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Intramolecular Base-Free Catalytic Wittig Reaction: Synthesis of Benzoxepinones

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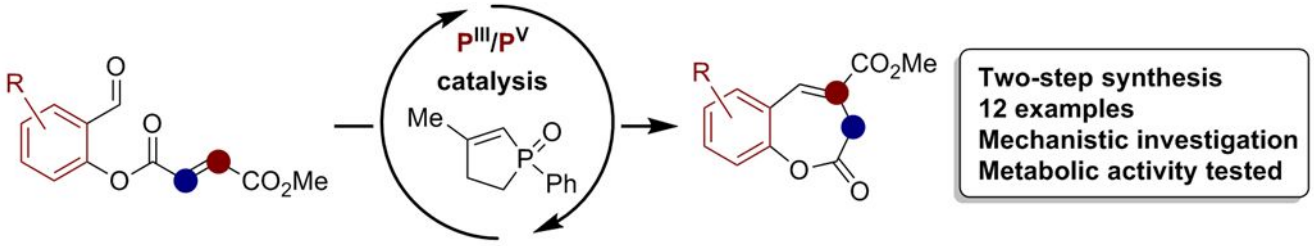
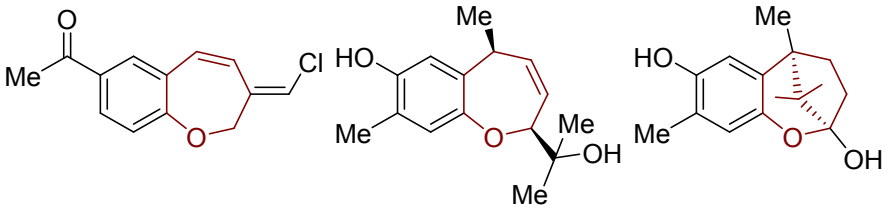


ABSTRACT

A straightforward two-step synthesis of benzoxepinones was developed via base-free phosphane-catalyzed Wittig reaction. 3-Methyl-1-phenyl-2-phospholene 1-oxide was used as a precatalyst and trimethoxysilane as a reducing agent. Additionally benzoic acid is employed as a catalyst to facilitate the reduction of the phosphane oxide. Mechanistic investigation revealed the formation of a coumarin as a side product, which was identified via 2D NMR experiments. First results of metabolic activity tests on the prepared benzoxepinones are reported.

INTRODUCTION

The Wittig reaction between phosphonium ylides and ketones or aldehydes is among the most frequently used methods for the synthesis of alkenes.[1, 2] A disadvantage of the Wittig reaction is the need of a relatively strong base to generate stoichiometric amount of phosphonium ylide: these conditions are not compatible with base-sensitive substrates.[3-5] Furthermore, the formation of stoichiometric phosphane oxide waste from the phosphonium ylide not only complicates purification of the product, but also reduces the atom economy of the Wittig reaction.[6, 7] The latter disadvantage was mitigated by the introduction of Wittig reaction conditions, employing catalytic amount of phosphane.[8, 9] Several applications of the phosphane-catalyzed Wittig reaction were reported since then,[10, 11] however the presence of stoichiometric base was still required in these works. Lee et al. were the first to accomplish an intramolecular Wittig reaction using catalytic amount of base.[12] Recently, we have developed a base-free intermolecular phosphane-catalyzed Wittig reaction, which proceeded under virtually neutral conditions.[13, 14] The base-free phosphane-catalyzed Wittig reaction has already been used for the synthesis of pyrrolizine and indole derivatives.[15] Herein, we report an application of our base-free phosphane-catalyzed Wittig reaction in the synthesis of benzoxepinones, synthetically valuable and easy-to-modify precursors of benzoxepines.[16-23]



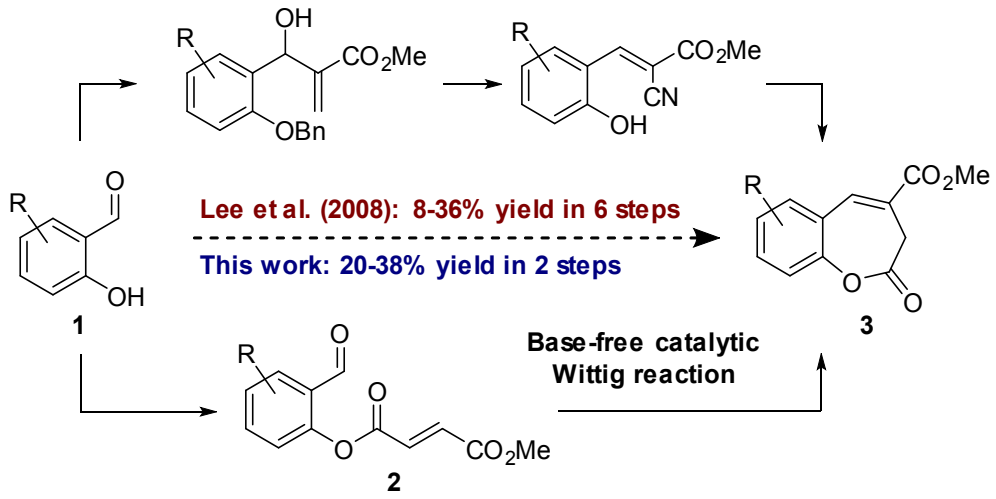
Pterulone **Heliannuol B** **Enokipodin A**

Figure 1. Natural products based on benzoxepine core.

The benzoxepine scaffold is encountered in a number of biologically active natural products.[24-29] For example, fungi metabolite pterulone has antibacterial properties,[30] and Enokipodin A , a sesquiterpenoid from enokitake, shows antimicrobial activity.[24] Further, Heliannuol B was isolated from sunflowers showing allelopathic activity[29] (Figure 1). Furthermore, several benzoxepine derivatives have been synthesized as anticancer drugs.[31,

[32] Thus, we were interested in developing an efficient synthetic route to access the benzoxepine scaffold and evaluate the anti-proliferative activities. Benzoxepinones have been synthesized by Lewis-acid mediated rearrangement of dihydrofurans[33] or from cyclobutanone by rhodium-catalyzed C–C bond cleavage in the presence of CO.[34] These heterocycles were also prepared in a long six-step sequence from 2-hydroxybenzaldehyde derivatives in 8–36 % overall yield (Scheme 1).[35] We realized that the long synthetic route from 2-hydroxybenzaldehyde (**1a**) could be reduced to a two-step sequence comprising an initial formation of ester **2a**, followed by an intramolecular base-free catalytic Wittig as the key step (Scheme 1).

Scheme 1. Synthesis of Benzoxepinones from salicylic aldehydes.



RESULTS AND DISCUSSION

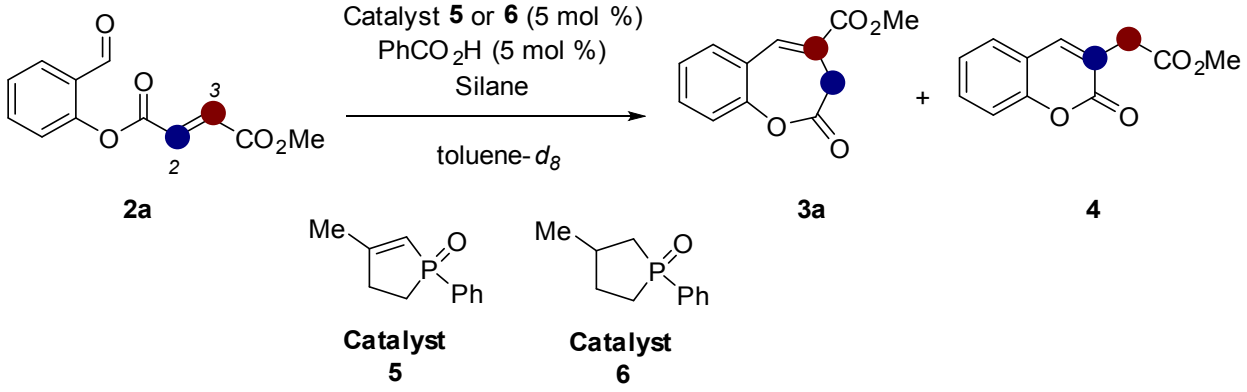
The Wittig reaction conditions from our previously published work[13] were employed as the starting point for the development of cyclization of **2a** to benzoxepinone **3a**. Accordingly, the use of Bu_3P as a catalyst, phenylsilane as a reducing agent, benzoic acid as an additive and toluene as a solvent afforded the desired benzoxepinone **3a** in 27% yield (Table 1, entry 1). The cyclization without the added benzoic acid led to slightly improved yield (34%, entry 2). Further improvement was achieved by using phospholene **5** as the catalyst and $(MeO)_3SiH$ as

the reducing agent leading to **3a** in 41% yield under previously reported conditions[14] (entry 3). Structurally closely related phospholane **6** was equally efficient as the catalyst (38%, entry 4). Variations in the amount of catalyst **5** had minor influence on the yield of lactone **3a**. Thus, both increased (10 mol %) and reduced (2.5 mol %) catalyst loading afforded comparable yield of lactone **3a**.[36] Further decrease of the catalyst amount to 1 mol % resulted in an incomplete conversion of **2a**.[36] Phenylsilane and hexylsilane were less efficient as reducing agents compared to $(MeO)_3SiH$ (19% and 33%, respectively; see entries 5 and 6). Variations of $(MeO)_3SiH$ amount did not improve the yield of **3a**.[36] Attempted cyclization of **2a** in various solvents such as 1,4-dioxane, THF and MeOH resulted in reduced yields of the desired benzoxepinone **3a**.[36] Prolongation of the reaction time to 48 h decreased the yield of lactone **3a** to 33% (entry 7). Variations of the cyclization temperature did not help to increase yield of lactone **3a**. Thus, lowering the temperature to 80 °C gave 25% of **3a** (entry 8), whereas at higher temperature (120 °C) lactone **3a** was formed in 33% yield (entry 9). Interestingly, microwave heating allowed for the full conversion to be achieved within 3 h, giving the desired lactone **3a** in 38% yield (entry 10).

We hypothesized that moderate yields of the desired lactone **3a** could be attributed to the concomitant formation of a six-membered side product **4** under all tested conditions (Table 1). Indeed, the formation of coumarin **4** (up to 10%) was observed using Bu_3P as a catalyst (entries 1 and 2). The 6-membered side product **4** was separated from the desired lactone **3a** by chromatography on silica gel and isolated in a pure form. Coumarin **4** was not observed by NMR under the phospholene-catalyzed cyclization conditions (entry 3). However, its formation cannot be excluded, because a control experiment showed that coumarin **4** is not stable under the phospholene-catalyzed cyclization conditions (entry 3), and it undergoes rapid decomposition. Possibly, the formation of transient coumarin **4** consumes the starting aldehyde **2a**, thus leading to moderate yields of the desired benzoxepinone **3a**. We also realized that the undesired Michael addition of phospholene **5** to position 2 of fumarate **2a**

(See graphics of Table 1) could be avoided by the replacement of methoxycarbonyl moiety in **2a** with *N,N*-dialkylamide group. The presence of the less electron-withdrawing *N,N*-dialkylamide substituent could improve the regioselectivity of Michael addition, favoring the addition to position 3 of fumarate, which leads to the desired benzoxepinone. Unfortunately, *N,N*-diethylamide moiety-containing analog of **2a** turned out to be unstable, and it underwent rapid decomposition under the standard Wittig cyclization conditions.

Table 1. Catalyst screening and optimization of the reaction conditions.



entry	cat. (5 mol %)	silane (equiv)	*T* (°C)	*T* (h)	yield **3a** (%)[a]
1[b]	Bu_3P	$PhSiH_3$ (1)	125	24	27
2[c]	Bu_3P	$PhSiH_3$ (1)	125	24	34
3	**5**	$(MeO)_3SiH$ (3)	100	16	41
4	**6**	$(MeO)_3SiH$ (3)	100	16	38
5	**5**	$PhSiH_3$ (3)	100	16	19
6	**5**	$HexylSiH_3$ (3)	100	16	33
7	**5**	$(MeO)_3SiH$ (3)	100	48	33
8	**5**	$(MeO)_3SiH$ (3)	80	20	25
9	**5**	$(MeO)_3SiH$ (3)	120	20	33
10[d]	**5**	$(MeO)_3SiH$ (3)	100	3	38

[a]Yield was determined by NMR with mesitylene as an internal standard. [b]Lactone **4** was formed as a side product (10%). [c]Without $PhCO_2H$; 6-membered lactone **4** (9%) was formed. [d]Microwave heating was used.

Structures of both benzoxepinone **3a** and chromenone **4** were confirmed by NMR experiments. Thus, an NOE correlation between the lactone proton H^A (7.68 ppm) and aliphatic protons H^B and $H^{B'}$ (3.60 ppm) was observed for coumarin **4** (Figure 2). In contrast, the NOE crosspeaks between protons H^A and H^B could not be seen for the benzoxepinone **3a**. Additional structural support for the formation of lactone **3a** was obtained by X-ray crystallographic analysis.[36]

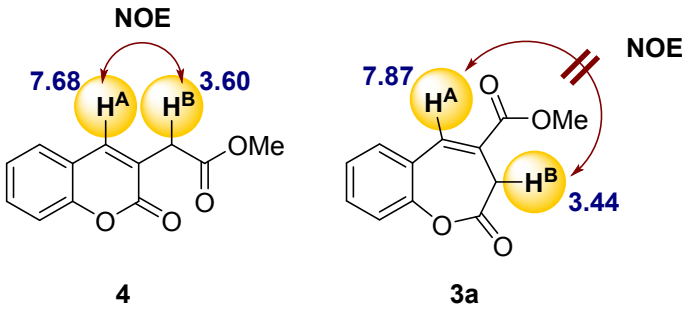
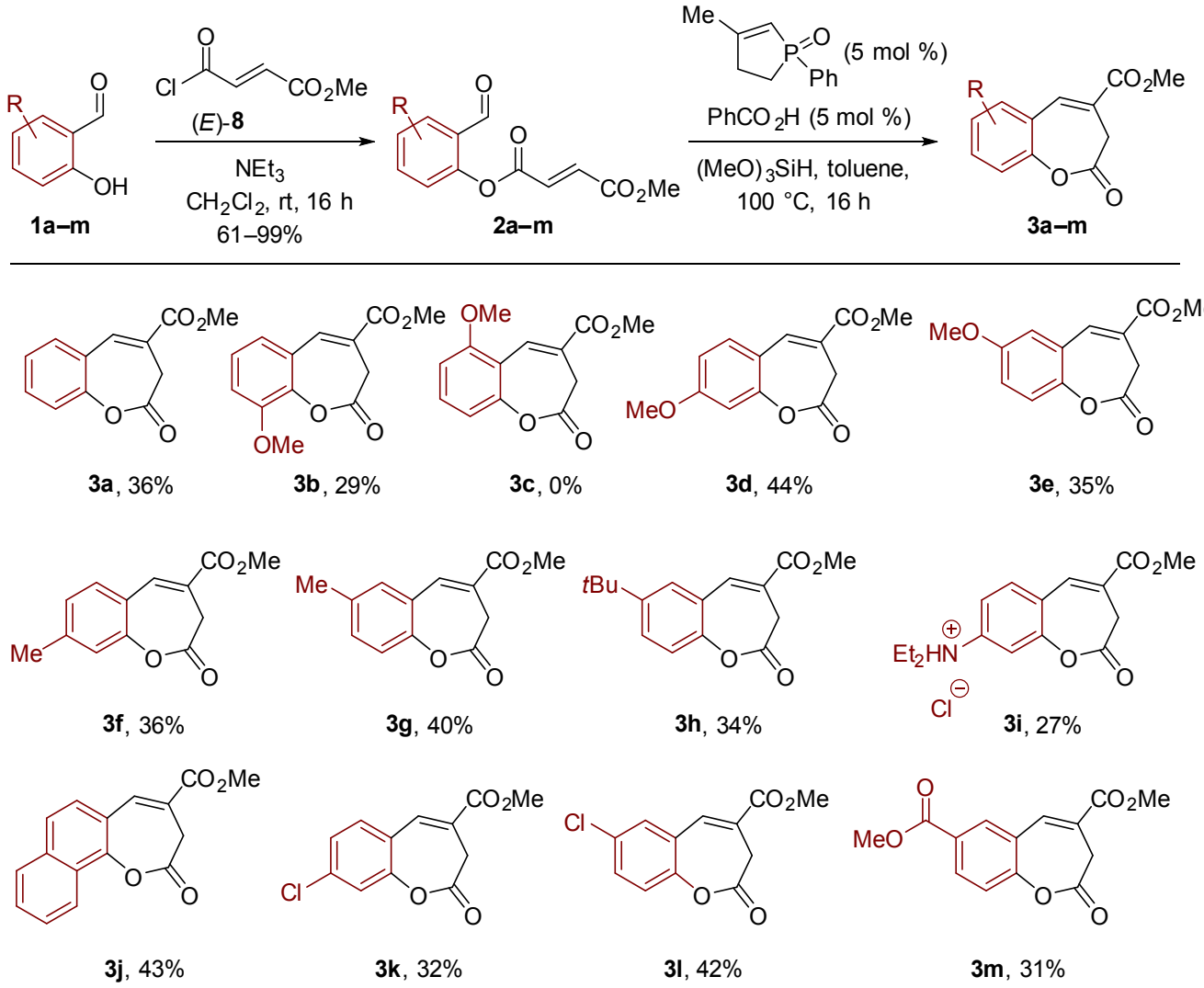


Figure 2. NOESY experiments for benzoxepinone **3a** and coumarin **4**.

To evaluate the substrate scope and limitations a series of substituted 2-formylphenyl fumarates **2a–m** were prepared from various 2-hydroxybenzaldehydes **1a–m** (Scheme 2). Under standard base-free catalytic Wittig reaction conditions esters **2a–m** were transformed into lactones **3a,b,d–m** (Scheme 2). It has to be mentioned that O-acylation of acceptor substituted substrates proved to be difficult. Moreover, the conversion of the respective esters under the standard reaction conditions usually led to complex reaction mixtures due to side reactions such as reduction of the aldehyde. However, aldehydes **2a**–**h** with electron donating substituents such as MeO, methyl and *t*-Bu groups as well as with electron-withdrawing substituents such as chloride (**3k** and **3l**), ester moiety (**3m**) and protonated amine (**3i**) afforded heterocycles **3a**–**m** in 27-44% yield. An exception is substrate **2c**, which contains a methoxy substituent in the ortho position to the aldehyde. In this case no formation of

benzoxepinone **3c** was observed. In contrast, aldehyde **2b** and **2j** possessing a substituent ortho to the phenolic oxygen are suitable as substrates for the base-free Wittig reaction.

Scheme 2. Substrate scope of the intramolecular base-free catalytic Wittig reaction.[a]

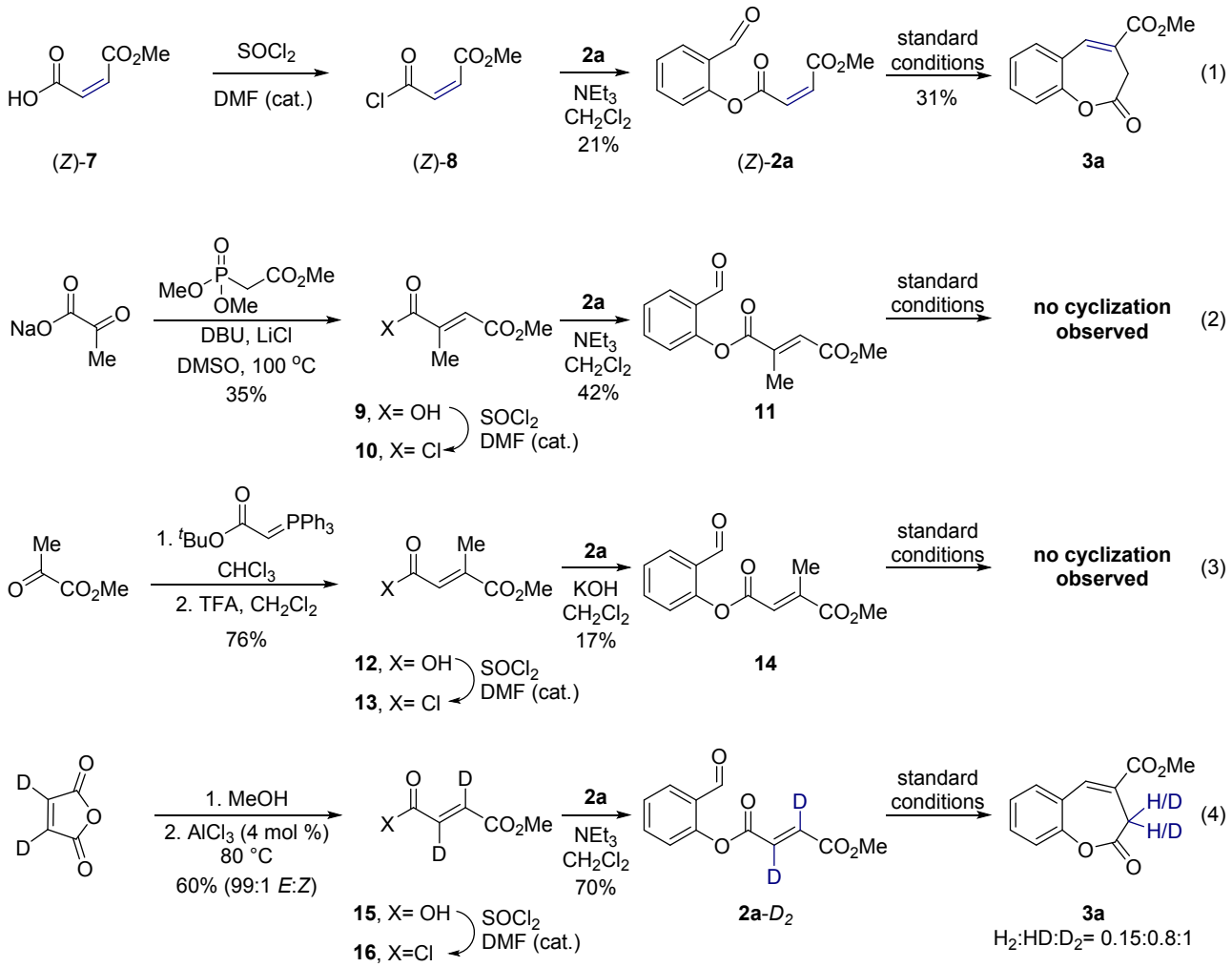


[a]Standard reaction conditions: **2a–m** (1.00 equiv), catalyst **5** (0.05 equiv), co-catalyst $PhCO_2H$ (0.05 equiv), silane (3.00 equiv), toluene (0.5 M), 100 °C for 16 h. Isolated yields are given.

To gain more insight into the reaction mechanism, we synthesized *Z*-isomer (***Z*-2a**) of the model substrate. Under the standard reaction conditions, the same reactivity was observed and NMR experiments showed no significant difference in the reaction outcome for ***E*-2a** and ***Z*-2a** (Scheme 3). Additionally, compounds **11** and **14** were also prepared as substrates for the cyclization. Ester **11** was synthesized by an initial reaction of sodium pyruvate with trimethyl phosphonoacetate under Horner-Emmons conditions, followed by formation of acid chloride **10** and condensation with aldehyde **2a** (Scheme 3). The first step in the synthesis of isomeric

ester **14** was the condensation of methyl pyruvate with phosphorus ylide under Wittig reaction conditions. Subsequent synthesis involved the formation of acid chloride **13** and condensation with **2a** (Scheme 3, equations 2 and 3). Unfortunately, the formation of the cyclization product from both esters **11** and **14** was not observed under the standard Wittig reaction conditions and only starting material or a mixture of several side products were observed. This is likely due to the increased steric hindrance hampering the initial step (the Michael addition of the phosphane).

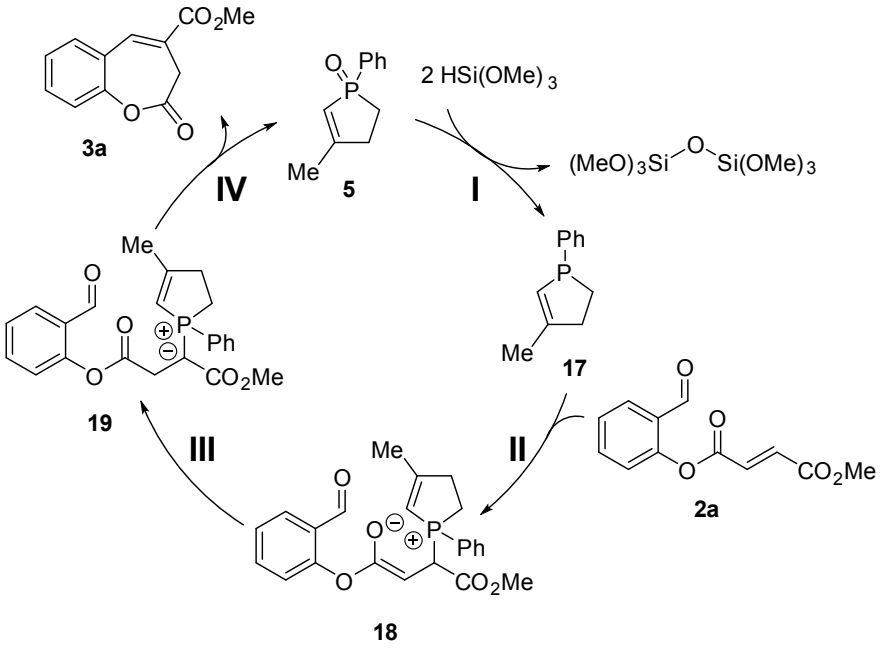
Scheme 3. Control experiments and investigation of the reaction mechanism.



Based on our previous findings and the above control experiments, a plausible catalytic cycle starts with the reduction of precatalyst **5** to phosphane **17** (step I, Scheme 4). This is probably promoted by the Brønsted acid additive.[13, 37, 38] The second step is the Michael

addition of the in situ formed phosphane to the activated olefin **2a**, which leads to the formation of enolate **18** (step II).[14] The product of the Michael addition was not observed by in situ NMR spectroscopy. However, the control experiments with the corresponding *Z* isomer (***Z*-2a**) clearly indicate the formation of such an adduct. Subsequent 1,2-proton shift or a protonation/ deprotonation sequence generates ylide **19**. This step might also be catalyzed by the Brønsted acid (step III).[39, 40] Finally, the intramolecular Wittig reaction between the aldehyde and the phosphonium ylide affords the desired lactone **3a** and liberates precatalyst **5**, which re-enters the catalytic cycle (step IV).

Scheme 4. Plausible catalytic cycle for intramolecular base-free catalytic Wittig reaction.



To gain more insight into the reaction mechanism, we synthesized the deuterated analogue **2a-D_2** in a three-step sequence from maleic anhydride-d_2 (Scheme 3, equation 4). Under the standard reaction conditions a significant amount of hydrogen in the product **3a** at the α-position was observed, excluding a purely intramolecular mechanism of the ylide formation. Other control experiments using a 1:1 mixture of **2a-H_2** and **2a-D_2** as starting materials showed a similar result, indicating at least a partial involvement of another molecule in the ylide forming step. For this reason, we investigated the reaction using $PhCO_2D$ (50 mol

%) as a Brønsted acid additive and could detect a significantly increased deuterium incorporation in the product.[36] Apparently, the Brønsted acid additive is involved in the formation of ylide **19** from enolate **18** (step III, see Scheme 4), however extensive mechanistic studies are required to get better insight into this intriguing mechanistic question.

Due to the use of benzoxepine derivates as anticancer drugs, we investigated the anti-proliferative activities of the synthesized substrates **3a, b, d–m** using human leukemia cell line SEM as an experimental model.[36] The data was obtained from one experiment performed in triplicates. Our results demonstrated that none of the tested compound influenced metabolic activity compared to DMSO treated control cells (= 100%) significantly.[36] Metabolic activity in the compound-treated cells ranged from 95.1 to 108.5 (5 μM) as well as from 91.0 to 108.5 (10 μM). However further studies concerning the biological activity of these compounds are currently in progress.

CONCLUSION

Herein we reported a straightforward two-step synthesis of benzoxepinones from 2-hydroxybenzaldehydes using an intramolecular base-free catalytic Wittig reaction. A commercially available phospholene oxide was used as a precatalyst (5 mol %) in a combination with benzoic acid as co-catalyst (5 mol %) and trimethoxysilane as a reducing agent. Moderate cyclization yields (29–44%) are compensated by the short synthesis and simplified workup due to the reduced amounts of phosphane and phosphaneoxide byproduct (5 mol %).

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used as received without further purification. Thin layer chromatography was performed on *Merck* TLC-plates with fluorescence indication (silica type 60, F_{254}), spots were visualized using UV-

light or $KMnO_4$ stains. Flash chromatography was performed using silica with a grain size of 40–63 µm from *Macherey-Nagel*. Deuterated chloroform was purchased from *Deutero*. NMR spectra were recorded on *Bruker 300 Fourier*, *Bruker AV 300* and *Bruker AV 400* spectrometers. The chemical shifts (δ) for ^1H and ^{13}C in $CDCl_3$ are given in parts per million (ppm) and referenced to 7.26 and 77.16 ppm, respectively. Coupling constants are expressed in Hertz (Hz). The following abbreviations are used: s= singlet, d= doublet, t= triplet, q= quadruplet, m= multiplet. IR spectra were recorded on a *Nicolet iS10 MIR* FT-IR-spectrometer from *Thermo Fisher Scientific*. Gas chromatography was performed on *Agilent 7890A GC System*, mass spectra were measured on downstream *5975C inert XL MSD* mass detector also from *Agilent*. Elementary analysis was performed on a *TruSpec CHNS Micro* from *Leco*. High resolution mass spectra (HRMS) were obtained either from a *MAT 95 XP* from *Thermo* (EI) or from an *HPLC system 1200* and downstream *ESI-TOF-MS 6210* from *Agilent* (ESI).

General procedure 1 (GP1) for the synthesis of fumarates 2a-m. Fumaric acid monomethyl ester (1 equiv) was dissolved in CH_2Cl_2 (2 mL·mmol^{-1}). After DMF (0.03 mL·mmol^{-1}) was added the mixture was cooled to 0 °C and thionyl chloride (1.1 equiv) was added dropwise. The resulting mixture was refluxed for 3 h. The solvent was distilled off and the obtained (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride *(E)*-**8** was used without further purification. Salicylderivative **1a–m** (1 equiv) was dissolved in CH_2Cl_2 (5 mL·mmol^{-1}) and acid chloride (*E*)-**8** (1.1–2.0 equiv) was added dropwise. The mixture was cooled to 0 °C and NEt_3 (1.6–2.0 equiv) was added dropwise. The resulting mixture was stirred at 23 °C for 16 h. The mixture was carefully quenched with H_2O (2.5 mL·mmol^{-1}) and washed with saturated aqueous $KHCO_3$ solution (2 × 2.5mL·mmol^{-1}). The organic layer was dried over Na_2SO_4. All volatiles were removed in vacuum and the product was purified by column chromatography on silica gel (cyclohexane:EtOAc).

2-Formylphenyl methyl fumarate (**2a**).[41] Obtained according GP1 from 2-hydroxybenzaldehyde (**1a**, 500 mg, 0.44 mL, 4.09 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 668 mg, 4.50 mmol) and NEt_3 (662 mg, 0.91 mL, 6.54 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc= 20:1) gave **2a** as a yellow oil (925 mg, 3.95 mmol, 97 %). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.32; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.87 (s, 3H), 7.08 (d, 1H, *J* = 15.8 Hz), 7.13 (d, 1H, *J* =15.8 Hz), 7.23–7.26 (m, 1H), 7.43–7.48 (m, 1H), 7.65–7.70 (m, 1H), 7.92 (dd, 1H, *J* = 7.7, 1.7 Hz), 10.10 (s, 1H).

2-Formyl-6-methoxyphenyl methyl fumarate (**2b**). Obtained according GP1 from 2-hydroxy-4-methoxybenzaldehyde (**1b**, 400 mg, 2.63 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 430 mg, 2.89 mmol) and NEt_3 (426 mg, 0.59 mL, 4.21 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) gave **2b** as a colorless solid (605 mg, 2.29 mmol, 87%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.18; Mp 122–124 °C; IR (neat, cm^{-1}): 1721 (C=O), 1694 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 3.37 (s, 3H), 7.08 (d, 1H, *J* = 15.8 Hz), 7.15 (d, 1H, *J* = 15.8 Hz), 7.22–7.26 (m, 1H), 7.34–7.41 (m, 1H), 7.46–7.50 (m, 1H), 10.11 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, δ): 52.7, 56.5, 118.0, 121.6, 127.4, 129.2, 132.1, 135.6, 140.9, 151.7, 162.7, 165.2, 188.5. HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_6$ $[M]^+$ 264.0628, found 264.0628; MS (EI, 70 eV): m/z (%) = 264 (2) $[M^+]$, 152 (15), 113 (100), 85 (19), 54 (12), 40 (41).

2-Formyl-3-methoxyphenyl methyl fumarate (**2c**). Obtained according GP1 from 2-hydroxy-6-methoxybenzaldehyde (**1c**, 400 mg, 2.63 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 430 mg, 2.89 mmol) and NEt_3 (426 mg, 0.59 mL, 4.21 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) gave **2c** as a colorless solid (546 mg, 2.07 mmol, 79%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.18; IR (neat, cm^{-1}): 1720 (C=O), 1684 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.84 (s, 3H), 3.94 (s, 3H), 6.71–6.74 (m, 1H), 6.92–6.95 (m, 1H), 7.04 (d, 1H, *J* = 15.8 Hz), 7.10 (d, 1H, *J* = 15.8 Hz), 7.53–7.58 (m, 1H), 10.40–10.41 (m, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$, δ): 52.5, 56.4, 110.0, 115.6, 117.0,

133.0, 135.0, 135.9, 150.0, 163.26, 163.34, 165.4, 188.1. Anal. calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.08; H, 4.51.

2-Formyl-5-methoxyphenyl methyl fumarate (**2d**). Obtained according GP1 from 2-hydroxy-3-methoxybenzaldehyde (**1d**, 400 mg, 2.63 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 430 mg, 2.89 mmol) and NEt_3 (426 mg, 0.59 mL, 4.21 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) gave **2d** as a colorless solid (472 mg, 1.79 mmol, 68%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.18; Mp 90–92 °C; IR (neat, cm^{-1}): 1723 (C=O), 1681 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 3.89 (s, 3H), 6.72 (d, 1H, *J* = 2.4 Hz), 6.93 (dd, 1H, *J* = 8.7, 2.4 Hz), 7.06 (d, 1H, *J* = 15.8 Hz), 7.12 (d, 1H, *J* = 15.8 Hz), 7.83 (d, 1H, *J* = 8.7 Hz), 9.93 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 52.7, 56.1, 108.8, 112.7, 121.5, 132.3, 133.7, 135.7, 152.6, 163.1, 165.1, 165.3, 187.3. HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_6$ $[M]^+$ 264.0628, found 264.0627; MS (EI, 70 eV): m/z (%) = 264 (1) $[M^+]$, 232 (9), 151 (19), 113 (29), 40 (100).

2-Formyl-4-methoxyphenyl methyl fumarate (**2e**). Obtained according GP1 from 2-hydroxy-5-methoxybenzaldehyde (**1e**, 400 mg, 2.63 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 430 mg, 2.89 mmol) and NEt_3 (426 mg, 0.59 mL, 4.21 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1). After recrystallization from EtOH compound **2e** was obtained as a light yellow solid (560 mg, 2.12 mmol, 81%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.29; Mp 76–78 °C; IR (neat, cm^{-1}): 1726 (C=O), 1693 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 3.87 (s, 3H), 7.06 (d, 1H, *J* = 15.8 Hz), 7.12 (d, 1H, *J* = 15.8 Hz), 7.13–7.21 (m, 2H), 7.36–7.38 (m, 1H), 10.07 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 52.7, 56.0, 113.4, 122.1, 124.3, 128.4, 132.3, 135.7, 145.1, 158.0, 163.7, 165.1, 188.0. HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_6Na$ $[M+Na]^+$ 287.0526, found 287.0526; MS (EI, 70 eV): m/z (%) = 264 (8) $[M^+]$, 152 (37), 113 (100), 85 (13), 54 (20), 40 (32).

2-Formyl-5-methylphenyl methyl fumarate (**2f**). Obtained according GP1 from 2-hydroxy-4-methylbenzaldehyde (**1f**, 400 mg, 2.94 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid

chloride ((*E*)-**8**, 480 mg, 3.23 mmol) and NEt_3 (476 mg, 0.66 mL, 4.70 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) gave **2f** as a yellow oil (**2f**, 625 mg, 2.52 mmol, 86%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.34; IR (neat, cm^{-1}): 1726 (C=O), 1692 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.44 (s, 3H), 3.86 (s, 3H), 7.02–7.04 (m, 1H), 7.06 (d, 1H, *J* = 15.8 Hz), 7.12 (d, 1H, *J* = 15.8 Hz), 7.21–7.26 (m, 1H), 7.75–7.82 (m, 1H), 10.02 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 21.9, 52.6, 123.8, 125.6, 127.9, 131.8, 132.4, 135.6, 147.3, 150.8, 163.3, 165.1, 188.2. HRMS-ESI (m/z) calcd for $C_{13}H_{13}O_5$ $[M+H]^+$ 249.0758, found 249.0760. MS (EI, 70 eV): m/z (%) = 216 (17), 135 (21), 113 (54), 40 (100).

2-Formyl-4-methylphenyl methyl fumarate (**2g**). Obtained according GP1 from 4-methyl-2-hydroxybenzaldehyde (**1g**, 500 mg, 3.67 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 818 mg, 5.51 mmol) and NEt_3 (594 mg, 0.82 mL, 5.87 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 3:1) gave **2g** as a yellow oil (875 mg, 3.52 mmol, 96%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.42; IR (neat, cm^{-1}): 1724 (C=O), 1684 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.43 (s, 3H), 3.85 (s, 3H), 7.06 (d, 1H, *J* = 15.8 Hz), 7.11 (d, 1H, *J* = 15.8 Hz), 7.12 (d, 1H, *J* = 8.2 Hz), 7.43–7.48 (m, 1H), 7.68–7.70 (m, 1H), 10.05 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 20.9, 52.7, 123.1, 127.5, 131.8, 132.4, 135.6, 136.1, 137.0, 148.9, 163.4, 165.1, 188.7. Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.91; H, 4.97. MS (EI, 70 eV): m/z (%) = 248 (1) $[M^+]$, 216 (13), 135 (26), 113 (100), 85 (17), 59 (17), 44 (11).

4-(tert-Butyl)-2-formylphenyl methyl fumarate (**2h**). Obtained according GP1 from 5-*tert*-butyl-2-hydroxybenzaldehyde (**1h**, 450 mg, 2.52 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 561 mg, 3.78 mmol) and NEt_3 (581 mg, 0.63 mL, 4.54 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 20:1) gave **2h** as a yellow oil (661 mg, 2.46 mmol, 90%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.45; IR (neat, cm^{-1}): 1729 (C=O), 1691 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 1.36 (s, 9H), 3.86 (s, 3H), 7.07 (d, 1H, *J* = 15.8 Hz), 7.13 (d, 1H, *J* = 15.8 Hz), 7.16 (d, 1H, *J* = 8.6 Hz), 7.68 (dd, 1H, *J* = 8.6, 2.6 Hz), 7.90 (d,

1H, *J* = 2.6 Hz), 10.09 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, δ): 31.3, 34.9, 52.7, 122.8, 127.3, 128.3, 132.4, 132.8, 135.6, 148.8, 150.3, 163.5, 165.1, 188.9. Anal. calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.33; H, 6.18; MS (EI, 70 eV): m/z (%) = 290 (7) [M^+], 258 (9), 177 (18), 163 (25), 113 (95), 85 (11), 40 (100).

5-(Diethylamino)-2-formylphenyl methyl fumarate (**2i**). Obtained according GP1 from 4-diethylamino-2-hydroxybenzaldehyde (**1i**. 500 mg, 2.59 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 576 mg, 3.88 mmol) and NEt_3 (459 mg, 0.58 mL, 4.14 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 3:1) gave **2i** as a green oil (580 mg, 1.90 mmol, 73%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.21; IR (neat, cm^{-1}): 1762 (C=O), 1711 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.21 (t, 6H, *J* = 7.2 Hz), 3.42 (q, 4H, *J* = 7.2 Hz), 3.85 (s, 3H), 6.31 (d, 1H, *J* = 2.5 Hz), 6.57 (dd, 1H, *J* = 8.9, 2.5 Hz), 7.06 (d, 1H, *J* = 15.8 Hz), 7.12 (d, 1H, *J* = 15.8 Hz), 7.66 (d, 1H, *J* = 8.9 Hz), 9.73 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, δ): 12.6, 45.0, 52.6, 104.3, 108.9, 116.0, 132.9, 134.3, 135.1, 153.1, 153.2, 163.4, 165.3, 186.4. Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.94; H, 6.28; N, 4.73. MS (EI, 70 eV): m/z (%) = 305 (24) [M^+], 290 (52), 281 (24), 193 (16), 178 (76), 150 (13), 113 (12), 73 (21), 44 (100).

2-Formylnaphthalen-1-yl methyl fumarate (**2j**). Obtained according GP1 from 1-hydroxy-2-naphthylaldehyde (**1j**, 400 mg, 2.32 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 520 mg, 3.48 mmol) and NEt_3 (376 mg, 0.52 mL, 3.71 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 20:1). After recrystallization from EtOH compound **2j** was obtained as a colorless solid (400 mg, 1.41 mmol, 61%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.37; Mp 113–115 °C; IR (neat, cm^{-1}): 1719 (C=O), 1675 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.90 (s, 3H), 7.22 (d, 1H, *J* = 15.8 Hz), 7.30 (d, 1H, *J* = 15.8 Hz), 7.50–7.71 (m, 2H), 7.85–7.97 (m, 4H), 10.25 (s, 1H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$, δ): 52.8, 122.6, 124.1, 124.3, 126.7, 127.2, 127.9, 128.5, 129.8, 131.8, 136.4, 137.6, 149.6,

163.4, 165.0, 188.4. Anal. calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.55; H, 4.04; MS (EI, 70 eV): m/z (%) = 284 (2) [M^+], 172 (13), 113 (57), 40 (100).

5-Chloro-2-formylphenyl methyl fumarate (**2k**). Obtained according GP1 from 4-chloro-2-hydroxybenzaldehyde (**1k**, 400 mg, 2.55 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 568 mg, 3.83 mmol) and NEt_3 (476 mg, 0.57 mL, 4.08 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) gave **2k** as a colorless solid (, 474 mg, 1.91 mmol, 69%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.42; Mp 91–93 °C; IR (neat, cm^{-1}): 1715 (C=O), 1695 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.87 (s, 3H), 7.07–7.11 (m, 2H), 7.30 (d, 1H, *J* = 1.9 Hz), 7.43 (dd, 1H *J* = 8.3, 1.9 Hz), 7.85 (d, 1H, *J*=8.3 Hz), 10.05 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 52.8, 124.0, 126.5, 127.5, 131.8, 132.4, 136.3, 141.4, 151.3, 162.8, 164.9, 187.3. Anal. calcd for $C_{12}H_9ClO_5$: C, 53.65; H, 3.38. Found: C, 54.10; H, 3.01; MS (EI, 70 eV): m/z (%) = 191 (4), 119 (39), 44 (100).

4-Chloro-2-formylphenyl methyl fumarate (**2l**). Obtained according GP1 from 5-chloro-2-hydroxybenzaldehyde (**1l**, 500 mg, 3.19 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 712 mg, 4.79 mmol) and NEt_3 (581 mg, 0.80 mL, 5.74 mmol). Purification by column chromatography on silica gel (cyclohexane:EtOAc 5:1) was followed by recrystallization from EtOH to afford **2l** as a colorless solid (551 mg, 2.06 mmol, 64%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.37; Mp 79–81 °C IR (neat, cm^{-1}): 1720 (C=O), 1682 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 7.07–7.12 (m, 2H), 7.22 (d, 1H, *J* = 8.7 Hz), 7.61 (dd, 1H, *J* = 8.7, 2.6 Hz), 7.87 (d, 1H, *J* = 2.6 Hz), 10.05 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 52.8, 124.9, 128.9, 130.8, 131.8, 132.9, 135.3, 136.2, 149.5, 163.0, 165.0, 187.0. Anal. calcd for $C_{12}H_9ClO_5$: C, 53.65; H, 3.38. Found: C, 53.51; H, 3.42. ; MS (EI, 70 eV): m/z (%) = 268 (1) [M^+], 155 (16), 113 (100), 85 (18), 44 (42).

2-Formyl-4-(methoxycarbonyl)phenyl methyl fumarate (**2m**). Obtained according GP1 from methyl-3-formyl-4-hydroxybenzoate (**1m**, 400 mg, 2.22 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid chloride ((*E*)-**8**, 494 mg, 3.33 mmol) and NEt_3 (0.359 g, 0.50 mL, 3.55 mmol) as a

light brown solid (**2m**, 646 mg, 2.21 mmol, 99%). Mp 118–120 °C; IR (neat, cm^{-1}): 1719 (C=O), 1686 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 3.96 (s, 3H), 7.05–7.16 (m, 2H), 7.35 (d, 1H, *J* = 8.5 Hz), 8.32 (dd, 1H, *J* = 8.5, 2.2 Hz), 8.57 (d, 1H, *J* = 2.2 Hz), 10.11 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 52.7, 52.8, 123.8, 127.9, 129.2, 131.9, 133.5, 136.2, 136.4, 153.9, 162.7, 165.0, 165.3, 187.8. Anal. calcd for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.55; H, 4.07. MS (EI, 70 eV): m/z (%) = 260 (15), 180 (25), 149 (34), 113 (100), 85 (18), 59 (13), 44 (91).

General procedure 2 (GP2) for the synthesis of benzoxepinones 3ab,d–m. Fumarate derivative **2a-m** (1 equiv) was dissolved in anhydrous toluene (2 mL·$mmol^{-1}$). 3-Methyl-1-phenyl-2-phospholen 1-oxide (**5**, 0.05 equiv.), benzoic acid (0.05 equiv) and $(MeO)_3SiH$ (3 equiv) were added under argon. The mixture was heated to 100 °C and stirred for 16 h. After cooling to 23 °C all volatiles were removed. The product was purified by column chromatography on silica gel (cyclohexane:EtOAc).

*Methyl 2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3a**).*[35] Obtained according to GP2 from **2a** (300 mg, 1.28 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 12 mg, 0.064 mmol), benzoic acid (8 mg, 0.06 mmol) and $(MeO)_3SiH$ (469 mg, 0.48 mL, 3.74 mmol) as a colorless solid (101 mg, 0.463 mmol, 36%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.34; Mp 91–93 °C; ^1H NMR (400 MHz, $CDCl_3$, δ): 3.44 (s, 2H), 3.88 (s, 3H), 7.26–7.31 (m, 2H), 7.41–7.51 (m, 2H), 7.87 (s, 1H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 33.4, 52.9, 121.6, 125.0, 125.2, 125.8, 131.1, 131.5, 137.8, 150.9, 165.1, 167.8; MS (EI, 70 eV): m/z (%) = 218 (100) [M^+], 186 (44), 175 (42), 158 (26), 147 (34), 131 (87), 115 (17), 102 (35), 77 (49), 63 (15), 51 (20).

*Methyl 9-methoxy-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3b**)*. Obtained according GP2 from **2b** (160 mg, 0.606 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 6 mg, 0.03 mmol), benzoic acid (4 mg, 0.03 mmol) and $(MeO)_3SiH$ (222 mg, 0.23 mL, 1.82 mmol) as a colorless solid (0.044 g, 0.178 mmol, 29%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.21; Mp 103–105 °C; IR (neat, cm^{-1}): 1761 (C=O), 1702 (C=O). ^1H NMR (300 MHz, $CDCl_3$,

δ): 3.44 (s, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 6.96–7.00 (m, 1H), 7.02–7.07 (m, 1H), 7.18–7.24 (m, 1H), 7.86 (s. 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 33.6, 52.9, 56.3, 113.4, 121.9, 125.1, 125.3, 125.5, 127.0, 137.8, 150.9, 165.1, 167.8. HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_5Na$ $[M+Na]^+$ 271.0577, found 271.0579; MS (EI, 70 eV): m/z (%) = 248 (100) $[M^+]$, 233 (35), 216 (22), 205 (22), 188 (23), 161 (55), 146 (15), 118 (27), 89 (19), 40 (78).

*Methyl 8-methoxy-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3d**).* Obtained according to GP2 from **2d** (200 mg, 0.757 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 7 mg, 0.04 mmol), benzoic acid (5 mg, 0.04 mmol) and $(MeO)_3SiH$ (278 mg, 0.29 mL, 2.27 mmol) as a colorless solid (83 mg, 334 mmol, 44%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.27; Mp 121–123 °C; IR (neat, cm^{-1}): 1749 (C=O), 1699 (C=O). ^1H NMR (400 MHz, $CDCl_3$, δ): 3.43 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.78 (d, 1H, *J* = 2.5 Hz), 6.85 (dd, 1H, *J* = 8.7, 2.5 Hz), 7.32 (d, 1H, *J* = 8.7 Hz), 7.82 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 33.4, 52.7, 55.9, 105.8, 112.7, 118.5, 122.3, 132.1, 137.9, 152.2, 162.3, 165.4, 167.3. Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.86; H, 4.50; MS (EI, 70 eV): m/z (%) = 248 (100) $[M^+]$, 217 (23), 205 (87), 189 (28), 161 (66), 146 (12), 118 (31), 89 (21), 40 (38).

*Methyl 7-methoxy-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3e**)*. Obtained according GP2 from **2e** (300 mg, 1.14 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 11 mg, 0.06 mmol), benzoic acid (7 mg, 0.06 mmol) and $(MeO)_3SiH$ (416 mg, 0.43 mL, 3.41 mmol) as a colorless solid (98 mg, 0.40 mmol, 35%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.29; Mp 85–87 °C; IR (neat, cm^{-1}): 1766 (C=O), 1708 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.43 (s, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 6.85 (d, 1H, *J* = 3.1 Hz), 7.01 (dd, 1H, *J* = 9.0, 3.1 Hz), 7.20 (d, 1H, *J* = 9.20 Hz), 7.82 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 33.3, 52.9, 55.9, 113.8, 118.1, 122.7, 125.3, 126.5, 137.7, 145.1, 156.3, 165.1, 168.2. HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_5Na$ $[M+Na]^+$ 271.0577, found 271.0579; MS (EI, 70 eV): m/z (%) = 248 (44) $[M^+]$, 216 (90), 205 (63), 189 (20), 161 (100), 146 (12), 118 (46), 89 (29), 63 (15), 40 (43).

*Methyl 8-methyl-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3f**).* Obtained according GP2 from **2f** (300 mg, 1.21 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 12 mg, 0.06 mmol), benzoic acid (7 mg, 0.06 mmol) and $(MeO)_3SiH$ (444 mg, 0.46 mL, 3.63 mmol) as a colorless solid (101 mg, 435 mmol, 36%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.32; Mp 130–132 °C; IR (neat, cm^{-1}): 1758 (C=O), 1699 (C=O). ^1H NMR (400 MHz, $CDCl_3$, δ): 2.42 (s, 3H), 3.42 (s, 2H), 3.87 (s, 3H), 7.07–7.11 (m, 2H), 7.28–7.31 (m, 1H), 7.84 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 21.5, 33.4, 52.8, 121.8, 123.0, 124.0, 126.3, 130.9, 138.0, 142.6, 150.8, 165.3, 167.7. Anal. calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.43; H, 4.95; MS (EI, 70 eV): m/z (%) = 232 (100) [M^+], 201 (28), 189 (36), 173 (22), 161 (12), 145 (65), 128 (11), 115 (44), 91 (13), 40 (82).

*Methyl 7-methyl-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3g**).* Obtained according GP2 from **2g** (300 mg, 1.21 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 12 mg, 0.06 mmol), benzoic acid (7 mg, 0.06 mmol) and $(MeO)_3SiH$ (444 mg, 0.46 mL, 3.63 mmol) as a colorless solid (112 mg, 482 mmol, 40%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.39; Mp 108–110 °C; IR (neat, cm^{-1}): 1756 (C=O), 1712 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.38 (s, 3H), 3.42 (s, 2H), 3.87 (s, 3H), 7.16 (d, 1H, *J* = 8.5 Hz), 7.19–7.21 (m, 1H), 7.25–7.29 (m, 1H), 7.82 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 20.7, 33.4, 52.8, 121.3, 124.8, 125.4, 131.0, 132.4, 135.0, 138.1, 149.0, 165.2, 168.0. Anal. calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.51; H, 5.08; MS (EI, 70 eV): m/z (%) = 232 (86) [M^+], 200 (87), 189 (53), 173 (34), 161 (22), 145 (100), 128 (11), 115 (79), 91 (29), 77 (15), 63 (15), 51 (14).

*Methyl 7-(tert-butyl)-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3h**).* Obtained according GP2 from **2h** (300 mg, 1.03 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 10 mg, 0.05 mmol), benzoic acid (6 mg, 0.05 mmol) and $(MeO)_3SiH$ (378 mg, 0.39 mL, 3.09 mmol) as a colorless solid (96 mg, 0.35 mmol, 34%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.45; Mp 78–80 °C; IR (neat, cm^{-1}): 1762 (C=O), 1711 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 1.34 (s, 9H), 3.44 (s, 2H), 3.88 (s, 3H), 7.20 (d, 1H, *J* = 8.6 Hz), 7.38 (d, 1H, *J* = 2.5 Hz), 7.50

(dd, 1H, *J* = 8.6, 2.5 Hz), 7.88 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 31.4, 33.4, 34.6, 52.8, 121.1, 124.6, 125.1, 127.6, 129.0, 138.4, 148.3, 148.9, 165.3, 168.1. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.22; H, 6.47; MS (EI, 70 eV): m/z (%) = 274 (55) [M^+], 259 (63), 242 (87), 231 (100), 199 (30), 187 (16), 171 (26), 157 (21), 128 (30), 115 (21), 77 (12).

*N,N-Diethyl-4-(methoxycarbonyl)-2-oxo-2,3-dihydrobenzo[b]oxepin-8-aminium chloride (**3i**)*. Obtained according GP2 from **2i** (300 mg, 0.983 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 9 mg, 0.05 mmol), benzoic acid (6 mg, 0.05 mmol) and $(MeO)_3SiH$ (360 mg, 0.38 mL, 2.95 mmol) as a yellow oil (98 mg, 0.34 mmol). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.37. The crude was dissolved in Et_2O (1.5 mL) and 2M HCl solution in Et_2O (0.20 mL, 0.406 mmol) was added. Precipitates were collected by filtration yielding **3i** as a colorless solid (85 mg, 294 mmol, 27%). Mp 161–163 °C; IR (neat, cm^{-1}): 1763 (C=O), 1703 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 1.28 (t, 6H, *J* = 7.2 Hz), 3.47 (s, 2H), 3.52 (q, 4H, *J* = 7.2 Hz), 3.88 (s, 3H), 7.45–7.50 (m, 1H), 7.54 (d, 1H, *J*=8.5 Hz), 7.67–7.75 (m, 1H), 7.85 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 10.8, 33.5, 52.3, 53.0, 100.1, 104.6, 113.8, 118.9, 125.6, 132.9, 136.4, 151.6, 164.8, 166.3. HRMS-ESI (m/z) calcd for $C_{16}H_{20}NO_4$ $[M]^+$ 290.1397, found 290.1394. MS (EI, 70 eV): m/z (%) = 289 (60), 274 (81), 246 (100), 207 (66), 186 (13), 158 (41), 133 (9), 73 (13), 44 (74).

*Methyl 2-oxo-2,3-dihydronaphtho[1,2-b]oxepine-4-carboxylate (**3j**).* Obtained according GP2 from **3j** (300 mg, 1.06 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 10 mg, 0.05 mmol), benzoic acid (6 mg, 0.05 mmol) and $(MeO)_3SiH$ (389 mg, 0.40 mL, 3.18 mmol) as a yellow solid (122 mg, 0.455 mmol, 43%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.39; Mp 156–158 °C; IR (neat, cm^{-1}): 1756 (C=O), 1692 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.49 (s, 2H), 3.91 (s, 3H), 7.45 (d, 1H, *J* = 8.5 Hz), 7.59–7.66 (m, 2H), 7.71 (d, 1H, *J* = 8.5 Hz), 7.84–7.91 (m, 1H), 7.99 (s, 1H), 8.36–8.43 (m, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 34.0, 52.9, 121.3, 123.0, 125.0, 125.1, 126.4, 126.5, 127.5, 127.8, 128.4, 135.0, 138.1, 147.0, 165.1, 167.5.

HRMS-ESI (m/z) calcd for $C_{16}H_{12}O_4Na$ $[M+Na]^+$ 291.0628, found 291.0628; MS (EI, 70 eV): m/z (%) = 268 (84) [M^+], 236 (31), 225 (10), 209 (45), 181 (100), 152 (71), 127 (11), 91 (13), 76 (14), 40 (80).

*Methyl 8-chloro-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3k**).* Obtained according GP2 from **2k** (300 mg, 1.12 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 11 mg, 0.056 mmol), benzoic acid (7 mg, 0.056 mmol) and $(MeO)_3SiH$ (411 mg, 0.43 mL, 3.36 mmol) as a colorless solid (91 mg, 0.36 mmol, 32%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.32; Mp 116–118 °C; IR (neat, cm^{-1}): 1767 (C=O), 1703 (C=O). ^1H NMR (400 MHz, $CDCl_3$, δ): 3.44 (s, 2H), 3.88 (s, 3H), 7.26–7.29 (m, 1H), 7.29–7.31 (m, 1H), 7.35–7.38 (m, 1H), 7.83 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 33.4, 53.0, 121.9, 124.3, 125.2, 125.7, 131.9, 136.9, 137.1, 151.0, 164.9, 166.8. Anal. calcd for $C_{12}H_9ClO_4$: C, 57.05; H, 3.59. Found: C, 57.09; H, 3.61; MS (EI, 70 eV): m/z (%) = 252 (19) [M^+], 220 (13), 209 (10), 193 (6), 165 (19), 102 (8), 75 (6), 40 (100).

*Methyl 7-chloro-2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3l**).* Obtained according to GP2 from **2l** (300 mg, 1.12 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 11 mg, 0.056 mmol), benzoic acid (7 mg, 0.06 mmol) and $(MeO)_3SiH$ (411 mg, 0.43 mL, 3.36 mmol) as a colorless solid (118 mg, 0.467 mmol, 42%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.37; Mp 110–112 °C; IR (neat, cm^{-1}): 1768 (C=O), 1706 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.44 (s, 2H), 3.89 (s, 3H), 7.20–7.25 (m, 1H), 7.39–7.45 (m, 2H), 7.79 (s, 1H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 33.4, 53.0, 123.1, 126.2, 127.1, 130.3, 130.6, 131.4, 136.5, 149.3, 164.8, 167.1. HRMS-ESI (m/z) calcd for $C_{12}H_{10}ClO_4$ $[M+H]^+$ 253.0262, found 253.0262; MS (EI, 70 eV): m/z (%) = 252 (14) [M^+], 220 (25), 209 (12), 193 (7), 180 (6), 165 (21), 102 (12), 40 (100).

*Dimethyl 2-oxo-2,3-dihydrobenzo[b]oxepine-4,7-dicarboxylate (**3m**).* Obtained according to GP2 from **2m** (300 mg, 1.03 mmol), 3-methyl-1-phenyl-2-phospholen 1-oxide (**5**, 10 mg, 0.05 mmol), benzoic acid (6 mg, 0.05 mmol) and $(MeO)_3SiH$ (378 mg, 0.39 mL, 3.09

mmol) as a colorless solid (87 mg, 0.315 mmol, 31%). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.24; Mp 134–136 °C; IR (neat, cm^{-1}): 1774 (C=O), 1721 (C=O), 1705 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.46 (s, 2H), 3.89 (s, 3H), 3.94 (s, 3H), 7.33 (d, 1H, *J* = 8.5 Hz), 7.90 (s, 1H), 8.10-8.16 (m, 2H). $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$, δ): 33.5, 52.7, 53.0, 122.0, 125.6, 125.8, 127.3, 132.4, 133.1, 137.1, 153.7, 164.8, 165.6, 166.6. Anal. calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 61.06; H, 4.08; MS (EI, 70 eV): m/z (%) = 276 (63) [M^+], 244 (100), 233 (41), 216 (62), 205 (21), 189 (83), 157 (18), 130 (47), 102 (29), 76 (21), 59 (22), 44 (30).

*Methyl 2-(2-oxo-2H-chromen-3-yl)acetate (**4**).*[43] To a solution of compound **2a** (500 mg, 2.13 mmol) in dry toluene (3 mL) PBu_3 (432 mg, 2.13 mmol, 0.53 mL) was added. The solution was stirred at room temperature under argon for 22 h. Volatiles were evaporated. The crude was purified by column chromatography on silica gel (cyclohexane:EtOAc 20:1) yielded coumarin **4** as a white solid (91 mg, 0.417 mmol, 20 %). R_f (SiO_2, cyclohexane:EtOAc= 3:1)= 0.22; ^1H NMR (400 MHz, $CDCl_3$, δ): 3.61 (s, 2H), 3.75 (s, 3H), 7.26–7.31 (m, 1H), 7.32–7.36 (m, 1H), 7.46–7.54 (m, 2H, 7.69 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 35.9, 52.5, 116.7, 119.2, 122.6, 124.6, 127.8, 131.5, 141.7, 153.6, 161.4, 170.6.

Synthesis of compounds for Control Experiments (Scheme 3).

Synthesis of *2-Formylphenyl methyl maleate* (*Z*-2a).[42]

*(Z)-4-Methoxy-4-oxobut-2-enoic acid chloride ((Z)-**8**)*. To a solution of (*Z*)-4-methoxy-4-oxobut-2-enoic acid ((*Z*)-**7**, 1.00 g, 7.69 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added DMF (0.10 mL). The mixture was cooled to 0 °C and thionyl chloride (1.08 g, 0.66 mL, 9.11 mmol, 1.2 equiv) was added dropwise. The resulting mixture was refluxed for 10 min. The solvent was distilled off and the obtained product (*Z*)-**8** was used without further purification

2-Formylphenyl methyl maleate (***Z*-2a**).[42] Obtained according to GP1 from aldehyde **1a** (909 mg, 0.80 mL, 7.44 mmol, 1 equiv), acid chloride (*(Z)*-**8**, 1.14 g, 7.69 mmol, 1.0 equiv) and NEt_3 (1.24 g, 1.70 mL, 12.3 mmol, 1.6 equiv). Purification by column chromatography on silica gel (cyclohexane:EtOAc= 20:1) gave ***Z*-2a** as a yellow oil (408 mg, 1.64 mmol, 21%). R_f (SiO_2,

cyclohexane:EtOAc= 5:1)= 0.35; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.81 (s, 3H), 6.44 (d, *J* = 12.0 Hz, 1H), 6.58 (d, *J*= 12.0 Hz, 1H), 7.32–7.47 (m, 2H), 7.62–7.72 (m, 1H), 7.88–7.96 (m, 1H), 10.2 (s, 1H) ppm.

Synthesis of 2-formylphenyl methyl fumarate-d_2 (2a-D_2)

*(E)-4-Methoxy-4-oxobut-2-enoic-2,3-d_2 acid chloride (**16**)*. Maleic anhydride-d_2 (1.00 equiv, 1.00 g, 10.2 mmol) was melted in a Schlenk flask at 70 °C under argon. MeOH (1.00 equiv, 326 mg, 0.413 mL, 10.2 mmol) was added and the mixture was allowed to stir for 16 h at 23 °C. The reaction mixture was heated to 80 °C and $AlCl_3$ (0.04 equiv, 54.4 mg, 0.408 mmol) was added. After 10 min most of the mixture solidified and was heated for additional 2 h. The colorless solid was then cooled down to 23 °C. 1 M HCl (25 mL) was added and the resulting mixture was extracted with EtOAc (3×40 mL). The organic phase was washed with water (40 mL) and saturated NaCl solution (40 mL) and dried with Na_2SO_4. After removal of all volatiles in vacuo the crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc 5:1 + 1% HOAc). Fractions of different *E*/*Z* ratios were collected and recrystallized from water to yield (*E*)-4-methoxy-4-oxobut-2-enoic-2,3-d_2 acid (**15**) as colorless crystals (60%, 808 mg, 6.12 mmol, E/Z >99:1). R_f (SiO_2, cyclohexane:EtOAc:HOAc= 1:2:0.01) = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.83 (s, 3H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$, δ): 52.5, 165, 170 ppm. Other signals could not be identified; IR (ATR): $\tilde{\nu}$= 2960 (br), 2647 (br), 2543 (br), 2280 (s), 1716 (s), 1672 (s), 1611 (m), 1437 (m), 1423 (m), 1283 (s), 1248 (s), 1058 (w), 1030(m), 911.7 (s), 856.6 (w), 786.7 (s), 722.8 (m), 652.9 (w), 642.8 (m), 536.9 (w), 403.8 (m) cm^{-1}; MS (EI, 70 eV)): *m/z* (%):132 (0.9) [M^+], 115 (5), 101 (100), 87 (60), 45 (86); HRMS (EI): *m/z* calcd for $C_5H_4D_2O_4$ [$M]^+$ 132.0392, found: 132.0389.

Acid **15** (1.10 g, 8.33 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL). After DMF (0.15 mL) was added the mixture was cooled to 0 °C and thionyl chloride (1.15 g, 0.70 mL, 9.66 mmol, 1.2 equiv) was added dropwise. The resulting mixture was refluxed for 3 h. The solvent was distilled off and the obtained acid chloride **16** was used without further purification.

2-Formylphenyl methyl fumarate-d_2 (**2a-D_2**). Obtained according GP1 from aldehyde **1a** (909 mg, 0.80 mL, 7.44 mmol, 1 equiv), acid chloride **16** (1.25 g, 8.33 mmol, 1.1 equiv) and NEt_3 (1.24 g, 1.70 mL, 12.3 mmol, 1.7 equiv). Purification by column chromatography on silica gel (cyclohexane:EtOAc= 20:1) gave the product **2a-D_2** as a yellow oil (1.23 g, 5.21 mmol, 70%). R_f (SiO_2, cyclohexane:EtOAc= 5:1)= 0.41; IR (neat, cm^{-1}): 1724 (C=O), 1695 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 3.82 (s, 3H), 7.19–7.23 (m, 1H), 7.39–7.44 (m, 1H), 7.60–7.66 (m, 1H), 7.85–7.90 (m, 1H), 10.1 (s, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 52.4, 123.1, 126.7, 127.6, 131.4, 135.3, 150.6, 162.9, 164.8, 188.3 ppm. Other signals could not be identified; MS (EI, 70 eV)): m/z (%):236 (0.9) [M+], 149 (7), 121 (35), 115 (100); HRMS-ESI (m/z) calcd for $C_{12}H_8D_2O_5$ $[M]^+$ 236.0648 found: 236.0649.

Synthesis of 1-(2-formylphenyl) 4-methyl 2-methylfumarate (11).

*(E)-4-methoxy-2-methyl-4-oxobut-2-enoic acid chloride (**10**).* Trimethyl phosphonoacetate (3.00 g, 16.5 mmol, 1.0 equiv), DBU (3.67 g, 3.60 mL, 24.1 mmol, 1.5 equiv) and LiCl (1.20 g, 28.3 mmol, 1.7 equiv) were dissolved in anhydrous DMSO (45 mL) and stirred under argon at room temperature for 15 min. Subsequently, sodium pyruvate (1.80 g, 16.4 mmol, 1.0 equiv) was added portion wise to the solution. The resulting mixture was heated to 100 °C under an argon atmosphere for 16 h. The solution was allowed to cool to room temperature, quenched with 20 mL of 1 M HCl and extracted with EtOAc (3 × 40 mL). The organic phase was dried with Na_2SO_4, all volatiles were removed in vacuo. After purification by column chromatography on silica gel (cyclohexane:EtOAc:AcOH= 5:1:0.01). The resulting mixture of *endo* and *exo*-alkene product (mesaconic acid and itaconic acids, respectively) was recrystallized from pentane to yield (*E*)-4-methoxy-2-methyl-4-oxobut-2-enoic acid (**9**) as colorless crystals (838 mg, 5.81 mmol, 35%). R_f (SiO_2, cyclohexane:EtOAc:HOAc= 1:2:0.01) = 0.77; ^1H NMR (300 MHz, $CDCl_3$, δ): 2.25 (d, *J*= 1.6 Hz, 3H), 3.75 (s, 3H), 6.86 (m, 1H), 12.0 (br, 1H) ppm.

To a solution of the acid **9** (440 mg, 3.06 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added DMF (0.10 mL). The mixture was cooled to 0 °C and thionyl chloride (575 mg, 0.35 mL, 4.83 mmol, 1.6 equiv) was added dropwise. The resulting mixture was refluxed for 3 h. The solvent was distilled off and the obtained product **10** was used without further purification.

*1-(2-Formylphenyl) 4-methyl 2-methylfumarate (**11**).* Obtained according to the GP1 from aldehyde **1a** (454 mg, 0.40 mL, 3.72 mmol, 1.2 equiv), crude acid chloride **10** (498 mg, 3.06 mmol, 1.0 equiv) and NEt_3 (802 mg, 1.10 mL, 7.96 mmol, 2.6 equiv). Purification by column chromatography on silica gel (cyclohexane:EtOAc= 20:1) gave the product **11** as a yellow oil (320 mg, 1.30 mmol, 42%). R_f (SiO_2, cyclohexane:EtOAc= 5:1)= 0.41; IR (neat, cm^{-1}): 1720 (C=O), 1694 (C=O). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.39 (d, *J*= 1.6 Hz, CH3, 3H), 3.75 (s, OCH3, 3H), 7.00 (q, *J*= 1.5 Hz, 1H), 7.15–7.19 (m, 1H), 7.35–7.39 (m, 1H), 7.57–7.63 (m, 1H), 7.82–7.86 (m, 1H), 10.0 (s, 1H) ppm; $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$, δ): 14.2, 51.6, 123.1, 126., 127.7, 128.2, 131.5, 135.3, 151.0, 165.3, 165.7, 188.3 ppm; MS (EI, 70 eV)): m/z (%):248 (0.6) [M+], 217 (6), 161 (5), 145 (3), 127 (100), 121 (35), 99 (66); HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_5$ $[M]^+$ 248.0679 found: 248.0680.

Synthesis of 4-(2-formylphenyl) 1-methyl 2-methylfumarate (14)

*(E)-4-methoxy-3-methyl-4-oxobut-2-enoic acid chloride (**13**)*. Methyl pyruvate (512 mg, 5.02 mmol, 1 equiv) was dissolved in $CHCl_3$ (10 mL) and *tert*-butyl 2-(triphenyl-γ5-phosphaneylidene)acetate (2.61 g, 6.93 mmol, 1.4 equiv) was added. The reaction mixture was heated to reflux overnight under Ar, then filtered through silica, (CH_2Cl_2 as eluent) and then concentrated in vacuo. The residue was dissolved in TFA/ CH_2Cl_2 (1:2, 5 mL) and stirred at 23 °C for 24 h. Afterwards, all volatiles were removed and the crude product was purified by column chromatography on silica gel (cyclohexane:EtOAc= 5:1 with 1% AcOH) to yield *E*-4-methoxy-3-methyl-4-oxobut-2-enoic acid (**12**) as a colorless solid (550 mg, 3.82 mmol, 76%). R_f (SiO_2, cyclohexane:EtOAc:HOAc= 1:1:0.01) = 0.67; ^1H NMR (300 MHz, $CDCl_3$, δ): 2.32 (d, *J*= 1.6 Hz, 3H), 3.82 (s, 3H), 6.80 (q, *J*= 1.6 Hz, 1H), 11.7 (br, 1H) ppm.

To a solution of acid **12** (315 mg, 2.19 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added DMF (0.10 mL). The mixture was cooled to 0 °C and thionyl chloride (312 mg, 0.19 mL, 2.62 mmol, 1.2 equiv) was added dropwise. The resulting mixture was refluxed for 3 h. The solvent was distilled off and the obtained product **13** was used without further purification.

4-(2-Formylphenyl) 1-methyl 2-methylfumarate (**14**). To a solution of potassium 2-formylphenolate (1.05 g, 6.57 mmol, 3.0 equiv; prepared from KOH and aldehyde **1a** in MeOH) in DCM (25 mL) was dropwise added a solution of crude acid chloride (**13**) in CH_2Cl_2 (25 mL) at 0 °C and stirred for 15 min at 0 °C. The reaction was then allowed to warm to room temperature and stirred for 90 min. The mixture was quenched with H_2O (2×2.5 mL·mmol^{-1}) and washed with saturated aqueous $KHCO_3$ solution (2×2.5 mL·mmol^{-1}). The organic layer was dried over Na_2SO_4, and the volatiles were removed under vacuum. Purification by column chromatography on silica gel (cyclohexane:EtOAc= 20:1) gave the product **14** as a yellow oil (90 mg, 0.36 mmol, 17%). R_f (SiO_2, cyclohexane:EtOAc= 5:1)= 0.41; IR (neat, cm^{-1}): 1717 (C=O), 1694 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.38 (d, *J*= 1.6 Hz, 3H), 3.86 (s, 3H), 7.00 (q, *J*= 1.5 Hz, 1H), 7.20–7.25 (m, 1H), 7.39–7.46 (m, 1H), 7.62–7.69 (m, 1H), 7.88–7.93 (m, 1H), 10.1 (s, 1H) ppm; ^{13}C{1H} NMR (100 MHz, $CDCl_3$, δ): 14.6, 52.8, 123.1, 124.9, 126.6, 127.9, 131.0, 135.3, 147.2, 151.1, 163.9, 167.1, 188.5 ppm; MS (EI, 70 eV)): m/z (%):248 (0.5) [M+], 216 (3), 161 (4), 127 (100), 121 (14), 99 (18), 39 (81); HRMS-ESI (m/z) calcd for $C_{13}H_{12}O_5$ $[M]^+$ 248.0679 found: 248.0682.

Associated Content

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXX.

Details of the control experiments and metabolic activity tests, ^{1}H and ^{13}C NMR spectra (PDF); X-ray crystallographic data for benzoxepinone **3a** (CIF).

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. Wittig, G.; Geissler, G., Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate. *Liebigs Ann. Chem.* **1953,** *580*, 44–57.

2. Wittig, G.; Schöllkopf, U., Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien. *Chem. Ber.* **1954,** *87*, 1318–1330.

3. Edmonds, M.; Abell, A., *Modern Carbony Olefination*. Wiley-VCH: Weinheim, 2004; p 1–17.

4. Edmonds, M.; Abell, A., *Organophosphorus Reagents*. Oxford University Press: Oxford, 2004; p 99–127.

5. Kolodiazhnyi, O., *Phosphorus Ylides*. Wiley-VCH: Weinheim, 2007; p 359–538.

6. van Kalkeren, H. A.; Blom, A. L.; Rutjes, F. P. J. T.; Huijbregts, M. A. J., On the usefulness of life cycle assessment in early chemical methodology development: the case of organophosphorus-catalyzed Appel and Wittig reactions. *Green Chem.* **2013,** *15*, 1255–1263.

7. van Kalkeren, H. A.; van Delft, F. L.; Rutjes, F. P. J. T., Organophosphorus Catalysis to Bypass Phosphine Oxide Waste. *ChemSusChem* **2013,** *6*, 1615–1624.

8. O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A., Recycling the Waste: The Development of a Catalytic Wittig Reaction. *Angew. Chem.* **2009,** *121*, 6968–6971.

9. Longwitz, L.; Werner, T., Recent advances in catalytic Wittig-type reactions based on P(III)/P(V) redox cycling. *Pure Appl. Chem.* **2018,** DOI: 10.1515/pac-2018-0920.

10. Tsai, Y.-L.; Lin, W., Synthesis of Multifunctional Alkenes from Substituted Acrylates and Aldehydes via Phosphine-Catalyzed Wittig Reaction. *Asian J. Org. Chem.* **2015,** *4*, 1040–1043.

11. Wang, L.; Sun, M.; Ding, M.-W., Catalytic Intramolecular Wittig Reaction Based on a Phosphine/Phosphine Oxide Catalytic Cycle for the Synthesis of Heterocycles. *Eur. J. Org. Chem.* **2017,** *2017*, 2568–2578.

12. Lee, C.-J.; Chang, T.-H.; Yu, J.-K.; Madhusudhan Reddy, G.; Hsiao, M.-Y.; Lin, W., Synthesis of Functionalized Furans via Chemoselective Reduction/Wittig Reaction Using Catalytic Triethylamine and Phosphine. *Org. Lett.* **2016,** *18*, 3758–3761.

13. Schirmer, M.-L.; Adomeit, S.; Werner, T., First Base-Free Catalytic Wittig Reaction. *Org. Lett.* **2015,** *17*, 3078–3081.

14. Schirmer, M.-L.; Adomeit, S.; Spannenberg, A.; Werner, T., Novel Base-Free Catalytic Wittig Reaction for the Synthesis of Highly Functionalized Alkenes. *Chem. Eur. J.* **2016,** *22*, 2458-2465.

15. Saleh, N.; Voituriez, A., Synthesis of 9H-Pyrrolo[1,2-a]indole and 3H-Pyrrolizine Derivatives via a Phosphine-Catalyzed Umpolung Addition/Intramolecular Wittig Reaction. *J. Org. Chem.* **2016,** *81*, 4371–4377.

16. Gruijters, B. W. T.; van Veldhuizen, A.; Weijers, C. A. G. M.; Wijnberg, J. B. P. A., Total Synthesis and Bioactivity of Some Naturally Occurring Pterulones. *J. Nat. Prod.* **2002,** *65*, 558–561.

17. Huang, S.-T.; Kuo, H.-S.; Chen, C.-T., Total synthesis of NADH:ubiquinone oxidoreductase (complex I) antagonist pterulone and its analogue. *Tetrahedron Lett.* **2001,** *42*, 7473–7475.

18. Lemaire, P.; Balme, G.; Desbordes, P.; Vors, J.-P., Efficient syntheses of pterulone, pterulone B and related analogues. *Org. Biomol. Chem.* **2003,** *1*, 4209–4219.

19. Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O., Alternative routes to pterulone. *Tetrahedron* **2002,** *58*, 5203–5208.

20. Izquierdo, J.; Orue, A.; Scheidt, K. A., A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations. *J. Am. Chem. Soc.* **2013,** *135*, 10634–10637.

21. Ghosh, S.; Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V., Synthesis of heliannuols A and K, allelochemicals from cultivar sunflowers and the marine metabolite helianane, unusual sesquiterpenes containing a benzoxocane ring system. *Tetrahedron* **2007,** *63*, 644–651.

22. Biswas, B.; Sen, P. K.; Venkateswaran, R. V., The synthesis of heliannuol C, an allelochemical from Helianthus annuus. *Tetrahedron Lett.* **2006,** *47*, 4019–4021.

23. Biswas, B.; Sen, P. K.; Roy, A., Synthesis of (±)-heliannuol C. *Synth. Commun.* **2017,** *47*, 1692–1701.

24. Ishikawa, N. K.; Yamaji, K.; Tahara, S.; Fukushi, Y.; Takahashi, K., Highly oxidized cuparene-type sesquiterpenes from a mycelial culture of Flammulina velutipes. *Phytochemistry* **2000,** *54*, 777–782.

25. Bruder, M.; Haseler, P. L.; Muscarella, M.; Lewis, W.; Moody, C. J., Synthesis of the Oxepinochromone Natural Products Ptaeroxylin (Desoxykarenin), Ptaeroxylinol, and Eranthin. *J. Org. Chem.* **2010,** *75*, 353–358.

26. Kim, S.; Su, B.-N.; Riswan, S.; Kardono, L. B. S.; Afriastini, J. J.; Gallucci, J. C.; Chai, H.; Farnsworth, N. R.; Cordell, G. A.; Swanson, S. M.; Kinghorn, A. D., Edulisones A and B, two epimeric benzo[b]oxepine derivatives from the bark of Aglaia edulis. *Tetrahedron Lett.* **2005,** *46*, 9021–9024.

27. Vyvyan, J. R.; Looper, R. E., Total synthesis of (±)-heliannuol D, an allelochemical from Helianthus annuus. *Tetrahedron Lett.* **2000,** *41*, 1151–1154.

28. Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swarts, H. J.; Frankland, J. C.; Field, J. A., Novel monochlorinated metabolites with a 1-benzoxepin skeleton from Mycena galopus. *Tetrahedron Lett.* **1999,** *40*, 5767–5770.

29. Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R., Structural Elucidation and Chemistry of a Novel Family of Bioactive Sesquiterpenes: Heliannuols. *J. Org. Chem.* **1994,** *59*, 8261–8266.

30. Engler, M.; Timm, A.; Sterner, O., Pterulinic Acid and Pterulone, Two Novel Inhibitors of NADH: Ubiquinone Oxidoreductase (Complex I) Produced by a Pterula Species. *J. Antibiot.* **1997,** *50*, 330–333.

31. Saidachary, G.; Veera Prasad, K.; Divya, D.; Singh, A.; Ramesh, U.; Sridhar, B.; China Raju, B., Convenient one-pot synthesis, anti-mycobacterial and anticancer activities of novel benzoxepinoisoxazolones and pyrazolones. *Eur. J. Med. Chem.* **2014,** *76*, 460–469.

32. Rasolofonjatovo, E.; Provot, O.; Hamze, A.; Rodrigo, J.; Bignon, J.; Wdzieczak-Bakala, J.; Lenoir, C.; Desravines, D.; Dubois, J.; Brion, J.-D.; Alami, M., Design, synthesis and anticancer properties of 5-arylbenzoxepins as conformationally restricted isocombretastatin A-4 analogs. *Eur. J. Med. Chem.* **2013,** *62*, 28–39.

33. Rigby, J. H.; Aasuml, M., Synthesis of benzoxepins via rearrangement of dihydrofurans derived from carbonyl ylide [3+2] cycloaddition. *Tetrahedron Lett.* **2003,** *44*, 5029–5031.

34. Murakami, M.; Tsuruta, T.; Ito, Y., Lactone Formation by Rhodium-Catalyzed C−C Bond Cleavage of Cyclobutanone. *Angew. Chem. Int. Ed.* **2000,** *39*, 2484–2486.

35. Ahn, S.-H.; Lim, H. N.; Lee, K.-J., Application of the acetate of baylis-hillman adducts of salicylaldehydes in the synthesis of methyl 2-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylates. *J. Heterocycl. Chem.* **2008,** *45*, 1701–1706.

36. For additional information see Supporting Information.

37. O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J., Breaking the Ring through a Room Temperature Catalytic Wittig Reaction. *Chem. Eur. J.* **2013,** *19*, 5854-5858.

38. Li, Y.; Lu, L.-Q.; Das, S.; Pisiewicz, S.; Junge, K.; Beller, M., Highly Chemoselective Metal-Free Reduction of Phosphine Oxides to Phosphines. *J. Am. Chem. Soc.* **2012,** *134*, 18325–18329.

39. Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X., Mechanism, Regioselectivity, and the Kinetics of Phosphine-Catalyzed [3+2] Cycloaddition Reactions of Allenoates and Electron-Deficient Alkenes. *Chem. Eur. J.* **2008,** *14*, 4361–4373.

40. Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X., An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenoates and Alkenes. *J. Am. Chem. Soc.* **2007,** *129*, 3470–3471.

41. Pospíšil, J.; Potáček, M., Microwave-assisted solvent-free intramolecular 1,3-dipolar cycloaddition reactions leading to hexahydrochromeno[4,3-b]pyrroles: scope and limitations. *Tetrahedron* **2007,** *63*, 337–346.

42. Wolff, M.; Seemann, M.; Grosdemange-Billiard, C.; Tritsch, D.; Campos, N.; Rodríguez-Concepción, M.; Boronat, A.; Rohmer, M., Isoprenoid biosynthesis via the methylerythritol phosphate pathway. (E)-4-Hydroxy-3-methylbut-2-enyl diphosphate: chemical synthesis and formation from methylerythritol cyclodiphosphate by a cell-free system from Escherichia coli. *Tetrahedron Lett.* **2002,** *43*, 2555–2559.

43. Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P., A Novel Palladium-Catalyzed Dicarbonylation Process Leading to Coumarins. *J. Org. Chem.* **2008,** *73*, 756–759.