Limno-CP: A Natural-Product-Inspired 5-Aryl-3(2*H*)-furanone as Scaffold for a Library of α-Modified Enones

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Abstract: A library of 5-aryl-3(2*H*)-furanones that are modified in the α-position of the α,β-unsaturated carbonyl system was prepared via simple one- to three-step transformations from one common scaffold. The ^{13}C NMR characterization of the enone system showed a strong influence of the α-substituents, especially on the shifts of the α- and β-carbon atoms. Probing the addition chemistry of nucleophiles versus our α-modified enones, a 1,2-addition–elimination was found, but no 1,4-addition.

Key words: furanones, substituent effects, enones, spiro compounds, 1,2-addition–elimination

3(2*H*)-Furanones represent an important subgroup of α,β-unsaturated carbonyl compounds, which contain a number of very attractive, biologically active natural products. Geiparvarin,[1] eremantholides,[2] and jatrophone[3] possess antitumor activity, and pseurotin[4] is known to inhibit immunoglobulin E production. Therefore, the synthesis of 3(2*H*)-furanones is not only important as part of the total synthesis of more complex natural products, but also effective to get an easy access to these compounds for a potential application in drug development.[5] Importantly, when not substituted, the α-position of the α,β-unsaturated carbonyl unit can be used to introduce different substituents while maintaining the reactive enone system (Figure 1).[6]

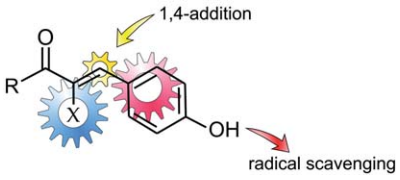


Figure 1 Substituent X can have a significant influence both on Michael acceptor activity, but also on antioxidative properties

Despite the fact that the formation of α-modified enones seems to be an attractive regime, this concept has not been used very extensively. Nevertheless, there are examples for chalcones (1,3-diphenylpropenoids),[7] benzenemalononitriles, and related compounds (tyrphostins),[8] as well as triterpenoids (Figure 2).[9] And, in that way the biological activities could be strongly influenced by the α-substituent X.[7,9,10] The underlying reactivities addressed were either Michael acceptor based, or in the case of phenolic compounds, also particularly antioxidative activity.

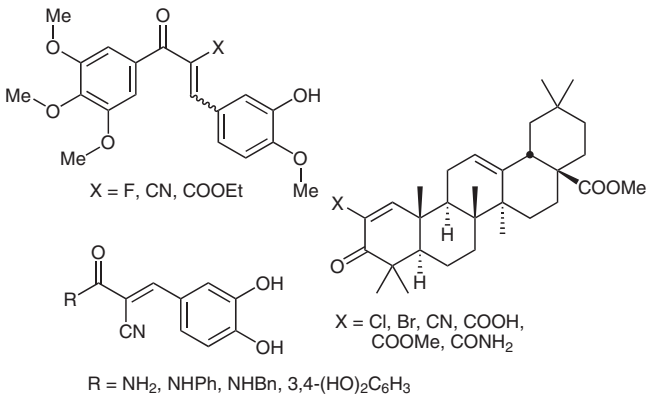
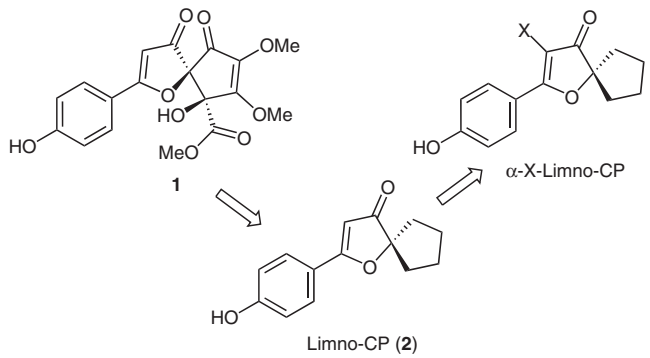


Figure 2 α-Modified enone compounds with biological activity

Compounds featuring both potential reactivities are referred to as bifunctional antioxidants since they can either induce anti-inflammatory and cytoprotective enzymes via thiol-dependent Michael additions or scavenge radicals/act as reductants.[11]

So far, no systematic studies on the influence of substituent X on the biological activity exist for scaffolds with the 3(2*H*)-furanone unit. To introduce a system where X possesses certain variability, for example, halogen, nitrile, or aryl, a natural product where α-substituted variants could be produced would be a good target. As a point of inspiration, the highly oxidized plant ingredient limnophilaspiroketone (**1**) (Scheme 1) was chosen. This compound was isolated from *Limnophila geoffrayi*, whose extracts are used in the traditional medicine of Thailand for detoxification.[12]



Scheme 1 Natural product limnophilaspiroketone (**1**), model compound Limno-CP (**2**), and α-modified derivatives thereof

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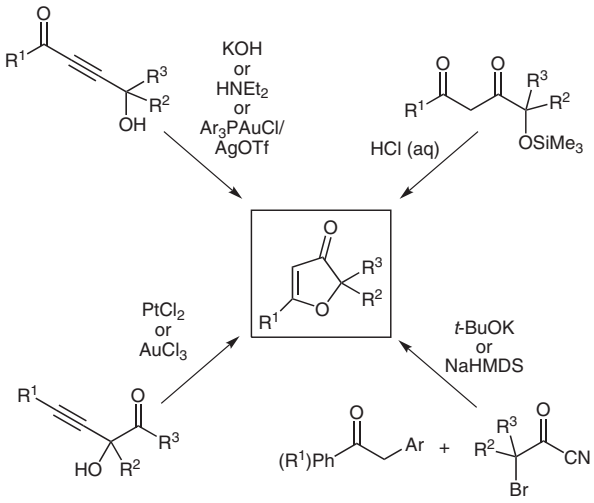
Limnophilaspiroketone (**1**) has two major features, which caught our interest: (1) the two orthogonal, spirocyclic α,β-unsaturated carbonyl systems, and (2) the phenolic unit conjugated with one of the enone units. To be able to test the influence of α-substituent X on the 3(2*H*)-furanones, it was decided to use a simple model system derived from **1** (Scheme 1). Model compound Limno-CP (**2**) contains the α-unsubstituted (α-H)-3(2*H*)-furanone unit of natural product **1** whereas the second α,β-unsaturated carbonyl unit, the spirocyclic 2,3-dimethoxycyclopent-2-enone-5,5-diyl system, was replaced by a simple spirocyclopentane-1,1-diyl (CP) unit.

The underlying 1-oxaspiro[4.4]non-2-en-4-one motif of **1** and **2** is found in only one natural product apart from **1**, namely jatrophone, in which this moiety is part of a larger ring system.[3] Similarly, pseurotins contain a spiro-3(2*H*)-furanone-γ-lactam (1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione) unit.[13] It is known that 3(2*H*)-furanones display a rather weak Michael acceptor activity,[14] which makes them an ideal skeleton to start modifications from. The phenolic unit in **2** allows apart from its potential antioxidant activity additional modifications such as the attachment of chromophores or affinity tags, which could be useful for biological studies.

In this work, we present a straightforward synthetic scheme for an easy access to a rational library of α-substituted derivatives of 3(2*H*)-furanones, namely, the simple model compound Limno-CP (**2**), as a starting point for a later biological characterization of these α,β-unsaturated carbonyl compounds.

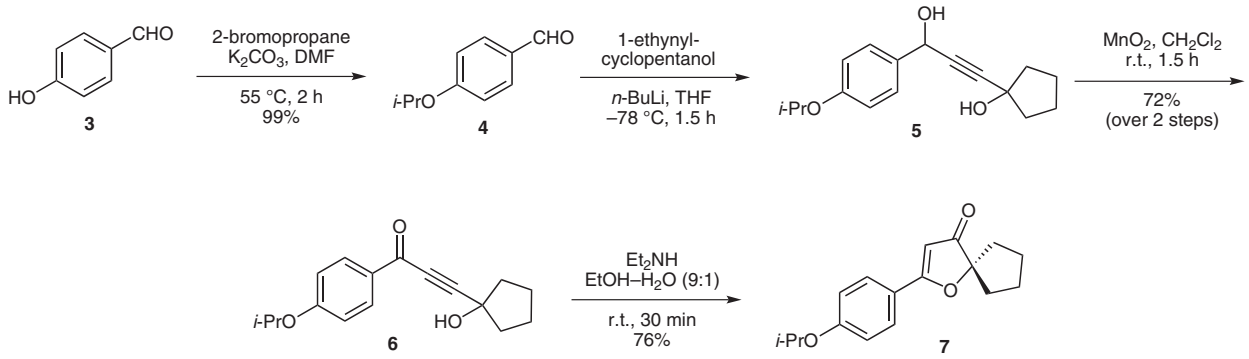
Instead of finding the best route to any of the potential α-modified variants of **2**, where the α-substituent could be for example any halogen, an aryl, or a nitrile group we decided to synthesize the parent compound *i*-Pr-α-H-Limno-CP (**7**) (see Scheme 3) as a common precursor to produce all other derivatives based on this molecule. A synthetic access to this spirocyclic structure has been known since 1966,[15] and until now several different approaches have been used (Scheme 2).[16,17]

For the synthesis of **7**, a strategy was used that was applied in the formation of novel COX-2 inhibitors, namely 5-aryl-2,2-dialkyl-4-phenyl-3(2*H*)-furanone derivatives[18] (see Scheme 2, upper left). We picked this particular sequence, since **7** can be prepared in four simple transformations with inexpensive standard reagents requiring only two chromatographic separations (Scheme 3).



Scheme 2 Syntheses of 3(2*H*)-furanones

The synthesis was carried out by first protecting 4-hydroxybenzaldehyde (**3**) quantitatively as its isopropyl ether **4**.[19] The orthogonal behavior of phenolic isopropoxy versus methoxy groups is essential for further studies towards methoxy-substituted compounds such as **1**. Additionally, the isopropyl ethers, which should be quite stable under physiological conditions, give rise to a second set of potentially biologically active compounds, where the phenolic hydroxy group is blocked. From 4-propoxybenzaldehyde (**4**), diol **5** was obtained by a coupling with lithiated 1-ethynylcyclopentanol. Diol **5** was subjected to a standard MnO_2 oxidation without prior purification to give ketone **6** in an overall yield of 72% over two steps. Initial attempts to form the 5-aryl-3(2*H*)-furanone unit in pure ethanol under literature conditions[18] (Table 1, entry 1) gave low yields. But the reaction was optimized accordingly (Table 1, entry 3).



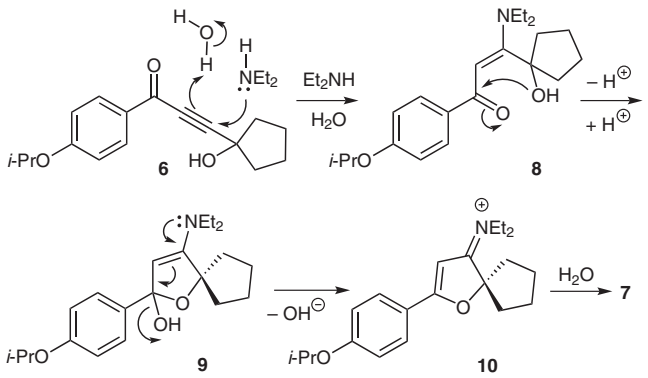
Scheme 3 Synthesis of *i*-Pr-α-H-Limno-CP (**7**)

Table 1 Formation of *i*-Pr-α-H-Limno-CP (**7**) by Cyclization of **6** with Different Nucleophiles/Bases

Entry	Nuc/Base	Solvent	Temp	Time (h)	**7** (%)[a]
1	Et_2NH	EtOH (100%)	r.t.	0.5	26
2	Et_2NH	EtOH (100%)	reflux	4	35
3	Et_2NH	EtOH–H_2O (9:1)	r.t.	0.5	90
4	-	EtOH–H_2O (9:1)	reflux	4	7
5	Et_3N	EtOH–H_2O (9:1)	reflux	4	8
6	KOH	EtOH–H_2O (9:1)	r.t.	0.5	35
7	KOH	EtOH–H_2O (9:1)	reflux	4	90

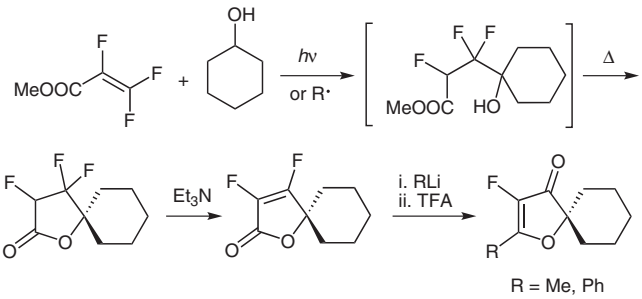
[a] Estimated by ^{1}H NMR spectroscopy.

It was found that water is needed to gain an effective protonation within the addition of diethylamine to the acetylene unit of precursor **6**. Ethanol is not sufficiently acidic. In the earlier given mechanism of the bullatenone synthesis from 1958, which is the basis for our considerations, this issue was not addressed.[20] Furthermore, potassium hydroxide in water–ethanol was not as effective (Table 1, entries 6 and 7) indicating that the harder nucleophile hydroxide is inferior to diethylamine. Triethylamine, or no additional base at all, gave only very poor product formation. A plausible mechanism is shown in Scheme 4.[21] The purification by chromatography and recrystallization gave *i*-Pr-α-H-Limno-CP (**7**) in a total yield of 54% over four steps.



Scheme 4 Reaction mechanism for the formation of **7**

With compound **7** in our hands, the preparation of the corresponding α-substituted derivatives of **7** was continued. First, the halogen series were probed. In the literature, single examples for related α-halogen 3(2*H*)-furanones as precursors for aryl compounds (α-Br[22] and α-I[23]) are known as well as α-Cl, α-F, α-Br,[24] and α-OH[25] derivatives with the 1-oxaspiro[4.4]non-2-ene-4-on system partially attached to the steroid skeleton. Moreover, an α-F[26] and an α-CN analogue[27] of a very similar spirocyclic 3(2*H*)-furanone were described. A series of α-modified enones were prepared from isopropyl-protected Limno-CP **7** by very simple one- to three-step modifications (Table 2). *i*-Pr-α-Cl-Limno-CP (**12**), *i*-Pr-α-Br-Limno-CP (**13**), and *i*-Pr-α-I-Limno-CP (**14**) could be prepared directly from **7** using the corresponding *N*-halosuccinimides as electrophile sources in 88 to 91%. These reagents were applied likewise in the more reactive 3(2*H*)-pyrrolone system.[28] Alternative conditions with a common addition–elimination pathway using bromine and triethylamine[29] gave α-Br compound **13** in 92% yield. The iodine substituent could also be installed with I_2 and catalytic amounts of PDC[30] to afford the α-I derivative **14** in 72% yield. Introducing a fluorine substituent in the α-position was exceedingly more challenging and the two examples that have been reported in the literature (where one is a patent from 1981 about steroidal spirodihydrofuranones)[24] have the F-atoms already installed prior to the cyclization transformations. Paleta and co-workers started from a trifluorinated acyclic starting material[31] and prepared a compound very similar to our target substance **11** (Scheme 5).[26] Initially, we used Selectfluor, a common reagent for electrophilic fluorinations,[32] to introduce the F-substituent directly into the 3(2*H*)-furanone system. This reagent together with **7** yielded complex mixtures in *N*,*N*-dimethylformamide, acetone, or acetonitrile at a reaction temperature of 0 °C, whereas refluxing tetrahydrofuran, chloroform, ethyl acetate, and toluene gave the desired product, but with very low conversions.

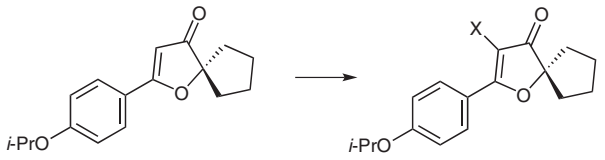


Scheme 5 Preparation of α-F-substituted enones of a 3(2*H*)-furanone by Paleta[26,31]

N-Fluorobenzenesulfonimide (NFSI) was slightly better. Overall, *i*-Pr-α-F-Limno-CP (**11**) could be successfully prepared in 5% isolated yield in refluxing tetrahydrofuran. When a reaction time of 16 hours was not exceeded, 87% of unreacted starting material could be reisolated. Otherwise the formation of other, unidentified fluorination products that were hard to separate was observed. Experiments to develop a gold-catalyzed fluorination using $Au(PPh_3)Cl/AgSbF_6$ as catalyst together with Selectfluor failed.

An adapted Rosenmund von Braun reaction of bromo compound **13** with sodium cyanide and nickel(II) bromide led to the corresponding nitrile **15** in 89%.[33] The best yields in the microwave-assisted formation of **15** could be achieved when the pressure did not rise above the ambient pressure. *i*-Pr-α-CN-Limno-CP (**15**) could be hydrolyzed in basic media[34] to yield amide **16** in 73% yield. Acid hydrolysis of amide **16** to the corresponding carboxylic acid

Table 2 Synthesis of α-Modified Derivatives of *i*-Pr-α-H-Limno-CP



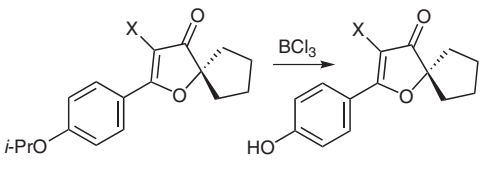
i-Pr-α-H-Limno-CP (**7**) *i*-Pr-α-X-Limno-CP

SM[a]	Conditions[b]	Product	X	Yield (%)[c]
7	NFSI, THF, reflux, 16 h	**11**	F	5
7	NCS, MeOH, reflux, 16 h	**12**	Cl	91
7	NBS, MeCN, 0 °C, 30 min	**13**	Br	88
7	Br_2, Et_3N, CH_2Cl_2, 0 °C, 3 h	**13**	Br	92
7	NIS, MeCN, reflux, 16 h	**14**	I	88
7	I_2, PDC, CH_2Cl_2, r.t., 3 h	**14**	I	72
13	NaCN, $NiBr_2$, NMP, μw, 200 °C, 10 min	**15**	CN	89
15	aq 12 M NaOH–1,4-dioxane (1:1), r.t., 1.5 h	**16**	$CONH_2$	73
13	$PhB(OH)_2$, $Pd_2(dba)_3$, PPh_3, Et_2NH, toluene–EtOH–H_2O, reflux, 20 h	**17**	Ph	79

[a] SM: starting material.
[b] NFSI: *N*-fluorobenzenesulfonimide; NMP: *N*-methyl-2-pyrrolidone.
[c] Isolated yield.

as well as attempts to directly hydrolyze nitrile **16** failed, complex, inseparable mixtures were obtained under various conditions. In a Suzuki reaction, the α-phenyl derivative **17** could be synthesized in 79% yield.[35]

To complete the syntheses of Limno-CP (**2**) and its α-modified variants, the isopropyl compounds could be successfully deprotected using six equivalents of boron trichloride in dichloromethane in very good to excellent isolated yields after chromatography (Scheme 6).



i-Pr-α-X-Limno-CP α-X-Limno-CP

Scheme 6 Deprotection of isopropyl ethers of α-X-Limno-CPs

In comparing the ^{13}C NMR chemical shifts, it was found that we were indeed able to modify the properties of the α,β-unsaturated carbonyl system (Table 3). As especially pivotal for Michael-addition chemistry the chemical shifts of the β-position could be significantly changed. 'Transforming' α-H compound **2** with a value of 183.0 ppm to a shift of 166.8 ppm in the case of α-F **18** proved the very strong effect of a fluorine substituent in the α-position. This finding is in complete agreement with the literature.[26]

Table 3 ^{13}C NMR Chemical Shifts of *i*-Pr-α-X-Limno-CPs and α-X-Limno-CPs

Product	X	R[a]	C=O, δ[b]	α-C, δ	β-C, δ
7	H	O*i*-Pr	205.7	98.8	183.6
11	F	O*i*-Pr	193.4[c]	140.5[d]	167.2[e]
12	Cl	O*i*-Pr	199.2	104.9	175.6
13	Br	O*i*-Pr	200.0	92.2	176.9
14	I	O*i*-Pr	202.5	62.8	179.1
15	CN	O*i*-Pr	199.6	86.5	185.3
16	$CONH_2$	O*i*-Pr	193.0	95.1	179.7
17	Ph	O*i*-Pr	204.3	113.6	178.3
2	H	OH	203.8	97.3	183.0
18	F	OH	191.6[f]	139.4[g]	166.8[h]
19	Cl	OH	197.5	103.1	175.4
20	Br	OH	198.5	90.8	176.7
21	I	OH	201.9	63.3	178.8
22	CN	OH	199.0	84.8	185.1
23	$CONH_2$	OH	191.6	93.6	178.5
24	Ph	OH	202.8	112.3	177.9

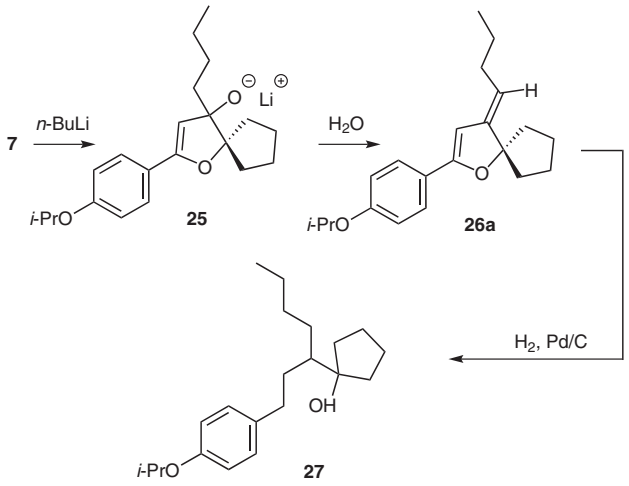
[a] Substituent at position 4 of the aromatic ring.
[b] Carbonyl carbon of 3(2*H*)-furanone.
[c] d, $^2J_{C,F}$ = 10.1 Hz.
[d] d, $^1J_{C,F}$ = 259.3 Hz.
[e] d, $^2J_{C,F}$ = 13.7 Hz.
[f] d, $^2J_{C,F}$ = 10.1 Hz.
[g] d, $^1J_{C,F}$ = 256.5 Hz.
[h] d, $^2J_{C,F}$ = 14.0 Hz.

But, the system could be only slightly pushed towards even more low field-shifted values as seen for α-CN **22** with a shift of 185.1 ppm (185.3 ppm for *i*-Pr-α-CN **15**).

The introduction of further substituents in the α-position was attempted by α-metalation–electrophile addition sequences. A direct deprotonation of **7** with *tert*-butyllithium that Takeda et al. used for the analogous proton abstraction of a 2(5*H*)-furanone[36] led only to the decomposition of **7**. Also, no reaction was observed with lithium diisopropylamide, which was reported to undergo a Baylis–Hilman-type reaction with pyranones.[37] Alternative experiments using halogenated compounds **13** and **14** also failed with lithium, tin,[38] or magnesiumorganic compounds.[39,40]

In order to determine whether the α-modified enones display differential reactivities, nucleophilic additions with alkyllithium reagents and Gilman cuprate were per-

formed. Indeed, with *n*-alkyllithium reagents, such as *n*-butyl-, *n*-hexyl-, and methyllithium, a 1,2-addition to the enone system of **7** was observed. This addition was unexpected and has not been described for a 3(2*H*)-furanone entity. The reaction is only possible because a subsequent elimination to the corresponding alkylidene compounds occurs instantaneously. More precisely, when *n*-butyllithium was used together with **7**, 3-methylene-2,3-dihydrofuran **26a** was obtained (Scheme 7).



Scheme 7 Addition of *n*-butyllithium to enone **7** and ring opening to form alcohol **27**

Compound **26a** is formed within three minutes and could be isolated through an aqueous workup together with the *Z*-isomer as the only two products in an *E*/*Z* ratio of 95:5 in 87% yield (Table 4 and Figure 3). A full characterization was easy to achieve when done quickly after its formation. Nevertheless, **26a**, **26b** are not stable even at –20 °C and decompose within hours at this temperature. Different attempts to trap **26a**, **26b** with electrophiles or nucleophiles did not succeed.

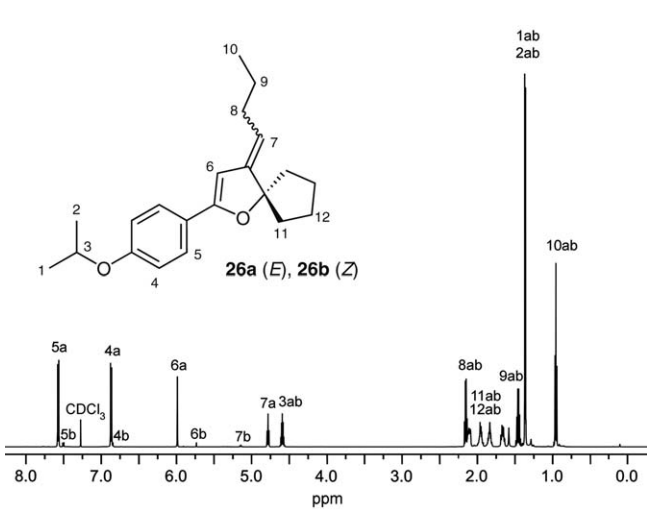


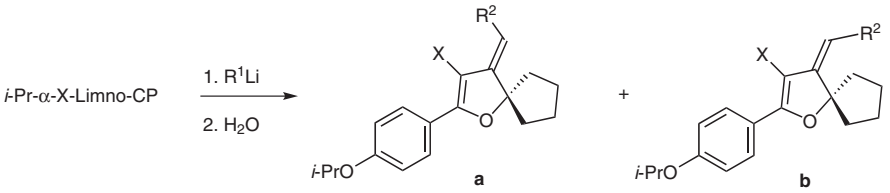
Figure 3 Crude ^{1}H NMR spectrum of **26a** and **26b** as obtained directly after aqueous workup from reaction of **7** with *n*-BuLi

Hydrogenation using hydrogen over palladium-on-carbon, however, gave ring-opened, stable product **27** in 89% yield as the only product (Scheme 6). Employing *n*-hexyllithium gave the analoguous products **28a**, **28b** in the same isomeric ratio of 95:5 and an isolated yield of 91%. MeLi on the other hand yielded exomethylene compound **29**, but only in 38% as determined from a mixture by the use of an internal standard. Since phenyllithium and *tert*-butyllithium lack α-methylenic groups no formation of the corresponding alkylidene products **a**, **b** was anticipated. Indeed, only complex mixtures were observed. Adding *n*-butyllithium to our *i*-Pr-α-modified enones gave different ratios of *E*/*Z*-isomers **a**, **b** in the case of *i*-Pr-α-F **11**, *i*-Pr-α-Cl **12**, and *i*-Pr-α-Ph derivatives **17**, where X is inert to the reaction conditions (Table 4).

Interestingly, α-Cl derivatives **31a**, **31b** were found in an opposite isomeric ratio than observed in the other cases, which might be explained by the greater steric demand of the chloro substituent. Both *i*-Pr-α-Br **13** and *i*-Pr-α-I compounds **14** gave mixtures with dehalogenation products either of elimination products or the corresponding starting materials, leading to **26a** and **7**. This shows that a protonation of the α-lithiated compounds must be very fast and explains why we could not get other α-modified enones by the use of electrophiles such as diethyl carbonate, tributyltin chloride or trimethylborate. These are inferior to H^+ in our system. Primarily an addition to the nitrile group was observed with *i*-Pr-α-CN compound **15**. Using more than 1.0 equivalent of *n*-butyllithium gave additionally 1,2-addition–elimination products in a range of 20%. Amide **16** gave very little conversion and no 1,2-addition–elimination product could be proven. This is probably because the deprotonation of the amide-H_2 group is faster than a nulcleophilic attack at the 2-position.

Attempts to perform classical 1,4-additions with lithium dimethylcuprate (Gilman cuprate) failed under conditions where we were able to fully convert 2,2-dimethyl-3(2*H*)-furanone into its conjugate addition product within minutes at –30 °C.[42] Instead, when using Gilman cuprate with *i*-Pr-α-H **7** or *i*-Pr-α-F **11** we could not get any reaction at –30 °C within six to eight hours. Warming to 0 °C resulted in a slow decomposition. Two reasons for the diminished reactivity towards a conjugate addition could come into play: (1) the relatively large aryl-substituent at the β-position, and, (2) the low to moderate electrophilicity as judged from the ^{13}C NMR chemical shifts. Comparing **7** and **11** with 2,2-dimethyl-3(2*H*)-furanone, at least **11** should be reactive enough to be a Michael acceptor since its shift of 167.2 ppm is even more up-field than the one of 2,2-dimethyl-3(2*H*)-furanone with a value of 176.2 ppm. Typically, enone systems with chemical shifts of 120–170 ppm show intermediate to high reactivities in conjugate additions. Especially, exomethylenic enone entities like in helenalin with a ^{13}C NMR value of 122.1 ppm are very reactive.[43] In this case the 1,4-addition is responsible for its antitumor activity/cytotoxicity. We are aiming for a moderate to low reactivity, which could be expected in the range of chemical shifts of our compounds. Since

Table 4 Reaction of *i*-Pr-α-X-Limno-CPs with Different Alkyl(aryl)lithium Reagents[a]



Entry	Product	X	R^1Li	Conversion	Product	Yield (%), **a**/**b**[b]
1	**7**	H	*n*-BuLi	quant	**26a**, **26b**	87,[c] 95:5
2	**7**	H	*n*-HexLi	quant	**28a**, **28b**	91,[c] 95:5
3	**7**	H	MeLi	94%	**29**	38
4	**7**	H	PhLi	quant	-[d]	-
5	**7**	H	*t*-BuLi	quant	-[d]	-
6	**11**	F	*n*-BuLi	quant	**30a**, **30b**	52, 65:35
7	**12**	Cl	*n*-BuLi	quant	**31a**, **31b**	86, 10:90
8	**13**	Br	*n*-BuLi	quant	**7**, **26a**[e]	-
9	**14**	I	*n*-BuLi	89%	**7**, **26a**[f]	-
10	**15**	CN	*n*-BuLi	quant	-[g]	-
11	**16**	$CONH_2$	*n*-BuLi	<5%	n.d.[h]	-
12	**17**	Ph	*n*-BuLi	quant	**32a**, **32b**	33, 60:40

[a] Reaction procedure: addition of R^1Li (1.0 equiv) in *n*-hexane or Et_2O dropwise at –78 °C to a solution of 3(2*H*)-furanone (1.0 equiv) in THF, then addition of H_2O. R^2 contains (n – 1) carbon atoms of R^1.
[b] Determined by ^1H NMR with hexamethyldisilane as internal standard.[41]
[c] Isolated yield.
[d] Complex mixture.
[e] Yield of **7**: 67%; **26a**: 15%.
[f] Yield of **7**: 44%; **26a**: 22%; **14**: 11%.
[g] Addition products to nitrile group.
[h] Not determined.

no reaction was found, it is clear that the ^{13}C NMR chemical shifts alone are not sufficient to predict reactivity in 1,4-additions. This is particularly true when steric hindrance in the β-position interferes with the addition of the nucleophile.

In preparing α-substituted variants of Limno-CP via a facile synthesis we could demonstrate that the α-substituent has a very strong influence on the ^{13}C NMR chemical shifts of the 3(2*H*)-furanone system. This distinction together with the variation in sterical demand give a strong indication for differential activities as seen in the formation of the 1,2-addition–elimination products. Importantly, we were able to access a ^{13}C NMR chemical shift for the β-position of up to 167 ppm – a range where the very potent, biologically active synthetic triterpenoids are found.[9] Nevertheless, a Michael addition reaction was not observed with Gilman cuprate. Further studies concerning antioxidant activity and inhibition of the proinflammatory enzyme inducible NO synthase (iNOS) are ongoing and show first promising results. Moreover, the modification regime could be applied to modulate the activity of known, biologically active 3(2*H*)-furanones such as geiparvarin derivatives and eremantholides since these compounds possess unsubstituted α-positions in their corresponding 3(2*H*)-furanone unit.

All reactions were carried out under N_2 atmosphere in oven-heated glassware (110 °C), when dry conditions were required, and monitored by TLC on silica gel plates 60 F_{254} by Merck. Spots were detected under UV light (λ = 254 and 366 nm) or visualized by staining with vanillin/H_2SO_4 (6 g vanillin in 100 mL 95% EtOH–concd H_2SO_4 100:1). Column chromatography was performed on silica gel Geduran Si 60 (0.063–0.200 mm) by Merck. Melting points are determined with a Büchi SMP 20 apparatus, they are uncorrected. IR spectroscopy was carried out on a Specac Golden Gate Diamond Single Reflection ATR System Excalibur Series FTS3000MX by BIO-RAD. NMR spectra were recorded on Bruker Avance 300, Bruker Avance 400, and Bruker Avance III 600 spectrometers. ^1H NMR spectra are referenced to $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 ppm); ^{13}C NMR spectra to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.43 ppm). Mass spectra were obtained on Varian MAT 311A, Finnigan MAT 95 or Thermoquest Finnigan TSQ 7000 instruments.

4-Isopropoxybenzaldehyde (**4**) was prepared according to a literature procedure[19] in 99% yield.

1-[3-Hydroxy-3-(4-isopropoxyphenyl)prop-1-ynyl]cyclopentanol (5)

To a suspension of 1-ethynylcyclopentanol (5.00 g, 45.4 mmol, 1.3 equiv) in THF (100 mL) was added dropwise a 1.6 M solution of *n*-BuLi in *n*-hexane (45.8 mL, 73.3 mmol, 2.1 equiv) at –78 °C. After stirring for 30 min, aldehyde **4** (5.64 g, 34.4 mmol, 1.0 equiv) was added dropwise and the solution allowed to warm to r.t. After 1.5 h, the solvent was removed and the residue dissolved in H_2O (100 mL). The solution was neutralized with aq 1 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (100 mL), dried ($MgSO_4$), and the solvent evaporated. Crude diol **5** (yellow solid, 8.82 g) obtained was used without further purification. A sample of **5** was purified (SiO_2, hexanes–EtOAc, 4:1) for obtaining analytical and spectral data; mp 108 °C; R_f = 0.1 (SiO_2, hexanes–EtOAc, 4:1).

IR (neat): 3273, 2973, 2870, 1609, 1506, 1381, 1240, 1180, 1122, 994, 958, 844, 812, 728, 631, 597, 567, 530 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.67–1.88 (m, 4 H, CH_2), 1.90–2.00 (m, 4 H, CH_2), 2.46 (s, 1 H, OH), 2.78 (s, 1 H, OH), 4.54 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 5.41 (s, 1 H, CH), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 7.41 (d, *J* = 8.6 Hz, 2 H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 23.4, 42.2, 64.1, 69.9, 74.4, 83.0, 90.2, 115.8, 128.1, 132.6, 157.9.

MS (EI, 70 eV): *m*/*z* (%) = 274.2 (100, [M^+]), 214.1 (33), 185.1 (66), 157.0 (48), 147.0 (36), 121.0 (82), 120.1 (68), 107.0 (64), 95.1 (32), 55.1 (24).

HRMS (EI): *m*/*z* (M^+) calcd for $C_{17}H_{22}O_3$: 274.1569; found: 274.1567.

3-(1-Hydroxycyclopentyl)-1-(4-isopropoxyphenyl)propynone (6)

A suspension of crude diol **5** (8.82 g) and an excess of MnO_2 (27.8 g, 0.320 mol) in CH_2Cl_2 (200 mL) was stirred for 1.5 h at r.t. The suspension was filtered through a pad of Celite, evaporated to dryness, and the product purified by flash chromatography (FC) (SiO_2, hexanes–EtOAc, 6:1) to give ketone **6** as a yellow solid (6.76 g, 24.8 mmol, 72% over two steps); mp 82 °C; R_f = 0.4 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 3339, 2973, 2208, 1618, 1583, 1505, 1385, 1318, 1260, 1170, 1106, 1003, 946, 844, 757, 692, 632, 575 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.77–1.95 (m, 4 H, CH_2), 2.03–2.19 (m, 5 H, CH_2, OH), 4.66 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.91 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}), 8.07 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 23.6, 42.4, 70.3, 74.4, 81.1, 96.4, 115.1, 129.5, 132.1, 163.1, 176.5.

MS (EI, 70 eV): *m*/*z* (%) = 272.2 (68, [M^+]), 201.2 (40), 173.1 (100), 121.1 (66).

HRMS (EI): *m*/*z* (M^+) calcd for $C_{17}H_{20}O_3$: 272.1412; found: 272.1411.

2-(4-Isopropoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (7)

To a solution of ketone **6** (1.86 g, 6.83 mmol, 1.0 equiv) in EtOH–H_2O (35 mL, 9:1) was added dropwise Et_2NH (0.750 g, 10.3 mmol, 1.5 equiv) at r.t. After 30 min, the solvent was removed and the crude product purified by FC (SiO_2, hexanes–EtOAc, 20:1). Recrystallization from hexanes yielded the furanone **7** as light yellow crystals (1.42 g, 5.21 mmol, 76%); mp 93 °C; R_f = 0.45 (SiO_2, hexanes–EtOAc, 3:1).

IR (neat): 2972, 1674, 1603, 1562, 1499, 1429, 1366, 1298, 1253, 1182, 1109, 1074, 1051, 948, 893, 820, 666 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.90–2.14 (m, 8 H, CH_2), 4.65 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 5.88 (s, 1 H, CH), 6.94 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}), 7.75 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 25.7, 37.1, 70.2, 98.2, 98.8, 115.6, 121.3, 129.1, 161.6, 183.6, 205.7.

MS (EI, 70 eV): *m*/*z* (%) = 272.1 (40, [M^+]), 231.1 (62), 189.0 (100), 118.0 (86).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{17}H_{20}O_3$: 272.1412; found: 272.1410.

3-Fluoro-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (11)

A solution of furanone **7** (300 mg, 1.10 mmol, 1.0 equiv) and *N*-fluorobenzenesulfonimide (382 mg, 1.21 mmol, 1.1 equiv) in anhyd THF (30 mL) was heated under reflux for 16 h. The solution was evaporated in the presence of SiO_2 and purified by FC [SiO_2 (dry-load), hexanes–EtOAc, 20:1 to 5:1] to afford α-F-furanone **11** as a white solid (17.0 mg, 0.0586 mmol, 5%); mp 94 °C; R_f = 0.36 (SiO_2, hexanes–EtOAc, 5:1). Additionally, 261 mg (0.958 mmol, 87%) of starting material **7** was reisolated.

IR (neat): 2970, 1701, 1616, 1566, 1511, 1432, 1404, 1385, 1306, 1259, 1178, 1153, 1118, 948, 885, 837, 745, 647, 632, 517, 490, 445 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.96–2.11 (m, 8 H, CH_2), 4.66 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.97 [d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 7.90 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.3, 70.2, 96.2 (d, *J* = 7.1 Hz), 115.7, 119.4 (d, *J* = 5.1 Hz), 129.3 (d, *J* = 6.6 Hz), 140.5 (d, *J* = 259.3 Hz), 161.6 (d, *J* = 1.8 Hz), 167.2 (d, *J* = 13.7 Hz), 193.4 (d, *J* = 10.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –181.0.

MS (EI, 70 eV): *m*/*z* (%) = 290.1 (34, [M^+]), 249.1 (12), 220.0 (16), 207.0 (100), 136.0 (11), 121.0 (12).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{17}H_{19}FO_3$: 290.1318; found: 290.1321.

3-Chloro-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (12)

A stirred solution of furanone **7** (200 mg, 0.734 mmol, 1.0 equiv) and *N*-chlorosuccinimide (118 mg, 0.881 mmol, 1.2 equiv) in MeOH (10 mL) was refluxed for 16 h. After removal of solvent and addition of sat. aq $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (5 × 10 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (SiO_2, hexanes–EtOAc, 10:1) gave α-Cl-furanone **12** (204 mg, 0.665 mmol, 91%) as light yellow crystals; mp 94 °C; R_f = 0.62 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2977, 1698, 1603, 1561, 1501, 1428, 1351, 1298, 1261, 1188, 1086, 949, 926, 834, 747, 631, 445 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.95–2.18 (m, 8 H, CH_2), 4.66 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.97 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 8.15 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.4, 70.2, 96.8, 104.9, 115.4, 120.4, 130.3, 161.7, 175.6, 199.1.

MS (EI, 70 eV): *m*/*z* (%) = 306.1 (24, [M^+]), 265.1 (12), 225.0 (31), 223.0 (100), 152.0 (18), 121.0 (14).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{17}H_{19}ClO_3$: 306.1023; found: 306.1025.

3-Bromo-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (13)

Method A: To a stirred solution of furanone **7** (500 mg, 1.84 mmol, 1.0 equiv) in MeCN (20 mL) was added *N*-bromosuccinimide (359 mg, 2.02 mmol, 1.1 equiv) in portions at 0 °C. After 30 min, sat. aq $NaHCO_3$ (20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed. Recrystallization from EtOAc gave α-Br-furanone **13** (570 mg, 1.62 mmol, 88%) as white crystals.

Method B: A solution of furanone **7** (500 mg, 1.84 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was treated with a solution of Br_2 (293 mg, 1.84 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C. After 20 min, a solution of Et_3N (557 mg, 5.51 mmol, 3.0 equiv) in CH_2Cl_2 (3 mL) was added dropwise to the mixture. The solution was stirred for 1 h at 0 °C and 2 h at r.t., then diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (SiO_2, hexanes–EtOAc, 10:1) afforded **13** (592 mg, 1.69 mmol, 92%), mp 94 °C; R_f = 0.58 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2954, 1696, 1601, 1556, 1497, 1425, 1347, 1293, 1256, 1187, 1106, 1070, 951, 919, 831, 746 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.95–2.18 (m, 8 H, CH_2), 4.66 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.97 (d, *J* = 9.1 Hz, 2 H, CH_{Ar}), 8.19 (d, *J* = 9.1 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.5, 37.5, 70.2, 92.2, 96.8, 115.3, 120.7, 130.5, 161.6, 176.9, 200.0.

MS (EI, 70 eV): *m*/*z* (%) = 350.0 (26, [M^+]), 309.0 (15), 269.0 (84), 267.0 (84), 145.0 (100), 121.0 (29).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{17}H_{19}BrO_3$: 350.0518; found: 350.0512.

3-Iodo-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (14)

Method A: A stirred solution of furanone **7** (100 mg, 0.367 mmol, 1.0 equiv) and *N*-iodosuccinimide (90.9 mg, 0.404 mmol, 1.1 equiv) in MeCN (10 mL) was refluxed for 16 h. Sat. aq $NaHCO_3$ (10 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent removed. Recrystallization from EtOAc gave α-I-furanone **14** (592 mg, 1.49 mmol, 88%) as light yellow crystals.

Method B: To a solution of furanone **7** (50 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (1.2 mL) were added I_2 (70 mg, 0.28 mmol, 1.5 equiv) and pyridinium dichromate (21 mg, 55 μmol, 0.3 equiv). The reaction flask was covered with aluminum foil and the mixture stirred for 3 h at r.t. The contained solids were filtered off and the filtrate washed with H_2O (3 mL), sat. aq $Na_2S_2O_3$ (3 mL), and brine (3 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated. Purification by FC (SiO_2, hexanes–EtOAc 10:1) afforded **14** (52 mg, 0.13 mmol, 72%); mp 135 °C; R_f = 0.57 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2955, 1677, 1599, 1545, 1491, 1422, 1342, 1291, 1253, 1175, 1107, 1060, 950, 915, 832, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.95–2.16 (m, 8 H, CH_2), 4.66 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.96 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}), 8.21 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.4, 37.6, 62.8, 70.2, 96.4, 115.2, 121.2, 130.9, 161.6, 179.1, 202.5.

MS (EI, 70 eV): *m*/*z* (%) = 398.0 (37, [M^+]), 357.0 (14), 315.0 (62), 145.0 (100), 121.0 (17).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{17}H_{19}IO_3$: 398.0379; found: 398.0379.

2-(4-Isopropoxyphenyl)-4-oxo-1-oxaspiro[4.4]non-2-ene-3-carbonitrile (15)

In a microwave glass tube with a magnetic stirring bar were placed α-bromofuranone **13** (0.20 g, 0.57 mmol, 1.0 equiv), NaCN (56 mg, 1.1 mmol, 2.0 equiv), and $NiBr_2$ (0.12 g, 0.57 mmol, 1.0 equiv) in *N*-methylpyrrolidinone (4 mL). The sealed reaction vessel was put into the cavity of a CEM Discover S microwave synthesis system reactor using a noncontact, infrared sensor for temperature control and heated up to 200 °C. Once the temperature was reached, the brown mixture was held at 200 °C for 10 min. Then the green mixture was allowed to cool down to r.t., diluted with H_2O (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 × 5 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (SiO_2, hexanes–EtOAc, 8:1) gave nitrile **15** as white crystals (0.15 g, 0.50 mmol, 89%); mp 126 °C; R_f = 0.6 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2984, 2221, 1706, 1603, 1578, 1504, 1429, 1387, 1314, 1261, 1190, 1156, 1127, 1102, 951, 842, 758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.95–2.20 (m, 8 H, CH_2), 4.69 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 7.00 (d, *J* = 9.1 Hz, 2 H, CH_{Ar}), 8.19 (d, *J* = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 25.6, 37.3, 70.7, 86.5, 100.2, 113.4, 115.9, 119.0, 131.0, 163.6, 185.3, 199.6.

MS (EI, 70 eV): *m*/*z* (%) = 297.2 (21, [M^+]), 255.2 (7), 214.1 (100), 143.1 (20), 121.0 (9).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{18}H_{19}NO_3$: 297.1365; found: 297.1362.

2-(4-Isopropoxyphenyl)-4-oxo-1-oxaspiro[4.4]non-2-ene-3-carboxylic Acid Amide (16)

Nitrile **15** (0.10 g, 0.34 mmol, 1.0 equiv) was dissolved in a 1:1 solution of aq 12 M NaOH–1,4-dioxane (9 mL) and the mixture stirred at r.t. for 2 h. After dilution with aq 1 M HCl (5 mL) and extraction with EtOAc (3 × 10 mL), the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was evaporated. Recrystallization from EtOAc gave amide **16** as white crystals (81 mg, 0.25 mmol, 73%); mp 175 °C; R_f = 0.47 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 3321, 3183, 2966, 1597, 1483, 1245, 1184, 1121, 1045, 947, 931, 855, 830, 792, 652, 608, 545, 480 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 [d, *J* = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.84–1.94 (m, 6 H, CH_2), 2.07–2.18 (m, 2 H, CH_2), 4.63 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.03 (s, 1 H, NH), 6.89 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}), 7.92 (d, *J* = 8.9 Hz, 2 H, CH_{Ar}), 9.28 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 25.4, 36.7, 69.8, 95.1, 99.7, 114.3, 130.4, 131.3, 161.2, 179.7, 189.0, 193.0.

MS (EI, 70 eV): *m*/*z* (%) = 315.2 (47, [M^+]), 272.2 (23), 232.1 (100), 138.0 (86), 121.0 (73), 95.0 (33).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{18}H_{21}NO_4$: 315.1471; found: 315.1467.

2-(4-Isopropoxyphenyl)-3-phenyl-1-oxaspiro[4.4]non-2-en-4-one (17)

To solution of α-bromofuranone **13** (20 mg, 57 μmol, 1.0 equiv) in toluene (0.32 mL) and EtOH (0.10 mL) were added $Pd_2(dba)_3$ (2.6

mg, 2.8 μmol, 0.05 equiv), PPh_3 (1.5 mg, 5.7 μmol, 0.1 equiv), and $PhB(OH)_2$ (8.3 mg, 68 μmol, 1.2 equiv). After stirring for 10 min, Et_2NH (7.5 μL) and H_2O (0.10 mL) were added and the mixture was refluxed for 16 h. The solution was diluted with EtOAc (3 mL) and washed successively with aq 0.2 M NaOH (3 mL), aq 0.05 M HCl (3 mL), and brine (3 mL). The organic layer was dried ($MgSO_4$) and the solvent removed. Purification by FC (SiO_2, hexanes–EtOAc, 6:1) afforded α-Ph-furanone **17** as colorless crystals (16 mg, 45 μmol, 79%); mp 119 °C; R_f = 0.33 (SiO_2, toluene–MeOH, 99:1).

IR (neat): 2969, 1686, 1603, 1486, 1384, 1252, 1168, 1106, 1045, 948, 835, 695, 623, 514, 447 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.92–2.21 (m, 8 H, CH_2), 4.57 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.80 (d, J = 9.0 Hz, 2 H, CH_{Ar}), 7.27–7.39 (m, 5 H, CH_{Ar}), 7.59 (d, J = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 25.7, 37.5, 70.0, 96.8, 113.6, 115.1, 121.9, 127.3, 128.6, 129.7, 130.3, 130.6, 160.8, 178.3, 204.3.

MS (EI, 70 eV): m/z (%) = 348.2 (98, [M^+]), 307.2 (75), 265.1 (100), 194.1 (58), 165.0 (24), 121.0 (18).

HRMS (EI-MS): m/z (M^+) calcd for $C_{23}H_{24}O_3$: 348.1725; found: 348.1727.

Deprotection of Isopropyl Ethers; General Procedure

Protected furanone (8.0–20 mg, 28 μmol–57 mol, 1.0 equiv) was dissolved in anhyd CH_2Cl_2 (0.5 mL) and a solution of 1 M BCl_3 in *n*-hexane (6.0 equiv) was added slowly at –78 °C to the solution. The solution was warmed to r.t. and stirred until the reaction was complete (1 to 40 h). THF (0.5 mL) and aq 1 M HCl (0.5 mL) were added and the solvent was removed. The residue was taken up in EtOAc (10 mL) and H_2O (10 mL), extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Absorption on SiO_2 was done from a solution of EtOH and purification achieved by FC [SiO_2 (dryload), hexanes–EtOAc–EtOH (40:10:1) and $CHCl_3$–EtOH (25:1)] to yield the deprotected furanones. For the purification of amide **23**, only $CHCl_3$–EtOH (25:1) was applied.

2-(4-Hydroxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (2)

Compound **7** (10 mg, 37 μmol) gave after 16 h of reaction time, 8.4 mg (36 μmol, 99%) of **2**; mp 231 °C; R_f = 0.15 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2918, 2728, 2609, 1638, 1548, 1501, 1431, 1366, 1234, 1161, 1051, 895, 789, 592 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.73–1.94 (m, 8 H, CH_2), 6.13 (s, 1 H, CH), 6.90 (d, J = 8.7 Hz, 2 H, CH_{Ar}), 7.77 (d, J = 8.7 Hz, 2 H, CH_{Ar}), 10.44 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.1, 36.4, 97.3, 97.4, 115.7, 119.3, 129.2, 161.7, 183.0, 203.8.

MS (EI, 70 eV): m/z (%) = 230.1 (26, [M^+]), 189.0 (86), 118.0 (100), 89.1 (13), 44.0 (16), 40.1 (32).

HRMS (EI-MS): m/z (M^+) calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0944.

3-Fluoro-2-(4-hydroxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (18)

Compound **11** (8.0 mg, 28 μmol) gave after 3 h of reaction time, 6.7 mg (27 μmol, 98%) of **18**; mp 208 °C; R_f = 0.33 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3121, 2946, 1675, 1563, 1508, 1414, 1285, 1154, 1107, 961, 843, 743, 581, 512, 413 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.99 (m, 8 H, CH_2), 6.98 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 7.78 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 10.61 (s, 1 H, OH).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 24.8, 36.5, 95.5 (d, J = 7.6 Hz), 116.2, 117.1 (d, J = 5.0 Hz), 129.2 (d, J = 6.2 Hz), 139.4 (d, J = 256.5 Hz), 162.0 (d, J = 1.2 Hz), 166.8 (d, J = 14.0 Hz), 191.6 (d, J = 10.1 Hz).

^{19}F NMR (282 MHz, DMSO-d_6): δ = –181.5.

MS (EI, 70 eV): m/z (%) = 248.2 (47, [M^+]), 220.2 (18), 207.1 (100), 136.1 (23), 121.1 (29).

HRMS (EI-MS): m/z (M^+) calcd for $C_{14}H_{13}FO_3$: 248.0849; found: 248.0853.

3-Chloro-2-(4-hydroxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (19)

Compound **12** (10 mg, 33 μmol) gave after 16 h of reaction time, 8.2 mg (31 μmol, 95%) of **19**; mp 209 °C; R_f = 0.43 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3139, 2924, 1670, 1606, 1552, 1489, 1370, 1284, 1170, 1095, 933, 837, 744, 659, 505, 450 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.81–2.00 (m, 8 H, CH_2), 6.98 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 8.03 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 10.65 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.9, 36.7, 96.1, 103.0, 115.9, 118.3, 130.2, 162.1, 175.3, 197.5.

MS (EI, 70 eV): m/z (%) = 264.1 (35, [M^+]), 225.0 (30), 223.0 (100, [$M^+ - C_3H_5$], 152.0 (33), 145.1 (16), 121.0 (24).

HRMS (EI-MS): m/z (M^+) calcd for $C_{14}H_{13}ClO_3$: 264.0553; found: 264.0548.

3-Bromo-2-(4-hydroxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (20)

Compound **13** (20 mg, 57 μmol) gave after 16 h of reaction time, 16 mg (53 μmol, 93%) of **20**; mp 216 °C; R_f = 0.48 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3158, 2958, 1666, 1603, 1552, 1484, 1361, 1281, 1235, 1171, 1079, 921, 846, 747, 665, 597, 438 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.75–2.03 (m, 8 H, CH_2), 6.97 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 8.07 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 10.63 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.9, 36.8, 90.8, 96.0, 115.7, 118.7, 130.5, 162.0, 176.7, 198.5.

MS (EI, 70 eV): m/z (%) = 308.0 (32, [M^+]), 268.9 (79), 267.0 (82), 145.0 (100), 121.0 (28).

HRMS (EI-MS): m/z (M^+) calcd for $C_{14}H_{13}BrO_3$: 308.0048; found: 308.0047.

2-(4-Hydroxyphenyl)-3-iodo-1-oxaspiro[4.4]non-2-en-4-one (21)

Compound **14** (20 mg, 50 μmol) gave after 1 h of reaction time, 15 mg (41 μmol, 82%) of **21**; mp 201 °C; R_f = 0.43 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3139, 2923, 1656, 1600, 1545, 1476, 1352, 1279, 1231, 1168, 1070, 915, 841, 746, 665, 594, 523, 450 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.76–1.98 (m, 8 H, CH_2), 6.96 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 8.08 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 10.55 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.0, 36.9, 63.3, 95.5, 115.5, 119.6, 130.8, 161.7, 178.8, 201.9.

MS (EI, 70 eV): m/z (%) = 355.9 (65, [M^+]), 314.9 (80), 145.0 (100), 121.0 (17).

HRMS (EI-MS): m/z (M^+) calcd for $C_{14}H_{13}IO_3$: 355.9909; found: 355.9902.

2-(4-Hydroxyphenyl)-4-oxo-1-oxaspiro[4.4]non-2-ene-3-carbonitrile (22)

Compound **15** (10 mg, 34 μmol) gave after 40 h of reaction time, 8.4 mg (33 μmol, 98%) of **22**; mp 255 °C; R_f = 0.35 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3200, 2972, 2231, 1701, 1605, 1559, 1505, 1382, 1286, 1170, 1117, 956, 845, 707, 665, 575, 510 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.82–2.07 (m, 8 H, CH_2), 7.04 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 8.05 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 11.09 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.9, 36.5, 84.8, 99.8, 113.7, 116.4, 117.3, 131.0, 164.2, 185.1, 199.0.

MS (EI, 70 eV): m/z (%) = 255.1 (20, [M^+]), 214.1 (100, [M^+ – C_3H_5]), 143.0 (45), 121.0 (13).

HRMS (EI-MS): m/z (M^+) calcd for $C_{15}H_{13}NO_3$: 255.0895; found: 255.0889.

2-(4-Hydroxyphenyl)-4-oxo-1-oxaspiro[4.4]non-2-ene-3-carboxylic Acid Amide (23)

Compound **16** (10 mg, 32 μmol) gave after 16 h of reaction time, 7.3 mg (27 μmol, 84%) of **23**; mp 190 °C; R_f = 0.09 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 3283, 3057, 2962, 1610, 1581, 1452, 1274, 1244, 1024, 1000, 934, 789, 710, 636, 605, 525, 480, 440 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.80–1.99 (m, 8 H, CH_2), 6.75 (d, J = 8.7 Hz, 2 H, CH_{Ar}), 7.68 (d, J = 8.7 Hz, 2 H, CH_{Ar}), 9.00 (s, 1 H, NH), 9.28 (s, 1 H, NH), 10.01 (s, 1 H, OH).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 24.9, 36.1, 93.5, 97.4, 113.9, 129.7, 131.1, 160.6, 178.5, 187.1, 191.6.

MS (EI, 70 eV): m/z (%) = 273.1 (38, [M^+]), 232.0 (49, [M^+ – C_3H_5], 138.0 (43), 121.0 (100), 93.0 (37), 65.1 (44).

HRMS (EI-MS): m/z (M^+) calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0994.

2-(4-Hydroxyphenyl)-3-phenyl-1-oxaspiro[4.4]non-2-en-4-one (24)

Compound **17** (10 mg, 29 μmol) gave after 16 h of reaction time, 8.3 mg (27 μmol, 94%) of **24**; mp 221 °C; R_f = 0.45 (SiO_2, hexanes–EtOAc, 2:1).

IR (neat): 3260, 2919, 1670, 1604, 1562, 1483, 1397, 1287, 1219, 1168, 1052, 841, 701, 594, 524, 450 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.79–2.04 (m, 8 H, CH_2), 6.77 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 7.22–7.25 (m, 2 H, CH_{Ar}), 7.29–7.46 (m, 5 H, CH_{Ar}), 10.35 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.2, 36.8, 95.8, 112.3, 115.4, 119.8, 127.2, 128.4, 129.4, 130.0, 130.6, 161.0, 177.9, 202.8.

MS (EI, 70 eV): m/z (%) = 306.1 (48, [M^+]), 265.1 (100, [M^+ – C_3H_5]), 194.1 (51), 121.0 (16).

HRMS (EI-MS): m/z (M^+) calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1252.

Reaction of *i*-Pr-α-X-Limno-CPs with Alkyllithium Reagents With *n*-BuLi

To a stirred solution of respective 3(2*H*)-furanone (5.0–20 mg, 14–73 μmol, 1.0 equiv) in anhyd THF (1.0 mL) was added a 1.6 M solution of *n*-BuLi in *n*-hexane (1.0 equiv) dropwise at –78 °C. Then H_2O (0.5 mL) was added, the mixture warmed to r.t., diluted with sat. aq $NaHCO_3$ (0.5 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and the solvent was evaporated to give the dihydrofuran, which decomposed within hours even at –20 °C. The yield was determined by dissolving the crude material in 600 μL of a 3.77 mM hexamethyldisilane (internal standard) solution in $CDCl_3$ or a 1.89 mM hexamethyldisilane solution in $CDCl_3$–C_6D_6 (1:1) in the case of phenyl compound **32a**, **32b**. Yields of compounds **26a**, **26b** and **28a**, **28b** were isolated yields of homogenous materials without internal standard, but were verified by using the internal standard.

4-Butylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-enes (26a, 26b)

Compound **7** (20 mg, 73 μmol, 1.0 equiv) gave 20 mg (64 μmol, 87%) of **26a**, **26b** as a colorless oil; R_f = 0.97 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2927, 1609, 1504, 1245, 1119, 1058, 953, 833, 770, 638, 601 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 312.3 (56, [M^+]), 283.2 (100), 241.2 (21), 121.0 (40).

HRMS (EI-MS): m/z (M^+) calcd for $C_{21}H_{28}O_2$: 312.2089; found: 312.2087.

26a

^1H NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.3 Hz, 3 H, CH_3, Bu), 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.43 (sext, J = 7.3 Hz, 2 H, CH_2, Bu), 1.61–1.66 (m, 2 H, CH_2), 1.78–1.85 (m, 2 H, CH_2), 1.90–1.96 (m, 2 H, CH_2), 2.06–2.10 (m, 2 H, CH_2), 2.13 (q, J = 7.3 Hz, 2 H, CH_2, Bu), 4.57 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.76 (dt, J = 7.4, 0.7 Hz, 1 H, =CH, Bu), 5.97 (d, J = 0.8 Hz, 1 H, =CH), 6.85 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 7.56 (d, J = 8.9 Hz, 2 H, CH_{Ar}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.8, 22.0, 23.4, 24.9, 31.5, 42.4, 69.9, 96.3, 97.5, 110.7, 115.6, 123.9, 126.8, 147.7, 158.4, 159.0.

26b

^1H NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.3 Hz, 3 H, CH_3, Bu) 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.43 (sext, J = 7.3 Hz, 2H, CH_2, Bu), 1.61–1.66 (m, 2H, CH_2), 1.78–1.85 (m, 2 H, CH_2), 1.90–1.96 (m, 2 H, CH_2), 2.06–2.10 (m, 2 H, CH_2), 2.13 (q, J = 7.3 Hz, 2 H, CH_2, Bu), 4.57 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 5.13 (t, J = 8.0 Hz, 1 H, =CH, Bu), 5.72 (s, 1 H, =CH), 6.85 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 7.49 (d, J = 8.9 Hz, 2 H, CH_{Ar}).

4-Butylidene-3-fluoro-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-enes (30a, 30b)

Compound **11** (7.7 mg, 27 μmol, 1.0 equiv) gave 4.6 mg (14 μmol, 52%) of **30a**, **30b**; R_f = 0.81 (SiO_2, hexanes–EtOAc, 5:1).

30a

^1H NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.41–1.49 (m, 2 H, CH_2, Bu), 1.58–1.68 (m, 3 H, CH_2), 1.77–2.02 (m, 5 H, CH_2), 2.34 (q, J = 7.5 Hz, 1 H, CH_2, Bu), 4.58 [sept, J = 6.0 Hz, 1 H, $(CH_3)_2CH$], 4.80 (t, J = 8.0 Hz, 1 H, =CH, Bu), 6.89 (d, J = 9.0 Hz, 2 H, CH_{Ar}), 7.62 (d, J = 8.9 Hz, 2 H, CH_{Ar}).

30b

^1H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.41–1.49 (m, 2 H, CH_2, Bu), 1.58–1.68 (m, 3 H, CH_2), 1.77–2.02 (m, 5 H, CH_2), 2.14 (q, J = 7.5 Hz, 1 H, CH_2, Bu), 4.57 [sept, J = 6.0 Hz, 1 H, $(CH_3)_2CH$], 5.16 (t, J = 8.1 Hz, 1 H, =CH, Bu), 6.89 (d, J = 9.0 Hz, 2 H, CH_{Ar}), 7.59 (d, J = 8.9 Hz, 2 H, CH_{Ar}).

30a, 30b

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.6, 13.8, 22.0, 23.7, 23.8, 24.5, 25.0, 29.3, 29.4, 39.9, 42.5, 69.9, 93.9 (d, J = 6.2 Hz), 94.6 (d, J = 8.4 Hz), 111.9 (d, J = 4.0 Hz), 112.6 (d, J = 7.6 Hz), 115.6, 122.0 (d, J = 5.8 Hz), 126.8 (d, J = 6.3 Hz), 127.0 (d, J = 6.9 Hz), 137.8 (d, J = 12.8 Hz), 137.9 (d, J = 14.8 Hz), 138.2 (d, J = 19.5

Hz), 141.1 (d, J = 21.2 Hz), 142.5 (d, J = 255.8 Hz), 143.8 (d, J = 257.5 Hz), 157.8, 158.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –174.4, –170.7.

MS (EI, 70 eV): m/z (%) = 330.2 (81, [M^+]), 301.2 (100), 259.1 (23), 121.0 (29).

HRMS (EI-MS): m/z (M^+) calcd for $C_{21}H_{27}FO_2$: 330.1995; found: 330.1993.

4-Butylidene-3-chloro-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-enes (31a, 31b)

Compound **12** (5.0 mg, 16 μmol, 1.0 equiv) gave 4.9 mg (14 μmol, 86%) of **31a**, **31b**; R_f = 0.61 (SiO_2, hexanes–EtOAc, 5:1).

MS (EI, 70 eV): m/z (%) = 346.2 (76, [M^+]), 317.1 (100), 121.0 (46).

HRMS (EI-MS): m/z (M^+) calcd for $C_{21}H_{27}ClO_2$: 346.1700; found: 346.1696.

31a

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.47 (sext, J = 7.4 Hz, 2 H, CH_2, Bu), 1.79–2.10 (m, 8 H, CH_2), 2.58 (q, J = 7.5 Hz, 2 H, CH_2, Bu), 4.59 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.88 (t, J = 7.9 Hz, 1 H, =CH, Bu), 6.89 (d, J = 9.0 Hz, 2 H, CH_{Ar}), 7.86 (d, J = 9.0 Hz, 2 H, CH_{Ar}).

31b

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.47 (sext, J = 7.4 Hz, 2 H, CH_2, Bu), 1.79–2.10 (m, 8 H, CH_2), 2.16 (q, J = 7.3 Hz, 2 H, CH_2, Bu), 4.59 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 5.26 (t, J = 8.1 Hz, 1 H, =CH, Bu), 6.89 (d, J = 9.0 Hz, 2 H, CH_{Ar}), 7.86 (d, J = 9.0 Hz, 2 H, CH_{Ar}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 22.0, 23.9, 25.2, 29.2, 40.0, 69.8, 95.3, 104.9, 114.4, 115.3, 122.5, 128.5, 143.3, 150.5, 158.4.

4-Butylidene-2-(4-isopropoxyphenyl)-3-phenyl-1-oxaspiro[4.4]non-2-enes (32a, 32b)

Compound **17** (5.0 mg, 14 μmol, 1.0 equiv) gave 1.8 mg (4.7 μmol, 33%) of **32a**, **32b**.

MS (EI, 70 eV): m/z (%) = 388.3 (89, [M^+]), 359.2 (100), 121.0 (91).

HRMS (EI-MS): m/z (M^+) calcd for $C_{27}H_{32}O_2$: 388.2402; found: 388.2404.

32a

^{1}H NMR (600 MHz, $CDCl_3$–C_6D_6, 1:1): δ = 0.61 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.01 or 1.03 or 1.05 [d, J = 6.0 Hz, 6 H, $(CH_3)_2CH$], 1.07–1.16 (m, 2 H, CH_2, Bu), 1.50–1.54 (m, 2 H, CH_2, Bu), 1.57–1.65 (m, 2 H, CH_2), 1.67–1.76 (m, 2 H, CH_2), 1.86–1.98, (m, 2 H, CH_2), 2.13–2.18 (m, 2 H, CH_2), 4.16 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.74 (t, J = 7.9 Hz, 1 H, =CH, Bu), 6.49 or 6.52 or 6.54 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 7.06–7.29 (m, 7 H, CH_{Ar}).

32b

^{1}H NMR (600 MHz, $CDCl_3$–C_6D_6, 1:1): δ = 0.78 (t, J = 7.4 Hz, 3 H, CH_3, Bu), 1.01 or 1.03 or 1.05 [d, J = 6.0 Hz, 6 H, $(CH_3)_2CH$], 1.19–1.26 (m, 2 H, CH_2, Bu), 1.57–1.65 (m, 2 H, CH_2), 1.67–1.76 (m, 2 H, CH_2), 1.86–1.98 (m, 2 H, CH_2), 1.99–2.04 (m, 2 H, CH_2, Bu), 2.13–2.18 (m, 2 H, CH_2), 4.11 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.83 (t, J = 8.0 Hz, 1 H, =CH, Bu), 6.49 or 6.52 or 6.54 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 7.06–7.29 (m, 7 H, CH_{Ar}).

With *n*-Hexyllithium

4-Hexylidene-2-(4-isopropoxyphenyl)-1-oxaspiro[4.4]non-2-enes (28a, 28b)

To a stirred solution of furanone **7** (5.0 mg, 18 μmol, 1.0 equiv) in anhyd THF (0.5 mL) was added dropwise a solution of 2.45 M *n*-HexLi in *n*-hexane (9.0 μL, 22 μmol, 1.2 equiv) at –78 °C. Workup and isolation of the product were done as in the case of *n*-BuLi. Dihydrofurans **28a**, **28b** were obtained as a colorless oil (6.2 mg, 18 μmol, 91%); R_f = 0.88 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 2924, 1608, 1503, 1245, 1179, 1119, 1057, 952, 834, 770, 637, 601 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 340.3 (38, [M^+]), 284.2 (20), 283.2 (100, [$M^+ - C_4H_9$]), 241.1 (19), 163.1 (17), 121.0 (35).

HRMS (EI-MS): m/z (M^+) calcd for $C_{23}H_{32}O_2$: 340.2402; found: 340.2397.

28a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3, Hex), 1.30–1.34 [m, 10 H, $(CH_3)_2CH$, CH_2, Hex), 1.38–1.43 (m, 2 H, CH_2, Hex), 1.60–1.66 (m, 2 H, CH_2), 1.77–1.84 (m, 2 H, CH_2), 1.89–1.97 (m, 2 H, CH_2), 2.06–2.10 (m, 2 H, CH_2), 2.14 (q, J = 7.4 Hz, 2 H, CH_2, Hex), 4.57 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.76 (dt, J = 7.3, 0.3 Hz, 1 H, =CH, Hex), 5.96 (d, J = 0.6 Hz, 1 H, =CH), 6.85 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 7.56 (d, J = 8.8 Hz, 2 H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.0, 22.6, 24.9, 29.5, 30.0, 31.5, 42.4, 69.9, 96.2, 97.5, 111.0, 115.6, 123.9, 126.8, 147.5, 158.4, 158.9.

28b

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3, Hex), 1.30–1.34 [m, 10 H, $(CH_3)_2CH$, CH_2, Hex], 1.38–1.43 (m, 2 H, CH_2, Hex), 1.60–1.66 (m, 2 H, CH_2), 1.77–1.84 (m, 2 H, CH_2), 1.89–1.97 (m, 2 H, CH_2), 2.06–2.10 (m, 2 H, CH_2), 2.14 (q, J = 7.4 Hz, 2 H, CH_2, Hex), 4.57 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 5.12 (t, J = 8.0 Hz, 1 H, =CH, Hex), 5.71 (s, 1 H, =CH), 6.85 (d, J = 8.8 Hz, 2 H, CH_{Ar}), 7.49 (d, J = 8.8 Hz, 2 H, CH_{Ar}).

With MeLi

2-(4-Isopropoxyphenyl)-4-methylene-1-oxaspiro[4.4]non-2-ene (29)

To a stirred solution of furanone **7** (5.0 mg, 18 μmol, 1.0 equiv) in anhyd THF (0.5 mL) was added dropwise a 1. 6 M solution of MeLi in Et_2O (12 μL, 18 μmol, 1.0 equiv) at –78 °C. The reaction was worked up as described for the reaction of **7** with *n*-BuLi. Dihydrofuran **29** was obtained in 38% yield (1.9 mg, 7.0 μmol); R_f = 0.92 (SiO_2, hexanes–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 [d, J = 6.1 Hz, 6 H, $(CH_3)_2CH$], 1.65–2.15 (m, 8 H, CH_2), 4.38 (s, 1 H, =CH_2), 4.58 [sept, J = 6.1 Hz, 1 H, $(CH_3)_2CH$], 4.69 (s, 1 H, =CH_2), 5.88 (s, 1 H, =CH), 6.86 (d, J = 8.9 Hz, 2 H, CH_{Ar}), 7.55 (d, J = 8.9 Hz, 2 H, CH_{Ar}).

With PhLi and *t*-BuLi

The reactions of furanone **7** (1.0 equiv) with 1.8 M PhLi in Bu_2O (1 equiv) or 1.6 M *t*-BuLi in pentane (1 equiv) were carried out as described for the *n*-BuLi. No product was observed.

1-{1-[2-(4-Isopropoxyphenyl)ethyl]pentyl}cyclopentanol (27)

To a stirred solution of dihydrofurans **26a**,**26b** (20 mg, 64 μmol, 1.0 equiv) in anhyd EtOAc (0.5 mL) was added 10% Pd/C (6.8 mg, 6.4 μmol, 0.1 equiv) at r.t. The mixture was stirred under H_2 atmosphere for 2 h. Filtration and evaporation of the solvent gave pure tertiary alcohol **27** as a colorless oil (18 mg, 57 μmol, 89%); R_f = 0.61 (SiO_2, hexanes–EtOAc, 5:1).

IR (neat): 3421, 2928, 1509, 1239, 1179, 632, 536, 497 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.31–1.35 [m, 11 H, $(CH_3)_2CH$], 1.40–1.44 (m, 1 H), 1.53–1.66 (m, 9 H), 1.76–1.83 (m, 3 H), 2.54 (ddd, *J* = 13.8, 10.8, 6.1 Hz, 1 H, $ArCH_2$), 2.69 (ddd, *J* = 13.8, 11.0, 5.3 Hz, 1 H, $ArCH_2$), 4.57 [sept, *J* = 6.1 Hz, 1 H, $(CH_3)_2CH$], 6.81 (d, *J* = 8.6 Hz, 2 H, CH_{Ar}), 7.09 (d, *J* = 8.6 Hz, 2 H, CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.1, 23.3, 23.8, 30.8, 31.2, 33.5, 34.3, 38.6, 38.7, 47.2, 69.9, 86.2, 115.9, 129.2, 135.0, 155.9.

MS (EI, 70 eV): *m*/*z* (%) = 318.2 (6, [M^+]), 162.1 (100), 120.0 (74), 107.0 (43).

HRMS (EI-MS): *m*/*z* (M^+) calcd for $C_{21}H_{34}O_2$: 318.2559; found: 318.2559.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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