New Cyclohexadienone Derivatives: Preparation and Chiral Discrimination in High-Pressure Diels–Alder Cycloadditions

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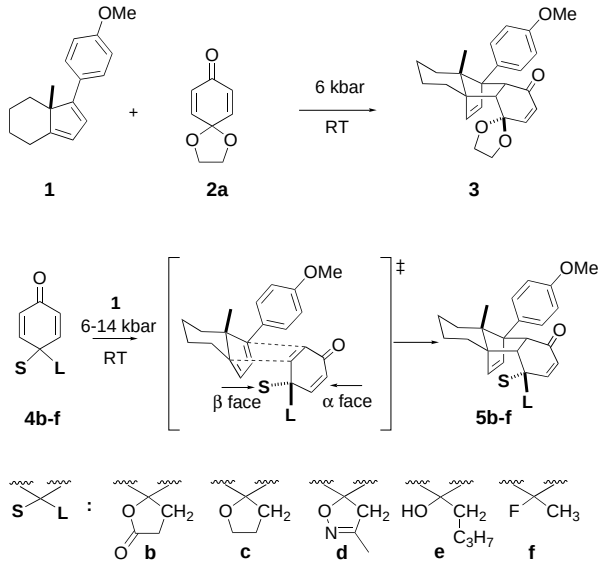
Abstract: A wide range of cyclohexadienones has been synthesised in order to study their reactivity and their regio- and stereoselectivity with the enantiopure diene **1** under high-pressure conditions. Computational investigations were used to point out some parameters which affect the reactivity in this high chiral discrimination process. In addition, the resulting [4+2] cycloadducts allowed the preparation of new polyfunctional cyclohexenone derivatives.

Keywords: asymmetric synthesis · chiral resolution · cyclohexadienones · Diels–Alder cycloadditions · high-pressure chemistry

Introduction

For many years, we have been investigating chiral recognition phenomena in Diels–Alder processes by means of high-pressure cycloadditions with the enantiopure cyclopentadiene **1**[1] (see Scheme 1). While **1** reacts with *p*-benzoquinone ethylene-monoketal **2a** to give a high yield of only one cycloadduct, **3**,[2] (i.e., absolutely *endo*- and regioselective), reactions with all prochiral cyclohexadienones **4b–f** showed, in addition, a high π-facial differentiation affording only **5b–c**,[3] **5d**,[4] **5e**[1b] and **5f**,[5] respectively.

The synthetic value of cycloadducts **3** and **5b–f** is their ability to undergo highly diastereoselective transformations in subsequent steps. The resulting intermediates finally released enantiopure polyfunctional cyclohexenones by an exothermic retro-Diels–Alder reaction.[2–5] The stereogenic centre controlling this π-facial differentiation in the Diels–Alder process was, in all these cases, located in the α position to the electron-poor *dienone* double bond: the substituent **S** (oxygen or fluorine atoms) was orientated into the resulting molecular cage to produce a weaker hindrance with the cyclopentene ring compared to that of **L** (-CH_2- or –CH_3 group), as demonstrated by Houk and co-workers with their theoretical calculations.[4b, 6] Furthermore, the electronic properties of substituents **S** and **L**,[5, 6a] as well as the size of these



Scheme 1. Diels–Alder cycloadditions of enantiopure diene **1** with various cyclohexadienones gave rise to only one diastereoisomer under high-pressure conditions.

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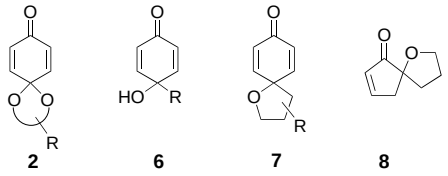
groups should have an influence on the rate or the efficiency of the cycloaddition. By extension, we assume that such effects should probably have consequences on the reactivity of cycloadduct **5** as well.

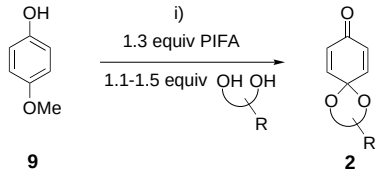
In this paper, we first report on the synthesis of a range of new dienophiles, *p*-benzoquinone spiro-monoketals **2**, 4-hydroxy-4-substituted cyclohexadienone (*p*-quinols) **6** and a new family of spiro-cyclohexadienones **7** by developed or



improved convenient general methods. These compounds permitted us to begin an extensive and systematic study of their [4+2] cycloaddition to enantiopure cyclopentadiene **1**. These experiments aimed to define those parameters that influence the cycloaddition rate and to demonstrate the general character of this π-facial differentiation rule. Computational investigations contributed to these experimental results. Transformations of the remaining enone double bond in cycloadduct **5** and subsequent thermal retro-reaction additionally lead to new, optically pure, polyfunctional cyclohexenone derivatives. Recently, a stereoselective induction from a chiral centre located in the α position of the *enone* carbonyl group was also reported.[7] Therefore, we also checked cyclopentenone **8**, which could give results comparable to those of **4c**.

Results and Discussion

Synthesis of *p*-benzoquinone spiro-monoketals: *p*-Benzoquinone monoketal is of quite some synthetic value as an electron-poor 2π partner. It offers an attractive source to allow various transformations and to build up polyfunctional cyclohexane derivatives.[8] In our case, there was the additional opportunity to examine thoroughly how the steric effect from the ketal groups (size and substituents) could influence the reactivity in Diels–Alder cycloadditions. For this purpose, a range of *p*-benzoquinone spiro-monoketals **2** (Scheme 2 and Table 1) was prepared by a convenient procedure developed in our laboratory.



Scheme 2. Straightforward synthesis of 1,4-benzoquinone spiro-monoketals **2**: i) 45 min, 4 °C → RT, CH_2Cl_2; PIFA: phenyliodonium bis(trifluoroacetate).

Recent methods for the preparation of these compounds were mainly based on the oxidation of phenolic derivatives either by electrochemical processes[9] (which require investment in special equipment) or by the use of a mild hypervalent iodine reagent. Pelter and Elgendy[10] described the use of two equivalents of phenyliodonium diacetate (PIDA) with phenol in methanolic medium to give *p*-benzoquinone dimethyl ketal in high yield. Abrams and co-workers[11] used the same approach with ethylene glycol as the co-solvent in hexane to isolate **2a** (Scheme 2, Table 1) in moderate yields. Starting from the inexpensive *p*-methoxyphenol (**9**), generation of mixed *p*-benzoquinone monoketals was achieved in good yields, thus avoiding the use of two equivalents of oxidizing reagent.[12] Alternatively, Pirrung and co-workers[13] developed a BF_3-catalysed transketalisation by treating monoketal **10** (Table 2) with various diols. More recently, de March, Figueredo and co-workers[14a] directly condensed butane-2,3-diol with the simple *p*-benzoquinone to furnish the enantiopure (+) *p*-benzoquinone spiro-monoketal **2b** (Scheme 2, Table 1) in good yield. However, this method which is limited to secondary 1,2-diols, sometimes produced bis-ketals or mixtures of mono-and bis-ketals with other diols. Recently, these authors applied this approach to the synthesis of new, enantiomerically pure, *p*-benzoquinone monoketals from new C_2-symmetric diols.[14b]

We wish to report a direct and facile conversion of *p*-methoxyphenol (**9**, Scheme 2, Table 1) to various spiro-monoketals with only 1.1–1.5 equivalents of the corresponding diols and 1.3 equivalents of phenyliodonium bis(trifluoroacetate) (PIFA). Although no evidence concerning the mechanism has been established yet, this sequence is probably initiated by phenolic oxidation. Attack on the phenolic intermediate by one hydroxyl group of the diol should trigger the subsequent intramolecular transketalisation. This latter process should be catalysed by the trifluoroacetic acid (TFA) generated in situ.

Several *p*-benzoquinone spiro-monoketals **2a–i** have been prepared this way and the results are summarised in Table 1.

Table 1. Conversion of *p*-methoxyphenol **9** by PIFA oxidation with several diols into the corresponding *p*-benzoquinone spiro-monoketal **2a–i**.

Entry	Diol	Equiv	Product	Yield [%]
1	ethylene glycol[a]	1.5	**2a**	83
2	butane-2,3-diol[a, c]	1.2	**2b**	68
3	*meso*-1,2-diphenyl-ethane-1,2-diol[b]	1.1	**2c**	36
4	1-phenyl-ethane-1,2-diol[a]	1.5	**2d**	77
5	3,3-dimethyl-butane-1,2-diol[a]	1.5	**2e**	40
6	3-chloro-propane-1,2-diol[a]	1.5	**2f**	64
7	3-iodo-propane-1,2-diol[b]	1.1	**2g**	29
8	butane-1,4-diol[a]	1.5	**2h**	45
9	*meso*-pentane-2,5-diol[a]	1.2	**2i**	19

[a] Dissolved in CH_2Cl_2; [b] dissolved in CH_3CN (minimum volume). [c] Mixture of isomers D,L/*meso* = 30:1; only a racemic product that originated from D,L-diols was isolated.

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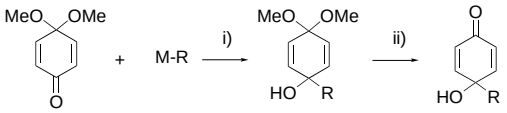
Table 2. Reaction of monoketal **10** with various organometallic reagents to give *p*-quinols **6a–f**.[a]



10 **11a-f** **12a-f** **6a-f**

Entry	Reagent	Equiv	Product	Yield [%]
1	**11a**	2.5	**6a**	76
2	**11b**	1.5	**6b**	54
3	**11c**	1.5	**6c**	80
4	**11d**	1.5	**6d**	81
5	**11e**	1.5	**6e**	76
6	**11f**	1.5	**6f**	91

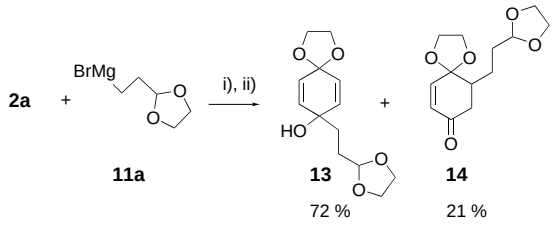
[a] i) **11** (1.5–2.5 equiv), THF, −78 °C; ii) flash chromatography (silica gel, EtOAc/light petroleum); **a**: M = BrMg, R = -$CH_2CH_2CH(OCH_2\text{-})_2$; **b**: M = ClMg, R = -$CH_2CH_2CH(OEt)_2$; **c**: M = Li, R = -$CH_3$; **d**: M = Li, R = -$CH_2CN$; **e**: M = Li, R = -CC-TIPS; **f**: M = Li, R = -CC-$CH(OEt)_2$.

CH_2Cl_2 was selected as the solvent of choice because i) PIFA is soluble and stable in this solvent (while PIDA is insoluble), ii) many commercially available diols are soluble in CH_2Cl_2, iii) the extraction work-up is simplified. When necessary, a minimum volume of dry acetonitrile (CH_3CN) was used to dissolve the diols (entries 3, 7). Slow addition into the ice-cooled PIFA solution prevented polymerisation or rapid degradation of the reagent observed under other conditions (which turned black immediately). Treatment with an excess of PIFA did not increase the yields. The reaction proved to be most efficient for five-membered ring closure with limited steric hindrance (entries 1, 2, 4). When CH_3CN was used as the co-solvent, lower yields were observed. The presence of halogen atoms on the diols seems to be quite well tolerated during the reaction (entries 6, 7). The high cost (entry 9) or low solubility in CH_2Cl_2 (entries 3, 7) of diols prompted us to employ only 1.1–1.2 equivalents. Although some yields remain low, this new route, which tolerates various substituents on the diol, provides the most expedient solution to furnish rapidly a range of various *p*-benzoquinone spiromonoketals.

Preparation of *p*-quinol intermediates: Hypervalent iodine reagents can also be employed to prepare *p*-quinols, as demonstrated by McKillop and co-workers.[15] This oxidation was performed in aqueous CH_3CN. However, various constraints in this method prompted us to pay much attention to the alternative "organometallic" route as well. Direct addition of organometallic reagents to *p*-benzoquinones gave mixtures with moderate-to-low yields of *p*-quinols,[16] owing mainly to the difficulty in avoiding unwanted double addition and to the intervention of quinone redox chemistry. To elude these side effects, the employment of *p*-benzoquinone monoketal **10** (Table 2) tends to be the general solution.[17, 4b]

We started our investigation by revisiting the existing *p*-quinol synthesis. It was reported[8e] that the reaction of Grignard reagent **11a** with **10** gave incomplete conversion to **12a** (Table 2). The following selective hydrolysis (oxalic acid, silica gel, CH_2Cl_2) finally led to **6a** in 46% overall yield from **10** (72% based on recovered starting materiel). In our hands, the use of 2.5 equivalents of **11a** resulted in a complete conversion into **12a** (observed by TLC). In addition, simple flash chromatography through silica gel with ethyl acetate/light petroleum as the eluent gave **6a** in 76% overall yield from **10**.

However, a minor, less polar, second spot observed in the TLC (not isolable) suggested that some 1,4 addition product had also been formed. This regioselectivity is better illustrated by addition of **11a** to the less sensitive[18] monoketal **2a** (Scheme 3). This addition afforded the protected compound **13** and the 1,4-adduct **14** in 72% and 21% yields, respectively.



11a **13** **14**
72% 21%

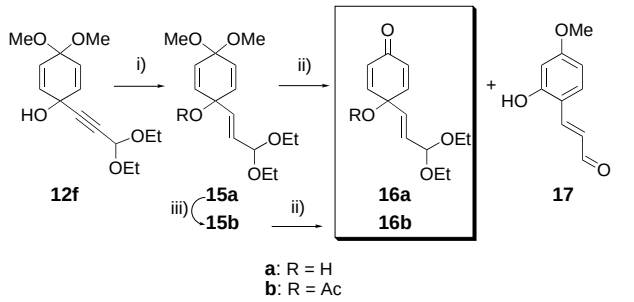
Scheme 3. i) **11a** (2.5 equiv), THF, −78 °C; ii) flash chromatography (silica gel, EtOAc/light petroleum).

The results with various organometallic reagents are summarised in Table 2. When organolithium reagents were added to **10**, only one intermediate (1,2 addition) was observed in TLC. Because of the difficulties in the preparation of Grignard reagent **11b**,[19] only 1.5 equivalents were used and therefore **6b** was only obtained in a moderate yield (54%).

The ability of **12a–f** to undergo hydrolysis by simple chromatography through silica gel gives access to a very convenient and mild approach to *p*-quinol derivatives, especially when other acid-sensitive groups are present (entries 1, 2, 5, 6).

However, depending on the nature of the substituted side-chain, some changes of the procedure had to be considered. We noticed, for instance, that electron-withdrawing functional groups, such as the cyano group (entry 4), induced a not entirely unexpected stabilisation of intermediate **12d**. It was thus necessary to employ double the amount of silica gel to convert **12d** completely into **6d**.

Another characteristic situation is illustrated in Scheme 4. After hydrometallation of the triple bond in **12f** with Red/Al to afford, after hydrolysis, only the unsaturated acetal **15a** with *E* configuration,[20] a subsequent standard chromatography afforded *p*-quinol **16a** and the unsaturated and rearranged aldehyde **17** in 13% and 42% overall yield, respectively. During acid hydrolysis, competitive rearrangements can obviously lead to more stable aromatic compounds.[21] This is particularly relevant for highly conjugated derivatives such as **17**. Assuming that the hydroxyl group acts as the leaving group, crude **15a** was converted by acetylation into **15b**. After standard chromatography, we managed to isolate, as expected, the acetylated cyclohexadienone **16b** in 47% yield from **12f**. With regards to the chemioselective

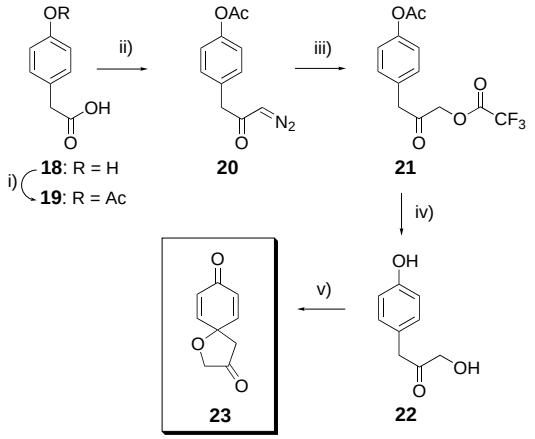


Scheme 4. i) Red/Al (1.5 equiv), THF, 0 °C, 15 min; ii) silica gel (EtOAc/light petroleum); iii) DMAP (2.5 equiv), Ac_2O (2.0 equiv), CH_2Cl_2, RT, 5 min.

hydrolysis of **15a**, we finally discovered that rapid filtrations (two or three times) of the highly diluted ethyl acetate/light petroleum solution (80:20) of **15a** through the same silica gel column followed by chromatography separation gave **16a** and **17** in 42% and 9% yields, respectively (from **10**).

Preparation of spiro-cyclohexadienones: Taking account of these results, we decided to tackle the synthesis of spiro-cyclohexadienones of type **7** (see above) by the use of the same operations, namely either phenolic oxidation or the organometallic approach.

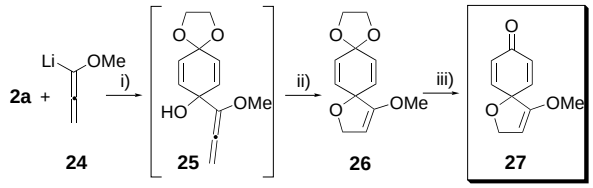
Synthesis by phenolic oxidation: The phenolic intermediate **22** (Scheme 5) was prepared by a modified Beames and Mander's procedure.[22] Treatment of the commercially available intermediate **18** with acetic acid anhydride resulted in the formation of the protected alcohol **19** (95%). This was treated successively with an excess of oxalyl chloride [$(COCl)_2$] in dry chloroform followed by an excess of diazomethane (CH_2N_2) in ether to afford phenolic diazoketone **20** (78%). Chatterjee and co-workers[23] had reported the formation of an unexpected hydroxymethyl ketone group by the reaction of the diazoketone group with TFA at −20 °C. We did not obtain the hydroxymethyl ketone directly, but the trifluoroacetate **21** (94%) first. A simple deprotection of both alcohol groups under mild basic conditions provided the hydroxymethyl ketone **22** (90%).



Scheme 5. i) Ac_2O, NaOH, H_2O/CH_2Cl_2, RT, 30 min, 95%; ii) $(COCl)_2$ (3 equiv), $CHCl_3$, RT, 2 h; CH_2N_2, Et_2O, 0 °C, 2 h, 78%; iii) TFA (2 equiv), CH_2Cl_2, −10 °C, 2 h, 94%; iv) $Na_2CO_3/NaHCO_3$, H_2O/MeOH, 90%; v) PIFA (1.2 equiv), CH_3CN/CH_2Cl_2, 43%.

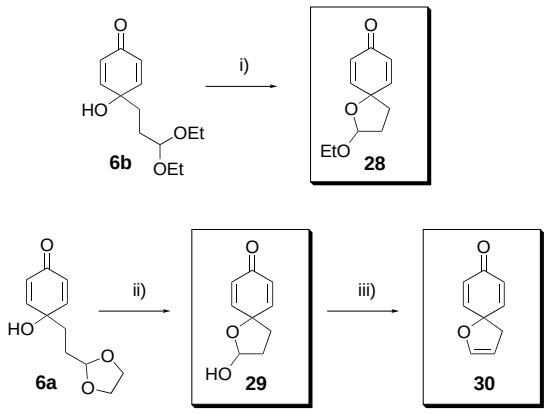
In the crucial oxidative cyclisation process, treatment of **22** with PIFA in dry CH_3CN/CH_2Cl_2 afforded spiro-dihydrofuranone **23** in 43% yield. Many attempts to improve the yield by changing the solvent, the temperature or the oxidant (by PIDA instead of PIFA) did not change the outcome.

Synthesis by organometallic techniques: Lithiated methoxyallene **24**[24] (Scheme 6) reacted with **2a** to give derivative **25**. This crude product was then directly converted into the corresponding tricyclic enol ether **26** (76% from **2a**) by treatment with potassium *tert*-butoxide (KO*t*Bu). Selective hydrolysis finally gave the spiro-enol ether **27** (88%).



Scheme 6. i) Et_2O, −78 °C; ii) KO*t*Bu (0.5 equiv), DMSO, RT, 30 min, 76%; iii) cat. *p*TsOH, H_2O/THF, reflux, 10 min, 88%.

We also investigated the cyclisation of *p*-quinols **6a–b** (Scheme 7). As expected, *p*-quinol **6b** in dry THF and in the presence of anhydrous camphor sulfonic acid (CSA) led to spiro-acetal **28** (63%). In the case of *p*-quinol **6a**, we first had to remove the dioxolane group in the presence of the acid-sensitive *p*-quinol. Standard conditions (aqueous HCl, H_2SO_4, CH_3CO_2H) gave a complex mixture.[21] Alternatively, the use of $[PdCl_2\cdot(MeCN)_2]$ has been reported.[8e] However, this smooth method had been described to be slow (3 d). Finally, we found that rapid treatment (30 min) of **6a** under mild acidic conditions (cat. *p*-TsOH, H_2O/THF, reflux) provided a satisfactory yield of spiro-lactol **29** (69%). Treatment with methanesulfonyl chloride (MsCl) and triethylamine (NEt_3) in CH_2Cl_2 subsequently afforded the spiro-enol ether **30** in 53% isolated yield.



Scheme 7. Cyclisation of *p*-quinols **6a–b**. i) CSA (0.25 equiv), THF, 5 h, RT, 63%; ii) cat. *p*TsOH, H_2O/THF, reflux, 30 min, 69%; iii) MsCl (3 equiv), NEt_3 (6 equiv), CH_2Cl_2, 0 °C → RT, 6 h, 53%.

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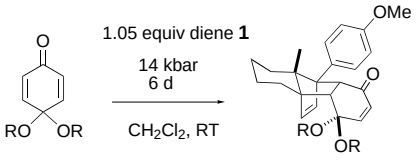
Reactivity and stereoselectivity in the Diels – Alder cycloaddition with diene 1: Now that a number of spiro-compounds were available, the reactivity of several dienones was compared by various competitive cycloaddition experiments.

p-Benzoquinone monoketal

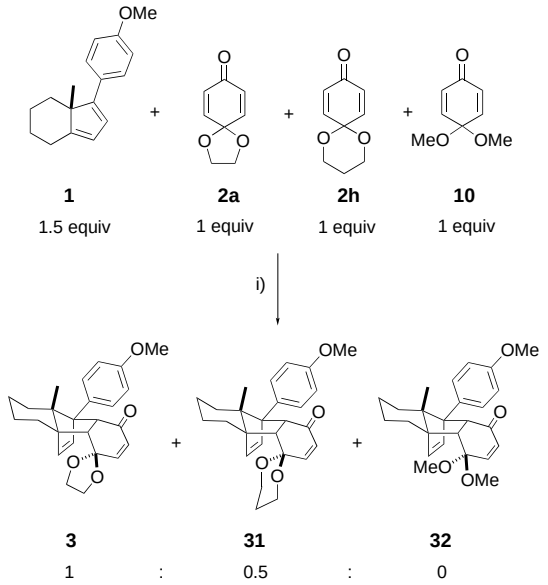
Synthesis of the corresponding cycloadducts: The dienophiles **2h** (Table 3, entry 1) and **10** (entry 2) were added to diene **1** in CH_2Cl_2 under high pressure (14 kbar, 25 °C) for 6 d. In each case, a single cycloadduct (**31** and **32**) was isolated (80 % and 78 % yield, respectively).

Table 3. Synthesis of monoketal cycloadducts **31** and **32** under high-pressure conditions.



Entry	Dienophile	R	Cycloadduct	Yield [%]
1	**2h**	$-CH_2-CH_2-CH_2-$	**31**	80
2	**10**	–Me	**32**	78

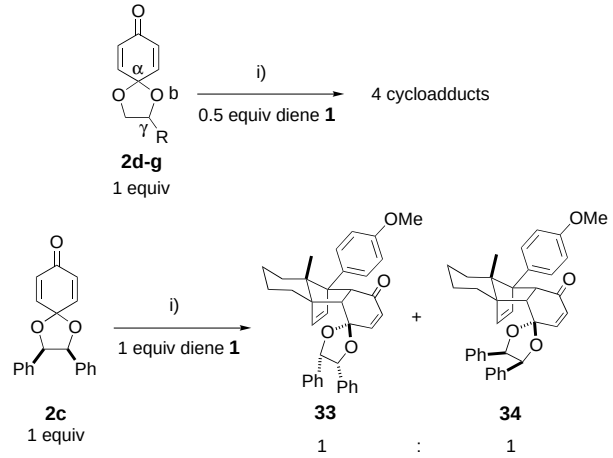
Kinetic comparison studies: The comparison between *p*-benzoquinone spiro-monoketals **2a**, **2h** and *p*-benzoquinone monoketal **10** (Scheme 8) in cycloadditions to diene **1** was carried out in order to demonstrate the structural influence of



Scheme 8. Structural influence of substituents located in the *para* position of dienone on the cycloaddition rate. i) 14 kbar, RT, CH_2Cl_2, 6 d.

the ketal moiety on the cycloaddition rate: 1 equivalent of each dienophile **2a**, **2h** and **10** with 1.5 equivalents of diene **1** in CH_2Cl_2 were sealed in the same Teflon tube which was held under high-pressure (14 kbar, 25 °C) for 6 d. The crude mixture was then analysed by ^1H NMR and the ratio of cycloadducts was concluded from integration and comparison of specific peaks. The ratio observed (**3**/**21**/**22** = 1:0.5:0) indicates that small and conformationally rigid groups (**2a**) produce weaker steric interactions compared to six-membered rings and especially to open-chain substituents (probably more hindrance by free rotation).

We also investigated the influence from stereogenic centers located in γ position from the dienone double bond. In the case of the five-membered ring (Scheme 9), the cycloaddition



Scheme 9. No diastereoselectivity in cycloaddition process from stereogenic centre in the γ position with the five-membered ring; i) 6.5 kbar, RT, CH_2Cl_2, 6 d.

of mono-substituted spiro-acetals **2d – g** (1 equivalent) with diene **1** (0.5 equivalent) gave rise to an inseparable mixture of four cycloadducts in every case.

Lack of any steric hindrance effect was confirmed by the addition of the *meso*-compound **2c** (1 equivalent) to diene **1** (1 equivalent) to afford a crude mixture of two separable cycloadducts **33** and **34** in a ratio of 1:1 (46 % and 45 % isolated yield, respectively). The conformation of cycloadduct **33** was assigned by means of the NOE signals (Figure 1).

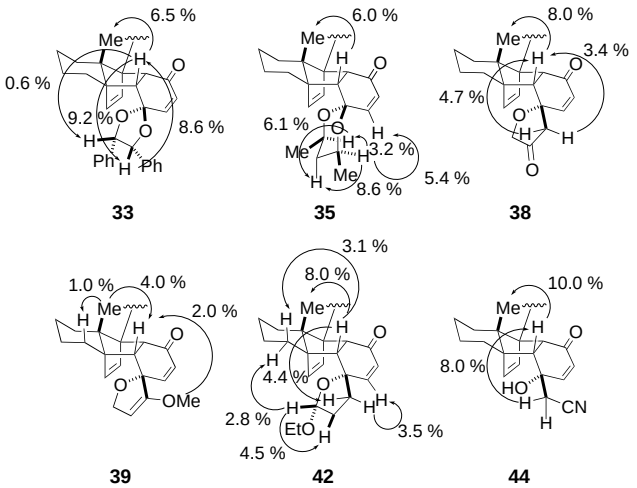
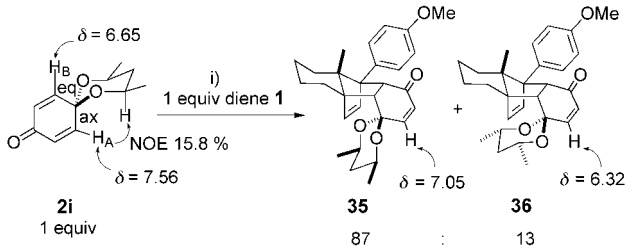


Figure 1. Stereochemistry assignment of **33**, **35**, **38**, **39**, **42** and **44** by NOE experiments.

These results are quite consistent with those obtained by de March, Figueredo and co-workers. These authors have also reported such lack of facial selectivity with this 1,3-dioxaspiro-[4,5]decane structure when the C_2-symmetric analogues were employed in reactions such as the conjugate addition of aromatic thiols[8f] or 1,3-dipolar cycloaddition to cyclic nitrones.[8g]

That stereogenic centres at this distance can still direct additions was illustrated with six-membered ring ketals which showed a moderate diastereoselectivity (Scheme 10). When

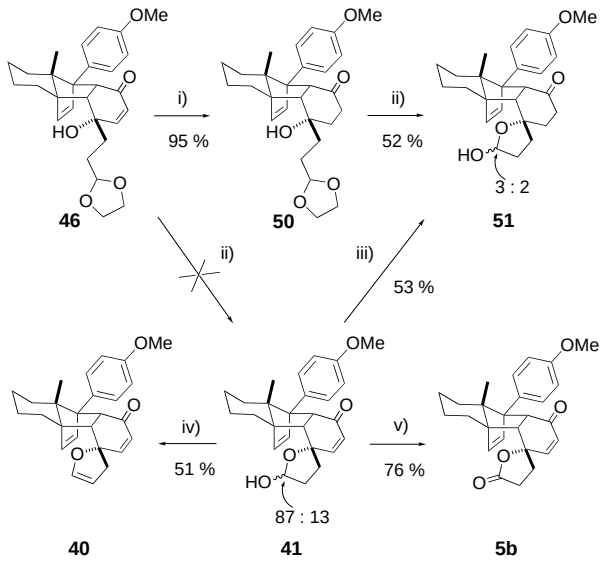


Scheme 10. Moderate diastereoselectivity resulting from a side differentiation induced by the conformation of the *meso* six-membered-ring ketal on the dienone **2i**; i) 14 kbar, RT, CH_2Cl_2, 6 d.

meso-compound **2i** (1 equivalent) was added to diene **1** (1 equivalent) under a pressure of 14 kbar for 6 d, an 87:13 ratio of **35** and **36** was obtained (^{1}H NMR measurements).

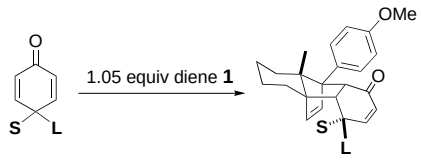
NOE experiments assigned the conformation of diastereoisomer **35** (Figure 1). This selectivity can be rationalised as a *side* differentiation induced by the conformation of the spiro-dienone **2i**. This differentiation is illustrated by the chemical shift in ^{1}H NMR: proton H_A ($\delta_{HA} = 7.56$) compared with proton H_B ($\delta_{HB} = 6.65$) exhibits a difference of 0.91 ppm. The presence of a NOE signal (15.8%) between the ketal protons and H_A indicates that a steric effect from the ketal group may well hinder the diene approach from one side.

At this stage, these results have pointed out that the configuration and conformation of an adjacent spiro-ketal ring generates steric effects which influence the cycloaddition rate. Whereas substituents tethered to the five-membered ketal ring of 1,3-dioxaspiro[4,5]decane structure do not induce any significant steric hindrance, a larger ring (six-membered) or open-ring monoketal manifests greater steric interaction with the diene during the [4+2]-cycloaddition process. The following investigations are devoted to the demonstration of the effect of electron-withdrawing or electron-donating substituents on the reactivity.



Scheme 11. Stereochemical assignment of **40**, **41** and **46** by chemical transformation; i) $Zn/NiCl_2 \cdot 6H_2O$ (1.5 equiv) in methoxyethanol/H_2O, sonification, 2.5 h, 95%; ii) cat. *p*TsOH, H_2O/THF, reflux, 45 min; iii) 10% Pd/C, H_2, THF, 3 h, 53%; iv) MsCl (1.5 equiv), NEt_3 (4 equiv), CH_2Cl_2, $-40\,^\circ C \rightarrow$ RT, 51%; v) PCC (1.5 equiv), molecular sieves, CH_2Cl_2, RT, overnight, 76%.

Table 4. Synthesis of the cycloadducts from diene **1** and various dienophiles.



Entry	Dienophile	Conditions[a]	Cycloadduct(s)	Yield [%]
1	**23**	i	**38**	85
2	**27**	i	**39**	89
3	**30**	i	**40**	74
4	**29**	ii	**41**	78
5	**28**	ii	**42/43**	34/29
6	**6d**	iii	**44**	89
7	**6c**	ii	**45**	79
8	**6a**	iv	**46**	87
9	**37**	iv	**47**	61
10	**16a**	i	**48**	77
11	**16b**	iv	**49**	51

[a] i) 14 kbar, RT, CH_2Cl_2, 6 d; ii) 14 kbar, RT, CH_2Cl_2, 13 d; iii) 14 kbar, RT, CH_3CN, 6 d; iv) 14 kbar, CH_2Cl_2, RT, 20 d.

Spiro-cyclohexadienones and *p*-quinol

Synthesis of the corresponding cycloadducts: These results are summarised in Table 4 and are, in most cases, examples of very selective reactions. At the beginning, all the dienophiles (1 equiv) were added to the enantiopure diene **1** (1.05 equiv) to furnish, in all cases, a single cycloadduct [except **28** (Scheme 7); Table 4, entry 5] in moderate-to-good yields. Whereas the cycloadduct **41** (Scheme 11 and Table 4, entry 4) was isolated as a thermodynamically controlled mixture of two diastereoisomers at the hemi-acetal centre (87:13, determined by ^{1}H NMR) in 78% yield, we obtained a 1:1 mixture as determined by ^{1}H NMR of separable diastereoisomers **42** and **43** that were isolated by chromatography in 34% and 29% yield, respectively.

To increase the steric hindrance close to the oxygen atom, we transformed the hydroxyl group of the dienophile **6a** into an acetate group (DMAP, acetic acid anhydride, CH_2Cl_2, 1 h) to obtain **37** (see Table 5) in 81% yield. Compounds **37** and **16b** (Scheme 4; Table 4, entries 9 and 11) were added to diene

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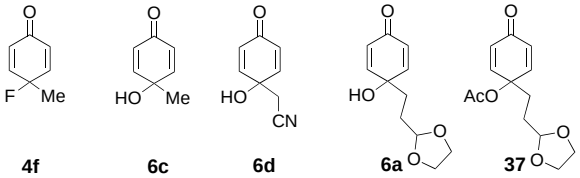
Table 5. Combination of electronic and steric effects on the relative rate of the cycloaddition. All experiments were carried out by mixing two different dienophiles (1 equiv each) with the diene **1** (1 equiv) under high-pressure conditions for 6 d. The dienophiles are ordered according to their relative reactivity observed experimentally (from left to right, more to less reactive).



	4f		**6c**		**6d**		**6a**		**37**
ratio 1	1	:	0[a]						
ratio 2			10	:			8.6		
ratio 3					10	:	2.2[c]		
ratio 4							5	:	1[b]

[a] 6 kbar, CH_2Cl_2; [b] 14 kbar, CH_2Cl_2; [c] 14 kbar, CH_2Cl_2/CH_3CN (1:1).

1 under a pressure of 14 kbar for 20 d to afford the cycloadducts **47** (61%) and **49** (51%) in moderate yield, respectively. *p*-Quinols **6e** and **6f** (Table 2) which bear an acetylene group did not give rise, however, to any corresponding cycloadducts, but to a mixture of polymers.

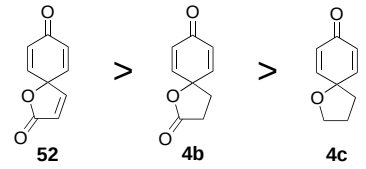
The configurations of **38**, **39**, **42**, and **44** were assigned by NOE experiments (Figure 1).

The structures of **40**, **41** and **46** were confirmed by chemical transformations (Scheme 11). Lactol **41** is readily oxidised by pyridinium chlorochromate (PCC) to afford the corresponding lactone **5d** (76%), the structure of which had been determined by a X-ray analysis at an earlier stage.[3] Acid hydrolysis of **46** did not furnish **41**, but mainly retro-Diels–Alder products. To overcome the retro-Diels–Alder process, the enone double bond was first reduced by Luche's procedure[25] to afford **50** in 95% yield. Hydrolysis of **50** gave rise to **51**, which displays a thermodynamic equilibrium of two diastereoisomers at the hemi-acetal centre (3:2 determined by ^{1}H NMR) in 52% yield. In the same way, the double bond of **41** was reduced by catalytic hydrogenation with Pd/C and the same hemi-acetal **51** was isolated in 53% yield. In addition, transformation of the hemi-acetal group of **41** into an enol-ether furnished cycloadduct **40** in 51% yield, which had also been obtained in the Diels–Alder cycloaddition of **30** with diene **1** (Scheme 7; Table 4, entry 3). Unfortunately, we did not manage to form the acetate **47** (cycloadduct from diene **1** and dienophile **37**, see Table 5) from **46** (Table 4, entries 8 and 9) which is probably caused by strong steric hindrances generated from the molecular cage formed around this hydroxyl group.

Kinetic comparison studies: We now set out to define the additional parameters that control the rate of the cycloaddition by simply comparing the kinetic behaviour of the different dienophiles in the presence of diene **1**. The comparison of various *p*-quinols was investigated first (Table 5).

These experiments have given us an initial improved understanding of the participation of each parameter. The comparison between **6c** and **6a** (ratio 2) demonstrated that the hindrance effect of the open side-chain weakly influences the rate (**6c**/**6a** = 10:8.6). A great deal of the acceleration observed with **6d** in comparison with **6a** (ratio 3, **6d**/**6a** = 10:2.2) can be attributed to the size and inductive effect from the electron-withdrawing property of the cyano group. This electronic induction is particularly noticeable when a stronger electron-withdrawing group, such as a fluoro group (**4f**) substitutes for the hydroxyl group (**6c**): all of diene **1** was consumed by **4f** exclusively and none of cycloadduct **45** was detected by ^{1}H NMR from the crude mixture (ratio 1). In this specific case, the steric parameter is also involved in the increase of the rate: because of its position close to the reactive centre, the fluoro group, which is smaller than a hydroxyl group, exerts less steric hindrance interaction as the cycloaddition evolves.[6] In contrast, the reactivity of the dienophile **37** decreases compared with **6a** (ratio 4, **6a**/**37** = 5:1). Although **37** carries an electron-withdrawing group on its oxygen atom, the enlargement of the steric hindrance resulting from the free rotation of this acyl group at this position affects the cycloaddition process by decreasing the reaction rate.

All these interpretations reveal the fact that it is not easy to quantify the steric and electronic effects at the same time and to make allowances for each factor. The kinetic comparison of the structurally rigid, five-membered ring, spiro-cyclohexadienones **7** offers the opportunity to exclude at least the steric hindrance factor since it has been demonstrated with the *p*-benzoquinone monoketal homologues (see above) that the hindrance from substituents at the γ position of the spiro five-membered ring have no significant influence on the reaction rate. Indeed, initial investigations in our laboratory[26] had already shown that **52** reacts faster than **4b** and **4b** is faster than **4c**.



The classification of the electron-withdrawing properties of these three different spiro-cyclohexadienones **7** is quite obvious (**52** > **4b** > **4c**) and is in good agreement with the experimental results. For greater accuracy, the electronic effects that result from the nature of the substituents themselves and to its location on the dienophile system is reflected in the shift of frontier molecular orbitals energies (FMO). In this context, we have studied further the inductive effects by the FMO method to a larger range of spiro-cyclohexadienones **7** in order to explore the viability of their convergence with the experimental results.

Computational investigations

Computational procedures

Reactants in the ground state: The conformations of the cycles belonging to the X-ray structure of the spiro-lactone adduct[3] were used to build the three-dimensional structure of the

reactants in the calculations. Geometries for all reactants were optimised by means of the gradient technique at the RHFAM1 level[27] with the MOPAC program (Version 5.0).[28]

Transition structures: All the RHFAM1 transition structures were located with the procedures implemented in the MOPAC program (Version 5.0).[28] All variables were optimised by minimising the sum of the squared scalar gradients (NLLSQ and SIGMA).[29] Force calculations were carried out to ensure that the transition structures located had one imaginary frequency. Final values of the gradient norms were <1 kcal Å^{-1} and each transition structure had only one negative eigenvalue in the Hessian matrix as required.

Definitions

The formation enthalpies of the fully optimised reactants in the ground state were calculated and summed to give the enthalpy of the reactants at infinite separation. The activation enthalpies ($E_{activation}$) were obtained by the difference between the enthalpies of the reactants at infinite separation with the formation enthalpy of the corresponding transition structures (ΔH_{TS}). The $\Delta E_{activation}$ or $\Delta\Delta H_{TS}$ were obtained by difference with the formation enthalpy of the most stable structure (ΔH_{TS} of **X**-*endo*β). The $E_{deformation}$ was obtained by the difference between the energy of the reactant moiety in the TS with the formation enthalpy of the reactant in the ground state.

FMO analysis

The evaluation of the difference in reactivities, rationalised with the FMO analysis, are summarised in Figure 2.

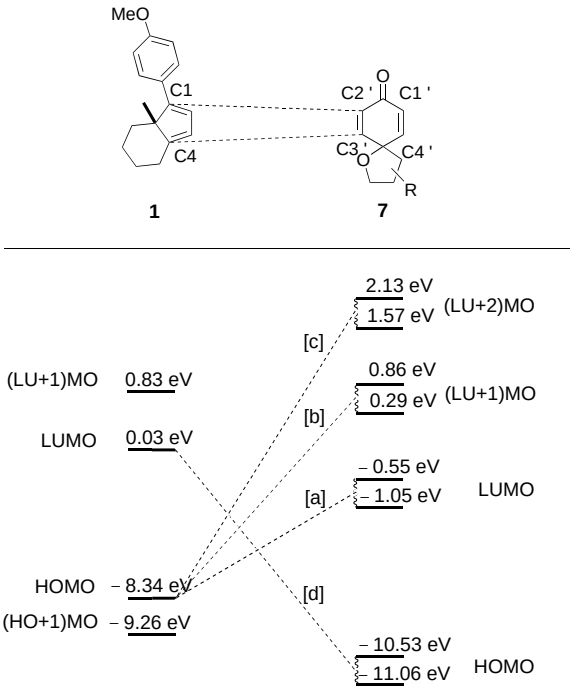


Figure 2. Diels–Alder $HOMO_{diene}$-controlled ([a] < [d]). Only LUMO of dienophiles **7** with favourable orbital coefficients relative to those of the HOMO in diene **1** are taken into account. [a] 7.29–7.79 eV, [b] 8.63–9.20 eV, [c] 9.91–10.47 eV, [d] 10.56–11.09 eV.

The conjugations of the π system of the diene with the π system of the phenyl ring on the one hand and of the π system of the dienophile with the π system of the carbonyl group on the other hand, give rise to several frontier molecular orbitals with p_z character. The relative disposition of the frontier orbitals for cyclopentadiene **1** [(HO + 1)MO(**1**) = − 9.26 eV, HOMO(**1**) = − 8.34 eV; LUMO(**1**) = + 0.03 eV] and dienophiles **7** [(HOMO(**7**) = − 11.06 to − 10.53 eV; LUMO(**7**) = − 1.05 to − 0.55 eV, (LU + 1)MO(**7**) = + 0.29 to + 0.86 eV] suggests that, on the basis of the narrower HOMO–LUMO gap, the reactions are predominantly HOMO-diene controlled ([a] < [d]). Under those conditions and in the further discussions, only $HOMO_{diene}$–[LUMO, (LU + 1)MO and $(LU + 2)MO]_{dienophile}$ interactions will be considered. The calculated relative reactivities of the different dienophiles are compared with the proportions of the corresponding products in the mixture obtained in each subsequent competition experiment in the same condition described previously (for the conditions, see Table 5). Assuming that the LUMO energy level ($n = 0$) of the dienophiles **7** acts as the dominant frontier orbital of the reactants, we have outlined the planning of our kinetic comparison following the lowest $LUMO_{dienophile}$ classification only. The results are summarised in Table 6. The results of the FMO calculation (**4b** > **23** > **30** > **29** > **27** ≥ **28** ≥ **4c**) showed a fairly good convergence (except for **27**) with the experimental findings.

We previously reported[2] that no reaction occurs between the spiro-cyclohexadienone **53** and the diene **1**. Steric hindrance interaction is used to explain such reactivity (a -CH_2- group has a higher steric demand than an oxygen atom). By comparing **53** with the closer but also the less reactive structural analogue **4c**, their LUMO energy levels also reveal that the presence of this endocyclic oxygen atom in the five-membered ring shifts, to a great extent, all the LUMOs to lower energy [**4c**/**53** $LUMO_{dienophile}$: − 0.55 eV < − 0.38 eV, (LU + 1)MO: + 0.76 eV < + 0.81 eV, LU(+2)MO: + 2.13 eV < + 2.36 eV]. The electronic impact of an oxygen atom caused by its relative electron-withdrawing property compared with the donating nature of a carbon atom set up at this position also seems to act as a favourable parameter for the activation of the cycloaddition.

The remarkable reactivity of the spiro-enol ether **27** with cyclopentadiene **1** compared with spiro-ethyl acetal **29** (ratio 8, **27**/**29** = 10:3) is surprising if only the interaction of the narrower $HOMO_{diene}$–$LUMO_{dienophile}$ gap [LUMO(**27**) > LUMO(**29**)] is considered. A structural analysis (Figure 3) of the π-orbital system in dienophiles **30** and **27** to a higher level (LU(+1)MO) reveals, however, that the p_z orbitals of the π system in the six-membered ring interact with the p_y of the double bond in the five-membered ring and cause the splitting of their LU(+1)MO into two unoccupied molecular orbitals LU(+1′)MO and LU(+1″)MO whose energy levels are + 0.62 and + 0.85 eV (**30**) and + 0.43 and + 0.86 eV (**27**).

Consequently, the LU(+1′)MO of **27** (+ 0.43 eV) is slightly lower compared to the LU(+1)MO of **29** (+ 0.70 eV) (Table 6). The higher reactivity observed with **27** compared to **29** can be better understood if one considers the interaction of the HOMO from diene **1** with all the LUMOs of dienophiles **7**, as indicated in the concept of frontier-controlled reactions.[30]

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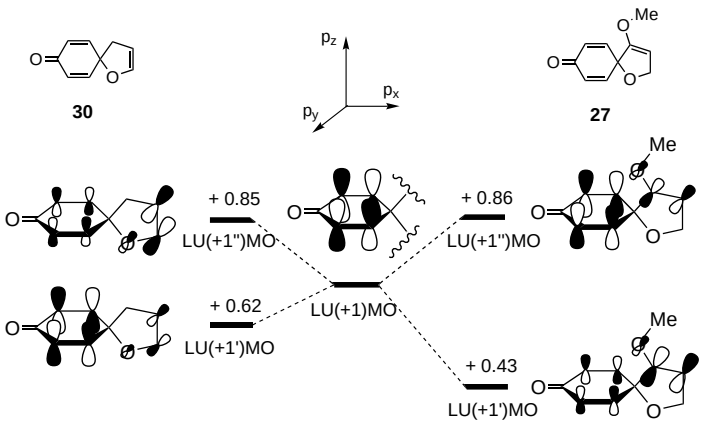

Figure 3. The LU(+1)MO of **30** and **27** split into two levels, LU(+1′)MO and LU(+1″)MO, consequential to the interaction between the π orbitals from their dienone group with those from double bonds located on their spiro five-membered ring.

However, the question still remains as to whether the electronic induction factors act as the sole significant parameter involved during the cycloaddition process in the case of the dienophile system **7**. As a matter of fact, the use of the FMO approach to predict the reactivity remains controversial.[31] Such a study consists of the comparison of the HOMO–LUMO gap of the starting material which might be different at the transition state (TS). Moreover, the formation of fused-ring structures requires that account is taken of ring strain parameters as well.

Hence, as an additional theoretical support to rationalise the experimental observations, the second part of our computational study is devoted to the location of the corresponding TS during the cycloaddition between **1** and the selected dienophiles **4b**, **23**, **27** and **53** (Table 6).

Transition states

Stereoselectivity: Houk and co-workers[4b] computed transition structures at the RHF/6-31G*//RHF/3-21G* level for the thermal reaction of a simple cyclopentadiene with the *p*-quinol as models and concluded that steric effects are responsible for the observed high π-facial diastereoselectivity. Recently, they[6] performed PM3 and RHF/6-31G* calculations for the Diels–Alder reactions of 1,5,5-trimethylcyclopentadiene with substituted cyclohexadienones. These calculations demonstrated that the high stereoselectivity, observed experimentally, arises from the lower steric demand of oxygen atom relative to a methylene group. The present study tends first to define the more stable TS during the cycloaddition between the cyclopentadiene **1** and the spiro-cyclohexadienone **4b**, for which the X-ray structure of the final product **5b** clearly indicates the stereoselectivity. In this case, the two real reactants are taken as a whole in the calculations at RHFAM1 level. Assuming that the dienophile approaches the less hindered face of the diene (the face by which the methyl group is set up), only eight possible transition structures were considered: **X** regio-chemical pathway C1(**1**)–C2′(**7**)/C4(**1**)–C3′(**7**) (for the numbering of the carbon atoms, see Figure 2) and **Y** regio-chemical pathway C1(**1**)–C3′(**7**)/C4(**1**)–C2′(**7**); stereofacial chemical pathways: *endoβ*, *exoβ* (the endocyclic oxygen atom of the five-membered ring pointing into the interior cage) and *endoα*, *exoα* (the -CH_2- group in the five-membered ring pointing into the interior cage). The formation enthalpies (ΔH_{TS}) and the relevant parameters for the eight transition structures involving cyclopentadiene **1** and spiro-cyclohexadienone **4b** (**X**, **Y**, *endo*, *exo*, *α* and *β* orientations of the dienophiles) are given in Table 7 and Table 8.

In their theoretical ab initio calculations of Diels–Alder reactions of cyclopentadiene with dienophiles, Jorgensen and co-workers[32] have found that the distances between the reacting centres are 2.066/2.357 Å for the *endo* TS and 2.100/2.326 Å for the *exo* TS in the cyclopentadiene/isoprene reaction at the MP3/6-31G*//6-31G* level. Houk[4b] has estimated that the distances between the reacting centres are 2.081/2.329 Å for the *endoβ* TS (*syn*) and 2.197/2.225 Å for the *endoα* TS (*anti*) in the cyclopentadiene/*p*-quinol reaction at the RHF/6-31G* level. Houk[6] has also illustrated that the distances between the reacting centres are 2.071/2.258 Å for the *endoβ* TS (*syn*), in the 1,5,5-trimethylcyclopentadiene/spiro-ether **4c** reaction at the RHF/6-31G* level. Our AM1 transition structures display comparable values (Table 7, **X**-*endoβ* TS, **X**-*exoβ* TS, **X**-*endoα* TS and **X**-*exoα* TS: C1(**1**)–C2′(**4b**)/C4(**1**)–C3′(**4b**) = 1.994/2.315 Å, 2.040/2.286 Å, 2.040/2.255 Å and 2.089/2.231 Å, respectively).

The corresponding bond lengths in the different theoretical treatments are equivalent to within 0.2 Å. It appears from the results of the energies in the RHFAM1 calculated TS of the reaction of diene **1** and spiro-cyclohexadienone **4b** that between the two stereochemical

Table 6. Frontier molecular orbitals (FMOs) of various dienophiles calculated at the RHFAM1 level as well as the experimentally observed product ratios.[a]

	52	**4b**	**23**	**30**	**29**	**27**	**28**	**4c**	**53**
LU(+2)MO	1.57	1.71	1.80	2.00	2.04	2.07	2.13	2.12	2.36
LU(+1)MO	0.29	0.39	0.48	0.62/0.85	0.70	0.43/0.86	0.76	0.77	0.81
LUMO	−1.05	−0.94	−0.85	−0.69	−0.62	−0.57	−0.56	−0.55	−0.38
ratio 5		5 : 1							
ratio 6			5 : 2						
ratio 7				2 : 1					
ratio 8					3 : 10				
ratio 9						10 : 2.3			
ratio 10							1 : 1		
ratio 11			10	:		9.5			
ratio 12					10 :		9		

[a] All experiments were performed at 14 kbar in CH_2Cl_2 for 13 d and following the same procedure described in Table 5. Dienophiles are classified according to their lowest LUMO value (in eV).

Table 7. The formation enthalpies and other relevant parameters for four transition structures of the *endo* stereofacial chemical pathway involving cyclopentadiene **1** and spiro-cyclohexadienone **4b** calculated at the AM1 level.

	X-*endoβ*	**X**-*endoα*	**Y**-*endoβ*	**Y**-*endoα*
ΔH_{TS} [kcal mol^{-1}][a]	−23.9	−18.9	−21.7	−21.2
$\Delta\Delta H_{TS}$ [kcal mol^{-1}][b]	0	5.0	2.2	2.7
C1(**1**)–C2′(**4b**) [Å][c]	2.315	2.255	1.957	1.999
C4(**1**)–C3′(**4b**) [Å][c]	1.994	2.040	2.329	2.289

[a] ΔH_{TS} = formation enthalpy of the corresponding TS. [b] $\Delta\Delta H_{TS}$ = difference between the formation enthalpy of the corresponding TS and the formation enthalpy of the most stable TS (i.e., **X**-*endoβ*). [c] Bonds being formed.

Table 8. The formation enthalpies and relevant parameters for four transition structures of the *exo* stereofacial chemical pathways involving cyclopentadiene **1** and spiro-cyclohexadienone **4b** calculated at the AM1 level.

	X-*exoβ*	**X**-*exoα*	**Y**-*exoβ*	**Y**-*exoα*
ΔH_{TS} [kcal mol^{-1}][a]	−16.1	−11.4	−13.7	−14.1
$\Delta\Delta H_{TS}$ [kcal mol^{-1}][b]	7.8	12.5	10.2	9.8
C1(**1**)–C2′(**4b**) [Å][c]	2.286	2.231	1.995	1.993
C4(**1**)–C3′(**4b**) [Å][c]	2.040	2.089	2.331	2.362

[a] ΔH_{TS} = formation enthalpy of the corresponding TS; [b] $\Delta\Delta H_{TS}$ = difference between the formation enthalpy of the corresponding TS with the formation enthalpy of the most stable one (i.e., **X**-*endoβ*, see Table 7); [c] bonds being formed.

pathways *endo* and *exo* [$\Delta H_{TS}(endo) = -23.9, -18.9, -21.7$ and -21.2 while $\Delta H_{TS}(exo) = -16.1, -11.4, -13.7$ and -14.1 kcal mol^{-1}] the *exo* TS are undoubtedly disfavoured compared with the *endo* TS. The differences between $\Delta H_{TS}(endo)$ and $\Delta H_{TS}(exo)$ are $\approx 7-8$ kcal mol^{-1}. Jorgensen and co-workers[32] have found that the preference for the *endo* approach of isoprene is ≈ 1.5 kcal mol^{-1} at the MP3 level. They have also mentioned that the TS of the *endo* addition in the cyclopentadiene dimerisation, computed as 2.7 kcal mol^{-1}, is consistent with the essentially exclusive observation of the *endo* dimer. They demonstrated that the much greater preference for the *endo* addition can be attributed to a steric clash between the hydrogen of the endocyclic methyl group in the *exo* transition state. Compared with the simple cyclopentadiene, our diene **1** presents the more bulky methyl group at this position instead of the hydrogen. The finding that the AM1-computed activation energies to form the *endo* cycloadducts are lower than the corresponding energies to the *exo* stereoisomers (7–8 kcal mol^{-1}) correlates nicely with the experimental as well as ab initio results.

The AM1-calculated energies also reveal that the **X**-*endoβ* TS (Table 7) is definitely the most stable. It is favoured over the **Y**-*endoβ* TS by 2.2 kcal mol^{-1} and over the **X**-*endoα* TS by 5.0 kcal mol^{-1}. This result is consistent with the exclusive formation of the **X**-*endoβ* cycloadduct. Houk[6] has interpreted this remarkable stereochemical outcome by invoking the steric effect between the formed cyclopentene and the substituent of **4c** (Table 6) spiro-cycle at TS. In our study, the entire real structure of the diene **1** interacting with the entire substrate has been considered.

It is noteworthy that a high-pressure environment may emphasise the chiral discrimination phenomenon as well. Ogoshi and co-workers[33] pointed out the role played by van der Waals forces in enantioselective processes and demonstrated that the resulting *chiral* recognition energy dramatically increases as external forces incline to restrict the volume of the system.

*Reactivity of **4b**, **23**, **27** and **53** estimated from TS analysis*: The calculations of three other TS that arise from the condensation of **23**, **27** and **53** (Table 6), respectively, with the diene **1** were also performed at the RHFAM1 level. According to the arguments discussed previously for **4b**, this procedure coincided sufficiently well with higher ab initio calculations to provide a good degree of confidence. In these conditions and in order to avoid some needless calculations, only the AM1 calculation of the **X**-*endoβ* TS of **23** and **27** and the **X**-*endoβ* TS of **53** were performed and these results are summarised in Table 9.

For the relative reactivity of **23** compared to **27** and taking into account the accuracy of the calculations (Table 9), their activation energies, calculated to be 46.8 and 47.3 kcal mol^{-1}, respectively, can be estimated as similar. This result correlates with the experimental observation (Table 6, 10:9.5, respectively) more closely than FMO results. The greater computed activation energy found for the **53** TS (Table 9, 51.6 kcal mol^{-1}) compared with those obtained for the reacting species **4b, 23** and **27** (45.7–47.3 kcal mol^{-1}) is in good agreement with the role played by a strong steric hindrance, which is probably associated with an unfavourable electronic disposition. Moreover, in order to have an appreciation of other possible steric influences on the reactivity, such as the angular strain in spirocyclic systems,[26] the activation energies of **4b**, **23**, **27** and **53** were partitioned and the relative stabilisation energies were analysed.

Table 9. The $E_{activation}$ and $E_{deformation}$ for the different transition states.[a]

Dienophiles **7**:	**4b** **X**-*endoβ*	**4b** **X**-*endoα*	**23** **X**-*endoβ*	**27** **X**-*endoβ*	**53** **X**-*endoβ*
$E_{activation}$ [kcal mol^{-1}]	45.7	50.7	46.8	47.3	51.6
diene moiety $E_{deformation}$ [kcal mol^{-1}]	24.1	25.3	24.0	24.1	26.1
dienophile moiety $E_{deformation}$ [kcal mol^{-1}]	17.1	21.3	17.5	17.2	20.5
remaining interaction energy [kcal mol^{-1}]	4.5	4.1	5.3	6.0	4.9
C4(**7**) bond angle deformation in the five-membered ring [°]	0.5	2.0	0.6	0.5	3.5
C1(**1**)–C2′(**7**) [Å][b]	2.315	2.255	2.319	2.312	2.240
C4(**1**)–C3′(**7**) [Å][b]	1.994	2.040	1.991	1.996	2.036

[a] $E_{activation}$ = difference between enthalpies of the reactants at infinite separation with the formation enthalpy of the corresponding transition structure; $E_{deformation}$ = difference between the energy of the reactant moiety in the TS with the formation enthalpy of the reactant in the ground state. [b] Bonds being formed.

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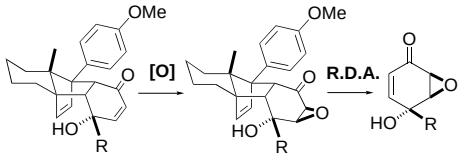
The energy of each reactant moiety (E_m) was evaluated by removing the atoms of the partner followed by single-point calculations, without altering the proposed geometry of the transition structure. The results reveal that the diene and dienophile moieties are more stable in the **X**-*endoβ* TS of **4b**, **23** and **27** than those in the **X**-*endoα* TS of **4b** and in the **X**-*endoβ* TS of **53**: The minimisation of the higher steric demand of the methylene group relative to the oxygen atom leads to a greater alteration of the structures of the reactants in **X**-*endoα* TS of **4b** and **X**-*endoβ* TS of **53**. These differences (Table 9) in stability are much more important in the dienophile moiety (17.1, 17.5, 17.2 compared with 21.3, 20.5) than in the diene moiety (24.1, 24.0, 24.1 compared with 25.3, 26.1). The exploration of the geometry of the dienophile moieties reveals that, in order to reduce the steric interaction, the C4′ bond angle in the five-membered ring is compressed. These angular deformations are much more important in the **X**-*endoα* TS of **4b** and in the **X**-*endoβ* TS of **53** (2.0° and 3.5°, respectively) than those in the **X**-*endoβ* TS of **4b**, **23** and **27** (≈0.5°). We believe that the angular strain from spiro-cyclohexadienones could also represent an additional and significant factor which influences the reactivity.

Epoxidation and retro-Diels – Alder reactions: The epoxidation of the remaining enone group has been shown to be completely diastereoselective (epoxidation of the less hindered face only) and efficient for the cycloadducts **3** and **5b** by the use of H_2O_2 under basic conditions (NaOH).[2, 3] When the same conditions were applied or a milder basic medium was used (K_2CO_3) for our *p*-quinol-cycloadducts **44**, **46** and **48**, only cycloadduct **44** reacted to give **54** in moderate yield (48%, with H_2O_2/K_2CO_3 only, Table 10, entry 1).

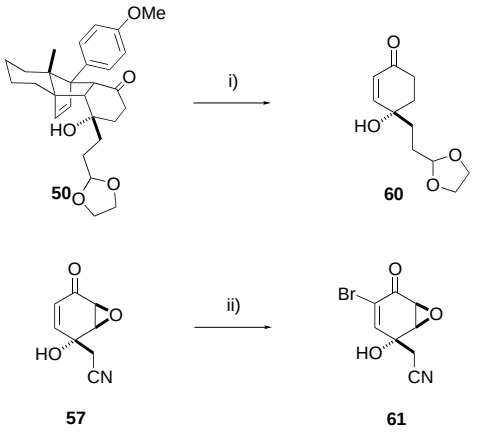
Table 10. Epoxidation and retro-Diels – Alder reactions.[a]



R			(Yield[%])		(Yield[%])
-CH_2-CN	**44**	i	**54** (48%)	iv	**57** (91%)
-C_2H_4-CH(OCH_2-)$_2$	**46**	ii	**55** (61%)	iv	**58** (96%)
-CH=CH-CH(OEt)$_2$	**48**	iii	**56** (57%)	iv	**59** (88%)

[a] i) H_2O_2/K_2CO_3, RT, 20 h; ii) LiO*O*t*Bu* (10 equiv), −25 °C for 5 h then 5 °C for 5 h; iii) LiO*O*t*Bu* (10 equiv), −25 °C for 5 h then −10 °C for 5 h; iv) 350 °C, 5×10^{-3} mbar.

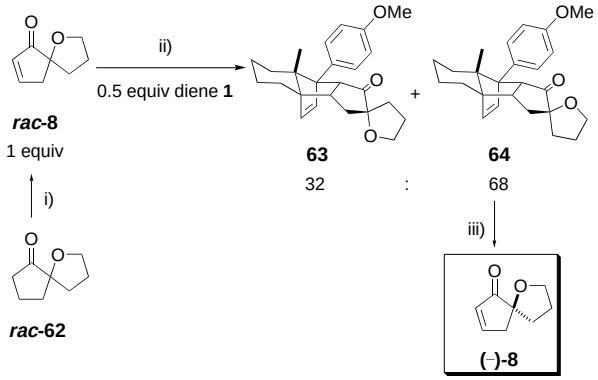
This reaction was also slower (20 h) and required a large excess of reagents. In fact, the efficiency of a cyclohexadienone in the Diels – Alder cycloaddition with the diene **1** correlates well with the reactivity of its corresponding cycloadduct toward the epoxidation process. This presumes again the participation of electronic inductions and steric effects. To increase the reactivity of the reactants, the use of lithium *tert*-butylhydroperoxide (LiO*O*t*Bu*) has been found to be efficient for the epoxidation of the cycloadduct **46** (entry 2) and **48** (entry 3) to provide the single diastereoisomers **55** and **56** respectively in moderate yields. The retro-Diels – Alder (R.D.A.) process by pyrolysis under reduced pressure (350 °C, 3×10^{-3} mbar) of **54** – **56** gave rise to the corresponding enantiopure enone compounds **57** – **59** in good yields (88 – 91%). Under the same conditions, the cycloadduct **50** (Scheme 12) gave the enantiopure compound **60** in good



Scheme 12. i) 350 °C, 5×10^{-3} mbar, 87%; ii) Br_2 (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, then NEt_3 (3 equiv), RT, 1 h, 68%.

yield (87%) whereas **51** failed to release the enone cleanly but gave a complex mixture instead. The enone **57** was converted into bromo-enone **61** (68%) which could find application as an intermediate in natural product synthesis.[34]

Chiral resolution with racemic α-spiro-ether cyclopentenone: Finally, we were interested in including further dienophile structures into our investigations. Starting from the racemic α-spiro-ether cyclopentanone *rac*-**62**[35] (Scheme 13), the racemic α-spiro-ether cyclopentenone *rac*-**8** was obtained in moderate yield (55%) using the Meyers' procedure.[36] The reaction with 0.5 equivalent of the diene **1** and 1 equivalent of *rac*-**8** under high pressure (20 kbar, 6 d) gave rise to a mixture of two cycloadducts **63** and **64** in a 32:68 ratio with 60% conversion referred to the diene **1** (determined by ^{1}H NMR).



Scheme 13. Kinetic resolution of the racemic mixture *rac*-**8** showed a moderate preference for the (−)-**8** enantiomer; i) $PhSO_2CH_3$ (1 equiv), KH (2.1 equiv), THF, RT, 1 h then reflux 2 h (toluene, Na_2CO_3), 55%; ii) 20 kbar, RT, CH_2Cl_2, 6 d, **63** (10%), **64** (40%); iii) 350 °C, 5×10^{-3} mbar, 93%.

Cycloadducts **63** and **64** were isolated in 10% and 40% yield, respectively (yields referred to the diene **1**). The structure of the majority diastereoisomer **64** was obtained by X-ray analysis[37] (Figure 4) and revealed that the -CH_2- of the

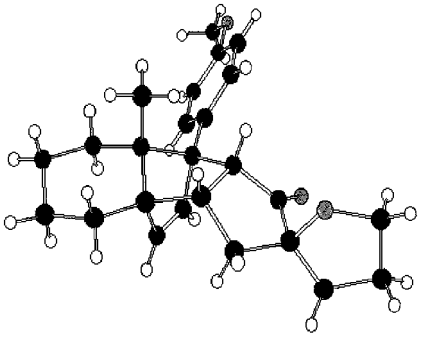


Figure 4. Structure of cycloadduct **64** as determined by X-ray analysis.

spiro-ether ring indeed points into the interior cage. This outcome proves that larger differences in spatial demands are clearly necessary to differentiate between α-carbonyl substituents **8**. The R.D.A. reaction by pyrolysis of **64** permitted the isolation of the enantiopure cyclopentenone (−)-**8** in good yield (93%).

Conclusions

We present here improved and simple preparations of various quinol derivatives and of spiro-dienophiles, in general. This is followed by investigations on the influence of their constitution and configuration on the rate and the stereoselectivity of Diels–Alder cycloadditions. The experimental results, which showed a high degree of selectivity, prove that although reaction rates can be influenced by electronic effects, the diastereoselectivity is a consequence of steric interactions. A very satisfactory theoretical interpretation of overall effects emerged from the computational investigations.

Experimental Section

General: All reactions involving Grignard reagents were carried out under a static pressure of N_2 in oven-dried glassware. Concentrations were defined by titration with the 2,2′-biquinoline colour test. Dry THF and Et_2O were distilled over sodium and benzophenone under N_2. CH_2Cl_2, $CHCl_3$, CH_3CN and triethylamine were distilled over calcium hydride under N_2. Light petroleum ether (PE) refers to the fraction with b.p. 45–60 °C. Optical rotations were recorded in $CHCl_3$ or MeOH with a Perkin–Elmer 241 polarimeter at the sodium-D line. Melting points were determined on a Büchi hotstage and were uncorrected. IR spectra were obtained on a Perkin—Elmer 580 in $CHCl_3$ or KBr (signal intensity: w = weak, m = medium, s = strong, vs = very strong). MS: Finnigan MAT 312 and VG Autospek and Kratos MS-80 instruments; HRMS: Finnigan MAT 312 and VG Autospek and Kratos MS-80 instruments. Electrospray ionisation mass spectrometry (ESI-MS) measurements on a LCT Micromass. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 or WP 400 instruments: δ_H values are given relative to tetramethylsilane ($\delta_H = 0$) and δ_C relative to $CDCl_3$ ($\delta_C = 77.14$). For flash chromatography, silica gel (300–600 mesh, Baker) was used. The high-pressure reactions were performed in a Hofer apparatus. *p*-Benzoquinone monoketal **10** was prepared following Pelter's procedure.[10] All liquid dialcohols were distilled with a kugelrohr apparatus prior to use.

General procedure for the synthesis of the spiro-monoketals 2a–i: *p*-Methoxyphenol (**8**, 1 equiv, 1M) and the corresponding dialcohol (1.0–1.5 equiv) in dry CH_2Cl_2 (when the dialcohol was insoluble in this solvent, dry CH_3CN was used) were injected dropwise to the stirred solution of phenyliodonium bis(trifluoacetate) (PIFA, 1.3 equiv, 0.1M) in dry CH_2Cl_2 at 4 °C (ice bath). The mixture was allowed to warm to room temperature for 45 min and was then neutralised with saturated Na_2CO_3 and decanted. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The corresponding spiro-monoketal **2** was purified by flash chromatography (silica gel, Et_2O/PE 1:4).

1,4-Dioxa-spiro[4.5]deca-6,9-dien-8-one (2a): *p*-Methoxyphenol (**9**, 3.0 g, 24.2 mmol) and ethylene glycol (2.23 g, 36.0 mmol, 1.5 equiv) mixed in CH_2Cl_2 were treated with PIFA (13.5 g, 31.4 mmol, 1.3 equiv) to yield spiro-monoketal **2a** (3.05 g, 83%) as colourless crystals after recrystallisation in Et_2O/PE. $R_f = 0.16$ (Et_2O/PE 2:3); m.p. 54 °C; IR ($CHCl_3$): $\tilde{\nu} = 2893$ (m), 1693 (s), 1678 (s), 1637 (s), 1382 (m), 1307 (m), 1115 (s), 1071 (m), 1012 (m), 975 (s), 947 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.63$ (d, $J = 10.1$ Hz, 2H), 6.17 (d, $J = 10.1$ Hz, 2H), 4.41 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.3$ (C), 143.3 (2 × CH), 129.0 (2 × CH), 98.3 (C), 65.9 (2 × CH_2); MS (70 eV): *m*/*z* (%): 152 (100) $[M]^+$, 128 (60); elemental analysis (%) calcd for $C_8H_8O_3$: C 63.14, H 5.30; found: C 63.16, H 5.31.

2,3-Dimethyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2b): *p*-Methoxyphenol (**9**, 500 mg, 4.0 mmol) and butane-2,3-diol (432 mg, 4.8 mmol, 1.2 equiv, mixture of isomers D,L/*meso* = 30:1) mixed in CH_2Cl_2 were treated with PIFA (2.25 g, 5.2 mmol, 1.3 equiv) to yield spiro-monoketal **2b** (486 mg, 68%) as a pale yellow solid after recrystallisation in Et_2O/PE. $R_f = 0.21$ (EtOAc/PE 2:3); m.p. 39 °C; IR ($CHCl_3$): $\tilde{\nu} = 2890$ (m), 1703 (s), 1681 (s), 1634 (s), 1380 (s), 1307 (s), 1102 (s), 1070 (s), 983 (s), 902 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.66$ (d, $J = 10.1$ Hz, 2H), 6.15 (d, $J = 10.1$ Hz, 2H), 3.83 (m, $J = 5.8$ Hz, 2H), 1.35 (m, $J = 5.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.6$ (C), 144.6 (2 × CH), 128.7 (2 × CH), 97.4 (C), 79.9 (2 × CH), 16.7 (2 × CH_3); MS (70 eV): *m*/*z* (%): 180 (100) $[M]^+$, 156 (6), 136 (86), 126 (40), 109 (42); HRMS: calcd for $C_{10}H_{12}O_3$: 180.0786, found: 180.0787.

***Meso*-2,3-Diphenyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2c)**: *p*-Methoxyphenol (**9**, 480 mg, 3.87 mmol) and 1,2-diphenyl-ethane-1,2-diol (911 mg, 4.26 mmol, 1.1 equiv) mixed in dry CH_3CN were treated with PIFA (2.19 g, 5.1 mmol, 1.3 equiv) to yield spiro-monoketal **2c** (422 mg, 36%) as clear yellow needles after recrystallisation in Et_2O/PE. $R_f = 0.44$ (EtOAc/PE 1:2); m.p. 154 °C; IR ($CHCl_3$): $\tilde{\nu} = 2916$ (w), 1676 (s), 1640 (s), 1384 (m), 131 (m), 1264 (m), 1176 (s), 1116 (vs), 1072 (s), 1004 (s), 852 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.15$ (dd, $J = 10.3$, 3.1 Hz, 1H), 7.14–7.08 (m, 5H), 7.07 (dd, $J = 10.3$, 3.1 Hz, 1H), 7.05–7.00 (m, 5H), 6.40 (dd, $J = 10.3$, 2.2 Hz, 1H), 6.26 (dd, $J = 10.3$, 2.2 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.2$ (C), 143.9 (CH), 141.8 (CH), 136.2 (2 × C), 131.3 (CH), 127.9 (CH), 127.88 (6 × CH), 126.9 (4 × CH), 98.6 (C), 82.4 (2 × CH); MS (EI, 90 °C): *m*/*z* (%): no molecular peak, 198 (100), 105 (46), 77 (49); MS (FAB+): *m*/*z* (%): 327 (12) $[M+Na]^+$, 305 (47) $[M+H]^+$, 198 (100), 154 (75), 136 (67), 105 (48); elemental analysis (%) calcd for $C_{20}H_{16}O_3$: C 78.92, H 5.30; found: C 78.69, H 5.24.

2-Phenyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2d): *p*-Methoxyphenol (**9**, 1.0 g, 8.06 mmol) and 1-phenyl-ethane-1,2-diol (1.67 g, 12.1 mmol, 1.5 equiv) mixed in CH_2Cl_2 were treated with PIFA (4.51 g, 10.5 mmol, 1.3 equiv) to yield spiro-monoketal **2d** (1.42 g, 77%) as a clear yellow oil. $R_f = 0.45$ (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu} = 3040$ (w), 2888 (w), 1676 (s), 1636 (s), 1496 (w), 1384 (m), 1304 (m), 1228 (m), 1180 (s), 1120 (vs), 1072 (m), 1016 (m), 976 (s), 852 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.43–7.32 (m, 5H), 6.78 (m, 1H), 6.76 (m, 1H), 6.22 (m, 1H), 6.19 (m, 1H), 5.27 (dd, $J = 8.3$, 6.0 Hz, 1H), 4.49 (dd, $J = 8.4$, 6.0 Hz, 1H), 3.89 (dd, $J =$ 8.4, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.3$ (C), 143.7 (CH), 143.2 (CH), 137.0 (C), 129.3 (CH), 128.83 (CH), 128.77 (2 × CH), 128.7 (CH), 126.2 (CH), 126.17 (CH), 99.1 (C), 79.2 (CH), 72.2 (CH_2); MS (70 eV): *m*/*z* (%): 228 (24) $[M]^+$, 199 (28), 122 (100), 104 (83), 91 (84), 77 (40); HRMS: calcd for $C_{14}H_{12}O_3$: 228.0786, found: 228.0796.

2-*tert*-Butyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2e): *p*-Methoxyphenol (**9**, 500 mg, 4.0 mmol) and 3,3-dimethyl-butane-1,2-diol (690 mg, 5.85 mmol, 1.5 equiv) mixed in CH_2Cl_2 were treated with PIFA (2.25 g, 5.2 mmol, 1.3 equiv) to yield spiro-monoketal **2e** (333 mg, 40%) as an amorphous white solid. $R_f = 0.45$ (Et_2O/PE 1:1); m.p. 61 °C; IR ($CHCl_3$):

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$\tilde{\nu}$ = 2964 (s), 2896 (w), 1676 (vs), 1636 (s), 1476 (w), 1384 (m), 1304 (m), 1228 (m), 1176 (s), 1120 (vs), 1072 (m), 1004 (s), 984 (s), 852 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.72 (dd, J = 10.1, 3.1 Hz, 1H), 6.61 (dd, J = 10.1, 3.1 Hz, 1H), 6.18 (dd, J = 10.1, 2.2 Hz, 1H), 6.13 (dd, J = 10.1, 2.2 Hz, 1H), 4.13 (dd, J = 8.2, 6.3 Hz, 1H), 4.03 (dd, J = 8.2, 6.3 Hz, 1H), 3.84 (t, J = 8.2 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.3 (C), 144.7 (CH), 143.3 (CH), 129.4 (CH), 128.0 (CH), 98.5 (C), 85.2 (CH), 66.7 (CH_2), 32.7 (C), 25.6 ($3\times CH_3$); MS (70 eV): m/z (%): 208 (4) $[M]^+$, 193 (2), 182 (2), 152 (100), 123 (41); HRMS: calcd for $C_{12}H_{16}O_3$: 208.1099, found: 208.1098.

2-Chloromethyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2f): *p*-Methoxyphenol (**9**, 1.0 g, 8.0 mmol) and 3-chloro-propane-1,2-diol (1.33 g, 12.1 mmol, 1.5 equiv) mixed in CH_2Cl_2 were treated with PIFA (4.51 g, 10.5 mmol, 1.3 equiv) to yield spiro-monoketal **2f** (1.03 g, 64%) as a clear yellow oil. R_f = 0.33 (EtOAc/PE 1:2); IR ($CHCl_3$): $\tilde{\nu}$ = 3048 (w), 2964 (m), 1680 (s), 1636 (s), 1444 (w), 1228 (w), 1180 (s), 1120 (s), 1072 (s), 980 (s), 852 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.69 (dd, J = 9.9, 3.1 Hz, 1H), 6.65 (dd, J = 9.9, 3.1 Hz, 1H), 6.21 (dd, J = 10.1, 2.2 Hz, 1H), 6.16 (dd, J = 10.1, 2.2 Hz, 1H), 4.57 (dddd, J = 6.8, 6.1, 4.4, 5.6 Hz, 1H), 4.32 (dd, J = 8.9, 6.1 Hz, 1H), 4.10 (dd, J = 8.9, 5.6 Hz, 1H), 3.68 (dd, J = 11.4, 4.4 Hz, 1H), 3.62 (dd, J = 11.4, 6.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 185.1 (C), 143.6 (CH), 142.3 (CH), 129.7 (CH), 128.5 (CH), 99.4 (C), 76.4 (CH), 68.4 (CH_2), 43.7 (CH_2); MS (70 eV): m/z (%): 202 (35) $[C_9H_9O_3{}^{37}Cl]^+$, 200 (57) $[C_9H_9O_3{}^{35}Cl]^+$, 151 (57), 109 (46), 82 (100), 68 (75); HRMS: calcd for $C_9H_9O_3{}^{35}Cl$: 200.0240, found: 200.0238.

2-Iodomethyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (2g): *p*-Methoxyphenol (**9**, 850 mg, 6.85 mmol) and 3-iodo-propane-1,2-diol (1.8 g, 8.9 mmol, 1.3 equiv) mixed in dry CH_3CN were treated with PIFA (3.83 g, 8.8 mmol, 1.3 equiv) to yield spiro-monoketal **2g** (580 mg, 29%) as a clear yellow solid. R_f = 0.38 (EtOAc/PE 2:3); m.p. 55 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3000 (w), 2960 (m), 1676 (s), 1636 (s), 1384 (w), 1224 (vs), 1180 (s), 1116 (s), 1072 (m), 976 (m), 852 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (m, 1H), 6.65 (m, 1H), 6.20 (m, 1H), 6.16 (m, 1H), 4.49 (dddd, J = 8.1, 5.9, 5.5, 4.4 Hz, 1H), 4.36 (ddd, J = 8.8, 5.5, 0.4 Hz, 1H), 3.98 (dd, J = 8.8, 5.9 Hz, 1H), 3.35 (ddd, J = 10.1, 4.4, 0.4 Hz, 1H), 3.25 (dd, J = 10.1, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1 (C), 143.8 (CH), 142.4 (CH), 129.8 (CH), 128.7 (CH), 99.9 (C), 76.8 (CH), 70.9 (CH_2), 4.8 (CH_2); MS (70 eV): m/z (%): 292 (74) $[M]^+$, 266 (20), 165 (75), 151 (92), 123 (100), 93 (92); HRMS: calcd for $C_9H_9O_3I$: 291.9596, found: 291.9598.

1,5-Dioxa-spiro[5.5]undeca-7,10-dien-9-one (2h): *p*-Methoxyphenol (**9**, 500 mg, 4.0 mmol) and 1,3-propandiol (460 mg, 6.0 mmol, 1.5 equiv) mixed in CH_2Cl_2 were treated with PIFA (2.25 g, 5.2 mmol, 1.3 equiv) to yield spiro-monoketal **2h** (302 mg, 45%) as a clear yellow solid. R_f = 0.29 (EtOAc/PE 2:3); m.p. 66 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 2964 (w), 1684 (vs), 1640 (vs), 1392 (m), 1316 (m), 1244 (m), 1180 (s), 1116 (s), 1076 (m), 1040 (m), 996 (vs), 932 (s), 848 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.16 (d, J = 10.3 Hz, 2H), 6.19 (d, J = 10.3 Hz, 2H), 4.10 (t, J = 5.6 Hz, 4H), 1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2 (C), 142.1 ($2\times$ CH), 128.3 ($2\times$ CH), 88.9 (C), 60.9 ($2\times CH_2$), 24.9 (CH_2); MS (70 eV): m/z (%): 166 (82) $[M]^+$, 138 (27), 124 (13), 108 (63), 82 (100); HRMS: calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0629.

2,4-Dimethyl-1,5-dioxa-spiro[5.5]undecan-7,10-dien-9-one (2i): *p*-Methoxyphenol (**9**, 994 mg, 8.0 mmol) and *meso*-pentane-2,3-diol (1.0 g, 9.6 mmol, 1.2 equiv) mixed in CH_2Cl_2 were treated with PIFA (4.47 g, 10.4 mmol, 1.3 equiv) to yield spiro-monoketal **2i** (290 mg, 19%) as a clear yellow solid after recrystallisation in Et_2O/PE. R_f = 0.28 (Et_2O/PE 1:1); m.p. 66 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3000 (w), 2979 (m), 2936 (w), 1679 (vs), 1638 (vs), 1505 (m), 1383 (s), 1345 (m), 1313 (m), 1229 (s), 1179 (s), 1174 (s), 1143 (s), 1114 (vs), 1075 (vs), 1009 (vs), 984 (s), 942 (s), 880 (m), 847 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 10.3, 3.0 Hz, 1H), 6.65 (dd, J = 10.3, 3.0 Hz, 1H), 6.19 (dd, J = 10.3, 3.0 Hz, 1H), 6.16 (dd, J = 10.3, 3.0 Hz, 1H), 4.22 (ddq, J = 11.6, 6.1, 2.4 Hz, 2H), 1.68 (dt, J = 13.4, 2.4 Hz, 1H), 1.38 (dt, J = 13.4, 11.6 Hz, 1H), 1.24 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.4 (C), 146.8 (CH), 138.9 (CH), 128.6 (CH), 127.9 (CH), 89.9 (C), 67.1 ($2\times$ CH), 39.9 (CH_2), 22.2 ($2\times CH_3$); MS (70 eV): m/z (%): 194 (13) $[M]^+$, 179 (2), 152 (6), 126 (18), 109 (100), 69 (31); HRMS: calcd for $C_{11}H_{14}O_3$: 194.0943, found: 194.0945.

4-[2-(1,3)Dioxalan-2-yl-ethyl]-4-hydroxy-cyclohexa-2,5-dienone (6a): 2-(2-Bromoethyl)-1,3-dioxolane (2.4 g, 13.2 mmol, 2.3 equiv) in dry THF (25 mL) was added dropwise to a magnetically stirred suspension of magnesium turnings (1.0 g, 41.1 mmol) in dry THF (1 mL). The reaction was initiated on injecting a few drops of 1,2-dibromoethane. The mixture was maintained below 40 °C by periodic cooling with a water bath. After completion of the addition (over a period of 1 h), the resulting Grignard reagent **11a** was stirred for 15 min at room temperature before use. The *p*-benzoquinone monoketal **10** (880 mg, 5.7 mmol) in dry THF (15 mL) was added dropwise to this stirred Grignard reagent at −78 °C (turned a deep blue colour) for 15 min. The reaction was stirred at 4 °C (ice bath) for 1 h. The mixture was quenched with a biphasic mixture of aqueous saturated NH_4Cl (100 mL) and EtOAc (100 mL) solutions and extracted with EtOAc ($3\times$100 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to afford **12a** as a yellow oil (crude). Purification/deprotection by flash chromatography (silica gel, EtOAc/PE 1:1) gave the *p*-quinol **6a** (910 mg, 76%) as a clear yellow oil. R_f = 0.28 (EtOAc/PE 4:1); IR ($CHCl_3$): $\tilde{\nu}$ = 3584 (m), 3000 (m), 2960 (m), 2888 (m), 1672 (s), 1628 (s), 1396 (s), 1228 (s), 1168 (m), 1140 (s), 1056 (s), 1028 (s), 944 (m), 864 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, J = 10.2 Hz, 2H), 6.17 (d, J = 10.2 Hz, 2H), 4.89 (t, J = 4.2 Hz, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 1.88 (m, 2H), 1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.7 (C), 151.6 ($2\times$ CH), 128.0 ($2\times$ CH), 103.6 (CH), 69.1 (C), 65.0 ($2\times CH_2$), 33.6 (CH_2), 28.0 (CH_2); MS (EI, RT): m/z (%): no molecular peak, 209 (1), 182 (3), 107 (8), 73 (100); MS (FAB+): m/z (%): 233 (7) $[M+Na]^+$, 211 (6) $[M+H]^+$, 210 (7), 209 (10), 176 (16), 154 (61), 149 (100), 137 (54), 107 (42); HRMS (FAB+): calcd for $C_{11}H_{14}O_4$: 210.0892, found: 210.0895.

4-(3,3-Diethoxy-propyl)-4-hydroxy-cyclohexa-2,5-dienone (6b): Freshly distilled 3-chloropropioaldehyde diethyl acetal (10.5 g, 63 mmol, 3 equiv) mixed with 1,2-dibromoethane (1.8 g, 9.6 mmol, 0.5 equiv) in dry THF (15 mL) was added dropwise to a magnetically stirred suspension of magnesium turnings (3.0 g, 123 mmol) in dry THF (1 mL). The mixture was maintained below 40 °C by periodic cooling with a water bath. After completion of the addition, the mixture was stirred for 1 h at room temperature and then additional dry THF (30 mL) was added. To this freshly prepared solution of **11b**, cooled to −78 °C, was added dropwise *p*-benzoquinone monoketal **10** (3.6 g, 23.4 mmol) in dry THF (20 mL) over a period of 10 min. The mixture was stirred at room temperature for 1 h and then was poured into a biphasic mixture of aqueous saturated NH_4Cl (250 mL) and EtOAc (250 mL) solutions. After decantation, the product was extracted with EtOAc ($3\times$250 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$) to afford **12b** as a crude yellow oil. Purification/deprotection by flash chromatography (silica gel, EtOAc/PE 1:3) gave the *p*-quinol **6b** (3.02 g, 54%) as a clear yellow oil. R_f = 0.18 (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu}$ = 3584 (w), 2976 (s), 2936 (m), 2884 (m), 1672 (vs), 1628 (m), 1376 (m), 1240 (m), 1124 (s), 1056 (s), 860 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.85 (d, J = 10.3 Hz, 2H), 6.17 (d, J = 10.3 Hz, 2H), 4.48 (t, J = 5.3 Hz, 1H), 3.65 (dq, J = 9.4, 7.1 Hz, 2H), 3.48 (dq, J = 9.4, 7.1 Hz, 2H), 1.84 (m, 2H), 1.66 (m, 2H), 1.20 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.7 (C), 151.7 ($2\times$ CH), 128.0 ($2\times$ CH), 102.4 (CH), 69.2 (C), 61.5 ($2\times CH_2$), 34.9 (CH_2), 28.1 (CH_2), 15.3 ($2\times CH_3$); MS (70 eV): m/z (%): no molecular peak, 194 (1), 149 (9), 103 (100), 75 (53); MS (FAB+): m/z (%): 263 (7) $[M+Na]^+$, 239 (17), 149 (9), 103 (100), 123 (42).

4-Hydroxy-4-methyl-cyclohexa-2,5-dienone (6c): *p*-Benzoquinone monoketal **10** (1.0 g, 6.49 mmol) in dry THF (50 mL) was added dropwise over a period of 5 min (the colour of the mixture remained yellow) to a stirred methyl lithium solution (**11c**, 5.4 mL, 1.2 M in pentane, 1.5 equiv) cooled to −78 °C. After the addition was complete, the mixture was stirred at room temperature for 30 min and quenched with an aqueous saturated NH_4Cl solution (150 mL). The compound was extracted with EtOAc ($3\times$250 mL) and dried ($MgSO_4$). The organic solvent was evaporated in vacuo to afford **12c** as a crude yellow oil. Purification/deprotection by flash chromatography (silica gel, EtOAc/PE 2:3) gave the *p*-quinol **6c** (644 mg, 80%) as a white solid. R_f = 0.16 (EtOAc/PE 2:3); m.p. 74 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3584 (m), 3420 (m), 3000 (m), 2984 (m), 1668 (vs), 1636 (vs), 1392 (m), 1304 (m), 1244 (m), 1172 (m), 1120 (m), 1056 (s), 1088 (s), 1044 (s), 912 (m), 860 (vs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, J = 10.1 Hz, 2H), 6.06 (d, J = 10.1 Hz, 2H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0 (C), 153.1 ($2\times$ CH), 126.7 ($2\times$ CH), 67.0 (C), 26.8 (CH_3); MS (70 eV): m/z (%): 124 (32) $[M]^+$, 109 (100), 96 (64), 81 (75), 77 (17); HRMS: calcd for $C_7H_8O_2$: 124.0524, found: 124.0524.

(1-Hydroxy-4-oxo-cyclohexa-2,5-dienyl)-acetonitrile (6d): *t*BuLi (40 mL, 1.5 M in pentane, 60.0 mmol) was injected by syringe to a stirred solution of

dry CH_3CN (2.5 g, 60.7 mmol, 1.7 equiv) in dry THF (30 mL) cooled to $-78\,^{\circ}C$. The resulting red-orange mixture was stirred for 15 min before use. To this freshly prepared solution of **11d** was added dropwise *p*-benzoquinone monoketal **10** (5.5 g, 35.7 mmol) in dry THF (10 mL) over a period of 5 min. After the addition was complete, the resulting dark solution was stirred at room temperature for 30 min and quenched with an aqueous saturated NH_4Cl solution (150 mL) and EtOAc. The compound was extracted with EtOAc (3×250 mL) and dried ($MgSO_4$). The organic solvent was evaporated in vacuo to afford **12d** as a crude yellow oil. Purification/deprotection by flash chromatography [silica gel (400 g), EtOAc/PE 2:3] gave the *p*-quinol **6d** (4.3 g, 81 %) as clear yellow crystals after recrystallisation in CH_2Cl_2/PE. $R_f = 0.14$ (EtOAc/PE 2:3); m.p. 83 °C; IR ($CHCl_3$): $\tilde{\nu} = 3580$ (w), 2256 (w), 1676 (vs), 1636 (m), 1392 (m), 1228 (m), 1072 (m), 1024 (m), 860 (s) cm^{-1}; ^1H NMR (400 MHz, CD_3OD): $\delta = 6.98$ (d, $J = 10.2$ Hz, 2H), 6.25 (d, $J = 10.2$ Hz, 2H), 2.41 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 186.9$ (C), 151.2 ($2 \times$ CH), 129.8 ($2 \times$ CH), 117.5 (C), 67.8 (C), 30.1 (CH_2); MS (70 eV): *m*/*z* (%): 149 (5) $[M]^+$, 109 (100), 81 (38); HRMS: calcd for $C_8H_7O_2N$: 149.0477, found: 149.0480.

4-Hydroxy-4-(triisopropylsilyl-ethynyl)-cyclohexa-2,5-dienone (6e): *t*BuLi (5.0 mL, 1.5 M in pentane, 7.5 mmol) was added dropwise to a stirred solution of ethynyl-triisopropylsilane (1.4 g, 7.7 mmol, 1.5 equiv) in dry THF (10 mL) cooled to $-78\,^{\circ}C$. After the addition was complete, the resulting organometallic reagent **11e** was stirred for 15 min at this temperature before use. Then *p*-benzoquinone monoketal **10** (800 mg, 5.2 mmol) in dry THF (5 mL) was added dropwise into the mixture over a period of 2 min (turned deep blue). The mixture was stirred at room temperature for 30 min. The excess reagent was quenched with a biphasic mixture of aqueous saturated NH_4Cl (50 mL) and EtOAc (100 mL) solutions. The product was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford **12e** as a crude yellow oil. Purification/deprotection by flash chromatography (silica gel, EtOAc/PE 3:17) gave the *p*-quinol **6e** (1.15 g, 76 %) as white needles after recrystallisation in CH_2Cl_2/PE. $R_f = 0.10$ (Et_2O/PE 1:1); m.p. 83 °C; IR ($CHCl_3$): $\tilde{\nu} = 3580$ (w), 2944 (s), 2864 (s), 1672 (vs), 1632 (m), 1460 (m), 1388 (m), 1228 (m), 1168 (m), 1108 (m), 1072 (m), 1016 (m), 884 (m), 860 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.90$ (d, $J = 10.1$ Hz, 2H), 6.19 (d, $J = 10.1$ Hz, 2H), 1.05 (br s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.3$ (C), 147.5 ($2 \times$ CH), 126.7 ($2 \times$ CH), 102.9 (C), 88.7 (C), 62.6 (C), 18.6 ($6 \times CH_3$), 11.1 ($3 \times$ CH); MS (70 eV): *m*/*z* (%): 290 (9) $[M]^+$, 247 (13), 219 (100), 177 (31); HRMS: calcd for $C_{17}H_{26}O_2Si$: 290.1702, found: 290.1703.

4-(3,3-Diethoxy-prop-1-ynyl)-4-hydroxy-cyclohexa-2,5-dienone (6f): *t*BuLi (23.3 mL, 1.5 M in pentane, 35 mmol) was added dropwise to a stirred solution of propioaldehyde diethyl acetal (4.48 g, 35 mmol, 1.5 equiv) in dry THF (70 mL) cooled to $-78\,^{\circ}C$. After the addition was complete, the resulting organometallic reagent **11f** was stirred for 15 min at this temperature. Then *p*-benzoquinone monoketal **10** (3.9 g, 25.3 mmol) in dry THF (20 mL) was added dropwise into the mixture over a period of 10 min (turned a clear blue colour). The mixture was stirred and warmed to room temperature for 30 min. The excess reagent was quenched with a biphasic mixture of aqueous saturated NH_4Cl (150 mL) and EtOAc (200 mL) solutions. The product was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford **12f** as a crude yellow oil. Purification/deprotection by flash chromatography (silica gel, EtOAc/PE 1:4) gave the *p*-quinol **6f** (5.43 g, 91 %) as pale yellow crystals after recrystallisation in CH_2Cl_2/PE. $R_f = 0.20$ (EtOAc/PE 2:3); m.p. 50 °C; IR ($CHCl_3$): $\tilde{\nu} = 3576$ (w), 2980 (m), 1672 (vs), 1632 (m), 1388 (m), 1356 (m), 1328 (vs), 1168 (m), 1140 (s), 1088 (s), 1052 (vs), 1020 (s), 856 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.92$ (d, $J = 10.1$ Hz, 2H), 6.19 (d, $J = 10.1$ Hz, 2H), 5.28 (s, 1H), 3.69 (dq, $J = 9.6$, 7.2 Hz, 2H), 3.57 (dq, $J = 9.6$, 7.2 Hz, 2H), 1.22 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.0$ (C), 146.8 ($2 \times$ CH), 127.1 ($2 \times$ CH), 91.1 (CH), 81.6 (C), 81.3 (C), 62.0 (C), 61.3 ($2 \times CH_2$), 15.0 ($2 \times CH_3$); MS (70 eV): *m*/*z* (%): no molecular peak, 235 (2) $[M-H]^+$, 191 (100), 107 (36), 77 (18); HRMS: calcd for $C_{13}H_{15}O_4$ $[M-H]^+$: 235.0970, found: 235.0961.

8-[2-(1,2)Dioxolan-2-yl-ethyl]-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-ol (13) and 10-[2-(1,3)dioxolan-2-yl-ethyl]-1,4-dioxa-spiro[4.5]dec-6-en-8-one (14): This synthesis was performed as described for **6a**: After treating *p*-benzoquinone monoketal **2a** (1.0 g, 6.57 mmol) with freshly prepared Grignard reagent **11a** (2.5 equiv), the crude product was purified by flash chromatography (silica gel, EtOAc/PE 2:3) to give the major compound **13** (1.21 g, 72 %) along with the 1,4-addition compound **14** (360 mg, 21.5 %), both as white crystals (recrystallisation in CH_2Cl_2/PE).

Cycloadduct 13: $R_f = 0.25$ (EtOAc/PE 4:1); m.p. 98 °C; IR ($CHCl_3$): $\tilde{\nu} = 3588$ (w), 3000 (w), 2888 (m), 1672 (s), 1628 (m), 1264 (s), 1128 (m), 1140 (s), 1116 (s), 1076 (m), 1032 (s), 964 (m), 864 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.99$ (d, $J = 10.2$ Hz, 2H), 5.81 (d, $J = 10.2$ Hz, 2H), 4.88 (t, $J = 4.2$ Hz, 1H), 4.04 (s, 4H), 3.90–3.80 (m, 4H), 1.79–1.73 (m, 2H), 1.68–1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.6$ ($2 \times$ CH), 127.1 ($2 \times$ CH), 104.1 (CH), 99.2 (C), 67.7 (C), 65.2 (CH_2), 65.1 (CH_2), 64.9 ($2 \times CH_2$), 33.8 (CH_2), 28.3 (CH_2); MS (70 eV): *m*/*z* (%): 254 (3) $[M]^+$, 73 (100); HRMS: calcd for $C_{13}H_{18}O_5$: 254.1154, found: 254.1151; elemental analysis (%) calcd for $C_{13}H_{18}O_5$: C 61.39, H 7.14; found: C 61.12, H 7.08.

Cycloadduct 14: $R_f = 0.37$ (EtOAc/PE 4:1); m.p. 93 °C; IR ($CHCl_3$): $\tilde{\nu} = 2954$ (s), 2888 (s), 1681 (vs), 1383 (s), 1126 (s), 1091 (vs), 948 (s), 881 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.63$ (d, $J = 10.1$ Hz, 1H), 5.97 (d, $J = 10.1$ Hz, 1H), 4.84 (t, $J = 4.7$ Hz, 1H), 4.18–4.08 (m, 3H), 4.00–3.90 (m, 3H), 3.83 (m, 2H), 2.66 (dd, $J = 16.4$, 4.1 Hz, 1H), 2.45 (dd, $J = 16.4$, 11.0 Hz, 1H), 2.33 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.64 (m, 1H), 1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.7$ (C), 146.7 (CH), 129.5 (CH), 105.9 (C), 104.4 (CH), 65.6 (CH_2), 65.1 (CH_2), 64.9 ($2 \times CH_2$), 42.5 (CH), 40.5 (CH_2), 31.2 (CH_2), 22.5 (CH_2); MS (70 eV): *m*/*z* (%): 254 (2) $[M]^+$, 128 (100), 98 (54), 73 (83); HRMS: calcd for $C_{13}H_{18}O_5$: 254.1154, found: 254.1155; elemental analysis (%) calcd for $C_{13}H_{18}O_5$: C 61.39, H 7.14; found: C 61.26, H 7.12.

4-(3,3-Diethoxy-propenyl)-4-hydroxy-cyclohexa-2,5-dienone (16a) and 3-(2-hydroxy-4-methoxy-phenol)-propenal (17): Red/Al (5.8 mL, 3.5 M in toluene, 1.5 equiv) diluted in dry THF (10 mL) at $-10\,^{\circ}C$ for 2 min was added dropwise to the stirred THF solution (10 mL) of the crude oil **12f** [see **6a** (see above), from propioaldehyde diethyl acetal (2.7 g, 21.0 mmol), *t*BuLi (14.0 mL, 1.5 M in pentane) and *p*-benzoquinone monoketal **10** (2.33 g, 15 mmol)]. After the addition was complete, the mixture was stirred at room temperature for 1 h. Excess reagent was quenched with an aqueous saturated NH_4Cl solution (100 mL). The crude compound **15a** was extracted with EtOAc (3×300 mL) and the combined organic layers were dried ($MgSO_4$). After addition of PE (150 mL), the resulting mixture was filtrated rapidly several times (3 to $4\times$) through the same column (silica gel, 200 g, EtOAc/PE 4:1). Then the column was washed with EtOAc (500 mL) and the combined organic solvents were evaporated in vacuo. After flash chromatography (silica gel, EtOAc/PE 3:17), *p*-quinol **16a** (1.51 g, 42 %) was isolated as a clear yellow oil and the aromatic compound **17** (240 mg, 9 %) as an yellow solid.

Cycloadduct 16a: $R_f = 0.22$ (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu} = 3584$ (m), 2980 (m), 1672 (vs), 1624 (m), 1388 (m), 1228 (m), 1120 (m), 1056 (s), 860 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (d, $J = 10.1$ Hz, 2H), 6.16 (d, $J = 10.1$ Hz, 2H), 5.95 (dd, $J = 15.7$, 4.5 Hz, 1H), 4.95 (dd, $J = 4.5$, 1.1 Hz, 1H), 3.62 (dq, $J = 9.4$, 7.1 Hz, 2H), 5.74 (dd, $J = 15.7$, 1.1 Hz, 1H), 3.49 (dq, $J = 9.4$, 7.1 Hz, 2H), 1.21 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.7$ (C), 150.1 ($2 \times$ CH), 132.6 (CH), 129.7 (CH), 127.4 ($2 \times$ CH), 100.3 (CH), 69.4 (C), 61.3 ($2 \times CH_2$), 15.2 ($2 \times CH_3$); MS (70 eV): *m*/*z* (%): no molecular peak, 237 (1.6), 193 (100), 165 (31), 147 (60), 119 (44), 99 (68); MS (FAB+): *m*/*z* (%): 261 (10) $[M+Na]^+$, 237 (14), 193 (100), 147 (45); MS (CI, CH_4): *m*/*z* (%): 221 (7) $[M-HO]^+$, 193 (100); HRMS (CI, CH_4) calcd for $C_{13}H_{17}O_3$ ($[M-HO]^+$): 221.1177, found: 221.1165.

Cycloadduct 17: $R_f = 0.24$ (EtOAc/PE 2:3); m.p. 108–110 °C; IR (KBr): $\tilde{\nu} = 3552$ (m), 1652 (vs), 1612 (s), 1504 (m), 1452 (m), 1284 (s), 1148 (s) cm^{-1}; ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.68$ (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 16.0$ Hz, 1H), 7.21 (d, $J = 2.9$ Hz, 1H), 6.94 (dd, $J = 9.0$, 2.9 Hz, 1H), 6.91 (dd, $J = 16.0$, 7.8 Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 195.0$ (CH), 152.5 (C), 151.4 (CH), 148.7 (C), 128.4 (CH), 121.1 (CH), 120.1 (C), 117.5 (CH), 112.1 (CH), 55.7 (CH_3); MS (70 eV): *m*/*z* (%): 178 (90) $[M]^+$, 177 (100), 161 (49), 135 (36), 77 (32); HRMS: calcd for $C_{10}H_{10}O_3$: 178.0630, found: 178.0628.

Acetic acid 1-(3,3-diethoxy-propenyl)-4-oxo-cyclohexa-2,5-dienyl ester (16b): 4-Dimethylaminopyridine (DMAP, 1.67 g, 13.7 mmol, 2 equiv) was added in one portion to the crude compound **15a** (5.5 mmol) in dry CH_2Cl_2 (15 mL). To this stirred mixture was injected through a septum acetic acid anhydride (1.12 g, 1.1 mmol, 2 equiv). After 1 h, the reaction was quenched by adding water (15 mL) and the product was extracted with Et_2O ($3 \times$ 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated

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in vacuo. After purification/deprotection (silica gel, EtOAc/PE 1:9), acetylated *p*-quinol **16b** (725 mg, 47 %) was isolated as a clear yellow oil. $R_f = 0.42$ (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu} = 2980$ (m), 1746 (s), 1668 (vs), 1624 (m), 1608 (s), 1368 (m), 1232 (vs), 1128 (s), 1060 (vs), 1012 (s), 856 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.84$ (d, $J = 10.2$ Hz, 2H), 6.28 (d, $J = 10.2$ Hz, 2H), 5.92 (dd, $J = 15.7$, 4.5 Hz, 1H), 5.69 (dd, $J = 15.7$, 1.2 Hz, 1H), 4.93 (dd, $J = 4.5$, 1.2 Hz, 1H), 3.62 (dq, $J = 9.4$, 7.1 Hz, 2H), 3.49 (dq, $J = 9.4$, 7.1 Hz, 2H), 2.10 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.0$ (C), 169.0 (C), 146.6 (2 × CH), 130.4 (CH), 129.9 (CH), 128.4 (2 × CH), 100.0 (CH), 75.7 (C), 61.3 (2 × CH_2), 21.3 (CH_3), 15.2 (2 × CH_3); MS (70 eV): *m*/*z* (%): no molecular peak, 251 (20), 235 (47), 192 (53), 177 (47), 165 (86), 161 (84), 147 (89), 119 (95), 103 (100), 75 (66); MS (FAB +): *m*/*z* (%) = 303 (20) $[M+Na]^+$, 279 (10), 235 (76), 177 (100), 107 (74).

(*p*-Acetoxyphenyl)-acetic acid (19): *p*-Hydroxyphenyl acetic acid (**18**, 5.0 g, 32.9 mmol) was added to a stirred biphasic mixture of aqueous 1N NaOH (100 mL) and CH_2Cl_2 (100 mL). Ac_2O (8.0 g, 78.4 mmol, 2.4 equiv) was added dropwise to this solution at room temperature. Stirring was continued for 1 h. 2N HCl aqueous solution was added until pH 2. The compound was extracted with CH_2Cl_2 (2 × 50 mL) and with EtOAc [2 × (50 mL+1 mL MeOH)]. The combined extracts were dried ($MgSO_4$) and evaporated to give the crude product. This was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2, 1:9) to give **19** (6.05 g, 95 %) as white crystals. $R_f = 0.5$ (MeOH/CH_2Cl_2, 1:4); m.p. 102 °C; IR ($CHCl_3$): $\tilde{\nu} = 3512$ (w), 3040 (m), 1756 (vs), 1712 (vs), 1608 (w), 1508 (s), 1368 (s), 1228 (vs), 1168 (s), 1120 (w), 916 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.7$ Hz, 2H), 7.16 (d, $J = 8.7$ Hz, 2H), 3.65 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 177.6$ (C), 169.6 (C), 149.9 (C), 131.0 (C), 130.5 (2 × CH), 121.7 (2 × CH), 40.4 (CH_2), 21.1 (CH_3); MS (70 eV): *m*/*z* (%): 194 (19) $[M]^+$, 152 (81), 107 (100), 91 (28), 77 (58); elemental analysis (%) calcd for $C_{10}H_{10}O_4$ (194.2): C 61.84, H 5.19; found: C 61.79, H 5.13.

4-(3-Diazo-2-oxo-propyl)phenyl acetate (20): Oxalyl chloride (8.98 g, 6.07 mL, 70.8 mmol, 3 equiv) followed by the addition of few drops of DMF was injected through a septum to a dry $CHCl_3$ solution (100 mL) of **19** (4.6 g, 23.6 mmol) under N_2. The mixture was stirred at room temperature until no further gas evolution was observed (≈1 h). The excess oxalyl chloride was evaporated and the resulting oil was diluted in dry CH_2Cl_2. This solution was added dropwise to a stirred solution of diazomethane in diethyl ether (large excess, 150 mL) at 0 °C. After 2 h, the mixture was carefully (in a fume cupboard) condensed under reduced pressure. Flash chromatography (silica gel, EtOAc/PE 3:7) of the residue gave **20** (4.0 g, 78 %) as a yellow solid. $R_f = 0.30$ (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2108 (vs), 1756 (s), 1636 (s), 1508 (s), 1360 (vs), 1296 (w), 1228 (s), 1196 (vs), 1164 (s), 912 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J =$ 8.6 Hz, 2H), 7.06 (d, $J = 8.6$ Hz, 2H), 5.17 (s, 1H), 3.60 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 192.2$ (C), 169.2 (C), 149.9 (C), 132.1 (C), 130.3 (2 × CH), 121.9 (2 × CH), 54.9 (CH), 47.0 (CH_2), 21.0 (CH_3); MS (70 eV): *m*/*z* (%): 218 (1) $[M]^+$, 190 (1), 176 (6), 148 (65), 120 (44), 107 (100), 91 (13), 77 (11); HRMS: calcd for $C_{11}H_{10}O_3N_2$: 218.0691, found: 218.0696.

3-(4-Acetoxy-phenyl)-2-oxo-propyl trifluoroacetate (21): Trifluoroacetic acid (3.14 g, 2.2 mL, 28 mmol, 2 equiv) was added dropwise at −10 °C to a stirred solution of diazomethyl ketone **20** (3.0 g, 14 mmol) in dry CH_2Cl_2 (50 mL) under N_2. The white mixture was stirred for 1 h at the same temperature. The solvent and the excess trifluoroacetic acid was then evaporated and the residue was dissolved in dry toluene. After evaporation, the isolated solid was thoroughly dried in vacuo to yield **21** (4.1 g, 97 %) as an amorphous white solid. $R_f = 0.14$ (EtOAc/PE 1:4); m.p. 102 – 104 °C; IR ($CHCl_3$): $\tilde{\nu} = 3040$ (w), 1796 (vs), 1748 (vs), 1508 (s), 1372 (s), 1196 (vs), 1148 (vs), 1072 (m), 912 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.7$ Hz, 2H), 7.09 (d, $J = 8.7$ Hz, 2H), 4.94 (s, 2H), 3.78 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.8$ (C), 169.4 (C), 156.8 (q, $J = 43.8$ Hz, C), 150.2 (C), 130.5 (2 × CH), 129.6 (C), 122.2 (2 × CH), 114.5 (q, $J = 283.5$ Hz, CF_3), 69.4 (CH_2), 45.1 (CH_2), 21.0 (CH_3); MS (70 eV): *m*/*z* (%): 304 (28) $[M]^+$, 262 (67), 166 (24), 107 (100), 91 (22), 77 (40); HRMS: calcd for $C_{13}H_{11}O_5F_3$: 304.0556, found: 304.0554.

1-Hydroxy-3-(4-hydroxyphenyl)-propan-2-one (22): Compound **21** (4.1 g, 13.5 mmol) in MeOH (30 mL) was added to a stirred solution of Na_2CO_3 (6.0 g) and $NaHCO_3$ (7.0 g) in water (70 mL). The mixture was stirred at room temperature for 1 h. The residue was extracted with MeOH/EtOAc (3:17, 4 × 30 mL). The combined organic extract was dried ($MgSO_4$) and evaporated in vacuo. After flash chromatography (silica gel, EtOAc/PE 2:3), the dialcohol **22** was isolated (2.0 g, 90 %) as an amorphous white solid. $R_f = 0.36$ (EtOAc/PE 4:1); IR ($CHCl_3$): $\tilde{\nu} = 3596$ (m), 1716 (s), 1616 (m), 1512 (vs), 1260 (m), 1172 (vs), 1116 (vs), 1068 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 4.28 (s, 2H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 210.5$ (C), 157.7 (C), 131.8 (2 × CH), 126.2 (C), 116.7 (2 × CH), 68.3 (CH_2), 45.6 (CH_2); MS (70 eV): *m*/*z* (%): 166 (17) $[M]^+$, 108 (100), 77 (12); HRMS: calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0638.

1-Oxa-spiro[4.5]deca-6,9-diene-3,8-dione (23): Dialcohol **22** (300 mg) dissolved in dry CH_3CN (10 mL) was added under N_2 Dialcohol **22** (300 mg) dissolved in dry CH_3CN (10 mL) to a stirred solution of PIFA (1.0 g, 3.34 mmol, 1.3 equiv) in dry CH_2Cl_2 (40 mL) cooled to 4 °C (ice bath) dropwise. The colour of the mixture changed from green into yellow after stirring at the same temperature for 30 min. The solution was concentrated to ≈5 mL and EtOAc (100 mL) was added. The excess reagent was quenched with saturated aqueous $NaHCO_3$ (50 mL). The product was extracted with EtOAc (3 × 100 mL) and the combined organic extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, EtOAc/PE 2:3) gave the spiro-cyclohexadienone **23** (128 mg, 43 %) as a white solid. $R_f = 0.27$ (EtOAc/PE 2:3); m.p. 63 °C; IR ($CHCl_3$): $\tilde{\nu} = 3040$ (w), 1764 (vs), 1716 (w), 1672 (vs), 1636 (vs), 1612 (w), 1440 (m), 1400 (s), 1324 (m), 1228 (s), 1176 (vs), 1072 (m), 1048 (vs), 984 (m), 916 (s), 856 (vs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.93$ (d, $J = 10.1$ Hz, 2H), 6.28 (d, $J = 10.1$ Hz, 2H), 4.21 (s, 2H), 2.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.3$ (C), 184.5 (C), 146.0 (2 × CH), 128.7 (2 × CH), 76.3 (C), 69.5 (CH_2), 45.6 (CH_2); MS (70 eV): *m*/*z* (%): 164 (51) $[M]^+$, 136 (20), 122 (7), 107 (53), 78 (100); HRMS: calcd for $C_9H_8O_3$: 164.0473, found: 164.0477.

12-Methoxy-1,4,9-trioxa-dispiro[4.2.4.2]tetradeca-6,11,13-triene (26): *n*BuLi (7.6 mL, 1.6 M in pentane, 1.3 equiv) was injected through a septum to a stirred solution of methoxyallene (850 mg, 12.7 mmol, 1.3 equiv) in dry Et_2O (20 mL)at −40 °C. After 15 min, the mixture was cooled to −78 °C and *p*-benzoquinone monoketal **2a** (1.5 g, 9.9 mmol) in dry Et_2O (20 mL) was added dropwise over a period of 10 min. After a further 30 min at this temperature, the mixture was quenched with powdered ammonium chloride. This was warmed to 4 °C (ice bath) and water was added. The adduct was extracted with EtOAc (3 × 100 mL), washed with brine, dried ($MgSO_4$) and concentrated. The resulting yellow oil was diluted in dry DMSO (1 mL) and added to a dry DMSO solution (20 mL) of potassium *tert*-butoxide (550 mg, 4.9 mmol) at room temperature. After 30 min, the reaction was quenched with ice water. The residue was extracted with Et_2O (5 × 80 mL). The combined extract was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (silica gel, EtOAc/PE 1:4) gave the spiro-monoketal **26** (1.62 g, 74 %) as a white solid. $R_f = 0.24$ (EtOAc/PE 2:3); m.p. 77 °C; IR ($CHCl_3$): $\tilde{\nu} = 2888$ (m), 2860 (m), 1664 (s), 1404 (s), 1348 (m), 1312 (m), 1244 (s), 1228 (m), 1116 (vs), 1060 (vs), 1024 (vs), 964 (vs), 944 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.97$ (d, $J = 10.3$ Hz, 2H), 5.91 (d, $J = 10.3$ Hz, 2H), 4.79 (t, $J = 1.7$ Hz, 1H), 4.70 (d, $J = 1.7$ Hz, 2H), 4.06 (s, 4H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.9$ (C), 132.9 (2 × CH), 128.5 (2 × CH), 98.8 (C), 91.8 (CH), 79.3 (C), 71.6 (CH_2), 65.4 (CH_2), 65.2 (CH_2), 58.2 (CH_3); MS (70 eV): *m*/*z* (%): 222 (17) $[M]^+$, 191 (30), 153 (100); HRMS: calcd for $C_{12}H_{14}O_4$: 222.0892, found: 222.0901.

4-Methoxy-1-oxa-spiro[4.5]deca-3,6,9-trien-8-one (27): Spiro-monoketal **26** (616 mg, 2.7 mmol) in THF (4 mL) was poured into a refluxing water/THF solution (3:1, 25 mL) containing *para*-toluenesulfonic acid (*p*TsOH, 50 mg) under vigorous stirring. After 10 min, the solution was cooled to room temperature (water bath). The residue was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (silica gel, EtOAc/PE 1:4) gave the spiro-dienone **27** (425 mg, 88 %) as a white solid. $R_f = 0.28$ (EtOAc/PE 2:3); m.p. 54 °C; IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 1668 (vs), 1628 (s), 1348 (m), 1248 (s), 1168 (m), 1092 (s), 1056 (s), 1020 (s), 944 (m), 852 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.76$ (d, $J =$ 10.1 Hz, 2H), 6.22 (d, $J = 10.1$ Hz, 2H), 4.93 (t, $J = 1.7$ Hz, 1H), 4.81 (d, $J =$ 1.7 Hz, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.4$ (C), 154.8 (C), 147.5 (2 × CH), 129.2 (2 × CH), 93.6 (CH), 80.7 (C), 72.5 (CH_2), 58.2 (CH_3); MS (70 eV): *m*/*z* (%): 178 (61) $[M]^+$, 163 (15), 150 (22), 147 (14), 107 (23), 96 (100), 91 (34), 77 (23); HRMS: calcd for $C_{10}H_{10}O_3$: 178.0630, found: 178.0633.

2-Ethoxy-1-oxa-spiro[4.5]deca-6,9-dien-8-one (28): Anhydrous camphor-10-sulfonic acid (CSA, 743 mg, 3.2 mmol, 0.25 equiv) was added to *p*-quinol **6b** (3.02 g, 12.6 mmol) in dry THF (100 mL). The mixture was stirred under N_2 for 5 h at room temperature. This was concentrated to ≈20 mL. Et_2O (200 mL) was added and this organic layer was washed with saturated $NaHCO_3$ (100 mL). The product was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography (silica gel, EtOAc/PE 1:2) gave the spiro-dienone **28** (1.53 g, 63 %) as a clear yellow oil. $R_f = 0.36$ (EtOAc/PE 2:3); IR ($CHCl_3$): $\tilde{\nu} = 2960$ (m), 2888 (m), 1672 (s), 1628 (m), 1604 (s), 1396 (m), 1266 (s), 1128 (m), 1140 (s), 1116 (s), 1076 (m), 1036 (s), 964 (m), 944 (m), 864 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.90$ (dd, $J = 10.1$, 2.7 Hz, 1H), 6.75 (dd, $J = 10.1$, 2.7 Hz, 1H), 6.15 (dd, $J = 10.1$, 1.9 Hz, 1H), 6.14 (dd, $J = 10.1$, 1.9 Hz, 1H), 5.32 (dd, $J = 3.4$, 2.6 Hz, 1H), 3.81 (dq, $J = 9.6$, 7.0 Hz, 1H), 3.49 (dq, $J = 9.6$, 7.0 Hz, 1H), 2.32 (m, 1H), 2.27 – 2.11 (m, 2H), 2.05 (m, 1H), 1.23 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.6$ (C), 151.8 (CH), 149.2 (CH), 127.2 (CH), 127.0 (CH), 105.4 (CH), 78.3 (C), 63.0 (CH_2), 34.3 (CH_2), 33.4 (CH_2), 15.2 (CH_3); MS (70 eV): *m*/*z* (%): 194 (8) $[M]^+$, 166 (2), 149 (33), 120 (39), 107 (22), 91 (63), 86 (100); HRMS: calcd for $C_{11}H_{14}O_3$: 194.0943, found: 194.0943.

2-Hydroxy-1-oxa-spiro[4.5]deca-6,9-dien-8-one (29): *p*TsOH (100 mg) was added to *p*-Quinol **6a** (910 mg, 4.33 mmol) in a mixed solution of THF/H_2O (3:10, 75 mL) and the mixture was immediately refluxed (oil bath at 140 °C) under vigorous stirring for 30 min. After cooling, EtOAc (100 mL) was added and the two layers were decanted. The product was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography (silica gel, EtOAc/PE 1:1) gave the spiro-dienone **29** (498 mg, 69 %) as a white solid. $R_f = 0.30$ (EtOAc/PE 4:1); m.p. 77 °C; IR ($CHCl_3$): $\tilde{\nu} = 3600$ (m), 3032 (m), 1672 (vs), 1632 (s), 1224 (s), 1172 (m), 1036 (s), 1012 (s), 952 (s), 856 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.01$ (dd, $J = 10.2$, 2.9 Hz, 1H), 6.76 (dd, $J = 10.2$, 2.9 Hz, 1H), 6.15 (dd, $J = 10.2$, 2.0 Hz, 1H), 6.12 (dd, $J = 10.2$, 2.0 Hz, 1H), 5.74 (dd, $J = 4.1$, 1.7 Hz, 1H), 2.37 (m, 1H), 2.25 – 2.13 (m, 2H), 2.04 (ddd, $J = 13.5$, 7.7, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.9$ (C), 152.2 (CH), 127.12 (CH), 127.07 (CH), 100.1 (CH), 78.5 (C), 34.1 (CH_2), 149.3 (CH), 33.9 (CH_2); MS (70 eV): *m*/*z* (%): 166 (25) $[M]^+$, 148 (14), 109 (100), 91 (54); HRMS: calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0630.

1-Oxa-spiro[4.5]deca-2,6,9-trien-8-one (30): Freshly distilled triethylamine (1.23 mg, 12 mmol, 4 equiv) was injected dropwise under N_2 through a septum to a solution of spiro-dienone **29** (506 mg, 3.05 mmol) in dry CH_2Cl_2 (15 mL) stirred at −40 °C. After 5 min, methanesulfonyl chloride (MsCl, 533 mg, 4.6 mmol, 1.5 equiv) was injected dropwise into the mixture. Stirring was continued for 15 min at −40 °C and then at room temperature for 5 – 7 h. The mixture was then poured into a biphasic mixture of H_2O/EtOAc (1:1, 200 mL). The product was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of oxalic acid, with brine, dried ($MgSO_4$) and evaporated. After purification by flash chromatography (silica gel, EtOAc/PE 1:4), spiro-dienone **30** (239 mg, 53 %) was isolated as a white solid. $R_f = 0.55$ (EtOAc/PE 2:3); m.p. 61 °C; IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 1672 (vs), 1632 (vs), 1248 (m), 1172 (m), 1144 (vs), 1044 (vs), 988 (m), 960 (m), 856 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.95$ (d, $J = 10.1$ Hz, 2H), 6.35 (dt, $J = 2.5$, 2.4 Hz, 1H), 6.19 (d, $J = 10.1$ Hz, 2H), 5.06 (dt, $J = 2.5$, 2.4 Hz, 1H), 2.77 (t, $J = 2.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.4$ (C), 147.1 (2 × CH), 144.5 (CH), 127.5 (2 × CH), 100.1 (CH), 80.0 (C), 39.8 (CH_2); MS (70 eV): *m*/*z* (%): 148 (38) $[M]^+$, 120 (25), 91 (100); HRMS: calcd for $C_9H_8O_2$: 148.0524, found: 148.0522.

General procedure for the synthesis of the cycloadducts 31 – 49: The optically pure diene (−)-**1** (1.05 equiv) and the corresponding cyclohexadienone (1.0 equiv) were dissolved in dry CH_2Cl_2, unless otherwise stated. This mixture was sealed in a Teflon tube and placed under elevated pressure (6.5 – 14 kbar) at room temperature for 6 – 20 d. After evaporation, purification by flash chromatography on silica gel (except **32** which was twice recrystallised in CH_2Cl_2/Et_2O) gave the corresponding cycloadduct (with only *endo* – *syn* selectivity).

Cycloadduct 31: Diene **1** (152 mg, 0.63 mmol) and the spiro-cyclohexadienone **2h** (100 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 6 d) into the cycloadduct **31** (195 mg, 80 %) as pale yellow crystals. $R_f = 0.17$ (Et_2O/PE 1:1); m.p. 136 °C; $[\alpha]_D^{20} = -232$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} =$ 3000 (w), 2956 (m), 2932 (m), 1668 (s), 1612 (w), 1516 (s), 1248 (s), 1180 (m), 1152 (m), 1112 (s), 1056 (w), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.8$ Hz, 2H), 7.09 (dd, $J = 10.5$, 1.1 Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.92 (d, $J = 10.5$ Hz, 1H), 5.85 (d, $J = 5.5$ Hz, 1H), 5.76 (d, $J = 5.5$ Hz, 1H), 4.08 (dt, $J = 11.8$, 3.1 Hz, 1H), 3.96 – 3.87 (m, 2H), 3.86 (d, $J = 8.0$ Hz, 1H), 3.79 (s, 3H), 3.79 – 3.72 (m, 1H), 2.91 (dd, $J = 8.0$, 1.1 Hz, 1H), 2.36 (br d, $J = 13.0$ Hz, 1H), 2.11 (m, 1H), 1.85 (dt, $J = 13.0$, 3.8 Hz, 1H), 1.60 (br d, $J = 12.7$ Hz, 1H), 1.48 – 1.30 (m, 3H), 1.28 (m, $J = 13.3$ Hz, 1H), 1.19 (m, $J = 13.0$, 3.7 Hz, 1H), 0.83 (s, 3H), 0.46 (br d, $J = 13.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.2$ (C), 158.3 (C), 141.6 (CH), 138.8 (CH), 134.8 (CH), 133.4 (CH), 129.3 (C), 129.2 (2 × CH), 113.1 (2 × CH), 97.0 (C), 70.7 (C), 62.0 (C), 61.1 (C), 59.6 (CH_2), 52.2 (CH), 51.1 (CH), 28.7 (CH_2), 27.7 (CH_2), 25.3 59.7 (CH_2), (CH_2), 24.0 (55.2 (CH_3), CH_2), 21.3 (CH_2), 15.3 (CH_3); MS (70 eV): *m*/*z* (%): 406 (3) $[M]^+$, 240 (100); HRMS: calcd for $C_{26}H_{30}O_4$: 406.2157, found: 406.2140; elemental analysis (%) calcd for $C_{26}H_{30}O_4$: C 76.81, H 7.44; found: C 76.43, H 7.42.

Cycloadduct 32: Diene **1** (327 mg, 1.36 mmol) and cyclohexadienone **10** (200 mg, 1.3 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 6 d) into cycloadduct **32** (399 mg, 78 %) as pale yellow crystals. $R_f = 0.27$ (Et_2O/PE 1:1); m.p. 155 °C; $[\alpha]_D^{20} = -247$ ($c = 1.1$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2936 (m), 1668 (s), 1612 (w), 1516 (s), 1248 (s), 1180 (s), 1152 (w), 1120 (s), 1068 (m), 1040 (s), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.41 (dd, $J = 10.3$, 1.4 Hz, 1H), 5.94 (d, $J = 10.3$ Hz, 1H), 5.87 (d, $J = 5.5$ Hz, 1H), 5.76 (d, $J = 5.5$ Hz, 1H), 3.83 (d, $J = 7.9$ Hz, 1H), 3.79 (s, 3H), 3.30 (s, 3H), 3.15 (s, 3H), 3.05 (dd, $J = 7.9$, 1.4 Hz, 1H), 2.25 (br d, $J = 13.0$ Hz, 1H), 1.87 (dt, $J = 13.0$, 3.9 Hz, 1H), 1.64 (br d, $J = 12.7$ Hz, 1H), 1.46 (dt, $J = 13.0$, 4.0 Hz, 1H), 1.40 (br d, $J = 13.3$ Hz, 1H), 1.32 (m, $J = 12.7$, 3.5 Hz, 1H), 1.18 (m, $J = 13.3$, 3.7 Hz, 1H), 0.84 (s, 3H), 0.48 (br d, $J = 13.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 200.0 (C), 158.3 (C), 145.3 (CH), 138.8 (CH), 134.4 (CH), 129.1 (2 × CH), 129.0 (C), 113.1 (2 × CH), 99.2 135.5 (CH), (C), 70.7 (C), 62.0 (C), 60.7 (C), 55.2 (CH_3), 51.5 (CH), 49.6 (CH_3), 48.2 (CH), 47.6 (CH_3), 28.8 (CH_2), 27.4 (CH_2), 24.0 (CH_2), 21.2 (CH_2), 15.4 (CH_3); MS (70 eV): *m*/*z* (%): 394 (1.4) $[M]^+$, 240 (100); HRMS: calcd for $C_{25}H_{30}O_4$: 394.2144, found: 394.2108.

Cycloadducts 33 and 34: Diene **1** (258 mg, 1.07 mmol) and the spiro-cyclohexadienone **2c** (311 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) were converted (6 kbar, 6 d) into the cycloadducts **33** (252 mg, 46 %) and **34** (247 mg, 45 %) both as a white amorphous solid.

Cycloadduct 33: $R_f = 0.44$ (EtOAc/PE 3:7); m.p. 87 °C; $[\alpha]_D^{21} = -163$ ($c =$ 1.0, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2928 (vs), 2856 (m), 1672 (vs), 1612 (w), 1512 (s), 1452 (m), 1452 (m), 1252 (vs), 1180 (s), 1128 (s), 1096 (m), 1032 (s), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (d, $J = 8.8$ Hz, 2H), 7.13 – 6.95 (m, 10H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.76 (dd, $J = 10.1$, 1.1 Hz, 1H), 6.11 (d, $J = 10.1$ Hz, 1H), 5.91 (d, $J = 5.7$ Hz, 1H), 5.65 (d, $J = 7.2$ Hz, 1H), 5.59 (d, $J = 7.2$ Hz, 1H), 3.93 (d, $J = 7.8$ Hz, 1H), 3.80 (s, 3H), 3.31 (dd, $J = 7.8$, 1.1 Hz, 1H), 2.46 (br d, $J = 13.0$ Hz, 1H), 1.88 (dt, $J = 12.8$, 3.8 Hz, 1H), 1.70 – 1.20 (m, 6H), 0.90 (s, 3H), 0.51 (br d, $J = 12.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.1$ (C), 158.4 (C), 145.8 (CH), 138.4 (CH), 136.8 (C), 136.5 (C), 135.7 (CH), 135.5 (CH), 129.3 (2 × CH), 128.8 (C), 127.8 (2 × CH), 127.7 (2 × CH), 127.2 (2 × CH), 126.9 (2 × C), 126.8 (2 × CH), 113.1 (2 × CH), 106.3 (C), 83.3 (CH), 80.4 (CH), 71.6 (C), 61.9 (C), 61.7 (C), 55.2 (CH_3), 50.5 (CH), 49.4 (CH), 28.6 (CH_2), 27.0 (CH_2), 24.0 (CH_2), 21.4 (CH_2), 15.4 (CH_3); MS (70 eV): *m*/*z* (%) = no molecular peak, 438 (2), 240 (100), 198 (95); MS (CI, CH_4): *m*/*z* (%): 545 (4) $[M+H]^+$, 240 (100); HRMS (CI, CH_4): calcd for $C_{37}H_{37}O_4$ $[M+H]^+$: 545.2692, found: 545.2714.

Cycloadduct 34: $R_f = 0.31$ (EtOAc/PE 3:7); m.p. 89 °C; $[\alpha]_D^{20} = -163$ ($c =$ 1.0, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2928$ (s), 2860 (m), 1668 (vs), 1516 (s), 1456 (m), 1384 (w), 1252 (vs), 1180 (s), 1112 (s), 1040 (s), 1004 (m), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.13 – 7.01$ (m, 10H), 6.89 (dd, $J = 10.3$, 1.1 Hz, 1H), 6.01 (d, $J = 5.7$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 2H), 5.98 (d, $J =$ 10.3 Hz, 1H), 5.90 (d, $J = 5.7$ Hz, 1H), 5.63 (d, $J = 7.6$ Hz, 1H), 5.42 (d, $J =$ 7.6 Hz, 1H), 4.02 (d, $J = 8.0$ Hz, 1H), 3.81 (s, 3H), 3.36 (dd, $J = 8.0$, 1.1 Hz, 1H), 2.64 (br d, $J = 13.0$ Hz, 1H), 1.90 (dt, $J = 13.0$, 3.9 Hz, 1H), 1.70 – 1.56 (m, 2H), 1.46 – 1.23 (m, 4H), 0.95 (s, 3H), 0.53 (br d, $J = 13.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.9$ (C), 158.4 (C), 143.7 (CH), 138.3 (CH), 137.3 (C), 136.5 (C), 135.6 (CH), 133.6 (CH), 129.3 (2 × CH), 128.9 (C), 127.8 (2 × CH), 127.7 (3 × CH), 127.5 (CH), 127.3 (2 × CH), 127.1 (2 × CH), 113.2 (2 × CH), 106.5 (C), 80.6 (CH), 80.0 (CH), 71.5 (C), 62.2 (C), 62.0 (C), 55.2 (CH_3), 50.8 (CH), 49.9 (CH), 28.7 (CH_2), 28.3 (CH_2), 24.1 (CH_2), 21.2 (CH_2), 15.4 (CH_3); MS (70 eV): *m*/*z* (%) = no molecular peak, 438 (1), 240 (86), 198 (100); MS (CI, CH_4): *m*/*z* (%): 545 (4) $[M+H]^+$, 240

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(100); HRMS (CI, CH_4): calcd for $C_{37}H_{37}O_4$ $[M+H]^+$: 545.2692, found: 545.2655.

Cycloadducts 35 and 36: Diene **1** (177 mg, 0.74 mmol) and the spiro-cyclohexadienone **2i** (136 mg, 0.7 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 6 d) into the cycloadducts **35** (195 mg, 64 %) and **36** (22 mg, 7 %) both as a white amorphous solid.

Cycloadduct 35: $R_f = 0.22$ (EtOAc/PE 1:4); m.p. 68 °C; $[\alpha]_D^{22} = -185$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (m), 2932 (s), 2864 (m), 1668 (vs), 1512 (vs), 1380 (m), 1252 (s), 1172 (s), 1116 (vs), 1092 (m), 1032 (s), 1004 (m), 984 (m), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.8$ Hz, 2H), 7.05 (dd, $J = 10.5$, 1.1 Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.89 (d, $J = 10.5$ Hz, 1H), 5.88 (d, $J = 5.6$ Hz, 1H), 5.75 (d, $J = 5.6$ Hz, 1H), 4.11 (ddq, $J = 6.1$, 2.6, 2.6 Hz, 1H), 3.85 (ddq, $J = 6.1$, 2.6, 2.6 Hz, 1H), 3.79 (s, 3H), 2.86 (dd, $J = 8.3$, 1.1 Hz, 1H), 2.42 (m, 1H), 1.86 (dt, $J = 12.9$, 3.6 Hz, 1H), 1.23 (d, $J = 6.1$ Hz, 3H), 1.60 – 1.15 (m, 8H), 1.09 (d, $J = 6.1$ Hz, 3H), 0.82 (s, 3H), 0.45 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.5$ (C), 158.2 (C), 142.6 (CH), 139.0 (CH), 134.5 (CH), 132.8 (CH), 129.4 (C), 129.2 (2 × CH), 113.1 (2 × CH), 97.4 (C), 70.7 (C), 65.6 (CH), 65.2 (CH), 61.9 (C), 61.1 (C), 55.2 (CH_3), 52.8 (CH), 51.4 (CH), 40.2 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 24.1 (CH_2), 22.3 (CH_3), 22.1 (CH_3), 21.4 (CH_2), 15.4 (CH_3); MS (70 eV): m/z (%): 434 (1.7) $[M]^+$, 240 (100), 225 (12), 109 (20); HRMS: calcd for $C_{28}H_{34}O_4$: 434.2457, found: 434.2466.

Cycloadduct 36: $R_f = 0.28$ (EtOAc/PE 1:4); m.p. 158 °C; $[\alpha]_D^{22} = -151$ ($c = 0.3$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2932 (m), 1668 (s), 1516 (s), 1380 (m), 1264 (vs), 1176 (s), 1156 (m), 1120 (s), 1036 (w), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 1H), 6.32 (dd, $J = 9.9$, 1.3 Hz, 2H), 5.91 (d, $J = 5.5$ Hz, 1H), 5.83 (d, $J = 9.9$ Hz, 1H), 5.77 (d, $J = 5.5$ Hz, 1H), 4.26 (ddq, $J = 6.1$, 2.6, 2.6 Hz, 1H), 4.06 (ddq, $J = 6.1$, 2.6, 2.6 Hz, 1H), 3.80 (s, 3H), 3.80 (d, $J = 7.7$ Hz, 1H), 3.54 (dd, $J = 7.7$, 1.3 Hz, 1H), 2.17 (br d, $J = 12.7$ Hz, 1H), 1.89 (dt, $J = 12.9$, 4.0 Hz, 1H), 1.65 (br d, $J = 13.0$ Hz, 1H), 1.60 – 1.15 (m, 6H), 1.21 (d, $J = 6.1$ Hz, 3H), 1.16 (d, $J = 6.1$ Hz, 3H), 0.88 (s, 3H), 0.49 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.7$ (C), 158.4 (C), 148.5 (CH), 138.9 (CH), 136.0 (CH), 134.0 (CH), 129.3 (2 × CH), 129.0 (C), 113.2 (2 × CH), 97.6 (C), 71.0 (C), 67.0 (CH), 65.2 (CH), 60.7 (C), 55.3 (CH_3), 51.2 (CH), 43.0 (CH), 39.5 (CH_2), 29.1 62.5 (C), (CH_2), 27.0 (CH_2), 24.1 (CH_2), 22.3 (CH_3), 21.9 (CH_3), 21.4 (CH_2), 15.6 (CH_3); MS (70 eV): m/z (%): 434 (1) $[M]^+$, 240 (100), 225 (8), 109 (10); HRMS (ESI-MS): calcd for $C_{28}H_{34}O_4Na$ $[M+Na]^+$: 457.2355, found: 457.2366.

1-[2-(1,3)Dioxolan-2-yl-ethyl]-4-oxo-cyclohexa-2,5-dienyl aceate (37): Ac_2O (971 mg, 9.52 mmol, 2 equiv) was added dropwise over a period of 5 min at room temperature to a stirred solution of *p*-quinol **6a** (1.0 g, 4.76 mmol) and DMAP (1.45 g, 11.9 mmol, 2.5 equiv) in dry CH_2Cl_2 (50 mL) under N_2. The mixture was stirred overnight and then poured into a biphasic mixture of H_2O (150 mL) and EtOAc (200 mL). After layer separation, the product was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash chromatography (silica gel, EtOAc/PE 1:3) gave **37** (975 mg, 81 %) as a white solid. $R_f = 0.47$ (EtOAc/PE 4:1); m.p. 44 °C; IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2956 (w), 2888 (w), 1744 (s), 1668 (vs), 1632 (s), 1444 (w), 1396 (m), 1368 (m), 1228 (vs), 1168 (w), 1140 (s), 1016 (s), 980 (w), 856 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.28$ (d, $J = 10.3$ Hz, 2H), 4.87 (t, $J = 4.3$ Hz, 1H), 3.94 (m, 2H), 3.85 (m, 2H), 2.06 (s, 3H), 1.96 (m, 2H), 1.69 (dt, $J = 7.9$, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.0$ (C), 169.3 (C), 148.1 (2 × CH), 129.1 (2 × CH), 103.3 (CH), 76.3 (C), 65.0 (2 × CH_2), 33.0 (CH_2), 27.7 (CH_2), 21.2 (CH_3); MS (70 eV): m/z (%): 252 (0.7) $[M]^+$, 210 (5), 148 (15), 73 (100); MS (FAB +): m/z (%): 275 (22) $[M+Na]^+$, 253 (8) $[M+H]^+$, 193 (22), 149 (100); HRMS: calcd for $C_{13}H_{16}O_5$: 252.0998, found: 252.1004.

Cycloadduct 38: Diene **1** (430 mg, 1.8 mmol) and the spiro-cyclohexadienone **23** (280 mg, 1.7 mmol) in CH_2Cl_2 (2 mL) were converted (14 kbar, 6 d) into the cycloadduct **38** (586 mg, 85 %) as a white amorphous solid. $R_f = 0.33$ (EtOAc/PE 2:3); m.p. 81 °C; $[\alpha]_D^{22} = -241$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2928(s), 2652 (s), 1760 (s), 1664 (s), 1516 (s), 1448 (w), 1252 (s), 1180 (s), 1036 (w), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.63 (dd, $J = 10.3$, 1.1 Hz, 1H), 6.08 (d, $J = 5.7$ Hz, 1H), 5.83 (d, $J = 5.7$ Hz, 1H), 5.81 (d, $J = 10.3$ Hz, 1H), 4.14 (d, $J = 17.5$ Hz, 1H), 4.07 (d, $J = 17.5$ Hz, 1H), 3.80 (d, $J = 8.1$ Hz, 1H), 3.79 (s, 3H), 2.76 (dd, $J = 8.1$, 1.1 Hz, 1H), 2.56 (d, $J = 18.0$ Hz, 1H), 2.50 (d, $J = 18.0$ Hz, 1H), 2.34 (br d, $J = 12.0$ Hz, 1H), 1.86 (dt, $J = 12.9$, 3.4 Hz, 1H), 1.63 (br d, $J = 12.9$ Hz, 1H), 1.47 – 1.10 (m, 4H), 0.80 (s, 3H), 0.47 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.9$ (C), 198.7 (C), 158.4 (C), 149.4 (CH), 138.6 (CH), 136.4 (CH), 131.5 (CH), 129.2 (2 × CH), 128.7 (C), 113.2 (2 × CH), 81.5 (C), 71.6 (C), 70.4 (CH_2), 62.2 (C), 61.6 (C), 55.2 (CH_3), 53.8 (CH_2), 50.8 (CH), 49.7 (CH), 28.7 (CH_2), 27.3 (CH_2), 23.9 (CH_2), 21.1 (CH_2), 15.5 (CH_3); MS (70 eV): m/z (%): 404 (0.35) $[M]^+$, 240 (100), 225 (20), 164 (11); MS (FAB +): m/z (%): 427 (5) $[M+Na]^+$, 405 (5) $[M+H]^+$, 240 (100), 176 (9), 165 (24); HRMS: calcd for $C_{26}H_{28}O_4$: 404.1999, found: 404.1987.

Cycloadduct 39: Diene **1** (383 mg, 1.6 mmol) and the spiro-cyclohexadienone **27** (270 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) were converted (14 kbar, 6 d) into the cycloadduct **39** (566 mg, 89 %) as a white amorphous solid. $R_f = 0.18$ (EtOAc/PE 1:4); m.p. 119 °C; $[\alpha]_D^{20} = -249$ ($c = 1.1$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (s), 2956 (s), 2936 (s), 2860 (s), 1736 (w), 1668 (vs), 1612 (m), 1512 (vs), 1464 (m), 1380 (m), 1308 (s), 1244 (vs), 1180 (vs), 1096 (vs), 1072 (s), 1036 (vs), 964 (m), 824 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.29 (dd, $J = 10.2$, 0.9 Hz, 1H), 6.05 (d, $J = 5.7$ Hz, 1H), 5.79 (d, $J = 5.7$ Hz, 1H), 4.67 (dd, $J = 10.5$, 1.6 Hz, 1H), 4.63 (dd, $J = 10.5$, 1.6 Hz, 1H), 4.60 (t, $J = 1.6$ Hz, 1H), 3.80 (s, 3H), 3.79 (d, $J = 8.5.78$ (d, $J = 10.2$ Hz, 1H), 3 Hz, 1H), 3.51 (s, 3H), 2.72 (dd, $J = 8.3$, 0.9 Hz, 1H), 2.41 (dd, $J = 8.0$, 2.6 Hz, 1H), 1.85 (dt, $J = 13.0$, 3.5 Hz, 1H), 1.59 (m, 1H), 1.41 – 1.08 (m, 4H), 0.78 (s, 3H), 0.43 (br d, $J = 13.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$ (C), 160.0 (C), 158.3 (C), 148.3 (CH), 138.9 (CH), 135.4 (CH), 131.1 (CH), 129.5 (C), 129.3 (2 × CH), 113.0 (2 × CH), 89.0 (CH), 84.4 (C), 71.6 (C), 71.2 (CH_2), 62.1 (C), 61.1 (C), 58.2 (CH_3), 55.2 (CH_3), 50.3 (CH), 49.3 (CH), 28.6 (CH_2), 27.5 (CH_2), 24.0 (CH_2), 21.3 (CH_2), 15.2 (CH_3); MS (70 eV): m/z (%): 418 (1) $[M]^+$, 240 (100); HRMS: calcd for $C_{27}H_{30}O_4$: 418.2144, found: 418.2145.

Cycloadduct 40

Method A: Diene **1** (182 mg, 0.76 mmol) and the spiro-cyclohexadienone **30** (107 mg, 0.72 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 6 d) into the cycloadduct **40** (207 mg, 74 %) as a white amorphous solid.

Method B: The cycloadduct **41** (300 mg, 0.77 mmol) in dry CH_2Cl_2 (30 mL) at −40 °C under N_2 and magnetic stirring was treated with triethylamine (298 mg, 2.9 mmol, 4 equiv) and methanesulfonyl chloride (129 mg, 1.1 mmol, 1.5 equiv). After the addition was complete, stirring was continued at the same temperature for 2 h and then at room temperature overnight. The white mixture was filtered through a short silica gel column (washed with CH_2Cl_2). After evaporation and purification by flash chromatography (silica gel, EtOAc/PE 1:9) the cycloadduct **40** (144 mg, 51 %) was isolated as a white amorphous solid. $R_f = 0.11$ (EtOAc/PE 1:9); m.p. 54 °C; $[\alpha]_D^{20} = -194$ ($c = 0.6$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2924 (s), 2856 (m), 1660 (vs), 1620 (s), 1516 (s), 1464 (w), 1444 (w), 1248 (s), 1180 (s), 1144 (s), 1052 (s), 960 (w), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.61 (dd, $J = 10.1$, 0.9 Hz, 1H), 6.28 (dt, $J = 2.3$, 2.3 Hz, 1H), 6.07 (d, $J = 5.7$ Hz, 1H), 5.83 (d, $J = 5.7$ Hz, 1H), 5.74 (d, $J = 10.1$ Hz, 1H), 4.88 (dt, $J = 2.3$, 2.3 Hz, 1H), 3.81 (d, $J = 8.3$ Hz, 1H), 3.79 (s, 3H), 2.91 (d, $J = 8.3$ Hz, 1H), 2.69 (dt, $J = 15.5$, 2.3 Hz, 1H), 2.65 (dt, $J = 15.5$, 2.3 Hz, 1H), 2.33 (m, 1H), 1.86 (dt, $J = 12.9$, 3.5 Hz, 1H), 1.61 (m, 1H), 1.41 – 1.13 (m, 4H), 0.81 (s, 3H), 0.45 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.3$ (C), 158.3 (C), 150.9 (CH), 144.5 (CH), 139.0 (CH), 135.4 (CH), 129.5 (CH), 129.4 (C), 129.2 (2 × CH), 113.1 (2 × CH), 98.3 (CH), 84.7 (C), 71.0 (C), 62.1 (C), 61.2 (C), 55.2 (CH_3), 50.9 (CH), 50.4 (CH), 48.7 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 24.0 (CH_2), 21.3 (CH_2), 15.4 (CH_3); MS (70 eV): m/z (%): 388 (0.7) $[M]^+$, 240 (100), 225 (17); HRMS: calcd for $C_{26}H_{28}O_3$: 388.2038, found: 388.2045.

Cycloadduct 41: Diene **1** (456 mg, 1.9 mmol) and the spiro-cyclohexadienone **29** (300 mg, 1.8 mmol) in CH_2Cl_2 (3 mL) were converted (14 kbar, 13 d) into the cycloadduct **41** (587 mg, 78 %, thermodynamic controlled mixture of two diastereoisomers at the hemi-acetal centre: 87:13) as a white amorphous solid. $R_f = 0.14$ (EtOAc/PE 2:3); m.p. 76 °C; $[\alpha]_D^{23} = -207$ ($c = 1.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3600$ (w), 3000 (w), 2936 (m), 2860 (w), 1732 (w), 1660 (s), 1612 (w), 1516 (s), 1464 (w), 1444 (w), 1380 (w), 1248 (s), 1180 (s), 1152 (w), 1092 (w), 1036 (s), 1000 (m), 964 (s), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.9$ Hz, 2H), 6.87 (d, $J = 8.9$ Hz, 2H), 6.57 (dd, $J = 10.3$, 1.0 Hz, 1H), 6.07 (d, $J = 5.5$ Hz, 1H), 5.83 (d, $J = 5.5$ Hz, 1H), 5.72 (d, $J = 10.3$ Hz, 1H), 5.57 (m, 1H), 3.79 (s, 3H), 3.73 (d, $J = 8.0$ Hz, 1H), 2.54 (dd, $J = 8.0$, 1.0 Hz, 1H), 2.33 (m, $J = 12.5$ Hz, 1H), 2.20 – 1.90 (m, 4H), 1.85 (m, 1H), 1.62 (m, 1H), 1.43 – 1.10 (m, 4H), 0.78 (s, 3H), 0.43 (br d, $J = 12.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$ (C),

158.3 (C), 155.0 (CH), 138.9 (CH), 135.6 (CH), 129.3 (3 × CH, C), 113.1 (2 × CH), 99.1 (CH), 83.3 (C), 71.6 (C), 62.1 (C), 61.2 (C), 55.3 (CH_3), 50.5 (CH), 50.3 (CH), 40.8 (CH_2), 32.2 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 24.1 (CH_2), 21.3 (CH_2), 15.3 (CH_3); MS (70 eV): *m/z* (%): 406 (0.3) $[M]^+$, 240 (100).

Cycloadducts 42 and 43: Diene **1** (298 mg, 1.23 mmol) and the spirocyclohexadienone **28** (229 mg, 1.18 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 13 d) into the cycloadducts **42** (173 mg, 34%) and **43** (150 mg, 29%) both as a white amorphous solid.

Cycloadduct 42: $R_f = 0.18$ (EtOAc/PE 1:4); m.p. 53 °C; $[\alpha]_D^{21} = -191$ ($c = 1.1$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2972 (m), 2924 (s), 2860 (m), 1660 (vs), 1612 (m), 1512 (vs), 1464 (m), 1444 (m), 1380 (m), 1248 (vs), 1180 (s), 1104 (m), 1060 (m), 1032 (vs), 1000 (vs), 968 (s), 860 (m), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.50 (d, $J = 10.2$ Hz, 1H), 6.07 (d, $J = 5.7$ Hz, 1H), 5.79 (d, $J = 5.7$ Hz, 1H), 5.68 (d, $J = 10.2$ Hz, 1H), 5.12 (dd, $J = 3.9$, 0.9 Hz, 1H), 3.79 (s, 3H), 3.76 (dq, $J = 9.6$, 7.0 Hz, 1H), 3.72 (d, $J = 8.1$ Hz, 1H), 3.46 (dq, $J = 9.6$, 7.0 Hz, 1H), 2.52 (d, $J = 8.1$ Hz, 1H), 2.35 (br d, $J = 12.5$ Hz, 1H), 2.12–1.72 (m, 5H), 1.59 (m, 1H), 1.40–1.15 (m, 4H), 1.21 (t, $J = 7.0$ Hz, 3H), 0.78 (s, 3H), 0.42 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$ (C), 158.2 (C), 155.2 (CH), 139.1 (CH), 135.1 (CH), 129.4 (C), 129.3 (2 × CH), 128.9 (CH), 113.0 (2 × CH), 104.2 (CH), 82.6 (C), 71.4 (C), 62.6 (CH_2), 62.1 (C), 61.0 (C), 55.2 (CH_3), 50.6 (CH), 50.4 (CH), 41.4 (CH_2), 31.6 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 24.1 (CH_2), 21.3 (CH_2), 15.33 (CH_3), 15.3 (CH_3); MS (70 eV): *m/z* (%): 434 (1) $[M]^+$, 240 (100), 225 (14), 197 (15), 91 (10); HRMS: calcd for $C_{28}H_{34}O_4$: 434.2457, found: 434.2451.

Cycloadduct 43: $R_f = 0.10$ (EtOAc/PE 1:4); m.p. 114 °C; $[\alpha]_D^{22} = -97$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (m), 2976 (m), 2924 (s), 2864 (m), 1660 (vs), 1612 (m), 1512 (vs), 1464 (m), 1444 (m), 1380 (m), 1288 (m), 1248 (vs), 1180 (vs), 1152 (m), 1108 (m), 1076 (s), 1036 (s), 1008 (s), 960 (m), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.45 (d, $J = 10.1$ Hz, 1H), 6.05 (d, $J = 5.5$ Hz, 1H), 5.81 (d, $J = 5.5$ Hz, 1H), 5.68 (d, $J = 10.1$ Hz, 1H), 5.18 (dd, $J = 4.8$, 3.1 Hz, 1H), 3.85 (dq, $J = 9.4$, 7.0 Hz, 1H), 3.79 (s, 3H), 3.79 (d, $J = 8.3$ Hz, 1H), 3.51 (dq, $J = 9.4$, 7.0 Hz, 1H), 2.75 (d, $J = 8.3$ Hz, 1H), 2.56 (br d, $J = 12.3$ Hz, 1H), 2.15–1.80 (m, 5H), 1.62 (br d, $J = 13.0$ Hz, 1H), 1.45–1.17 (m, 4H), 1.22 (t, $J = 7.0$ Hz, 3H), 0.81 (s, 3H), 0.46 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$ (C), 158.2 (C), 153.0 (CH), 139.2 (CH), 135.4 (CH), 129.9 (CH), 129. 6 (C), 129.1 (2 × CH), 113.0 (2 × CH), 105.2 (CH), 83.1 (C), 70.8 (C), 64.4 (CH_2), 62.1 (C), 61.4 (C), 55.2 (CH_3), 51.6 (CH), 51.1 (CH), 42.9 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 24.0 (CH_2), 21.3 (CH_2), 15.5 (CH_3), 15.2 (CH_3); MS (70 eV): *m/z* (%): 434 (0.7) $[M]^+$, 240 (100), 225 (20), 197 (20), 91 (19); HRMS: calcd for $C_{28}H_{34}O_4$: 434.2457, found: 434.2461.

Cycloadduct 44: Diene **1** (1.69 g, 7.0 mmol) and the *p*-quinol **6d** (1.0 g, 6.7 mmol) in CH_2Cl_2/CH_3CN (25 mL, 3:2) were converted (14 kbar, 6 d) into cycloadduct **44** (2.33 g, 89%) as a white amorphous solid. $R_f = 0.21$ (EtOAc/PE 2:3); m.p. 76 °C; $[\alpha]_D^{22} = -163$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3584$ (w), 2928 (s), 2864 (m), 2153 (w), 1732 (w), 1668 (s), 1516 (s), 1252 (s), 1180 (s), 1036 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD): $\delta = 7.29$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.54 (d, $J = 10.4$ Hz, 1H), 6.14 (d, $J = 5.7$ Hz, 1H), 5.81 (d, $J = 5.7$ Hz, 1H), 5.80 (d, $J = 10.4$ Hz, 1H), 3.92 (d, $J = 8.3$ Hz, 1H), 3.78 (s, 3H), 2.83 (dd, $J = 8.3$, 0.9 Hz, 1H), 2.78 (d, $J = 16.0$ Hz, 1H), 2.73 (d, $J = 16.0$ Hz, 1H), 2.51 (br d, $J = 13.0$ Hz, 1H), 1.87 (dt, $J = 13.0$, 3.3 Hz, 1H), 1.62 (m, 1H), 1.49 (dt, $J = 13.0$, 3.3 Hz, 1H), 1.41–1.20 (m, 3H), 0.86 (s, 3H), 0.37 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 201.6$ (C), 160.0 (C), 152.4 (CH), 140.4 (CH), 136.7 (CH), 132.3 (CH), 130.9 (C), 130.6 (2 × CH), 118.4 (C), 72.9 (C), 71.8 (C), 63.9 (C), 62.5 (C), 52.1 (CH), 52.9 (CH), 114.2 (2 × CH), 55.9 (CH_3), 36.9 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.5 (CH_2), 16.2 (CH_3); MS (70 eV): *m/z* (%): 389 (2.8) $[M]^+$, 240 (100); HRMS: calcd for $C_{25}H_{27}O_3N$: 389.1990, found: 389.1998.

Cycloadduct 45: Diene **1** (321 mg, 1.34 mmol) and *p*-quinol **6c** (158 mg, 1.27 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 13 d) into the cycloadduct **44** (399 mg, 79%) as a pale yellow solid. $R_f = 0.33$ (EtOAc/PE 2:3); m.p. 176 °C; $[\alpha]_D^{22} = -153$ ($c = 1.1$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3604$ (w), 3000 (m), 2932 (s), 2860 (m), 1660 (vs), 1612 (w), 1516 (vs), 1248 (vs), 1180 (s), 1108 (m), 1036 (s), 824 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.48 (d, $J = 10.1$ Hz, 1H), 6.13 (d, $J = 5.7$ Hz, 1H), 5.92 (d, $J = 5.7$ Hz, 1H), 5.74 (d, $J = 10.1$ Hz, 1H), 3.81 (d, $J = 8.7$ Hz, 1H), 3.79 (s, 3H), 2.73 (d, $J = 8.7$ Hz, 1H), 2.37 (br d, $J = 12.8$ Hz, 1H), 1.87 (dd, $J = 13.4$, 4.2 Hz, 1H), 1.62 (m, 1H), 1.50–1.15 (m, 4H), 1.42 (s, 3H), 0.82 (s, 3H), 0.47 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $[D_6]DMSO$): $\delta = 199.2$ (C), 157.8 (CH), 156.0 (C), 139.0 (CH), 134.5 (CH), 130.0 (C), 129.2 (2 × CH), 128.1 (CH), 112.8 (2 × CH), 70.6 (C), 69.5 (C), 61.7 (C), 60.6 (C), 55.1 (CH_3), 51.8 (CH), 50.9 (CH), 36.2 (CH_3), 28.7 (CH_2), 27.8 (CH_2), 23.9 (CH_2), 21.1 (CH_2), 15.5 (CH_3); MS (70 eV): *m/z* (%): 364 (0.5) $[M]^+$, 240 (100), 109 (16); MS (FAB+): *m/z* (%): 378 (6) $[M+Na]^+$, 365 (7) $[M+H]^+$, 240 (100), 125 (28); HRMS: calcd for $C_{24}H_{28}O_3$: 364.2038, found: 364.2035.

Cycloadduct 46: Diene **1** (840 mg, 3.5 mmol) and *p*-quinol **6a** (700 mg, 3.3 mmol) in CH_2Cl_2 (5 mL) were converted (14 kbar, 20 d) into the cycloadduct **46** (1.29 g, 87%) as a pale amorphous solid. $R_f = 0.21$ (EtOAc/PE 2:3); m.p. 122 °C; $[\alpha]_D^{20} = -180$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3600$ (w), 3436 (w), 3000 (m), 2936 (s), 2864 (m), 1728 (w), 1664 (vs), 1612 (w), 1512 (vs), 1248 (vs), 1180 (s), 1140 (m), 1360 (s), 992 (m), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.43 (d, $J = 10.3$ Hz, 1H), 6.10 (d, $J = 5.7$ Hz, 1H), 5.84 (d, $J = 5.7$ Hz, 1H), 5.76 (d, $J = 10.3$ Hz, 1H), 4.90 (t, $J = 3.7$ Hz, 1H), 4.00 (m, 2H), 3.89 (m, 2H), 3.76 (d, $J = 8.3$ Hz, 1H), 2.70 (d, $J = 8.3$ Hz, 1H), 2.43 3.80 (s, 3H), (br d, $J = 12.5$ Hz, 1H), 1.90–1.70 (m, 5H), 1.60 (m, 1H), 1.48–1.27 (m, $J = 13.0$, 3.1 Hz, 3H), 1.21 (m, $J = 13.0$ Hz, 1H), 0.82 (s, 3H), 0.44 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.7$ (C), 158.2 (C), 153.5 (CH), 138.9 (CH), 135.7 (CH), 129.8 (CH), 129.4 (C), 129.1 (2 × CH), 113.0 (2 × CH), 103.9 (CH), 72.4 (C), 71.7 (C), 65.0 (2 × CH_2), 62.1 (C), 61.3 (C), 55.1 (CH_3), 51.2 (CH), 50.7 (CH), 41.7 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 24.0 (CH_2), 21.2 (CH_2), 15.4 (CH_3); MS (70 eV): *m/z* (%): 450 (1) $[M]^+$, 240 (100), 73 (58); MS (FAB+): (%): 473 (8) $[M+Na]^+$, 451 (4) $[M+H]^+$, 240 (100); HRMS: calcd for $C_{28}H_{34}O_5$: 450.2406, found: 450.2428.

Cycloadduct 47: Diene **1** (300 mg, 1.25 mmol) and *p*-quinol **37** (300 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) were converted (14 kbar, 20 d) into the cycloadduct **47** (357 mg, 61%) as a white amorphous solid [105 mg *p*-quinol **37** was recovered (35%)]. $R_f = 0.23$ (EtOAc/PE 2:3); m.p. 63 °C; $[\alpha]_D^{21} = -159$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2932 (m), 1732 (s), 1668 (s), 1612 (w), 1228 (s), 1180 (s), 1036 (m), 1000 (m), 964 (w), 824 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.8$ Hz, 2H), 7.03 (dd, $J = 10.5$, 1.1 Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.00 (d, $J = 5.6$ Hz, 1H), 5.83 (d, $J = 5.6$ Hz, 1H), 5.77 (d, $J = 10.5$ Hz, 1H), 4.83 (t, $J = 4.5$ Hz, 1H), 3.98–3.81 (m, 4H), 3.80 (d, $J = 7.7$ Hz, 1H), 3.79 (s, 3H), 3.06 (d, $J = 7.7$ Hz, 1H), 2.26–2.11 (m, 2H), 2.09 (s, 3H), 1.85 (dt, $J = 12.9$, 3.8 Hz, 1H), 1.75–1.55 (m, 3H), 1.48 (m, $J = 12.9$, 3.6 Hz, 1H), 1.43–1.27 (m, 3H), 1.20 (m, $J = 13.0$, 3.7 Hz, 1H), 0.84 (s, 3H), 0.45 (br d, $J = 12.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.7$ (C), 169.8 (C), 158.3 (C), 147.6 (CH), 138.7 (CH), 135.9 (CH), 130.6 (CH), 129.2 (C), 129.1 (2 × CH), 113.1 (2 × CH), 103.6 (CH), 83.2 (C), 70.9 (C), 65.0 (2 × CH_2), 62.0 (C), 61.7 (C), 55.2 (CH_3), 51.7 (CH), 49.1 (CH), 37.2 (CH_2), 28.8 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 24.1 (CH_2), 22.5 (CH_3), 21.1 (CH_2), 15.6 (CH_3); MS (70 eV): *m/z* (%): 492 (0.3) $[M]^+$, 240 (100), 73 (87); MS (FAB+): *m/z* (%): 515 (3) $[M+Na]^+$, 491 (3) $[M-H]^+$, 240 (100); HRMS: calcd for $C_{30}H_{36}O_6$: 492.2512, found: 492.2505.

Cycloadduct 48: Diene **1** (125 mg, 0.52 mmol) and *p*-quinol **16a** (118 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) were converted (14 kbar, 6 d) into the cycloadduct **48** (182 mg, 77%) as a white amorphous solid. $R_f = 0.36$ (EtOAc/PE 2:3); m.p. 57 °C; $[\alpha]_D^{21} = -239$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3588$ (w), 3464 (w), 3000 (m), 2928 (s), 1660 (vs), 1612 (w), 1516 (vs), 1248 (vs), 1120 (m), 1044 (s), 1000 (m), 824 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.28 (dd, $J = 10.1$, 0.9 Hz, 1H), 6.13 (d, $J = 5.7$ Hz, 1H), 5.86 (dd, $J = 15.6$, 1.0 Hz, 1H), 5.85 (d, $J = 5.7$ Hz, 1H), 5.78 (d, $J = 10.1$ Hz, 1H), 5.61 (dd, $J = 15.6$, 4.7 Hz, 1H), 4.91 (dd, $J = 4.7$, 1.0 Hz, 1H), 3.79 (d, $J = 8.4$ Hz, 1H), 3.79 (s, 3H), 3.68–3.45 (m, 4H), 2.80 (d, $J = 8.4$ Hz, 1H), 2.39 (br d, $J = 12.0$ Hz, 1H), 1.85 (dt, $J = 13.0$ Hz, 1H), 1.61 (br d, $J = 12.7$ Hz, 1H), 1.46–1.30 (m, 3H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.19 (m, 1H), 0.70 (s, 3H), 0.45 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.5$ (C), 158.3 (C), 150.5 (CH), 141.8 (CH), 138.9 (CH), 136.0 (CH), 130.4 (CH), 129.3 (C), 129.1 (2 × CH), 124.8 (CH), 113.1 (2 × CH), 100.6 (CH), 73.2 (C), 71.0 (C), 62.2 (C), 61.6 (C), 61.4 (CH_2), 61.2 (CH_2), 55.2 (CH_3), 51.1 (CH), 50.9 (CH), 28.6 (CH_2), 28.2 (CH_2), 24.0 (CH_2), 21.1 (CH_2), 15.5 (2 × CH_3), 15.3 (CH_3); MS (70 eV): *m/z* (%): 478 (1) $[M]^+$, 240 (100), 73 (58); MS (FAB+): *m/z* (%): 479 (1) $[M+H]^+$, 433 (4), 240 (100), 133 (27); HRMS: calcd for $C_{30}H_{38}O_5$: 478.2719, found: 478.2722.

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Cycloadduct 49: Diene **1** (896 mg, 3.73 mmol) and dienone **16b** (995 mg, 3.55 mmol) in CH_2Cl_2 (5 mL) were converted (14 kbar, 20 d) into the cycloadduct **49** (950 mg, 51%) as a colourless oil [249 mg of dienone **16b** was recovered (32%)]. $R_f = 0.22$ (EtOAc/PE 1:4); $[\alpha]_D^{20} = -162$ ($c = 0.7$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (w), 2976 (m), 2928 (m), 1736 (s), 1668 (s), 1612 (w), 1516 (vs), 1368 (m), 1248 (vs), 1232 (vs), 1180 (m), 1124 (m), 1040 (s), 988 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.8$ Hz, 2H), 6.68 (dd, $J = 10.3$, 1.1 Hz, 1H), 6.67 (d, $J = 8.8$ Hz, 2H), 6.07 (dd, $J = 15.9$, 1.3 Hz, 1H), 6.04 (d, $J = 5.5$ Hz, 1H), 5.96 (d, $J = 10.3$ Hz, 1H), 5.85 (d, $J = 5.5$ Hz, 1H), 5.35 (dd, $J = 15.9$, 4.0 Hz, 1H), 4.94 (dd, $J = 4.0$, 1.1 Hz, 1H), 3.79 (s, 3H), 3.74 (d, $J = 8.3$ Hz, 1H), 3.63–3.41 (m, 4H), 3.01 (dd, $J = 8.4$, 1.1 Hz, 1H), 2.29 (br d, $J = 13.0$ Hz, 1H), 2.11 (s, 3H), 1.87 (dt, $J = 13.0$, 3.7 Hz, 1H), 1.65 (br d, $J = 13.0$ Hz, 1H), 1.51 (dt, $J = 13.0$, 3.3 Hz, 1H), 1.44–1.12 (m, 3H), 1.21 (t, $J = 7.1$ Hz, 6H), 0.82 (s, 3H), 0.47 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.6$ (C), 169.3 (C), 158.3 (C), 144.1 (CH), 138.7 (CH), 138.6 (CH), 136.0 (CH), 132.4 (CH), 129.0 (2 × CH), 128.9 (C), 127.1 (CH), 113.1 (2 × CH), 99.8 (CH), 81.4 (C), 70.4 (C), 71.0 (C), 62.2 (C), 62.0 (C), 60.8 (CH_2), 60.7 (CH_2), 55.2 (CH_3), 51.2 (CH), 50.9 (CH), 28.8 (CH_2), 28.0 (CH_2), 24.1 (CH_3), 22.3 (CH_3), 21.1 (CH_2), 15.3 (CH_3), 15.28 (CH_3); MS (70 eV): *m/z* (%): no molecular peak, 240 (100), 225 (19), 165 (21), 73 (58); MS (FAB+): *m/z* (%): 543 (2) $[M+Na]^+$, 521 (3) $[M+H]^+$, 475 (4), 240 (100); HRMS (ESI-MS): calcd for $C_{32}H_{40}O_6Na$ $[M+Na]^+$: 543.2723, found: 543.2706.

Cycloadduct 50: $NiCl_2 \cdot 6H_2O$ (464 mg, 2.3 mmol) and zinc powder (746 mg, 11.2 mmol) were added in one portion to a solution of cycloadduct **46** (700 mg, 1.5 mmol) in methoxyethanol (25 mL) and water (3.4 mL). The mixture underwent sonification for 2.5 hours and was then filtered through Celite. Water (150 mL) was added and the product was extracted with EtOAc (2 × 150 mL) and CH_2Cl_2 (1 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. After flash chromatography (silica gel, EtOAc/PE 1:1), **50** (668 mg, 95%) was isolated as colourless crystals. $R_f = 0.12$ (EtOAc/PE 2:3); m.p. 140 °C; $[\alpha]_D^{21} = +16$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3540$ (w), 3000 (m), 2932 (s), 2864 (m), 1704 (s), 1612 (w), 1516 (s), 1464 (s), 1180 (s), 1140 (s), 1036 (s), 984 (w), 944 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.15$ (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.29 (d, $J = 5.7$ Hz, 1H), 6.13 (d, $J = 5.7$ Hz, 1H), 4.90 (t, $J = 4.3$ Hz, 1H), 4.04–3.86 (m, 4H), 3.79 (s, 3H), 3.71 (d, $J = 10.3$ Hz, 1H), 2.73 (d, $J = 10.3$ Hz, 1H), 2.25–2.16 (m, 3H), 2.03–1.69 (m, 7H), 1.65 (br d, $J = 13.0$ Hz, 1H), 1.52–1.30 (m, 3H), 1.18 (dt, $J = 13.2$, 3.5 Hz, 1H), 0.78 (s, 3H), 0.53 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.7$ (C), 158.0 (C), 138.5 (CH), 137.0 (CH), 131.0 (C), 127.9 (2 × CH), 113.3 (2 × CH), 104.5 (CH), 72.7 (C), 65.5 (C), 65.0 (2 × CH_2), 62.5 (C), 60.1 (C), 55.2 (CH_3), 55.1 (CH), 54.8 (CH), 35.8 (CH_2), 34.9 (CH_2), 32.2 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 23.7 (CH_2), 21.0 (CH_2), 16.0 (CH_3); MS (70 eV): *m/z* (%): no molecular peak, 240 (100); MS (FAB+): *m/z* (%): 475 (7) $[M+Na]^+$, 451 (8), 240 (100); elemental analysis (%) calcd for $C_{28}H_{36}O_5$: C 74.29, H 8.02: found: C 74.24, H 7.98.

Cycloadduct 51

Method A: *p*-TsOH (100 mg, 1 equiv) was added in one portion to compound **50** (290 mg, 6.42 mmol) dissolved in a solution of THF/H_2O (10:15, 25 mL). The mixture was refluxed immediately under vigorous stirring (oil bath at 140 °C) for 45 min. After cooling, EtOAc (100 mL) was added and the two layers were decanted. The product was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography (silica gel, EtOAc/PE 2:3) gave **51** (136 mg, 52%) as mixture of two diastereoisomers in thermodynamic equilibrium at the hemi-acetal position (3:2, determined by ^1H NMR).

Method B: A catalytic amount of 10% Pd/C (22 mg) was added to cycloadduct **41** (215 mg, 6.18 mmol) dissolved in dry THF (10 mL). The mixture was then stirred under a hydrogen atmosphere for 3 h. After filtration over Celite and flash chromatography, **51** (114 mg, 53%) was isolated. $R_f = 0.14$ (EtOAc/PE 2:3); m.p. 78 °C; $[\alpha]_D^{23} = -14$ ($c = 1.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3600$ (w), 3000 (m), 2928 (s), 2864 (m), 1701 (s), 1612 (w), 1516 (vs), 1464 (m), 1288 (m), 1248 (vs), 1180 (s), 1036 (s), 984 (m), 820 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): major diastereoisomer: $\delta = 7.18$ (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.06 (d, $J = 5.7$ Hz, 1H), 6.01 (d, $J = 5.7$ Hz, 1H), 5.57 (t, $J = 2.9$ Hz, 1H), 3.79 (s, 3H), 3.67 (d, $J = 10.1$ Hz, 1H), 2.69 (d, $J = 10.1$ Hz, 1H), 2.50–1.62 (m, 11H), 1.45–1.13 (m, 4H), 0.75 (s, 3H), 0.49 (br d, $J = 12.5$ Hz, 1H); minor diastereoisomer: $\delta = 7.19$ (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.10 (d, $J = 5.9$ Hz, 1H), 6.07 (d, $J = 5.9$ Hz, 1H), 5.48 (dd, $J = 4.8$, 3.3 Hz, 1H), 3.79 (s, 3H), 3.69 (d, $J = 10.2$ Hz, 1H), 2.85 (d, $J = 10.2$ Hz, 1H), 2.50–1.62 (m, 11H), 1.45–1.13 (m, 4H), 0.77 (s, 3H), 0.52 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): major diastereoisomer: $\delta = 212.3$ (C). 157.9 (C), 139.4 (CH), 134.9 (CH), 131.4 (C), 128.1 (2 × CH), 113.2 (2 × CH), 99.4 (CH), 84.1 (C), 66.2 (C), 61.7 (C), 59.9 (C), 55.4 (CH), 55.2 (CH_3), 54.1 (CH), 36.6 (CH_2), 36.3 (CH_2), 35.1 (CH_2), 32.7 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 23.8 (CH_2), 21.3 (CH_2), 16.1 (CH_3); minor diastereoisomer: $\delta = 212.4$ (C), 157.9 (C), 139.9 (CH), 134.6 (CH), 131.5 (C), 128.1 (2 × CH), 113.2 (2 × CH), 98.9 (CH), 84.4 (C), 66.0 (C), 61.9 (C), 60.0 (C), 55.6 (CH), 55.2 (CH_3), 53.9 (CH), 35.5 (CH_2), 34.6 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 23.9 (CH_2), 21.3 (CH_2), 16.2 (CH_3); MS (70 eV): *m/z* (%): no molecular peak, 240 (100), 225 (8); MS (FAB+): *m/z* (%): 431 (6) $[M+Na]^+$, 407 (5), 391 (14), 240 (100); MS (CI, CH_4): *m/z* (%): 409 (1) $[M+H]^+$, 240 (100); HRMS (CI, CH_4): calcd for $C_{26}H_{33}O_4$ $[M+H]^+$: 409.2379, found: 409.2385.

Cycloadduct 5b from 41: Cycloadduct **41** (200 mg, 0.49 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at room temperature (water bath) under N_2 to the stirred solution of pyridinium chlorochromate (PCC, 160 mg, 0.74 mmol, 1.5 equiv) in dry CH_2Cl_2 (10 mL). After the addition was complete, powdered dry 4 Å molecular sieves (100 mg) was poured in one portion and the mixture was stirred overnight. The black solution was diluted with dry Et_2O (50 mL) and the resulting black precipitate was triturated several times with dry Et_2O. The combined organic layers were filtered through Celite. After evaporation and flash chromatography (silica gel, EtOAc/PE 2:3), **5b** (152 mg, 76%) was isolated as a white solid. $R_f = 0.15$ (EtOAc/PE 2:3); $[\alpha]_D^{23} = -194$ ($c = 1.4$, $CHCl_3$); physical data are in complete agreement with those obtained previously in our laboratory by an alternative route.[3]

Cycloadduct 54: A solution of H_2O_2 (5 mL, 30% in water) was poured at room temperature to a stirred solution of cycloadduct **44** in a mixture of THF (50 mL) and saturated aqueous solution of K_2CO_3 (50 mL). The resulting exothermic reaction was cooled with a water bath. After 1 h, additional H_2O_2 was added (5 mL) and the reaction was stirred overnight (20 h). The compound was extracted with EtOAc, washed with 5% $FeSO_4$ solution in H_2O and dried ($MgSO_4$). Purification by flash chromatography (silica gel, EtOAc/PE 1:4) gave **54** (149 mg, 48%) as a white amorphous solid. $R_f = 0.29$ (EtOAc/PE 2:3); m.p. 175 °C; $[\alpha]_D^{21} = -8$ ($c = 0.6$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3688$ (w), 3552 (w), 3000 (w), 2932 (m), 2856 (w), 2252 (w), 1716 (vs), 1612 (w), 1516 (vs), 1464 (w), 1444 (w), 1344 (w), 1292 (w), 1252 (vs), 1180 (m), 1036 (m), 908 (w), 820 (w) cm^{-1}; ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.14$ (d, $J = 8.9$ Hz, 2H), 6.85 (d, $J = 8.9$ Hz, 2H), 5.98 (d, $J = 5.7$ Hz, 1H), 5.92 (d, $J = 5.7$ Hz, 1H), 3.98 (d, $J = 10.5$ Hz, 1H), 3.73 (s, 3H), 3.50 (d, $J = 4.4$ Hz, 1H), 3.32 (d, $J = 4.4$ Hz, 1H), 3.10 (d, $J = 17.0$ Hz, 1H), 3.05 (d, $J = 17.0$ Hz, 1H), 2.74 (d, $J = 10.5$ Hz, 1H), 2.10 (br d, $J = 12.0$ Hz, 1H), 1.91 (dt, $J = 13.0$, 3.5 Hz, 1H), 1.60 (br d, $J = 12.0$ Hz, 1H), 1.41–1.02 (m, 4H), 0.69 (s, 3H), 0.38 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 206.0$ (C), 157.9 (C), 139.6 (CH), 134.2 (CH), 131.3 (C), 128.3 (2 × CH), 118.3 (C), 113.6 (2 × CH), 70.6 (C), 70.5 (C), 63.6 (C), 62.3 (CH), 61.0 (C), 59.9 (CH), 55.3 (CH_3), 53.4 (CH), 51.9 (CH), 30.6 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 23.6 (CH_2), 21.1 (CH_2), 15.9 (CH_3); MS (70 eV): *m/z* (%): 405 (1.5) $[M]^+$, 240 (100); HRMS: calcd for $C_{25}H_{27}O_4N$: 405.1940, found: 405.1938.

Cycloadduct 55: A solution of *tert*-butylhydroperoxide (HO*t*Bu) in decane (5.5 M, 2.1 mL, 10 equiv) diluted in dry THF (10 mL) was stirred at −50 °C under N_2. *t*BuLi (1.5 M in pentane, 7.53 mL) was added dropwise from a syringe and the mixture was stirred for further 15 min at this temperature. The mixture was warmed to −40 °C and the cycloadduct **46** (515 mg, 1.14 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred for 5 h at a temperature maintained between −30 °C and −20 °C and for 5 h between 0 °C and 10 °C. After hydrolysis with a saturated aqueous solution of NH_4Cl (150 mL), the product was extracted with EtOAc (3 × 100 mL) and dried ($MgSO_4$). After flash chromatography (silica gel, EtOAc/PE 3:7), the epoxide **55** (323 mg, 61%) was isolated as a white amorphous solid and 90 mg of cycloadduct **46** was recovered (17%). $R_f = 0.23$ (EtOAc/PE 2:3); m.p. 138 °C; $[\alpha]_D^{23} = -62$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3556$ (w), 3400 (w), 2932 (m), 2864 (w), 1712 (m), 1616 (w), 1516 (m), 1264 (s), 1248 (m), 1228 (m), 1180 (m), 1140 (m), 1036 (m), 908 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.28 (d, $J = 5.8$ Hz, 1H), 6.06 (d, $J = 5.8$ Hz, 1H), 4.93 (t, $J = 3.7$ Hz, 1H), 3.99 (m, 2H), 3.88 (m, 2H), 3.78 (s, 3H), 3.66 (d, $J =$

9.6 Hz, 1H), 3.24 (d, $J = 3.9$ Hz, 1H), 3.16 (d, $J = 3.9$ Hz, 1H), 2.65 (d, $J =$ 9.6 Hz, 1H), 2.43 (br d, $J = 12.0$ Hz, 1H), 1.94–1.77 (m, 5H), 1.61 (br d, $J =$ 12.0 Hz, 1H), 1.46–1.10 (m, 4H), 0.74 (s, 3H), 0.41 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.3$ (C), 158.2 (C), 140.9 (CH), 135.0 (CH), 129.2 (C), 128.9 (2 × CH), 113.0 (2 × CH), 103.9 (CH), 71.9 (C), 70.2 (C), 65.07 (CH_2), 65.06 (CH_2), 63.5 (CH), 62.8 (C), 62.2 (C), 56.4 (CH), 55.1 (CH_3), 52.7 (CH), 52.6 (CH), 36.5 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 23.9 (CH_2), 21.2 (CH_2), 16.1 (CH_3); MS (70 eV): m/z (%): 466 (1) $[M]^+$, 240 (100); HRMS: calcd for $C_{28}H_{34}O_6$: 466.2354, found: 466.2372.

Cycloadduct 56: A solution of HOO*t*Bu in decane (5.5 M, 0.66 mL, 10 equiv) diluted in dry THF (5 mL) was cooled at −50 °C. *t*BuLi (1.5 M, 2.4 mL) was added dropwise from a syringe into this solution and the mixture was stirred for 15 min at this temperature. The cycloadduct **48** (175 mg, 0.37 mmol) in dry THF (3 mL) was added dropwise into the mixture at −50 °C. The solution was stirred for 5 h at a temperature maintained between −30 °C and −20 °C and for 5 h at −10 °C. After hydrolysis with a saturated aqueous solution of NH_4Cl (50 mL), the product was extracted with EtOAc (3 × 100 mL) and dried ($MgSO_4$). After flash chromatography (silica gel, EtOAc/PE 1:3), the epoxide **56** (103 mg, 57%) was isolated as a white amorphous solid and 32 mg of cycloadduct **48** was recovered (18%). $R_f = 0.38$ (EtOAc/PE 2:3); m.p. 142 °C; $[\alpha]_D^{23} = -78$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3588$ (w), 3448 (w), 3000 (w), 2980 (m), 2928 (m), 2864 (w), 1688 (s), 1612 (w), 1516 (vs), 1464 (w),1444 (w), 1340 (w), 1264 (vs), 1248 (vs), 1180 (s), 1120 (m), 1044 (s), 892 (m), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J =$ 8.8 Hz, 2H), 6.29 (d, $J = 5.7$ Hz, 1H), 6.06 (d, $J = 5.7$ Hz, 1H), 6.00 (dd, $J = 15.7$, 1.0 Hz, 1H), 5.88 (dd, $J = 15.7$, 4.4 Hz, 1H), 4.98 (dd, $J = 4.4$, 1.0 Hz, 1H), 3.79 (s, 3H), 3.72 (d, $J = 9.4$ Hz, 1H), 3.66 (m, 2H), 3.53 (m, 2H), 3.28 (d, $J = 4.0$ Hz, 1H), 3.20 (d, $J = 4.0$ Hz, 1H), 2.74 (d, $J = 9.4$ Hz, 1H), 2.36 (m, 1H), 1.92 (dt, $J = 12.7$, 3.9 Hz, 1H), 1.61 (m, 1H), 1.24 (t, $J =$ 7.0 Hz, 6H), 1.40–1.10 (m, 4H), 0.73 (s, 3H), 0.44 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.9$ (C), 158.3 (C), 141.3 (CH), 138.1 (CH), 134.6 (CH), 129.2 (C), 128.9 (2 × CH), 126.4 (CH), 113.2 (2 × CH), 100.4 (C), 72.8 (C), 69.6 (C), 63.1 (C), 62.5 (CH), 62.1 (C), 61.25 (CH_2), 61.23 (CH_2), 55.7 (CH), 55.2 (CH_3), 53.7 (CH), 52.6 (CH), 29.0 (CH_2), 27.9 (CH_2), 23.8 (CH_2), 21.1 (CH_2), 16.2 (CH_3), 15.3 (2 × CH_3); MS (70 eV): m/z (%): no molecular peak, 240 (100).

(2-Hydroxy-5-oxo-7-oxa-bicyclo[4.1.0]hept-3-en-2-yl)-acetonitrile (57): The cycloadduct **54** (328 mg, 8.43 mmol) was placed in a flash vacuum pyrolysis apparatus at 200 °C and 1.5×10^{-2} mbar. Through sublimation at 350 °C, an oil was collected into a trap cooled with liquid N_2. After flash chromatography (silica gel, EtOAc/PE 3:7), **57** (126 mg, 91%) was isolated as white crystals. $R_f = 0.19$ (EtOAc/PE 2:3); m.p. 84 °C; $[\alpha]_D^{20} = -273$ ($c =$ 0.9, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3684$ (w), 3580 (w), 3412 (w), 3392 (w), 2252 (w), 1696 (vs), 1600 (w), 1268 (m), 1076 (m), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.98$ (dd, $J = 10.5$, 2.7 Hz, 1H), 5.97 (dd, $J = 10.5$, 1.9 Hz, 1H), 3.75 (dd, $J = 3.8$, 2.7 Hz, 1H), 3.50 (dd, $J = 3.8$, 1.9 Hz, 1H), 2.99 (d, $J = 16.7$ Hz, 1H), 2.92 (d, $J = 16.7$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 194.6$ (C), 146.9 (CH), 127.2 (CH), 117.7 (C), 67.5 (C), 60.4 (CH), 54.5 (CH), 28.3 (CH_2); MS (70 eV): m/z (%): 165 (6) $[M]^+$, 125 (26), 97 (100); HRMS: calcd for $C_8H_7O_3N$: 165.0426, found: 165.0424.

5-[2-(1,3)Dioxolan-2-yl-ethyl]-5-hydroxy-7-oxa-dicyclo[4.1.0]hept-3-en-2-one (58): From cycloadduct **55** (288 mg, 6.18 mmol) after pyrolysis (see conditions described for **57**) and flash chromatography (silica gel, EtOAc/PE 2:3), **58** (134 mg, 96%) was obtained as a colourless oil. $R_f = 0.13$ (EtOAc/PE 2:3); $[\alpha]_D^{21} = +181$ ($c = 1.1$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3671$ (w), 3572 (w), 3000 (m), 2950 (w), 2828 (w), 1692 (vs), 1408 (w), 1228 (m), 1144 (m), 1028 (m), 900 (m), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.85$ (dd, $J = 10.6$, 2.8 Hz, 1H), 5.89 (dd, $J = 10.6$, 2.1 Hz, 1H), 4.90 (t, $J = 4.2$ Hz, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 3.67 (dd, $J = 3.9$, 2.8 Hz, 1H), 3.48 (dd, $J = 3.9$, 2.1 Hz, 1H), 1.94–1.88 (m, 2H), 1.78–1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 193.3$ (C), 148.9 (CH), 124.7 (CH), 103.4 (CH), 70.5 (C), 65.1 (2 × CH_2), 58.3 (CH), 54.1 (CH), 32.5 (CH_2), 27.2 (CH_2); MS (70 eV): m/z (%): no molecular peak, 225 (1) $[M-H]^+$, 149 (5), 73 (100); HRMS: calcd for $C_{11}H_{13}O_5$ $[M-H]^+$: 225.0763, found: 225.0758.

5-(3,3-Diethoxy-propenyl)-5-hydroxy-7-oxa-bicyclo[4.1.0]hept-3-en-2-one (59): From cycloadduct **56** (79 mg, 0.17 mmol) after pyrolysis (see conditions described for **57**) and flash chromatography (silica gel, EtOAc/PE 1:4), **58** (38 mg, 88%) was obtained as a colourless oil. $R_f =$ 0.26 (EtOAc/PE 2:3); $[\alpha]_D^{20} = +331$ ($c = 1.7$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3576$ (w), 2980 (m), 2928 (w), 2880 (w), 1692 (vs), 1376 (w), 1228 (w), 1128 (s), 1048 (vs), 1004 (s), 900 (m), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 6.36 (dd, $J = 10.5$, 2.8 Hz, 1H), 5.98 (dd, $J = 15.8$, 4.1 Hz, 1H), 5.89 (dd, $J =$ 10.5, 2.0 Hz, 1H), 5.83 (dd, $J = 15.8$, 1.1 Hz, 1H), 4.08 (dd, $J = 4.1$, 1.1 Hz, 1H), 3.67 (dd, $J = 3.8$, 2.8 Hz, 1H), 3.64 (dq, $J = 9.4$, 7.1 Hz, 2H), 3.52 (dd, $J = 3.8$, 2.0 Hz, 1H), 3.51 (dq, $J = 9.4$, 7.1 Hz, 2H), 1.22 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 193.2$ (C), 147.6 (CH), 131.9 (CH), 131.5 (CH), 124.2 (CH), 99.9 (CH), 71.2 (C), 61.4 (CH_2), 61.3 (CH_2), 58.1 (CH), 54.0 (CH), 15.3 (2 × CH_3); MS (70 eV): m/z (%): 254 (1) $[M]^+$, 253 (1.4), 209 (100), 163 (25), 129 (45), 107 (41); HRMS: calcd for $C_{13}H_{18}O_5$: 254.1154, found: 254.1125.

4-[2-(1,3)Dioxolan-2-yl-ethyl)-4-hydroxy-cyclohex-2-enone (60): From cycloadduct **50** (340 mg, 7.52 mmol) after pyrolysis (see conditions described for **57**) and flash chromatography (silica gel, EtOAc/PE 3:2), **60** (139 mg, 87%) was obtained as a colourless oil. $R_f = 0.25$ (EtOAc/PE 4:1); $[\alpha]_D^{21} =$ +28 ($c = 0.8$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3676$ (w), 3596 (w), 3440 (w), 3000 (m), 2956 (m), 2888 (m), 1680 (vs), 1620 (w), 1412 (m), 1228 (s), 1140 (s), 1032 (m), 944 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (d, $J =$ 10.3 Hz, 1H), 5.90 (d, $J = 10.3$ Hz, 1H), 4.93 (t, $J = 3.9$ Hz, 1H), 4.03–3.84 (m, 4H), 2.62 (dt, $J = 17.3$, 6.1 Hz, 1H), 2.41 (dt, $J = 17.3$, 7.0 Hz, 1H), 2.10 (dd, $J = 7.0$, 6.1 Hz, 2H), 1.94–1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.4$ (C), 154.4 (CH), 128.2 (CH), 103.9 (CH), 69.2 (C), 65.0 (2 × CH_2), 34.8 (CH_2), 34.4 (CH_2), 33.3 (CH_2), 27.5 (CH_2); MS (70 eV): m/z (%): 212 (2) $[M]^+$, 184 (3), 73 (100); HRMS: calcd for $C_{11}H_{16}O_4$: 212.1049, found: 212.1050.

(4-Bromo-2-hydroxy-5-oxo-7-oxa-bicyclo[4.1.0]hept-3-en-2-yl)-acetonitrile (61): A solution of Br_2 diluted in dry CH_2Cl_2 (0.46 mL, 1 M, 1.1 equiv) was injected dropwise to a cooled solution (ice bath) of the enone **57** (69 mg, 0.42 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred for 1 h at this temperature and triethylamine (0.46 mL, 3 equiv) was added. As the triethylamine was injected dropwise, the orange-red solution turned colourless to black. After 1 h at room temperature, the solution was poured into a biphasic mixture of H_2O/Et_2O (1:1, 50 mL). After decantation, the product was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a solution of HCl (1 N, 150 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography (silica gel, EtOAc/PE 1:4) gave **61** (69 mg, 68%) as a pale yellow oil. $R_f =$ 0.32 (EtOAc/PE 2:3); $[\alpha]_D^{22} = -108$ ($c = 0.5$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3680$ (w), 3572 (w), 3392 (w), 3016 (w), 2252 (w), 1732 (s), 1708 (vs), 1612 (w), 1376 (w), 1264 (s), 1248 (m), 1084 (w), 1044 (m), 876 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.04$ (d, $J = 2.6$ Hz, 1H), 3.83 (dd, $J = 3.6$, 2.6 Hz, 1H), 3.74 (d, $J = 3.6$, 1H), 3.00 (d, $J = 16.7$ Hz, 1H), 2.89 (d, $J = 16.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 186.6$ (C), 144.3 (CH), 123.8 (C), 115.4 (C), 69.1 (C), 58.8 (CH), 53.4 (CH), 27.7 (CH_2); MS (70 eV): m/z (%): 245 (1.5) $[C_8H_6O_3{}^{81}BrN]^+$, 243 (1.6) $[C_8H_6O_3{}^{79}BrN]^+$, 205 (97), 203 (100), 177 (19.4), 175 (19.8); HRMS: calcd for $C_8H_6O_3{}^{79}BrN$: 242.9531, found: 242.9520.

***rac*-1-Oxa-spiro[4.4]non-7-en-6-one (*rac*-8)**: KH (272 mg, 6.8 mmol, washed with pentane prior to use) was added portionwise to spiro-ketone ***rac*-62**[35] (450 mg, 3.2 mmol) and methyl phenylsulfinate (490 mg, 3.2 mmol) in dry THF (10 mL). The mixture was stirred for 1 h at room temperature under N_2 (changed to a deep red colour). The solution was concentrated and the residue was partitioned between an aqueous solution H_3PO_4 (0.5 M) and CH_2Cl_2. The aqueous layer was extracted with additional CH_2Cl_2 (2 ×). The combined organic extracts were dried ($MgSO_4$) and the mixture was refluxed in toluene (40 mL) with Na_2CO_3 (1.87 g) for 2 h. After filtration through a pad of Celite, and several washings with EtOAc, the solvent was evaporated in vacuo (water bath below 40 °C). After flash chromatography (silica gel, Et_2O/PE 1:4), ***rac*-8** (243 mg, 55%) was isolated as a colourless oil. $R_f = 0.23$ (Et_2O/PE 1:1), IR ($CHCl_3$): $\tilde{\nu} = 2980$ (m), 3956 (m), 2998 (m), 2872 (w), 1716 (s), 1588 (w), 1456 (w), 1424 (w), 1344 (w), 1168 (w), 1104 (w), 1064 (s), 1024 (w), 992 (w), 948 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (ddd, $J = 6.3$, 2.9 Hz, 1H), 6.18 (ddd, $J = 6.3$, 2.4 Hz, 1H), 4.10 (dd, $J = 8.0$, 7.0 Hz, 1H), 4.03 (ddd, $J = 8.0$, 7.0, 4.6 Hz, 1H), 2.86 (dt, $J = 18.9$, 2.4 Hz, 1H), 2.72 (ddd, $J = 18.9$, 2.9, 2.0 Hz, 1H), 2.22 (m, 1H), 2.11 (dt, $J =$ 11.4, 7.0 Hz, 1H), 2.01 (dq, $J = 11.4$, 7.0 Hz, 1H), 1.84 (ddd, $J = 11.8$, 7.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 209.5$ (C), 161.8 (CH), 130.9 (CH), 83.9 (C), 69.6 (CH_2), 43.4 (CH_2), 35.4 (CH_2), 26.2 (CH_2); MS (70 eV): m/z (%): 138 (14) $[M]^+$, 110 (19), 84 (100), 82 (64), 68 (43); HRMS: calcd for $C_8H_{10}O_2$: 138.0681, found: 138.0689.

Cycloadducts 63 and 64: Diene **1** (996 mg, 4.15 mmol, 0.5 equiv) and racemic spiro-enone ***rac*-8** (1.15 g, 8.3 mmol, 1 equiv) in CH_2Cl_2 (10 mL)

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were converted under high pressure (20 kbar, 6 d) into a mixture of **63** and **64** in a ratio of 32:68 (determined by ^{1}H NMR). After flash chromatography, cycloadducts **63** (324 mg, 10 %) and **64** (1.25 g, 40 %) were isolated as colourless crystals and 460 mg of spiro-enone **8** (40 %) was recovered.

Cycloadduct 63: $R_f = 0.36$ (EtOAc/PE 1:4); m.p. 128 °C; $[\alpha]_D^{21} = -26$ ($c = 1.3$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (m), 2932 (vs), 2864 (m), 1740 (s), 1612 (m), 1516 (vs), 1464 (w), 1444 (w), 1288 (w), 1248 (vs), 1180 (s), 1152 (m), 1092 (w), 1064 (s), 1036 (m), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 8.9$ Hz, 2H), 6.87 (d, $J = 8.9$ Hz, 2H), 6.14 (d, $J = 5.9$ Hz, 1H), 5.97 (d, $J = 5.9$ Hz, 1H), 4.02 – 3.86 (m, 2H), 3.79 (s, 3H), 3.73 (d, $J = 9.6$ Hz, 1H), 2.71 (ddd, $J = 9.6$, 9.0, 8.7 Hz, 1H), 2.00 (dd, $J = 13.3$, 9.2 Hz, 1H), 1.99 – 1.80 (m, 5H), 1.65 (dd, $J = 13.3$, 8.3 Hz, 1H), 1.64 (m, 1H), 1.45 (br d, $J = 11.4$ Hz, 1H), 1.38 – 1.15 (m, 4H), 0.76 (s, 3H), 0.64 (br d, $J = 12.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 216.8$ (C), 15.1 (CH_3), 21.5 (CH_2), 23.2 (CH_2), 25.3 (CH_2), 26.1 (CH_2), 29.2 (CH_2), 34.7 (CH_2), 37.1 (CH_2), 39.9 (CH), 53.0 (CH), 55.3 (CH_3), 59.9 (C), 65.2 (C), 66.5 (C), 69.3 (CH_2), 91.0 (C), 113.5 (2 × CH), 128.5 (2 × CH), 130.7 (C), 138.5 (CH), 138.9 (CH), 158.3 (C); MS (70 eV): m/z (%): 378 (6) $[M]^+$, 266 (40), 251 (27), 240 (100); HRMS: calcd for $C_{25}H_{30}O_3$: 378.2195, found: 378.2163.

Cycloadduct 64: $R_f = 0.4$ (EtOAc/PE 1:4); m.p. 123 °C; $[\alpha]_D^{20} = -65$ ($c = 1.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3000$ (m), 2928 (vs), 2864 (m), 1736 (s), 1612 (m), 1516 (vs), 1464 (m), 1444 (m), 1308 (m), 1288 (m), 1248 (vs), 1180 (vs), 1152 (m), 1036 (s), 824 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.03 (d, $J = 5.8$ Hz, 1H), 5.93 (d, $J = 5.8$ Hz, 1H), 3.99 (d, $J = 9.6$ Hz, 1H), 3.87 (ddd, $J = 14.2$, 8.0, 4.8 Hz, 1H), 3.78 (s, 3H), 3.64 (ddd, $J = 14.2$, 7.2, 7.2 Hz, 1H), 2.93 (ddd, $J = 9.6$, 9.3, 7.4 Hz, 1H), 2.08 (dd, $J = 14.7$, 9.3 Hz, 1H), 2.04 – 1.77 (m, 5H), 1.63 (m, 1H), 1.49 (dd, $J = 4.7$, 7.4 Hz, 1H), 1.47 – 1.17 (m, 5H), 0.78 (s, 3H), 0.63 (br d, $J = 12.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.8$ (C), 158.2 (C), 138.8 (CH), 138.1 (CH), 130.6 (C), 128.6 (2 × CH), 113.4 (2 × CH), 91.2 (C), 68.0 (CH_2), 66.7 (C), 66.2 (C), 59.3 (C), 55.2 (CH_3), 54.6 (CH), 42.7 (CH), 34.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 23.2 (CH_2), 21.4 (CH_2), 15.1 (CH_3); MS (70 eV): m/z (%): 378 (20) $[M]^+$, 266 (94), 251 (42), 240 (100); HRMS: calcd for $C_{25}H_{30}O_3$: 378.2195, found: 378.2194.

(*S*)-(−)-1-Oxa-spiro[4.4]non-7-en-6-one [(*S*)-(−)-8]: From cycloadduct **64** (380 mg, 1 mmol) after pyrolysis (see conditions described for **57**) and flash chromatography (silica gel, MeOH/CH_2Cl_2 1:99), (*S*)-(−)-**8** (129 mg, 93 %) was obtained as a colourless oil. $[\alpha]_D^{20} = -116$ ($c = 1.5$, $CHCl_3$).

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[37] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151161. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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