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Hypervalent iodine(III)-mediated tandem oxidative reactions: application for the synthesis of bioactive polyspirocyclohexa-2,5-dienones

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ABSTRACT

In 2002, we reported the first total syntheses of potent antimalarial natural products, the aculeatins, employing the concept of tandem oxidative reactions mediated by hypervalent iodine(III) reagent to access to polyspirocyclohexa-2,5-dienone cores in very concise manner. Efforts in this field have allowed to identify cyclohexa-2,5-dienone group as a new potent class of pharmacophoric group for treating malaria disease. This article sums up recent contributions devoted to the synthesis of complex and diverse polycyclic structures using the concept of tandem oxidative activations, with *p*-phenol as co-reactant. More recently, we have explored a variant of the new tandem oxidative reactions that employs a catalytic amount of 4-iodotoluene in the presence of *m*CPBA as the stoichiometric oxidant (Kita's procedure).

1. Introduction

Hypervalent phenyliodine reagents have emerged as oxidants of choice for mediating various transformations in an efficient manner.[1] These mild organic oxidants possess low toxicity, thus providing a sustainable alternative to reagents based on harmful heavy metals, such as lead, mercury and thallium. The advent of techniques for the in situ generation of catalytic amounts of hypervalent iodine, by the use of appropriate co-oxidants or under anodic conditions, is realizing the promise of a green oxidizing agent[2] and it has culminated in the development of highly enantioselective oxidations.[3]

Trivalent iodine reagents, such as phenyliodine(III) diacetate ($PhI(OAc)_2$, PIDA or DIB) or phenyliodine(III) bis(trifluoroacetate) ($PhI(OCOCF_3)_2$, PIFA or BTI) (Fig. 1) are stable, commercially available, easily handled products, which are soluble in a wide range of organic solvents and are safer than pentavalent iodine reagents, such as 2-iodoxybenzoic acid (IBX) or Dess/Martin periodane. Oxidation with $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ releases only iodobenzene and weak nucleophilic carboxylic acids in the reaction medium (Scheme 1). Hypervalent phenyliodine(III) reagents convert phenols, such as **1** into a presumed electrophilic intermediate **3**, probably by the initial removal of one electron and one proton,

$PhI(OAc)_2$ = PIDA or DIB
$PhI(OCOCF_3)_2$ = PIFA or BTI

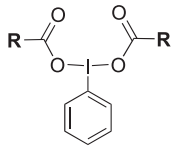

Figure 1. Hypervalent phenyliodine(III) reagents.

followed by the removal of a second electron (Scheme 1, Eq. 1). A great deal of valuable synthetic chemistry relies on the capture of **3** with appropriate nucleophiles,[4] that could be an oxygen, nitrogen, fluorine or carbon sp^2 atom, in inter-or intra-molecular fashion to yield **4**.[5] This cyclohexa-2,5-dienone functional group has the ability to react further as Michael acceptor or dienophile. Interestingly, an extra nucleophilic group arises from *p*-quinol (Nu=OH) and 4-aza-substituted cyclohexa-2,5-dienone ($Nu=NHCOR^3$).

For some years, we have been involved in the synthesis of biologically active natural products in which the cyclohexa-2,5-dienone moiety was identified as a new antimalarial pharmacophoric group (vide infra).[6] By anticipating the need for producing larger libraries in drug optimisation process, we planned to develop synthetic strategies that focus on 'one pot' transformations, especially those involving tandem or/and cascade reactions,

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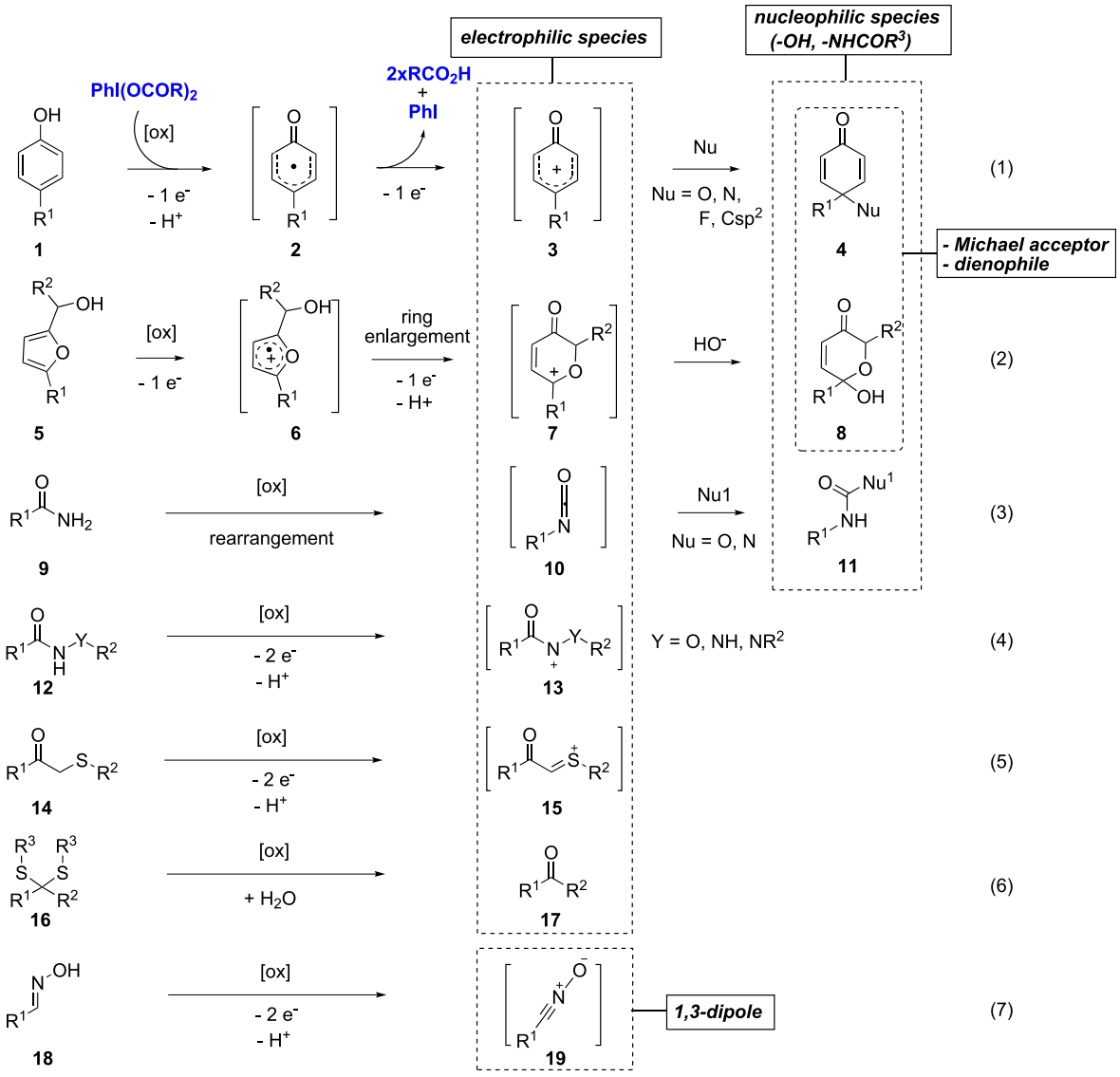


Scheme 1. Simple functional groups activated by hypervalent iodine(III) reagent.

maximizing the opportunity to make multiple bonds within a single synthetic step. No doubt that the benefices in term of atom, time, resources economies can make quite an impact on the accessibility of future libraries. In addition, tandem reaction processes provide a unique opportunity to bring distinct and unstable species to react together on the same reaction time scale, allowing transformations that would be hardly possible with other reaction conditions.

This article aims at exploring the effectiveness and the limitations of tandem oxidative reactions mediated by hypervalent phenyliodine(III) reagent, with *p*-phenol as co-reactant. One important challenge to face in this approach is the fine-tuning reactivity of distinct transient species, which can have different oxidation states. A comparison can be made with the successful use of SmI_2 for the tandem reductive reaction approach.[7] Indeed, in the course of phenolic oxidation mediated by hypervalent(III) iodine reagent, many reactive facets of an oxidized phenol **1** can be revealed like the radical intermediate **2**, the highly reactive electrophilic species **3**, or the cyclohexa-2,5-dienone product **4**. The difficulty rests on the identification of the best intramolecular partner to be paired off with the phenolic group. A few groups meet certain advantageous criteria like efficient activation by hypervalent iodine(III) reagent in compatible solvents with the phenolic oxidation, the requirement of none or at least minimum additive and the ability to be run within a reasonable reaction time (Scheme 1, Eq. 2–7).

For furanyl-2-methanols **5** (Eq. 2), good reaction condition for its conversion into the corresponding 5,6-dihydropyranone **8** was reported by using $PhI(OAc)_2$ in a mixture of $(CF_3)_2CHOH$/buffer solution (1:1) within a few minutes.[8] Like the phenolic oxidation, this ring enlargement sequence involves different oxidation states. A single electron transfer (SET) gave rise to a radical cation **6**.[9] This latter underwent a second mono-electronic oxidation allowing a rearrangement to occur and led to the formation of an electrophilic species **7**. The final trapping by a hydroxyl group afforded **8**. Other highly reactive electrophilic species can also be derived from very simple functional groups (Eq. 3–5). The oxidation of primary carboxamides **9** can rearrange into reactive isocyanates **10**. A subsequent nucleophilic addition would give either carbamate or urea derivatives **11** (Eq. 3). Other possible partners involve the precursor **12**, which is able to give *N*-acyl-nitrenium ions **13** under oxidative condition[10] (Eq. 4), and the conversion of α-acyl sulphide **14** into

the corresponding sulphonium salt **15** (Eq. 5). The robust protecting group dithioacetal **16** can be easily removed to form carbonyl group **17** (Eq. 6).[11] Finally, the oxidation of aldoxime **18** (Eq. 7) can afford the 1,3-dipolar nitrile oxide **19**, amenable to make a subsequent [3+2] cyclization (vide infra).[12]

The tandem, cascade or domino terminologies are used in this article according to the Tietze's definitions (Fig. 2).[13] For an intramolecular reaction, tandem reactions are restricted to two or more reactions occurring on the same molecule in isolation of one another, whereas only one initiating process should be considered for cascade or domino reaction. In the context of tandem reactions, once the simultaneous activations have occurred, the reactions can also further evolve to cascade processes.

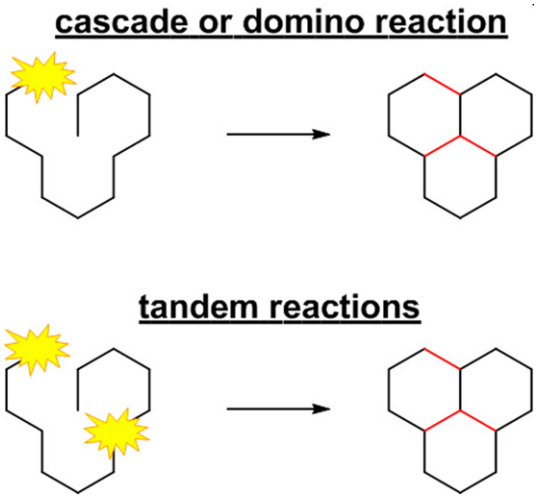
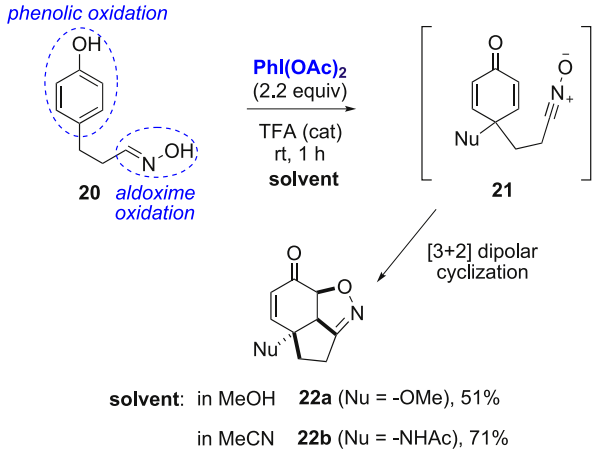


Figure 2. Each yellow flash means a chain-initiating process.

2. Ciufolini's tandem phenolic/aldoxime oxidative activations

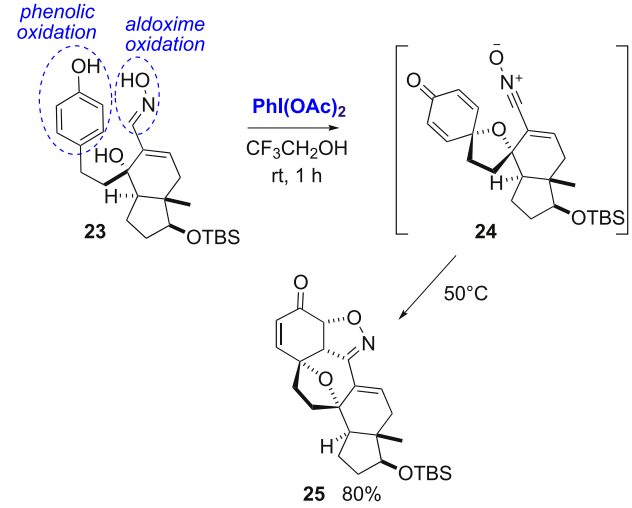
It was only recently demonstrated by Ciufolini and co-workers that phenol and aldoxime groups are compatible partners in tandem oxidative reactions (Scheme 2).[12] The phenolic oxidation condition that allowed the trapping of an external nucleophile coming from the reaction medium (MeOH or MeCN) was suitable for the tandem intramolecular conversion of aldoxime into the nitrile oxide group.



Scheme 2. Ciufolini's pioneer work in tandem phenolic/aldoxime oxidation reactions.

The resulting intermediate **21** underwent spontaneous intramolecular [3+2] dipolar cyclization to yield the fused polycycles **22a**,**b** in a highly diastereoselective manner. These authors pointed out that both activating processes were asynchronous, cyclohexa-2,5-dienone being formed almost instantaneously, whereas oxidation of aldoxime to nitrile oxides took about 45–60 min for complete conversion. This sequence of events was essential to ensure good yield by the gradual intramolecular trapping of the nascent nitrile oxide with the more stable cyclohexa-2,5-dienone intermediate group.

This elegant tactic has been recently exemplified by the works of Sorenson's group in which the tandem oxidative reactions was applied for the compound **23** bearing both phenol and aldoxime functional groups (Scheme 3). The oxidation of **23** with $PhI(OAc)_2$ in fluorous solvent gave the intermediate **24**, which then cyclized to yield selectively **25**, resulting in the formation of an advanced intermediate for the synthesis of (+)-cortistatin A.[14]



Scheme 3. Application of tandem phenolic/aldoxime oxidation reactions for total synthesis.

3. Tandem phenolic/thioacetal oxidative activations

A few years ago, we reported the first total synthesis of (±)-aculeatins A and B (Fig. 3) using a tandem phenolic/thioacetal oxidation activations as key final step (Scheme 4).[15] Since their first isolation in 2000 from the rhizome of *Amomum aculeatum* by Heilmann and co-workers,[16] this class of natural product has inspired numerous synthetic studies due to their challenging polyspirocyclic structure[17], their good cytotoxic activity, and their potent biological property as antimalarial agent.[16a] The syntheses of optically pure aculeatins A and B and their improved bioactive synthetic analogues (±)-**26** and **27**, which hold the pharmacophore group twice have allowed to confirm and clearly identify the cyclohexa-2,5-dienone as an important functional group responsible for the biological activity.[6] In addition, Kinghorn and coworkers showed that aculeatin A was also active against cancer cell lines (MCF-7, ED_{50}=0.2 μM).[18] Interestingly, a closely related natural product, EBC-23, was recently identified by Williams and coworkers to be potent anticancer agent.[19] This product shares with aculeatins many structural similarities, such as a lipophilic side chain, a spiroacetal moiety and a terminal cycle bearing at least one electron poor carbon–carbon double bond. Williams argued that the long aliphatic chain could be useful to control metabolism and enable cell membrane permeability.

Hence, we have developed several synthetic approaches based on tandem phenolic/thioacetal oxidation reactions. Our goal was to

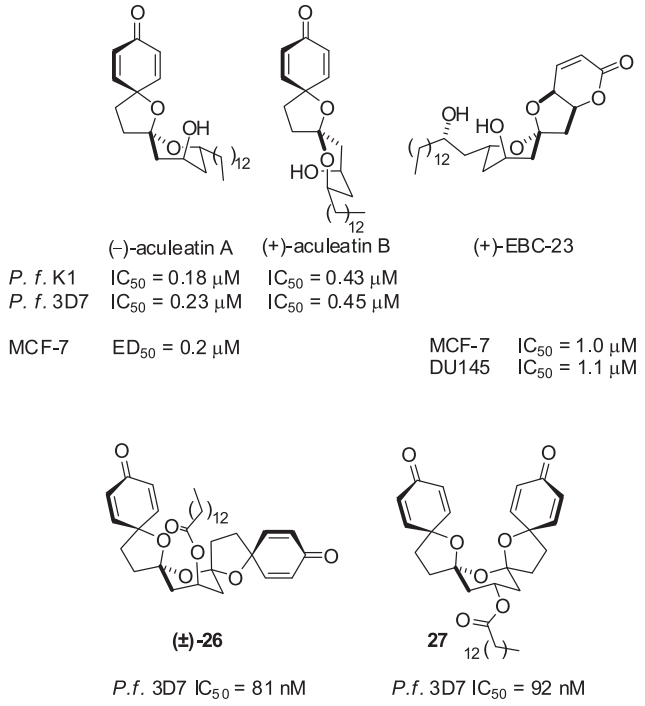
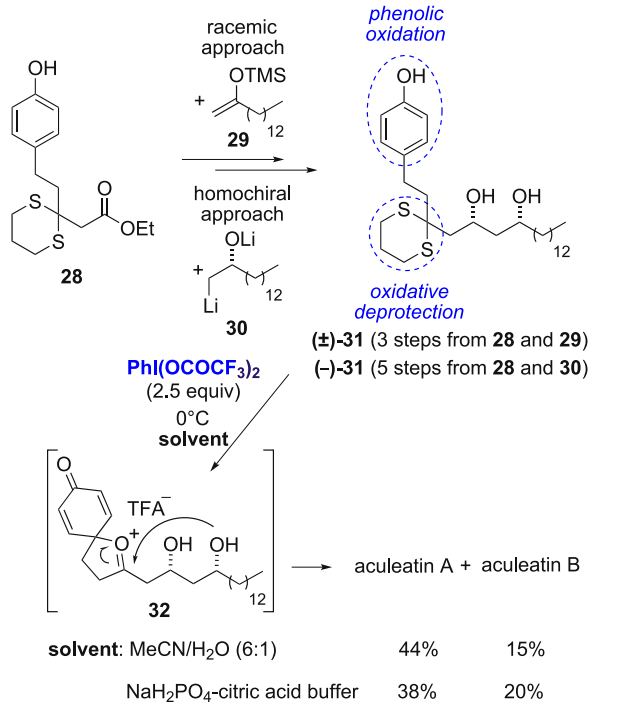


Figure 3. Natural and bioactive products, the aculeatins and EBC-23, and improved bioactive analogues (±)-**26** and **27**.

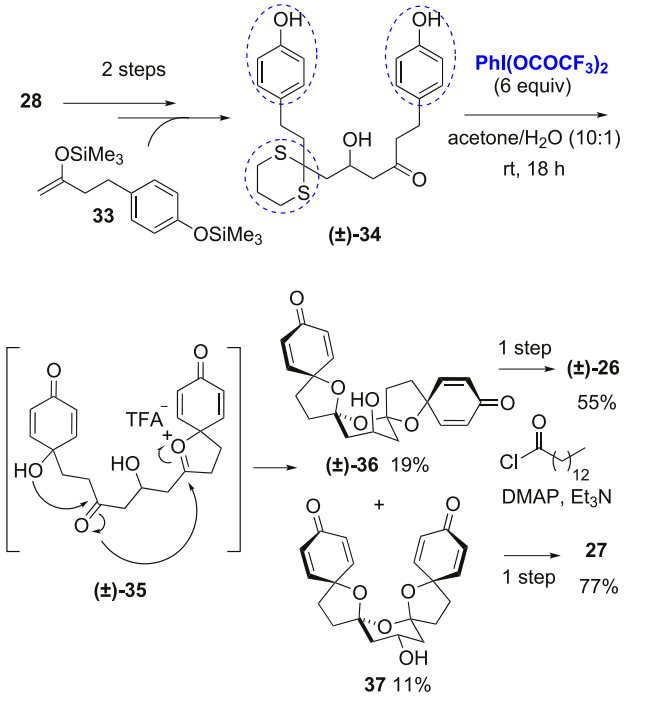


Scheme 4. Tandem phenolic/thioacetal oxidative activation for the synthesis of aculeatins.

keep intact the cyclohexa-2,5-dienone moiety (pharmacophore) and efforts have been mainly focused on triggering polyspiroannulation process initiated by phenolic oxidation (cascade reaction). In our strategy, the thioacetal protecting group plays a pivotal role. As a result, the arsenal of alkylating or reducing agents can be used enabling key intermediates, such as **31** to be assembled in racemic[15] or enantiopure form[17j] in only three or five steps, respectively, starting from the common precursor **28**.

At this stage, when carrying out the tandem oxidative reactions on **31** with $PhI(OCOCF_3)_2$ in wet MeCN at 0 °C, the removal of thioacetal was immediate, very likely at comparable rate to phenolic oxidation. Thus, initial spiro-oxocarbenium species **32** might arise from the trapping of phenoxenium ion by the newly deprotected carbonyl group, which then in turn triggers the second spiroannulation to give aculeatins. This is very likely the way that nature makes such compounds (biomimetic approach). This reaction works equally well in Wu's buffer condition that prevents conversion of aculeatin B into aculeatin A by thermodynamic equilibrium.

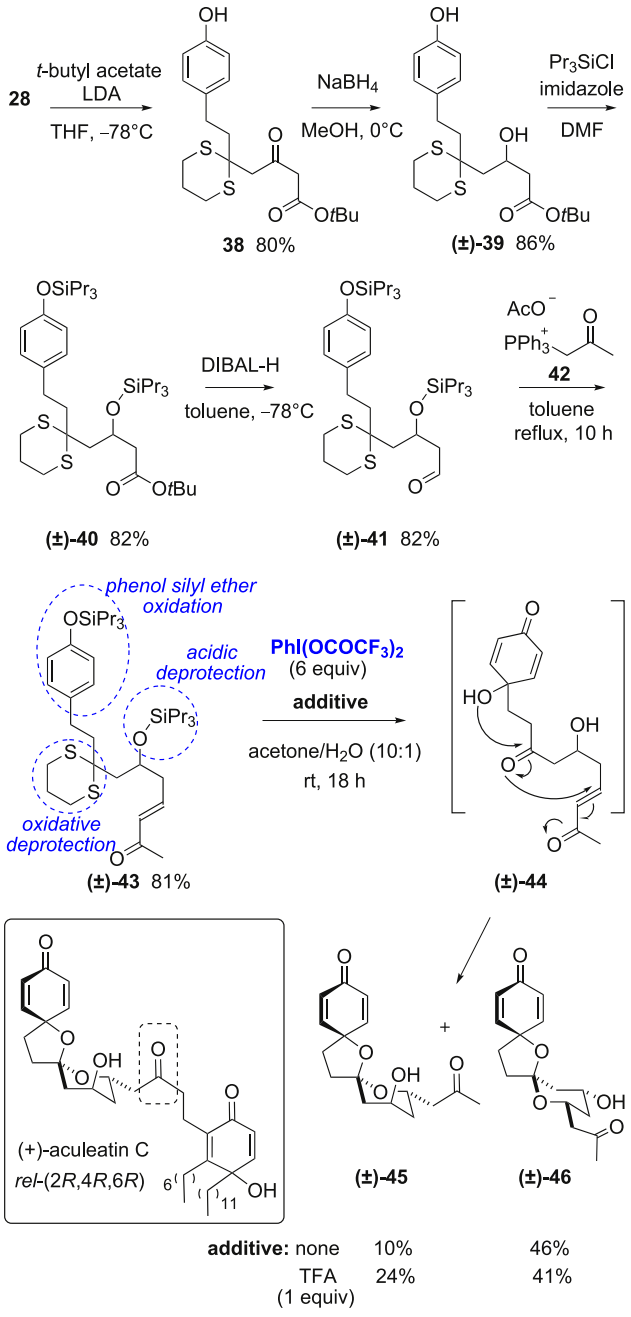
In the same vein, the polyphenolic compound **34** was obtained in only two steps starting from **28** (Scheme 5).[6] In the key step, three tandem oxidation reactions mediated by $PhI(OCOCF_3)_2$ were performed on the same molecule. We observed instantaneous formation of final products by TLC. However, we left the reaction running for 18 h at rt so that, after thermodynamic equilibrium catalyzed by the acidic medium, two major polyspirocyclic products **36** and **37** were isolated. Remarkably, only one step converts them into highly potent bioactive antimalarial agents **26** and **27**. Again, all these oxidative functional activations seem to occur at the same rate level. We postulate that the intermediate **35** may exist, with one oxidized phenol acting as strong electrophilic species (spiro-oxocarbenium ion), whereas the second one would intercept water to give the nucleophilic *p*-quinol, bringing out complementary partners to raise the final polyspirocyclic structures.



Scheme 5. Triple tandem oxidative reactions to convert linear precursor **34** into complex polyspirocyclic products.

4. Tandem phenol silyl ether/thioacetal oxidations and silyloxy deprotection reactions

To construct the spirocyclic core of aculeatin C (Scheme 6), a few years ago, we reported an approach that takes advantage of an existing carbonyl group lacking in aculeatins A and B.[17e] This allows to install on the synthetic precursor **43** a Michael acceptor acting as terminal acceptor for the polyspiroannulation process. On the opposite side of **43**, the phenolic group needs to be efficiently oxidized into *p*-quinol in order to play the role of nucleophilic counterpart.

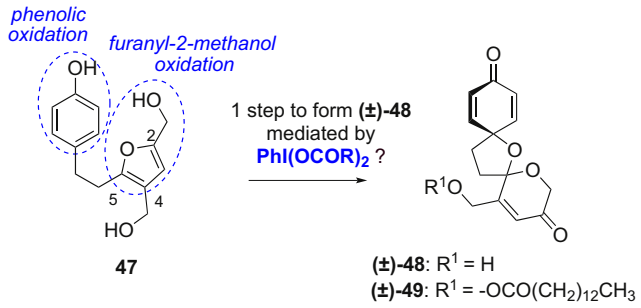


Scheme 6. Synthesis of aculeatin C central core.

This conversion is best performed starting from phenol silyl ether.[5d] This new approach opens up prospects to explore other functional groups able to be activated by $PhI(OCOR)_2$ reagents. The synthesis started by treating **28** with an excess of enolate of *tert*-butyl acetate to give the β-ketoester **38**. This latter was reduced by $NaBH_4$ to yield **39**, which then underwent silylation on both phenol and secondary alcohol to give **40**. DIBAL-H selectively reduced the ester to give aldehyde **41**. Wittig reaction proceeded with the phosphonium acetate reagent **42**[20] in reflux toluene to yield the desired intermediate **43**. When $PhI(OCOCF_3)_2$ was added to **43** in the optimized condition (acetone/H_2O, 10:1) at rt, the overall process turned out to be slow (18 h to run into complete conversion). Interestingly, the TFA generated by the reagent allowed the smooth in situ deprotection of silyl secondary alcohol. However, addition of TFA (1 equiv) with $PhI(OCOCF_3)_2$ was the best condition to obtain **45** and **46**.

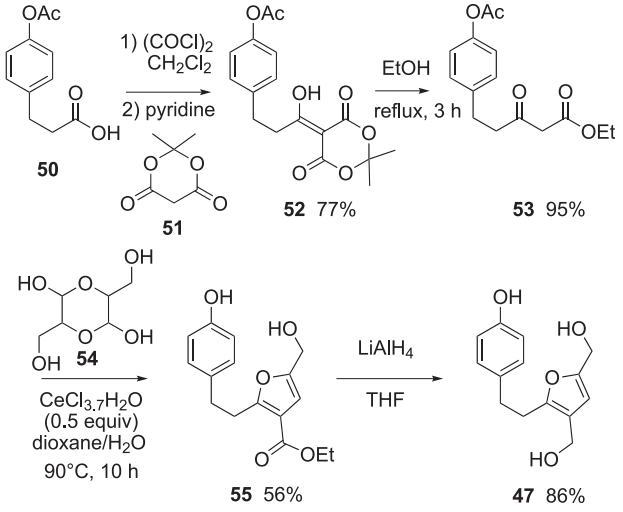
5. Study of a new approach by tandem phenolic/furanyl-2-methanol oxidative activations

Looking at aculeatin and EBC-23 structures (see Fig. 3), and being aware that fighting against malarial requires the access to inexpensive bioactive molecules, we though about developing the easy accessible new polyspirocyclic compound **49** (Scheme 7) that can be regarded as a hybrid molecule[21] derived from these two natural products. This product should arise from the intermediate **47** according to tandem phenolic/furanyl-2-methanol oxidative reactions. The combination on the same molecule of these two aromatic rings is quite challenging since both can generate different reactive species at different oxidation states. The furanyl group is polysubstituted at 2, 4 and 5 positions thus preventing competitive Friedel/Craft additions or dimerisation reactions by SET intermediates.



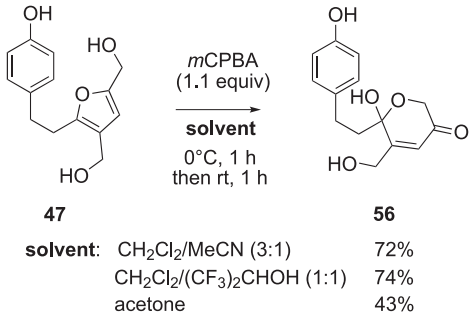
Scheme 7. A direct access to a new analogue **49** starting from a bis-aromatic molecule **47**.

We started our synthesis by converting the carboxylic acid **50**[22] into acyl chloride (Scheme 8). This latter reacted with Meldrum's acid **51** to give **52**. The corresponding β-ketoester **53** was obtained by refluxing **52** in anhydrous ethanol for 3 h. Garcia/Gonzalez's reaction with DL-glyceraldehyde dimer **54** and β-ketoester **53** using $CeCl_3 \cdot 7H_2O$ as catalyst gave the desired adduct **55** in moderate yield.[23] Finally, $LiALH_4$ reduction provided the key intermediate **47**.

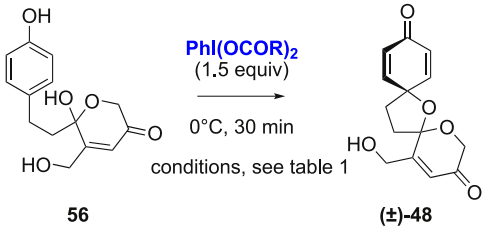


Scheme 8. Synthesis of key precursor **47**.

When **47** was subjected to $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ oxidation under various solvent conditions ($(CF_3)_2CHOH$/Buffer,[8] CF_3CH_2OH, CH_2Cl_2, MeCN, acetone/H_2O, THF), the desired product was not detected. Instead, a complex mixture was formed in every case. At this stage, it seems clear that activating both aromatic groups at the same time leads to unwanted reaction behaviours. We then decided to deconvolute the synthesis into two steps (Schemes 9 and 10), in order to localize the problematic events. *m*CPBA is the reagent of



Scheme 9. Selective oxidation of furanyl-2-methanol with *m*CPBA.



Scheme 10.

choice since it can easily convert furanyl-2-methanol group into 5,6-dihydropyranone without reacting with phenol. We observed that the conversion of **47** into **56** occurs in generally good yields. A polar solvent needs to be used or co-added to make **47** soluble in the reaction medium (Scheme 9).

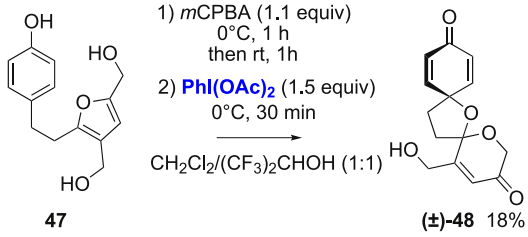
Having **56** in hand, we set out to study the second step using PhI(OAc)$_2$ as oxidizing reagent, in order to optimize the trapping of the intramolecular hemi-acetal group by the oxidized phenol species (Scheme 10, Table 1). Unexpectedly, this reaction was clearly solvent dependant and the use of the fluorous solvent $(CF_3)_2CHOH$ has

Table 1
Various solvent conditions for the phenolic oxidation reaction to convert **56** to **48**

Reagent	Solvent	(±)-**48** Yield %
PhI(OAc)$_2$	CH_2Cl_2	<1
PhI(OAc)$_2$	CH_2Cl_2/MeCN(3:1)	<1
PhI(OAc)$_2$	THF	<1
PhI(OAc)$_2$	Acetone	4
PhI(OAc)$_2$	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	74
PhI(OCOCF$_3$)$_2$	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	2

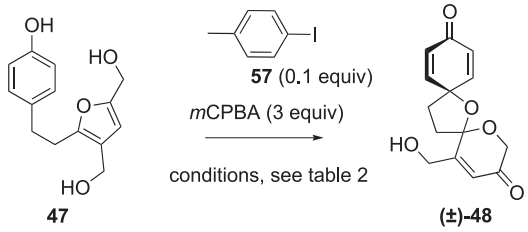
a dramatic beneficial effect (Table 1). This solvent condition allows for the conversion of phenol **56** into the desired polyspirocycle **48** in good yield (74%), whereas conventional solvents failed in giving less than 4% yield. Use of the more nucleophilic and less hindered CF_3CH_2OH solvent also gave **48** (as shown by NMR) but this latter was also contaminated by other inseparable products (data not shown). Addition of catalytic amount of TFA seems to decompose **56** rapidly. This can explain why PhI(OCOCF$_3$)$_2$ in the best solvent condition gave a very poor yield of **48** (2%).

Having selected the solvent condition $CH_2Cl_2/(CF_3)_2CHOH$ (1:1) and the oxidizing reagent (PhI(OAc)$_2$), we decided to run a 'one pot' transformation, by adding first the *m*CPBA (Scheme 11). Once the conversion of **47** to **56** was total (monitored by TLC), PhI(OAc)$_2$ was added. Again, we obtained a surprising yield of 18% for **48** (starting from **47**, the overall yield for the two steps sequences to give **48** was 55%). At this stage, it is worthy to note that the presence of the by-product *m*-chlorobenzoic acid burdens the purification of this polar and likely fragile product **48**. The repeated purification by silica gel or alumina chromatography may explain in part the lowering in yield. Still, the presence of *m*CPBA or *m*-chlorobenzoic acid might also be troublesome for the PhI(OAc)$_2$ reactivity.



Scheme 11. One pot procedure with PhI(OAc)$_2$ introduced as second reagent.

We decided to explore the in situ generation of a catalytic amount of hypervalent iodine(III) reagent using *m*CPBA as co-oxidants.[24] This approach should gradually consume reagent as this latter is being formed, ensuring a low concentration of hypervalent iodine(III) species. In this way, we hope to be able to mediate more selective tandem reactions. According to Kita's work, we selected 4-iodobenzene **57** as catalyst[24a] (Scheme 12). To begin with this study, we started with the 'one pot' sequential version, namely first addition of *m*CPBA (3 equiv) to convert all **47** into the 5,6-dihydropyranone **56**, and then addition of the catalyst **57** (Table 2, entries 1–4).



Scheme 12. 'One pot' transformation with *m*CPBA with 10 mol % of 4-iodotoluene **57**.

Under Kita's condition (entry 1) that involves the use of TFA, only traces of **48** were obtained, presumably due to the instability of **56** with strong Brønsted acid. Without TFA (entry 2), the reaction proceeded quite well as shown by TLC and permitted the isolation

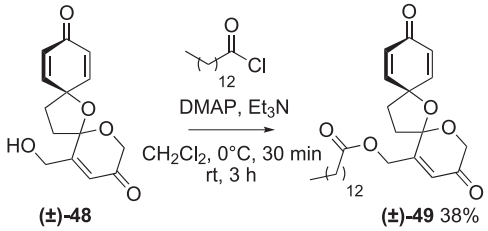
Table 2

Entry	Solvent	Procedure[a]	(±)-**48** Yield %
1	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	*m*CPBA, 1 h, 0 °C+1 h, rt, then addition of **57** at rt+TFA (1 equiv), then 15 min at rt	<1
2	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	*m*CPBA, 1 h, 0 °C+1 h, rt, then addition of **57** at rt, then 15 min at rt	22
3	Acetone	*m*CPBA, 1 h, 0 °C+1 h, rt, then addition of **57** at rt, then 48 h at rt	7
4	Acetone/H_2O (6:1)	*m*CPBA, 1 h, 0 °C+1 h, rt, then addition of **57** at rt, then 48 h at rt	<1
5	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	*m*CPBA+**57**, 1 h, rt	25

[a] The reaction was run until disappearance of **47** or **56**.

of **48** in 22% yield. At this stage, the purification was even more difficult due to the use of a larger amount of *m*CPBA. A non fluorous solvent like acetone gave a slower reaction and a lower yield (entries 3 and 4). Interestingly, when the catalyst and *m*CPBA were added simultaneously (entry 5), the reaction worked equally well to give **48** in 25% yield. We monitored this reaction by TLC and were able to see the formation of **56** at first, which was gradually consumed to give **48**. Very likely, *m*CPBA oxidation runs faster than the catalytic amount of hypervalent phenyliodine (III) species can drive phenolic oxidation into completion. It seems that the beneficial use of Kita's procedure cannot be attributed to the sole role of catalytic hypervalent iodine reagent in these tandem oxidative reactions.

Finally, **48** underwent acylation reaction (Scheme 13) to put the lipophilic side chain under the same reaction condition that led to the formation of **26** and **27** from **36** and **37**, respectively (see Scheme 5). The lower yield obtained for **49** (38%) may reflect somewhat the relative stability of **48**.



Scheme 13. Synthesis of the lipophilic analogue (±)-**49**.

In closing, hypervalent phenyliodine(III) reagent is an efficient promoter that enable a variety of intramolecular oxidation activations to occur selectively. The combination of these reactive and transient species can be exploited to make them to react and converge for assembling complex and diverse molecular structures in a very concise way. In addition, we are exploring the catalytic version to overcome cases unresolved by the use of stoichiometric amount of hypervalent phenyliodine(III) reagent in tandem oxidative activations process. Undoubtedly, the tandem oxidative reactions mediated by hypervalent iodine(III) reagents will disclose new attractive applications for the synthesis of complex natural products in near future.

6. Experimental

6.1. General

All reagents were used as purchased from commercial suppliers. Solvent was purified by conventional methods prior to use. For reactions performed under anhydrous conditions, glassware was oven-dried and reactions were performed under argon atmosphere. Buffer solution pH 7 (phosphate compound) was purchased by Roth (Art. Nr. A518.3). *m*CPBA (70–75%, balance with 3-chlorobenzoic acid and water) was purchased by Acros Organics and used as such. Reactions were monitored by thin-layer chromatography on precoated aluminium sheets (Merck, Silica gel 60, F_{254} and Macherey/Nagel, Aluminium oxide N/UV_{254}). Flash column chromatography was performed on silica gel: Macherey/Nagel 60 M, 0.04–0.063 mm (230–400 mesh), or on alumina: MP Alumina, activity II–III (0.05–0.2 mm). ^{1}H and ^{13}C NMR spectra were recorded at rt in deuterated solvents on a Bruker Avance 400 spectrometer. Chemical shifts δ are given relative to TMS as internal standard or relative to the solvent. IR spectra were collected on a Bruker Vector 22 spectrometer. UV spectra were obtained on a ThermoSpectronic Helios Gamma UV/Vis spectrophotometer in MeOH. Optical rotations were recorded on a Perkin/Elmer 341 polarimeter. Mass spectra (low resolution) were recorded with NERMAG R1010C (EI, CI, FAB), ZQ Waters (ESI) and Autoflex Bruker (MALDI) spectrometers. High resolution mass spectra were carried out on a Micromass GCT spectrometer (EI) or a Micromass ZAB-SPEC-TOF spectrometer (ESI, FAB) by CRMPO at the University of Rennes.

6.2. Synthesis of 4-hydroxy-2-(2-oxopropyl)-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (45) and (46)

*6.2.1. tert-Butyl 4-(2-(4-hydroxyphenethyl)-1,3-dithian-2-yl)-3-oxobutanoate (**38**).* To a stirred solution of HN^iPr_2 (4,3 mL, 30.48 mmol) in dry THF (30 mL) was slowly added a solution of *n*-BuLi 2.5 M in hexane (12.2 mL) at 0 °C under argon atmosphere. After 20 min, *tert*-butyl acetate (4.1 mL, 30.8 mmol) was added at −78 °C. After 30 min, a solution of **28** (1.99 g, 6.10 mmol) in dry THF (15 mL) was added. After 30 min at −78 °C then 30 min at 0 °C, the reaction was quenched by addition of AcOH (14 mL) then treated with a saturated aqueous solution of K_2CO_3 (30 mL). The organic phase was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 85:15) to give **38** (1.94 g, 80%) as a pale yellow oil; R_f (cyclohexane/EtOAc 7:3) 0.37; IR ν_{max} (film, cm^{-1}) 3447, 3406, 1728, 1709, 1514, 1258, 1150; UV (MeOH) 286, 277, 250, 224, 207 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, OC(CH_3)$_3$), 1.86–2.06 (m, 2H, SCH_2CH_2), 2.25–2.33 (m, 2H, $ArCH_2CH_2$), 2.68–2.75 (m, 2H, $ArCH_2$), 2.77–2.93 (m, 4H, 2×SCH_2), 3.25 (s, 2H, CH_2CO), 3.53 (s, 2H, $COCH_2CO$), 6.77 (d, J=8.4 Hz, 2H, 2×CH_{Ar}), 7.03 (d, J=8.4 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (SCH_2CH_2), 26.3 (2×SCH_2), 28.0 (OC(CH_3)$_3$), 29.7 ($ArCH_2$), 41.0 ($ArCH_2CH_2$), 49.4 (CH_2CO), 49.9 (*SCS*), 52.4 ($COCH_2CO$), 82.6 (*OC*(CH_3)$_3$), 115.4 (2×CH_{Ar}), 129.5 (2×CH_{Ar}), 132.9 (C_{Ar}), 154.2 (C_{Ar}), 166.7 (COO^tBu), 200.0 (*C*=O); MS (EI) m/z (%) 396 [M]$^+$ (18), 233 (100); HRMS (EI) m/z found 396.1422. $C_{20}H_{28}O_4S_2$ requires 396.1429.

*6.2.2. (±)-tert-Butyl 3-hydroxy-4-(2-(4-hydroxyphenethyl)-1,3-dithian-2-yl)butanoate ((±)-**39**).* To a stirred solution of **38** (3.47 g, 8.75 mmol) in MeOH (70 mL) was slowly added $NaBH_4$ (0.66 g, 17.50 mmol) at 0 °C. After 15 min the reaction mixture was concentrated. The residue was dissolved in H_2O and EtOAc. The organic phase was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 85:15) to give (±)-**39** (3.00 g, 86%) as a colourless oil; R_f (cyclohexane/EtOAc 7:3) 0.28; IR ν_{max} (film, cm^{-1}) 3418, 3368, 3331, 2976, 2936, 1720, 1514, 1368, 1265, 1240, 1154; UV (MeOH) 285, 279, 249, 225, 208 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H, OC(CH_3)$_3$), 1.86–2.08 (m, 3H, SCH_2CH_2, CH_aCHOH), 2.11–2.30 (m, 2H, $ArCH_2CH_2$), 2.37 (dd, J=15.2, 8.8 Hz, 1H, CH_bCHOH), 2.42 (dd, J=15.6, 4.8 Hz, 1H, CH_aCOO), 2.52 (dd, J=15.6, 7.6 Hz, 1H, CH_bCOO), 2.62–2.97 (m, 6H, $ArCH_2$, 2×SCH_2), 4.41–4.49 (m, 1H, *CH*OH), 6.76 (d, J=8.0 Hz, 2H, 2×CH_{Ar}), 7.03 (d, J=8.0 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (SCH_2CH_2), 26.1, 26.3 (2×−SCH_2−), 28.2 (−OC(CH_3)$_3$), 29.7 ($ArCH_2$), 41.9 ($ArCH_2CH_2$), 43.5 (CH_2COO), 44.0 (CH_2CHOH), 51.9 (*SCS*), 65.9 (*CH*OH), 81.5 (−*OC*(CH_3)$_3$), 115.5 (2×CH_{Ar}), 129.5 (2×CH_{Ar}), 133.2 (C_{Ar}), 154.4 (C_{Ar}), 171.6 (*COO*); MS (EI) m/z (%) 398 [M]$^+$ (13), 107 (100); HRMS (EI) m/z found 396.1569. $C_{20}H_{28}O_4S_2$ requires 396.1586.

*6.2.3. (±)-tert-Butyl 3-(tripropylsilyloxy)-4-(2-(4-(tripropylsilyloxy) phenethyl)-1,3-dithian-2-yl)butanoate ((±)-**40**).* To a stirred solution of (±)-**39** (1.31 g, 3.29 mmol) in dry DMF (12 mL) were added imidazole (6 equiv) and triisopropylsilyl chloride (3 equiv) at 0 °C. After stirring for 18 h, a saturated aqueous solution of NH_4Cl was added. The organic phase was extracted with Et_2O, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 95:5) to give (±)-**40**

(2.22 g, 95%) as a colourless oil; R_f (cyclohexane/EtOAc 9:1) 0.78; IR ν_{max} (film, cm^{-1}) 3423, 2961, 1721, 1640, 1509, 1258, 1154, 1063; UV (MeOH) 283, 236, 212 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56–0.64 (m, 6H, 3×SiCH$_2$CH_2), 0.69–0.75 (m, 6H, 3×SiCH$_2$CH_2), 0.93 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 0.97 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 1.29–1.45 (m, 12H, 6×SiCH_2), 1.46 (s, 9H, OC(CH_3)$_3$), 1.88–2.03 (m, 2H, SCH$_2$CH_2), 2.10 (dd, J=15.2, 7.2 Hz, 1H, CHH_aCHOSi), 2.18–2.24 (m, 2H, ArCH$_2$CH_2), 2.37 (dd, J=15.2, 4.0 Hz, 1H, CHH_bCHOSi), 2.49 (dd, J=14.8, 4.8 Hz, 1H, CHH_aCOO), 2.56 (dd, J=14.8, 7.6 Hz, 1H, CHH_bCOO), 2.71–2.93 (m, 6H, ArCH_2, 2×SCH_2), 4.44–4.52 (m, 1H, CHOSi), 6.76 (d, J=8.4 Hz, 2H, 2×CH_{Ar}), 7.04 (d, J=8.4 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 17.0, 17.1, 17.4, 18.5, 18.7 (6×SiCH$_2$CH$_2$CH$_3$), 25.3 (SCH$_2$CH$_2$), 26.2, 26.6 (2×SCH$_2$), 28.3 (-OC(CH$_3$)$_3$), 30.1 (ArCH$_2$), 42.0 (ArCH$_2$CH$_2$), 45.4 (CH$_2$COO, CH$_2$CHOSi), 52.6 (SCS), 67.8 (CHOSi), 80.7 (−OC(CH$_3$)$_3$), 119.9 (2×CH$_{Ar}$), 129.5 (2×CH$_{Ar}$), 134.7 (C$_{Ar}$), 153.7 (C$_{Ar}$), 170.8 (COO); MS (ESI$^+$) m/z (%) 733 [M+Na]$^+$ (100); HRMS (ESI$^+$) m/z found 733.4152. $C_{38}H_{70}O_4S_2Si_2Na$ requires 733.4152.

*6.2.4. (±)-3-(Tripropylsilyloxy)-4-(2-(4-(tripropylsilyloxy)phenethyl)-1,3-dithian-2-yl)butanal ((±)-**41**).* To a stirred solution of (±)-**40** (2.00 g, 2.81 mmol) in dry toluene (10 mL) was slowly added DIBAL-H (1.7 M in toluene, 1.05 equiv) at −78 °C. After stirring for 15 min, the reaction was quenched by addition of MeOH and the reaction mixture was warmed up to rt. After addition of an aqueous solution of NaOH 1 N, the organic phase was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 95:5) to give (±)-**41** (1.47 g, 82%) as a colourless oil; R_f (cyclohexane/EtOAc 9:1) 0.30; IR ν_{max} (film, cm^{-1}) 3429, 2958, 1724, 1609, 1509, 1455, 1259, 1206, 1064, 1005; UV (MeOH) 279, 224, 203 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58–0.64 (m, 6H, 3×SiCH$_2$CH_2), 0.69–0.75 (m, 6H, 3×SiCH$_2$CH_2), 0.94 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 0.97 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 1.30–1.47 (m, 12H, 6×SiCH_2), 1.90–1.98 (m, 2H, SCH$_2$CH_2), 2.15 (dd, J=14.8, 5.6 Hz, 1H, CHH_aCHOSi), 2.18–2.24 (m, 2H, ArCH$_2$CH_2), 2.27 (dd, J=14.8, 5.6 Hz, 1H, CHH_bCHOSi), 2.63 (ddd, J=16.4, 4.8, 2.4 Hz, 1H, CHH_aC=O), 2.72–2.83 (m, 6H, ArCH_2, 2×SCH_2), 2.87 (ddd, J=16.4, 5.6, 1.2 Hz, 1H, CHH_bC=O), 4.59–4.64 (m, 1H, CHOSi), 6.73 (d, J=8.4 Hz, 2H, 2×CH_{Ar}), 7.04 (d, J=8.4 Hz, 2H, 2×CH_{Ar}), 9.83 (t, J=2.0 Hz, 1H, O=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 16.9, 17.0, 17.3, 18.4, 18.6 (6×SiCH$_2$CH$_2$CH$_3$), 25.1 (SCH$_2$CH$_2$), 26.1, 26.4 (2×SCH$_2$), 30.2 (ArCH$_2$), 42.0 (ArCH$_2$CH$_2$), 46.2 (CH$_2$CHOSi), 52.2 (SCS), 52.7 (CH$_2$C=O), 66.0 (CHOSi), 119.8 (2×CH$_{Ar}$), 129.3 (2×CH$_{Ar}$), 134.3 (C$_{Ar}$), 153.8 (C$_{Ar}$), 201.6 (C=O); HRMS (ESI$^+$, CH_3CN) m/z found 661.3571. $C_{34}H_{62}O_3S_2Si_2Na$ requires 661.3570.

*6.2.5. (±)-(E)-6-(Tripropylsilyloxy)-7-(2-(4-(tripropylsilyloxy)phenethyl)-1,3-dithian-2-yl)hept-3-en-2-one ((±)-**43**).* To a stirred solution of (±)-**39** (368 mg, 0.58 mmol) in dry toluene (3 mL) was added 1-(triphenylphosphoranylidene)propan-2-one **42** (459 mg, 1.44 mmol) at rt. After refluxing for 10 h, the reaction mixture was concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 95:5) to give (±)-**41** (368 mg, 94%) as a colourless oil; R_f (cyclohexane/EtOAc 9:1) 0.40; IR ν_{max} (film, cm^{-1}) 2954, 2926, 2868, 1679, 1509, 1455, 1257, 1064; UV (MeOH) 279, 224, 203 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58–0.65 (m, 6H, 3×SiCH$_2$CH_2), 0.70–0.76 (m, 6H, 3×SiCH$_2$CH_2), 0.94 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 0.97 (t, J=7.2 Hz, 9H, 3×Si(CH$_2$)$_2$CH_3), 1.31–1.47 (m, 12H, 6×SiCH_2), 1.89–1.97 (m, 2H, SCH$_2$CH_2), 2.05 (dd, J=15.0, 5.6 Hz, 1H, CHH_aCHOSi), 2.12 (dd, J=15.0, 5.2 Hz, 1H, CHH_bCHOSi), 2.18–2.24 (m, 2H, ArCH$_2$CH_2), 2.25 (s, 3H, C=OCH_3), 2.42–2.51 (m, 1H, CHH_aCH=C), 2.59–2.88 (m, 7H, ArCH_2, 2×SCH_2, CHH_bCH=C), 4.28–4.34 (m, 1H, CHOSi), 6.15 (d, J=16.0 Hz, 1H, CH=CHC=O), 6.74 (d, J=8.2 Hz, 2H, 2×CH_{Ar}), 6.86 (dt, J=16.0, 7.2 Hz, 1H, CH=CHC=O), 7.03 (d, J=8.2 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7–18.5 (6×SiCH$_2$CH$_2$CH$_3$), 25.1 (SCH$_2$CH$_2$), 26.2, 26.4 (2×SCH$_2$), 26.7 (COCH$_3$), 30.3 (ArCH$_2$), 41.7 (ArCH$_2$CH$_2$), 42.2 (CH$_2$CH=CH), 46.0 (CH$_2$CHOSi), 52.5 (SCS), 68.7 (CHOSi), 119.8 (2×CH$_{Ar}$), 129.3 (2×CH$_{Ar}$), 133.9 (CH=CHC=O), 134.3 (C$_{Ar}$), 144.3 (CH=CHC=O), 153.8 (C$_{Ar}$), 198.1 (C=O); MS (ESI$^+$) m/z (%) 701 [M+Na]$^+$ (15), 679 [M+H]$^+$ (100); HRMS (ESI$^+$) m/z found 701.3888. $C_{37}H_{66}O_3S_2Si_2Na$ requires 701.3890.

*6.2.6. (±)-(2R,4R,6R)-4-Hydroxy-2-(2-oxopropyl)-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one ((±)-**45**) and (±)-(2R,4S,6R)-4-hydroxy-2-(2-oxopropyl)-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one ((±)-**46**).* To a stirred mixture of (±)-**43** (308 mg, 0.45 mmol) in acetone/H_2O (10:1; 15.4 mL) was injected TFA (37 mL) followed by the addition of solid PhI(OCOCF$_3$)$_2$ (1.17 g, 6 equiv) in one portion in darkness. The mixture was stirred for 18 h at rt and was quenched with a saturated solution of $NaHCO_3$. After extraction with EtOAc, the organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (100% CH_2Cl_2 then 1% MeOH in CH_2Cl_2) to give (±)-**45** (32 mg, 24%) and (±)-**46** (55 mg, 41%); (±)-**45**: R_f (CH_2Cl_2/MeOH 98:2) 0.46; IR ν_{max} (film, cm^{-1}) 3418, 2937, 1713, 1665, 1624, 1167, 1094, 1045; UV (MeOH) 338, 227, 204 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (ddd, J=13.1, 12.6, 2.6 Hz, 1H, CHH_aCHOH), 1.76–1.81 (m, 1H, CHH_bCHOH), 1.92–2.05 (m, 4H, CHOHCH_2COO, CHH_aCH$_2$-COO, CH$_2$CHH_aCOO), 2.15–2.24 (m, 1H, CH$_2$CHH_bCOO), 2.22 (s, 3H, CH_3), 2.27–2.38 (m, 1H, CHH_bCH$_2$COO), 2.47 (dd, J=16.4, 2.8 Hz, 1H, CHHC=O), 2.75 (dd, J=16.4, 9.7 Hz, 1H, CHHC=O), 4.13–4.18 (m, 1H, CHOH), 4.67–4.72 (m, 1H, CHOC), 6.11 (dd, J=10.0, 2.0 Hz, 1H, CH=CHC=O), 6.24 (dd, J=10.0, 2.0 Hz, 1H, CH=CHC=O), 6.77 (dd, J=10.0, 2.8 Hz, 1H, CH=CHC=O), 7.27 (dd, J=10.0, 2.8 Hz, 1H, CH=CHC=O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.5 (CH$_3$), 34.2 (CH$_2$CH$_2$COO), 37.7 (CH$_2$CHOH), 39.0 (CH$_2$COO), 39.1 (CHOHCH$_2$-COO), 49.2 (CH$_2$C=O), 62.0 (CHOC), 64.8 (CHOH), 80.3 (C), 109.0 (OCO), 127.3 (CH=CHC=O), 127. 7 (CH=CHC=O), 148.6 (CH=CHC=O), 151.7 (CH=CHC=O), 185.7 (C=O), 206.6 (CH$_3$C=O); MS (ESI$^+$) m/z (%) 292 [M]$^+$ (10), 280 (100), 258 (95); HRMS (ESI$^+$) m/z found 315.1202. $C_{16}H_{20}O_5Na$ requires 315.1208. Compound (±)-**46**: R_f (CH_2Cl_2/MeOH 98:2) 0.34; IR ν_{max} (film, cm^{-1}) 3425, 2930, 1712, 1668, 1628, 1385, 1167, 1053; UV (MeOH) 229, 200 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (ddd, J=11.8, 11.8, 11.8 Hz, 1H, CHH_aCHOH), 1.64 (dd, J=11.8, 11.8 Hz, 1H, CHOHCHH_aCOO), 1.92–2.04 (m, 2H, CHH_aCH$_2$COO, CHH_bCHOH), 2.05–2.12 (m, 1H, CHOHCHH_bCOO), 2.13–2.23 (m, 2H, CH$_2$CH_2COO), 2.21 (s, 3H, CH_3), 2.26–2.40 (m, 1H, CHH_bCH$_2$COO), 2.48 (dd, J=16.4, 3.1 Hz, 1H, CHH_aC=O), 2.76 (dd, J=16.4, 9.2 Hz, 1H, CHH_bC=O), 4.13–4.18 (m, 1H, CHOH), 4.33–4.38 (m, 1H, CHOC), 6.10 (dd, J=10.3, 2.1 Hz, 1H, CH=CHC=O), 6.19 (dd, J=10.3, 2.1 Hz, 1H, CH=CHC=O), 6.77 (dd, J=10.3, 2.8 Hz, 1H, CH=CHC=O), 7.15 (dd, J=10.3, 2.8 Hz, 1H, CH=CHC=O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5 (CH$_3$), 34.6 (CH$_2$COO), 38.8 (CH$_2$CH$_2$COO), 40.2 (CH$_2$CHOH), 42.8 (CHOHCH$_2$COO), 49.2 (CH$_2$C=O), 64.8 (CHOC), 65.3 (CHOH), 79.4 (C), 109.0 (OCO), 127.0 (CH=CHC=O), 127.3 (CH=CHC=O), 149.4 (CH=CHC=O), 152.4 (CH=CHC=O), 185.9 (C=O), 206.8 (CH$_3$C=O); MS (ESI$^+$) m/z (%) 607 [2M+Na]$^+$ (100), 315 [M+Na]$^+$ (75); HRMS (ESI$^+$) m/z found 315.1208. $C_{16}H_{20}O_5Na$ requires 315.1208.

6.3. Syntheses of 2-[5-(hydroxymethyl)-2*H*-Pyran-3-(6*H*)-one]-1-oxaspiro[4.5]deca-6,9-dien-8-one (48) and 2-[(5,6-dihydro-5-oxo-2*H*-pyran-3-yl)methyl tetradecanoate]-1-oxaspiro[4.5]deca-6,9-dien-8-one (49)

*6.3.1. 4-[3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-3-hydroxypropyl]-phenyl acetate (**52**).* To a solution of 3-(4-acetoxyphenyl) propanoic acid **50**[22] (16.4 g, 77.1 mmol) in dry CH_2Cl_2 (190 mL) was added dropwise oxalyl chloride (13.3 mL, 154 mmol) at rt followed by addition of few drops of DMF and the mixture was stirred for 3 h

at rt. The solvent was removed in vacuo to give a yellow oil. To a solution of Meldrum's acid **51** (11.21 g, 77.11 mmol) in dry CH_2Cl_2 (72 mL) was added dropwise at 0 °C dry pyridine (12.45 mL, 154.20 mmol). After stirring for 1 h, the freshly prepared acyl chloride in dry CH_2Cl_2 (30 mL) was added dropwise into the mixture. After stirring for 16 h at 0 °C and 2 h at rt, the mixture was quenched by addition of a HCl solution 1 N. The product was extracted with CH_2Cl_2, the combined solution dried over $MgSO_4$ and concentrated to give an orange oil, which crystallized in dry EtOH to give a pale yellow solid **52** (18.2 g, 77%); R_f (cyclohexane/EtOAc 8:2) 0.17; IR ν_{max} (film, cm^{-1}) 1739, 1665, 1578, 1508, 1409, 1292, 1197, 1019, 912; UV (MeOH) 263, 208 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 6H, OOC(CH_3)$_2$), 2.28 (s, 3H, OOCCH_3), 3.01 (t, J=7.2 Hz, 2H, ArCH$_2$CH_2), 3.40 (t, J=7.2 Hz, 2H, ArCH_2CH$_2$), 7.01 (d, J=8.7 Hz, 2H, 2×CH_{Ar}), 7.27 (d, J=8.7 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (OOCCH_3), 27.2 (CH_2CH_2), 32.9 (CH_2CH_2), 96.3 (OOCCOH), 104.6 (OOC(CH_3)$_2$), 121.5 (2×CH_{Ar}), 129.2 (2×CH_{Ar}), 138.1 (CH_2C_{Ar}), 186.6 (OHC_{Ar}); MS (ESI$^+$) m/z (%) 357 [M+Na]$^+$ (100); HRMS (ESI$^+$) m/z found 357.0945. $C_{17}H_{18}O_7Na$ requires 357.0948.

*6.3.2. Ethyl-5-(4-acetoxyphenyl)-3-oxopentanoate (**53**).* A solution of **52** (4.51 g, 13.5 mmol) in dry EtOH was stirred at reflux for 3 h. The solvent was removed in vacuo. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 80:20) to give **53** as a colourless oil (3.56 g, 95%); R_f (cyclohexane/EtOAc 8:2) 0.2; IR ν_{max} (film, cm^{-1}) 2984, 1748, 1647, 1509, 1369, 1318, 1196, 1098, 1019, 913, 848; UV (MeOH) 270 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H, CH_3CH$_2$), 2.28 (s, 3H, OOCCH_3), 2.78–2.80 (m, 4H, ArCH_2CH$_2$, ArCH$_2$CH_2), 3.41 (s, 2H, OCH_2O), 4.13 (q, J=7.1 Hz, 2H, OCH_2CH$_3$), 6.80 (d, J=8.6 Hz, 2H, 2×CH_{Ar}), 7.00 (d, J=8.6 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3CH_2), 20.3 (OOCCH_3), 28.7 (ArCH$_2$CH$_2$), 41.4 (ArCH$_2$CH$_2$), 48.9 (OCH$_2$O), 61.0 (CH$_3$CH$_2$), 121.5 (2×CH_{Ar}), 129.2 (2×CH_{Ar}), 138.1 (CH_2C_{Ar}), 148.5 (C_{Ar}), 168.1 (OCCH$_2$CH$_3$), 169.0 (OOCCH$_3$), 202.1 (C=O); MS (ESI$^+$) m/z (%) 301 [M+Na]$^+$ (100), 287 (45), 216 (37); HRMS (ESI$^+$) m/z found 301.1046. $C_{15}H_{18}O_5Na$ requires 301.1047.

*6.3.3. Ethyl-5-(hydroxymethyl)-2-(4-hydroxyphenyl)furan-3-carboxylate(**55**).* To a solution of **53** (0.78 g, 2.79 mmol) in 1,4-dioxanne (6 mL) were added distilled water (3.5 mL), $CeCl_3.7H_2O$ (0.5 g, 1.33 mmol) and DL-glyceraldehyde dimer **54** (0.30 g, 1.67 mmol). The mixture was stirred at 90 °C for 10 h. The mixture was concentrated by repeating co-evaporation with toluene. The residue was directly subjected to silica gel column chromatography (cyclohexane/EtOAc 65:35) to give **55** (1.06 g, 56%); R_f (cyclohexane/EtOAc 4:6) 0.19; IR ν_{max} (film, cm^{-1}) 3362, 2982, 1711, 1680, 1615, 1574, 1518, 1457, 1304, 1215, 1070, 1017, 827; UV (MeOH) 249, 202 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.1 Hz, 3H, CH_3CH$_2$O), 2.85 (t, J=8.0 Hz, 2H, ArCH$_2$CH_2), 3.23 (t, J=8.0 Hz, 2H, ArCH_2CH$_2$), 4.26 (q, J=7.1 Hz, 2H, CH$_3$CH_2O), 4.55 (s, 2H, CH_2OH), 6.54 (s, 1H, CH=CCH$_2$OH), 6.75 (d, J=8.4 Hz, 2H, 2×CH_{Ar}), 7.20 (d, J=8.4 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3CH_2O), 30.3 (ArCH$_2$CH$_2$), 33.6 (ArCH$_2$CH$_2$), 57.4 (CH_2OH), 60.6 (CH$_3$CH$_2$O), 109.0 (CHCCOH), 114.3 (CC=O), 115.4 (2×CH_{Ar}), 129.7 (2×CH_{Ar}), 132.9 (C_{Ar}CH$_2$), 152.1 (CCH$_2$OH), 154.3 (C_{Ar}OH), 162.5 (C=O) 164.2 (CH$_2$COC); MS (ESI$^+$) m/z (%) 313 (100) [M+Na]$^+$, 301 (75), 167 (40); HRMS (ESI$^+$) m/z found 313.1046. $C_{16}H_{18}O_5Na$ requires 313.1045.

*6.3.4. (5-(4-Hydroxyphenethyl)furan-2,4-diyl)dimethanol (**47**).* To a solution of **55** (0.91 g, 3.12 mmol) in dry THF (37 mL) was added dropwise at 0 °C and under argon a solution of $LiAlH_4$ in THF (15.6 mL, 15.6 mmol, 1 M in THF). The mixture was stirred at rt overnight. The mixture was quenched by carefully addition of EtOAc, followed by an aqueous solution of NH_4Cl. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 20:80) to give **47** (0.67 mg, 86%); R_f (cyclohexane/EtOAc 2:8) 0.30; IR ν_{max} (film, cm^{-1}) 3350, 2946, 2918, 1611, 1518, 1445, 1364, 1235, 1174, 1146, 1082, 1002, 827; UV (MeOH) 278, 225 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74–2.86 (m, 4H, ArCH_2CH_2), 4.14 (s, 2H, OCH_2OH), 4.45 (s, 2H, CH_2OH), 6.22 (s, 1H, CHCCH$_2$OH), 6.68 (d, J=8.5 Hz, 2H, 2×CH_{Ar}), 6.91 (d, J=8.5 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7 (ArCH$_2$CH$_2$), 35.1 (ArCH$_2$CH$_2$), 56.2 (CH_2OH), 57.5 (OCH$_2$OH), 110.1 (CCH$_2$OH), 116.1 (2×CH_{Ar}), 121.4 (CHCH$_2$OH), 130.5 (2×CH_{Ar}), 133.4 (CH_2C_{Ar}), 153.0 (OCCH$_2$OH), 153.7 (COC), 156.5 (C_{Ar}OH); MS (ESI$^+$) m/z (%) 271 [M+Na]$^+$ (100), 218 (20), 231 (15); HRMS (ESI$^+$) m/z found 271.0941. $C_{20}H_{28}O_4S_2$ requires 271.0943.

*6.3.5. 6-(4-Hydroxyphenethyl)-6-hydroxy-5-(hydroxymethyl)-2H-pyran-3(6H)-one (**56**).* To a solution of **47** (230 mg, 0.93 mmol) in CH_2Cl_2/1,1,1,3,3,3-hexafluoro-2-propanol (1:1) was added at 0 °C *m*CPBA (176 mg, 1.02 mmol). After stirring for 1 h at 0 °C and 1 h at rt, the mixture was quenched with an aqueous solution of $Na_2S_2O_3$. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 40:60) to give **56** (182.2 mg, 74%); R_f (cyclohexane/EtOAc 3:7) 0.29; IR ν_{max} (film, cm^{-1}) 3362, 1674, 1508, 1436, 1303, 1254, 1052, 1016, 826, 746; UV (MeOH) 278, 223 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92–2.07 (m, 2H, ArCH$_2$CH_2), 2.40–2.51 (m, 1H, OCOH), 2.67–2.79 (m, 1H, CH$_2$OH), 3.29–3.33 (m, 2H, ArCH_2CH$_2$), 4.07 (d, J=16.8 Hz, 1H, OCHH_aC=O), 4.35 (t, J=2 Hz, 2H, CH_2OH), 4.67 (d, J=16.8 Hz, 1H, OCHH_bC=O), 6.25 (t, J=1.6 Hz, 1H, C=CH), 6.28 (d, J=8.6 Hz, 2H, 2×CH_{Ar}), 6.98 (d, J=8.6 Hz, 2H, 2×CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (ArCH$_2$CH$_2$), 42.0 (ArCH$_2$CH$_2$), 61.2 (CH_2OH), 67.1 (OCH$_2$C=O), 96.5 (OCOH), 116.4 (2×CH_{Ar}), 122.1 (2×CH_{Ar}), 130.3 (C=CH), 133.8 (2×CH_{Ar}), 156.7 (CH_2C_{Ar}), 166.5 (HOC$_{Ar}$), 197.6 (C=O); MS (ESI$^+$) m/z (%) 287 [M+Na]$^+$ (100), 285 (28), 310 (27); HRMS (ESI$^+$) m/z found 287.0895. $C_{14}H_{16}O_5Na$ requires 287.0890.

*6.3.6. (±)-2[5-(Hydroxymethyl)-2H-pyran-3(6H)-one]-1-oxaspiro [4.5]deca-6,9-dien-8-one ((±)-**48**). Method a*: To a solution of **56** (11.3 mg, 0.043 mmol) in CH_2Cl_2/1,1,1,3,3,3-hexafluoro-2-propanol (1:1) (1 mL) was added at 0 °C PhI(OAc)$_2$ (21.0 mg, 0.065 mmol). After stirring for 30 min at 0 °C, solid $NaHCO_3$ was added. The solid was then removed by filtration and the solution was concentrated in vacuo. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 40:60) to give (±)-**48** (8.5 mg, 74%).

Method b: To a solution of **47** (160.4 mg, 0.65 mmol) in CH_2Cl_2/1,1,1,3,3,3-hexafluoro-2-propanol (6 mL) was added at 0 °C *m*CPBA (124.0 mg, 0.72 mmol). After stirring for 1 h at 0 °C and 1 h at rt, 4-iodotoluene **57** (14.2 mg, 0.065 mmol) was added at rt. After completion (about 15 min) solid $NaHCO_3$ was added. The solid was then removed by filtration and the solution was concentrated in vacuo. The residue was subjected to alumina column chromatography (cyclohexane/EtOAc 20:80) to give (±)-**48** (37.8 mg, 22%).

Method c: To a solution of **47** (30.9 mg, 0.12 mmol) in CH_2Cl_2/1,1,1,3,3,3-hexafluoro-2-propanol (2 mL) were added at rt *m*CPBA (45.0 mg, 0.26 mmol) and 4-iodotoluene **57** (2.7 mg, 0.012 mmol). After stirring until completion (1 h), solid $NaHCO_3$ was added. The solid was then removed by filtration and the solution was concentrated in vacuo. The residue was subjected to alumina column chromatography (cyclohexane/EtOAc 20:80) to give (±)-**48** (7.8 mg, 25%); R_f (cyclohexane/EtOAc 3:7) 0.25; IR ν_{max} (film, cm^{-1}) 3343, 2954, 1675, 1631, 1457, 1429, 1247, 1162, 1082, 1013, 860; UV (MeOH) 203 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17–2.26 (m, 1H, CCHH_aCH$_2$C), 2.29–2.35 (m, 1H, CCHH_bCH$_2$C), 2.43–2.57 (m, 2H, CCH$_2$CH_2C), 4.15 (d, J=17.2 Hz, 1H, OCHH_aC=O), 4.30 (dd, J=20.0, 2.0 Hz, 1H, CHH_aOH), 4.43 (dd, J=20.0, 2.0 Hz, 1H, CHH_bOH), 4.45 (d, J=17.2 Hz, 1H, OCHH_bC=O), 6.12 (dd, J=25.2, 2.0 Hz, 1H, CH=CHC

(O)CH=CH), 6.13 (dd, *J*=5.2, 1.6 Hz, 1H, CH=CHC(O)C*H*=CH), 6.29 (t, *J*=3.6 Hz, 1H, HOCH$_2$C=C*H*), 7.02 (dd, *J*=20.6, 4.0 Hz, 1H, C*H*=CHC(O)CH=CH), 7.03 (dd, *J*=7.2, 4.0 Hz, 1H, CH=CHC(O)CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.7 (C*C*H$_2$CH$_2$C), 36.0 (CCH$_2$*C*H$_2$C), 61.5 (*C*H$_2$OH), 68.1 (OCH$_2$C=O), 80.8 (CCH$_2$CH$_2$*C*O), 107.2 (*C*CH$_2$CH$_2$CO), 124.0 (HOCH$_2$C=*C*H), 128.0 (CH=*C*HC(O)CH=CH), 128.4 (CH=CHC(O)*C*H=CH), 150.6 (*C*H=CHC(O)CH=CH), 152.8 (CH=CHC(O)CH=*C*H), 162.0 (HOCH$_2$*C*=CH), 187.3 (CH=CH*C*(O)CH=CH), 196.8 (C=CH*C*=O); MS (ESI$^+$) *m*/*z* (%) 285 [M+Na]$^+$ (100), 263 (16%), 264 (2%); HRMS (ESI$^+$) *m*/*z* found 285.0733. $C_{14}H_{14}O_5Na$ requires 285.0736.

*6.3.7. (±)-2-[(5,6-Dihydro-5-oxo-2H-pyran-3-yl)methyl tetradecanoate]-1-oxaspiro[4.5]deca-6,9-dien-8-one ((+/−)-**49**).* To a solution of **48** (34.6 mg, 0.13 mmol) in dry CH_2Cl_2 (2 mL) were added at 0 °C DMAP (16.1 mg, 0.13 mmol), myristol chloride (42.4 mg, 0.17 mmol) and Et_3N (17.3 mg, 0.17 mmol). After 30 min at 0 °C and 2 h at rt, an aqueous solution of HCl 1 N was added. The product was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (cyclohexane/EtOAc 70:30) to give **49** (23.5 mg, 38%); R_f (cyclohexane/EtOAc 7:3) 0.18; IR ν_{max} (film, cm^{-1}) 2914, 2845, 1752, 1683, 1469, 1275, 1251, 1162, 1025, 1013, 900, 847; UV (MeOH) 221 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 3H, C*H*$_3$(CH$_2$)$_{10}$CH$_2$CH$_2$C=O), 1.26–1.28 (m, 20H, CH$_3$(C*H*$_2$)$_{10}$CH$_2$CH$_2$C=O), 1.67–1.75 (m, 2H, CH$_3$(CH$_2$)$_{10}$C*H*$_2$CH$_2$C=O), 2.19–2.29 (m, 2H, CC*H*$_2$CH$_2$C), 2.23–2.38 (m, 2H, CCH$_2$*CH*$_2$C), 2.52–2.60 (CH$_3$(CH$_2$)$_{10}$CH$_2$*CH*$_2$C=O), 4.18 (d, *J*=16.8 Hz, 1H, OCH-*H*$_a$C=O), 4.51 (d, *J*=16.8 Hz, 1H, OCH*H*$_b$C=O), 4.72 (dd, *J*=20.0, 1.6 Hz, 1H, CH=CCH*H*$_a$OC=O), 4.91 (dd, *J*=1.6 Hz, 1H, CH=CCH*H*$_b$OC=O), 6.19 (dd, *J*=11.6, 2.0 Hz, 1H, CH=C*H*C(O)CH=CH), 6.22 (dd, *J*=11.6, 2.0 Hz, 1H, CH=CHC(O)C*H*=CH), 6.25 (t, *J*=1.6 Hz, 1H, C*H*=CCH$_2$OC=O), 6.80 (dd, *J*=10.0, 3.2 Hz, 1H, CH=CHC(O)CH=C*H*), 6.89 (dd, *J*=10.0, 3.2 Hz, 1H, C*H*=CHC(O)CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$CH$_2$CH$_2$(CH$_2$)$_8$), 22.9 (CH$_3$*C*H$_2$CH$_2$(CH$_2$)$_8$), 25.0 (CH$_3$CH$_2$CH$_2$(CH$_2$)$_8$*C*H$_2$CH$_2$C=O), 29.2 (CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_8$), 30.1 (CH$_3$CH$_2$CH$_2$(CH$_2$)$_8$CH$_2$*C*H$_2$C=O), 61.7 (CH=CC*H*$_2$OC=O), 67.0 (O*C*H$_2$C=O), 79.7 (CCH$_2$CH$_2$*C*O), 105.9 (O*C*CH$_2$CH$_2$CO), 125.4 (*C*H=CCH$_2$OC=O), 128.0 (CH=*C*HC(O)*C*H=CH), 147.2 (*C*H=CHC(O)CH=*C*H), 149.7 (CH=*C*CH$_2$OC=O), 173.3 (CH=CCH$_2$OC=O), 185.1 (CH=CH*C*(O)CH=CH), 194.7 (C=CH*C*=O); MS (ESI$^+$) *m*/*z* (%) 495 [M+Na]$^+$ (100), 143 (95), 245 (65), 217 (40); HRMS (ESI$^+$) *m*/*z* found 495.2717. $C_{28}H_{40}O_6Na$ requires 495.2718.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.135.

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