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Synthesis of phenylpropanoids via Matsuda-Heck coupling of arene diazonium salts

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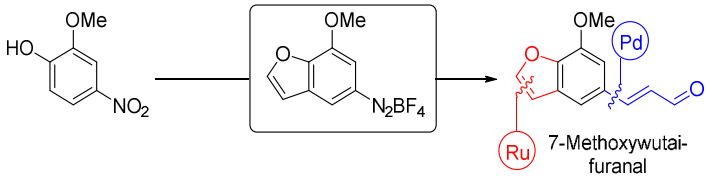


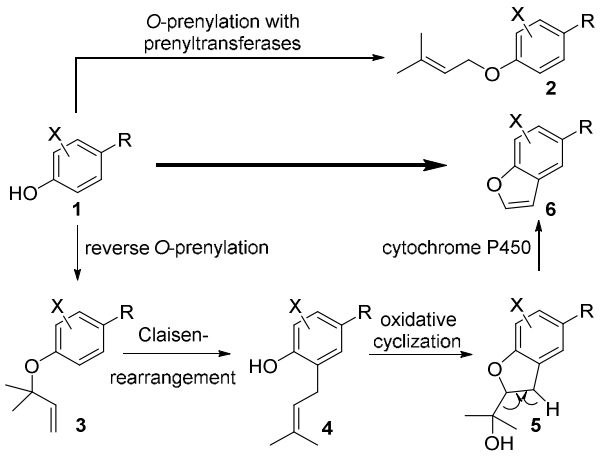
Abstract: The Pd-catalyzed Heck-type coupling (Matsuda-Heck reaction) of electron rich arene diazonium salts with electron deficient olefins has been exploited for the synthesis of phenylpropanoid natural products. Examples described herein are the naturally occurring benzofurans methyl wutaifuranate, wutaifuranol, wutaifuranal, their 7-methoxy derivatives and the *O*-prenylated natural products boropinols A and C.

Introduction

Phenylpropanoids are natural products with an oxygenated aromatic core substituted with a three carbon tail.[1] Biosynthetically phenylpropanoids are derived from L-phenylalanine and occasionally from L-tyrosine through the action of phenylalanine ammonia-lyase,[2] an enzyme that catalyzes the elimination of ammonia and thus yields *E*-cinnamic acid. Further down the biosynthetic pathway phenylpropanoids may be converted to other secondary metabolites, such as chalcones, flavones, coumarins or stilbenes.[3] Metabolites **1** with free phenols can undergo *O*-prenylation under the action of prenyltransferases, giving prenylethers **2**,[4-6] whereas a sequence of enzymatic reverse *O*-prenylation to *gem*-dimethylallylethers **3** and

Claisen rearrangement is a feasible route to *C*-prenylated phenylpropanoids **4**.[7] From these *C*-prenylated derivatives benzofurans **6** may arise via oxidative cyclization to **5** and cytochrom P-450 induced hydrogen abstraction, followed by homolytic scission of the exocyclic C-C-bond with formation of acetone (**Scheme 1**).[8]

Scheme 1. Biosynthetic relationship between phenols, prenylethers and benzofurans.[8]



There is evidence that phenylpropanoids are formed in plants in response to heat and excess light stress. They play a major role in the antioxidant defense system of plants by trapping reactive oxygen species.[9] These antioxidant and radical scavenging properties are also believed to contribute to several pharmacological activities reported for phenylpropanoids and their glycoconjugates or for medicinal plants containing these secondary metabolites, such as antibacterial and antiviral activities, antiinflammatory activity or antitumor activity.[10]

Several secondary plant metabolites of the general structure **2**, i. e. phenylpropanoids with prenyloxy side chains, have been isolated from the shrub *Boronia pinnata* Sm., which is native to New South Wales, Australia.[11] Preliminary bioactivity studies revealed a notable activity against the Epstein-Barr virus early antigen for boropinic acid (**7**), one of the prenyloxyphenylpropanoids described in this study. Later, antibacterial activity against *Helicobacter pylori*,[12] anti-inflammatory activity,[13] inhibitory activity against prenyltransferases,[14] farnesoid-X-receptor agonistic activity,[15] neuroprotective activity[16] and

an activating effect on the transient receptor potential protein TRPA1[17] were discovered for boropinic acid (**7**) and its reduced derivatives boropinal C (**8**) and boropinol A (**9**). The methyl ester of boropinic acid has also been isolated from a natural source, the plant *Hortia longifolia* which is native to Brazil. This compound was found to inhibit α-glucosidase and α-amylase moderately.[18] Related natural products with a benzofuranpropanoid structure have been isolated from the shrub *Zanthoxylum wutaiense*.[19] These compounds, named methyl wutaifuranate (**10a**), 7-methoxywutaifuranal (**11b**), wutaifuranol (**12a**) and 7-methoxywutaifuranol (**12b**), respectively, are active against *Mycobacterium tuberculosis* at a μg/mL level (**Figure 1**).

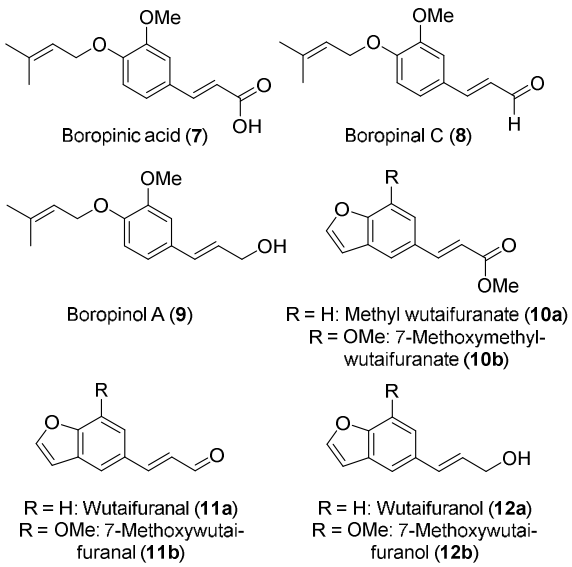


Figure 1. Secondary plant metabolites from *Boronia pinnata* and *Zanthoxylum wutaiense*.

Four publications report the synthesis of boropinic acid (**7**)[13,14,20] or its methyl ester[21] and one reports the syntheses of boropinal C (**8**) and boropinol A (**9**).[20] These syntheses proceed via *O*-prenylation of vanillin and subsequent carbonyl olefination or via direct *O*-prenylation of ferulic acid. No syntheses of benzofuranpropanoids **10** – **12** have been published so far.

In continuation of our studies on Pd-catalyzed Heck-type coupling reactions with electron rich phenol and alkoxyarene diazonium salts[22,23] we investigated the synthesis of benzofuran- and

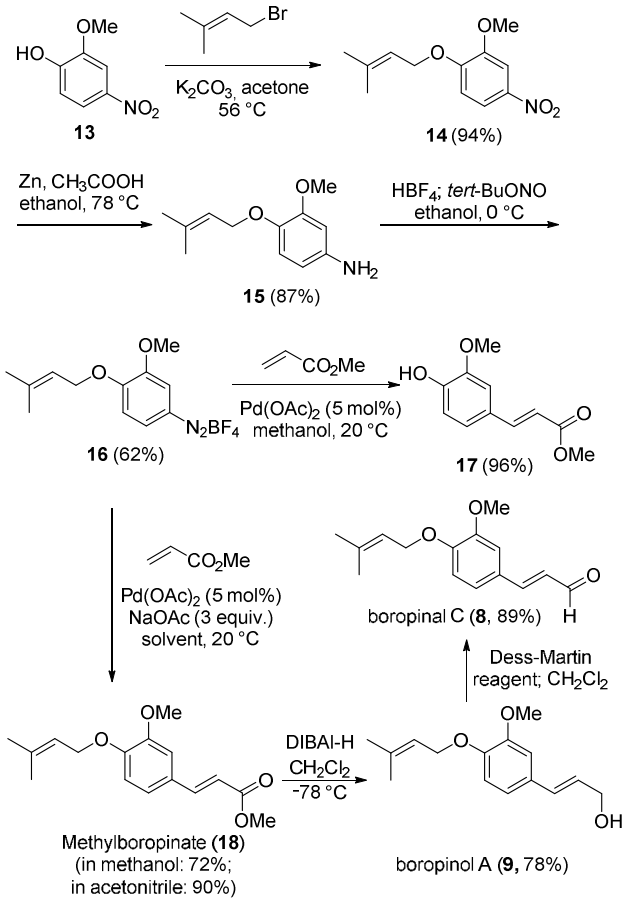
prenyloxyphenylpropanoids shown in figure 1, using this approach. The Heck-type coupling of arene diazonium salts is often described as "Matsuda-Heck-reaction".[24-36] Originally discovered by Matsuda and coworkers in the late 1970's,[37-39] the synthetic value of this variant of the Mizoroki-Heck reaction remained underrated for several decades. As for Heck reactions in general,[40] the Matsuda-Heck variant is synthetically particularly useful and high yielding when applied to electron deficient olefins, such as acrylates. At the outset of this project it was unclear whether prenyloxyarene and benzofuran moieties tolerate the strongly acidic conditions normally required to generate the respective diazonium salts, and if so, whether undesired Pd-catalyzed side reactions would occur. For instance, the prenylether might be cleaved or undergo a double bond migration, and in the case of benzofurans a Pd-catalyzed arylation at C2, similar to a recently reported C2-arylation of indoles with arene diazoniums salts,[41] is a conceivable competing reaction.

Results and discussion

Boropinic acid derivatives. Commercially available nitrophenol **13** was prenylated under standard conditions to furnish prenyl ether **14** in nearly quantitative yield. Chemoselective reduction of the nitrogroup to aniline **15** was accomplished with zinc and acetic acid. Diazotation of **15** with HBF_4 and *tert*-butyl nitrite worked well and led to the 4-prenyloxy arene diazonium salt **16**, which precipitated from the reaction mixture and could be isolated and characterized. For the Matsuda-Heck coupling of **16** and methyl acrylate we first tested methanol as a solvent without added base, because these base-free conditions had previously been identified to be superior for alkoxyarene diazonium salts in most cases.[22,42] A cinnamate coupling product **17** was indeed isolated in excellent yield, but quantitative deprenylation had occurred. The deprenylation could be fully suppressed by addition of NaOAc as a base, and the desired coupling product methylboropinate (**18**) was isolated in high yield. Both methanol and acetonitrile are suitable solvents for this transformation, but in combination with a base

the isolated yield is significantly higher in acetonitrile. Reduction of methylboropinate (**18**) with DIBAl-H furnished boropinol A (**9**) in good yield. Oxidation of **9** with Dess-Martin periodinane[43] worked well and gave boropinal C (**8**). The analytical data obtained by us for the synthetic compounds **8**,[11] **9**[11] and **18**[18,21] match those reported for the natural products (**Scheme 2**).

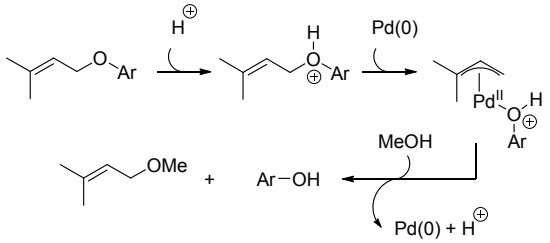
Scheme 2. Syntheses of methylboropinate, boropinal C and boropinol A.



Prenyl ethers have been reported to be stable only at very low concentrations of in situ generated Brønsted-acids[44] but are cleaved in the presence *p*-toluenesulfonic acid[45] or the Lewis-acid $Yb(OTf)_3$.[46] For these reasons it appears to be inconsistent that the equimolar amount of HBF_4 generated during a base-free Matsuda-Heck reaction is sufficient to induce a quantitative deprenylation, whereas an excess of HBF_4 is tolerated during the diazotation of

prenyloxy aniline **15**. This observation suggests that the deprenylative Matsuda-Heck reaction leading to **17** is cooperatively catalyzed by Pd(0) and Brønsted acid (**Scheme 3**): after protonation of the ether oxygen the cleavage of the *O*-prenyl bond by oxidative addition to the Pd-catalyst is facilitated. The solvent methanol subsequently attacks the dimethylallyl ligand, leading to prenylmethyl ether and the deprenylation product methylferulate (**17**), with regeneration of the Pd(0) catalyst and the Bronsted-acid.

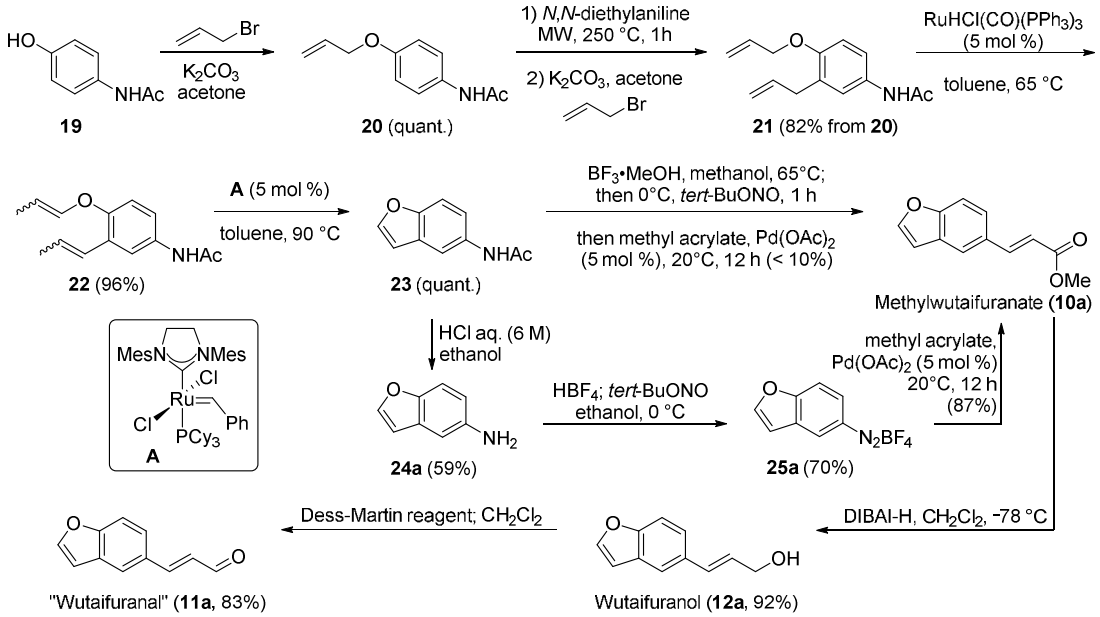
Scheme 3. Cooperatively Pd/H^+-catalyzed deprenylation.



Methylwutaifuranate, wutaifuranal and wutaifuranol. Construction of the benzofuran was accomplished along a sequence previously described by van Otterlo and coworkers for other benzofurans:[47] *O*-allylation of paracetamol (**19**) gave allyl ether **20**, which was converted to **21** by microwave-promoted Claisen-rearrangement[48] and repetition of the *O*-allylation step. Compound **21** was subjected to a Ru-hydride catalyzed isomerization.[49,50] Vinylether **22** was obtained in nearly quantitative yield, but as a mixture of all four geometrical isomers, without a clear preference for one of these. Ring closing metathesis[51-53] of **22** catalyzed by second generation Grubbs' catalyst **A**[54] furnished 5-acetamidobenzofuran (**23**) in quantitative yield. Originally, we envisaged the deacetylation-diazotation-coupling (DDC)-sequence recently developed in our laboratories for the synthesis of methylwutaifuranate (**10a**) from acetamide **23**.[55] This one-pot sequence involves a deacetylation mediated by borontrifluoride-methanol, a diazotation with *tert*-butyl nitrite and a Pd-catalyzed Matsuda-Heck-coupling of the *in situ* generated arene diazonium salt. The latter step is initiated by addition of methyl acrylate and a catalytic amount of $Pd(OAc)_2$ to the deacetylation-diazotation reaction mixture. Surprisingly,

the DDC-sequence was unsuccessful in this case, giving the desired product **10a** reproducibly in yields lower than 10%. Monitoring the one-pot reaction by TLC revealed that the deacetylation works well, but that the diazotation step appears to be inhibited under these conditions. For these reasons the transformation of **23** to methylwutaifuranate (**10a**) was performed step by step, starting with the deacetylation of acetamide **23** to 5-aminobenzofuran (**24a**), which was diazotized to **25a**, followed by Matsuda-Heck coupling with methyl acrylate under base-free conditions to furnish **10a** in 36% total yield based on acetamidobenzofuran **23**. Reduction of **10a** with DIBAl-H gave the natural product wutaifuranol (**12a**). This could be oxidized to the aldehyde "wutaifuranal" (**11a**), which has, in contrast to its 7-methoxy analogue **11b**, not yet been isolated from a natural source. Analytical data recorded for synthetic **10a** and **12a** match those reported for the natural products methyl wutaifuranate (**10a**)[19] and wutaifuranol (**12a**)[19] (**Scheme 4**).

Scheme 4. Methylwutaifuranate, wutaifuranol and wutaifuranal from paracetamol.



7-Methoxy derivatives of wutaifuranal and wutaifuranol and their ring-expanded analogues. For the synthesis of 7-methoxy methyl wutaifuranate (**10b**) and its reduced

derivatives **11b** and **12b** we chose commercially available 4-nitroguaiacol (**26**) as the starting material (**Scheme 5**). 4-Nitroguaiacol was first *O*-allylated, and the resulting allyl ether **27** was subjected to microwave irradiation in *N*,*N*-diethyl aniline at the same temperature (250 °C) and for the same reaction time (1 h) as the acetamide **20**. These conditions had previously been successfully applied in Claisen rearrangements by us[56] and we were therefore surprised to find that a complex mixture of products was formed in this particular case, which contained a large amount of highly polar products but apparently not the desired rearrangement product **28** (**Table 1**, entry 1). In order to improve the selectivity and increase the yield of **28** we varied the reaction time and temperature (**Table 1**).

Table 1. Optimization of reaction conditions for microwave promoted Claisen rearrangement.

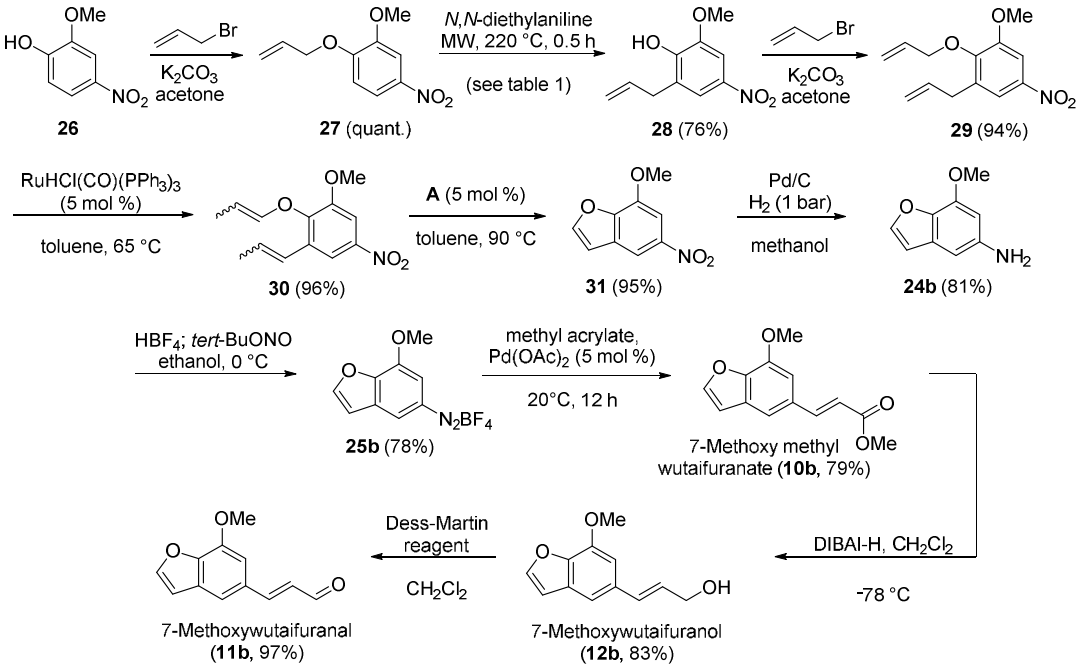
entry	T	Reaction time/minutes	Yield of **28**
1	250 °C	60	--[a)]
2	250 °C	7	54%
3	250 °C	7.5	62%
4	250 °C	15	51%
5	220 °C	10	52%
6	220 °C	15	61%
7	220 °C	20	72%
8	220 °C	30	76%
9	220 °C	60	72%
10	220 °C	90	70%

[a)]Complex mixture of products.

Compared to the standard conditions (entry 1) the yield of **28** was substantially improved to 62% by reducing the reaction time to 7.5 minutes (entry 3). Slightly shorter (entry 2) or longer (entry 4) reaction times resulted in lower yields. Controlling the selectivity through the

reaction time was unsatisfactory, and we therefore investigated a reduced temperature. At 220 °C the yield could be improved from 52% after microwave irradiation for 10 minutes (entry 5) to 76% after irradiation for 30 minutes (entry 8). Further prolongation of the reaction time was neither detrimental nor beneficial (entries 9 and 10).

Scheme 5. 7-Methoxywutaifuranate and congeners from 4-nitroguaiacol.



Phenol **28** was *O*-allylated under standard conditions and the resulting allyl ether **29** was converted to the 5-nitrosubstituted benzofuran **31** by Ru-catalyzed isomerization followed by RCM. Reaction conditions and yields are very similar to those for the acetamidobenzofuran **23**, apart from the Claisen rearrangement which required a reduced reaction temperature and proceeded in somewhat lower yields. In the next step the nitro group in compound **31** was reduced to an amino group by Pd/C-catalyzed hydrogenation, followed by diazotation and base-free Matsuda-Heck coupling to furnish 7-methoxy methyl wutaifuranate (**10b**). Reduction of **10b** with DIBAl-H gave the natural product 7-methoxy wutaifuranol (**12b**), which could be oxidized with Dess-Martin's reagent to 7-methoxy wutaifuranal (**11b**). In contrast to methyl wutaifuranate (**10a**) its 7-methoxy analogue (**10b**) has not been isolated

from natural sources so far and has not been described in the literature. The analytical data recorded for synthetic compounds **11b** and **12b** match those previously reported in the literature for the natural products from *Zanthoxylum wutaiense*.[19]

The convenient access to diallyl compound **29** prompted us to investigate whether the RCM/Matsuda-Heck-approach is a feasible route to ring-expanded analogues of the benzofuran propanoid natural products. We expected some difficulties along the way. The formation of benzoxepines by RCM[57-60] has been described in the literature but is known to be not as facile as that of five- and sixmembered analogues. It normally requires higher dilution and is occasionally hampered by competing double bond migration.[61] More serious problems were expected during the diazotation step and the Matsuda-Heck reaction, because the double bond generated by RCM is isolated and not part of an aromatic system, as in the benzofurans. This might result in acid-mediated isomerization, electrophilic addition or elimination reactions under diazotation conditions. Under Matsuda-Heck conditions Pd-catalyzed double bond migrations or arylations at the oxacycle might interfere with the intended coupling reaction.

In the first step **29** was subjected to RCM using second generation Grubbs' catalyst **A**. Under the conditions used for the RCM of **22** and **30** (initial substrate concentration 0.3 M, toluene, 90 °C) a complex mixture of products was formed, presumably because of uncontrolled double bond isomerizations. However, the expected benzoxepine **32** was obtained in high yield in dichloromethane at ambient temperature and with an initial substrate concentration of 0.1 M. Reduction of the nitro group in the presence of the endocyclic C-C-double bond was achieved with zinc in the presence of aq. NH_4Cl. The intermediate aniline **33** was isolated, but immediately diazotized without further purification to give the benzoxepin diazonium salt **34** in 83% yield over two steps. While the acidic diazotation conditions are tolerated without any problems, attempted Matsuda-Heck coupling of **34** with methyl acrylate under the standard conditions used for the benzofuran diazonium salts resulted in the formation of a complex

mixture of products. The desired coupling product **35** could be isolated from this mixture, but it was contaminated with impurities and the yield was lower than 10% (**Table 2**, entry 1). In an attempt to optimize this step, the addition of NaOAc as a base was tested. The product was indeed formed, but the conversion was lower than 10% (entry 2). In the next steps acetonitrile was tested as a solvent. In the absence of NaOAc no conversion was observed (entry 3), whereas addition of the base resulted again in a conversion below 10% (entry 4). For these reasons we returned to the solvent methanol and base-free reaction conditions, but reduced the initial substrate concentration from 0.1 M to 0.05 M, increased the excess of methyl acrylate to four equivalents and reduced the catalyst loading to 2.5 mol %. We reasoned that these measures should suppress the assumed competing Matsuda-Heck coupling at the endocyclic double bond. Gratifyingly, the alkenylated benzoxepine **35** was formed in high selectivity and isolated in good yield (entry 5).

Table 2. Optimization of reaction conditions for the Matsuda-Heck coupling of **34**.

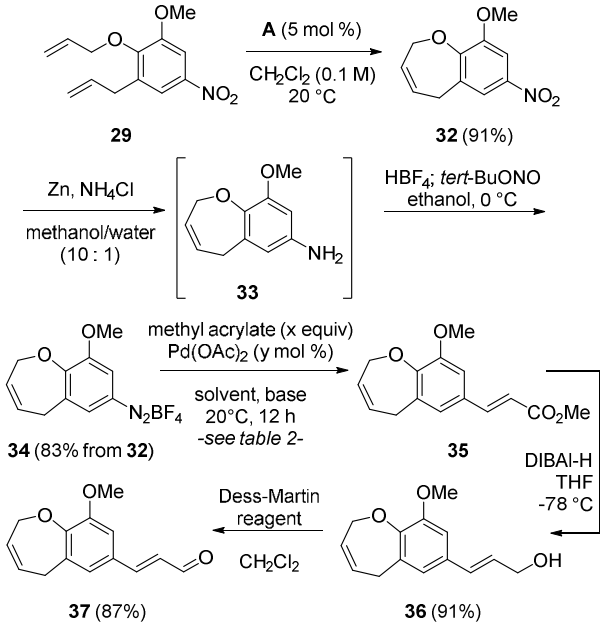
entry	methyl acrylate [equiv.]	$Pd(OAc)_2$ [mol %]	solvent	concentration[a] [mol•L^{-1}]	NaOAc [equiv.]	Yield of **35**
1	2	5.0	methanol	0.10	--	--[b]
2	2	5.0	methanol	0.10	3.0	--[c]
3	2	5.0	CH_3CN	0.10	--	--[d]
4	2	5.0	CH_3CN	0.10	3.0	--[c]
5	4	2.5	methanol	0.05	--	78%

[a]Initial concentration of diazonium salt **34**. [b]Complex mixture of products. [c]Conversion <10%. [d]No conversion.

Reduction of the ester group in **35** to the allylic alcohol **36** was accomplished with DIBAl-H, but surprisingly the conversion remained unsatisfactory in methylene chloride for this

particular substrate. A solvent switch to THF led to a substantially improved yield of 91%. Oxidation of **36** with Dess-Martin's reagent furnished the ring-expanded 7-methoxy wutaifuranal analogue **37** in high yield (**Scheme 6**).

Scheme 6. Synthesis of ring-expanded 7-methoxy wutaifuranate analogues.



Conclusions

In summary, naturally occurring phenylpropanoids isolated from the plants *Boronia pinnata* and *Zanthoxylum wutaiense* have been synthesized from paracetamol and 4-nitroguaiacol, respectively, using Pd-catalyzed couplings of prenyloxyarene- and benzofuran diazonium salts. Both types of arene diazonium salts have previously not been used in Matsuda-Heck reactions. The synthetic approach to benzofuran propanoids can be extended to ring-expanded analogues by using a benzoxepin diazonium salt. However, this coupling partner requires some modification of the reaction conditions, presumably because the endocyclic double bond of the oxepine moiety undergoes competing Pd-catalyzed reactions under the standard conditions.

Experimental Section

General methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra

were obtained at 300 MHz, 500 MHz or 600 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz, 125 MHz or 151 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal standard. Whenever the solubility or stability of the sample or signal separation were insufficient in $CDCl_3$, it was replaced by one of the following solvents: DMSO-d_6 (DMSO-d_5 as internal standard for ^1H NMR spectroscopy, δ = 2.50 ppm, DMSO-d_6 as internal standard for ^{13}C NMR spectroscopy, δ = 39.5 ppm); acetone-d_6 (acetone-d_5 as internal standard for ^1H NMR spectroscopy, δ = 2.05 ppm, CD_3COCD_3 as internal standard for ^{13}C NMR spectroscopy, δ = 29.8 ppm); methanol-d_4 (CD_2HOD as internal standard for ^1H NMR spectroscopy, δ = 3.31 ppm, CD_3OD as internal standard for ^{13}C NMR spectroscopy, δ = 49.2 ppm). IR spectra were recorded as ATR-FTIR spectra. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high resolution mass spectra were obtained by EI-TOF or ESI-TOF. Microwave reactions were carried out in an Anton-Paar-monowave-300 reactor at 250 °C (monowave, maximum power 850 W, temperature control via external IR-sensor) in sealed reaction vessels (volume of vials: 20 mL). Although most arene diazonium tetrafluoroborates are stable at elevated temperature, we generally advise against heating these compounds or recording melting points. Hexanes/MTBE mixtures of increasing polarity were used for column chromatography, starting with a hexanes : MTBE ratio of 10 : 1 (v/v), which was gradually reduced to 2 : 1 (v/v), if necessary.

2-Methoxy-1-((3-methylbut-2-en-1-yl)oxy)-4-nitrobenzene (14). A suspension of **13** (2.06 g, 12.1 mmol), K_2CO_3 (6.62 g, 48.0 mmol) and prenylbromide (2.68 g, 18.0 mmol) in acetone (60 mL) was heated at 65 °C for 12 h. The resulting suspension was filtered through a pad of celite which was washed with acetone. The filtrate was evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **14** (94%, 2.69 g, 11.3 mmol): yellow solid; mp 88-89 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.9, 2.6 Hz, 1H), 7.75 (d, J = 2.6 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H),

5.51 (tm, J = 6.8 Hz, 1H), 4.70 (d, J = 6.7 Hz, 2H), 3.96 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 149.2, 141.4, 139.4, 118.6, 117.8, 111.1, 106.6, 66.4, 56.4, 26.0, 18.5; IR (ATR) ν 1587 (m), 1504 (s), 1335 (s), 1272 (s), 1254 (s); HRMS (EI) calcd for $C_{12}H_{15}NO_4$ [M^+] 237.1001, found 237.1002.

3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)aniline (15). A suspension of **14** (95 mg, 0.4 mmol), Zn-dust (390 mg, 6.0 mmol) and acetic acid (344 µL, 6.0 mmol) in ethanol (5 mL) was heated to reflux for 10 minutes. After cooling to ambient temperature, the reaction mixture was filtered through a pad of celite, which was washed with ethanol. The filtrate was evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **15** (87%, 67 mg, 0.32 mmol): brownish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, J = 8.4 Hz, 1H), 6.28 (d, J = 2.6 Hz, 1H), 6.18 (dd, J = 8.4, 2.6 Hz, 1H), 5.49 (tm, J = 6.8 Hz, 1H), 4.46 (d, J = 6.7 Hz, 2H), 3.79 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 141.2, 141.1, 137.2, 120.6, 116.1, 106.5, 100.8, 66.9, 55.7, 25.8, 18.2; IR (ATR) ν 3349 (bw), 1625 (w), 1506 (s), 1450 (m), 1223 (s); HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ [M+H]$^+$ 208.1338, found 208.1327. According to a SciFinder search the compound is known and commercially available, but no references are listed and no data have been reported.

3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyldiazonium tetrafluoroborate (16). A solution of **15** (508 mg, 2.51 mmol) and HBF_4 (aq., 48 wt-%, 656 µL, 5.02 mmol) in ethanol (5 mL) was stirred for 5 minutes at ambient temperature and then cooled to 0 °C. *tert*-BuONO (668 µL, 5.02 mmol) was added dropwise. After 15 minutes at 0 °C the reaction mixture was warmed to ambient temperature and stirred for 1 h. Diethyl ether (50 mL) was added and the precipitate was filtered through a Büchner funnel. The solid was washed with diethyl ether and dried *in vacuo* to furnish **16** (62%, 475 mg, 1.55 mmol): colourless solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (dd, J = 8.1, 2.4 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.52 (d, J = 9.2 Hz, 1H), 5.47 (tm, J = 6.3 Hz, 1H), 4.84 (d, J = 6.9 Hz, 2H), 3.88 (s, 3H), 1.77 (s, 3H), 1.73

(s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.1, 154.4, 145.5, 135.9, 122.9, 119.5, 118.0, 107.6, 72.2, 61.8, 30.6, 23.3; IR (ATR) ν 2254 (m), 1568 (m), 1504 (m), 1245 8s), 1070 (s); HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2$ [M^+] 219.1134, found 219.1133.

Ferulic acid methyl ester (17).[62] To a solution of **16** (76.5 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 5 mol%) in methanol (2.5 mL) was added methyl acrylate (45 µL, 0.50 mmol) at ambient temperature and the reaction mixture was stirred until the gas evolution had ceased. The solvent was evaporated and the residue was dissolved in MTBE (10 mL). The soluton was washed with water (10 mL), the organic layer was separated and the aqueous layer was extracted three times with MTBE (10 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **17** (96%, 49 mg, 0.24 mmol): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 15.9 Hz, 1H), 7.07 (dd, J = 8.2, 1.7 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.30 (d, J = 15.9 Hz, 1H), 6.10 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 148.3, 147.2, 145.4, 127.3, 123.4, 115.5, 115.2, 109.8, 56.3, 52.0; IR (ATR) ν 3387 (w), 2950 (w), 1510 (s), 1263 (s), 1156 (s); HRMS (EI) calcd for $C_{11}H_{12}O_4$ [M^+] 208.0736, found 208.0741.

Methyl-(*E*)-3-(3-Methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)acrylate (18).[18,21] To a solution of **16** (76.5 mg, 0.25 mmol), NaOAc (61.5 mg, 0.75 mmol) and $Pd(OAc)_2$ (2.8 mg, 5 mol%) in CH_3CN (2.5 mL) was added methyl acrylate (45 µL, 0.50 mmol) and the reaction mixture was stirred until the gas evolution had ceased. The solvent was evaporated and the residue was dissolvend in MTBE (10 mL). The solution was washed with water (5 mL), the organic layer was separated and the aqueous layer was extracted three times with MTBE (5 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **18** (90%, 61 mg, 0.23 mmol). Following the same procedure but replacing CH_3CN by methanol also gave compound **18** (72%, 50 mg, 0.18 mmol): yellow

solid, mp 56-58 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.61 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.20 (dd, J = 8.3, 1.8 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 5.50 (tm, J = 6.6 Hz, 1H), 4.62 (d, J = 6.6 Hz, 2H), 3.89 (s, 3H), 3.74 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.9, 150.9, 150.0, 144.6, 137.3, 127.3, 122.6, 120.0, 115.2, 112.9, 110.4, 65.2, 55.2, 50.6, 24.9, 17.3; IR (ATR) ν 1712 (s), 1636 (m), 1510 (s), 1253 (s); HRMS (ESI) calcd for $C_{16}H_{20}O_4Na$ $[M+Na]^+$ 299.1259, found 299.1267.

Boropinol A (9).[11] To a solution of **18** (42 mg, 0.15 mmol) in THF (5 mL) was added DIBAl-H (1.0 M in CH_2Cl_2, 335 µL, 0.35 mmol) at −78 °C. After 30 minutes the reaction mixture was warmed to ambient temperature and stirred until the starting material was fully consumed. The reaction was quenched by addition of satd. aq. solution of NH_4Cl (10 mL) and the mixture was diluted with diethyl ether (10 mL). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether (10 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **9** (78%, 29 mg, 0.12 mmol): colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 1.6 Hz, 1H), 6.92 (dd, J = 8.3, 1.7 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 15.8 Hz, 1H), 6.26 (dt, J = 15.8, 5.9 Hz, 1H), 5.53 (tm, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 2H), 4.32 (dd, J = 5.9, 1.1 Hz, 2H), 3.90 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H), 1.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 148.6, 138.1, 131.6, 130.1, 126.8, 120.3, 120.0, 113.3, 109.5, 66.2, 64.3, 56.2, 26.2, 18.6; IR (ATR) ν 3471 (bw), 2918 (w), 1510 (s), 1261 (s), 1223 (m); HRMS (ESI) calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1310, found 271.1305.

Boropinal C (8).[11] To a solution of **9** (11.6 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin's reagent (23.4 mg, 0.55 mmol) at 0 °C. The reaction mixture was stirred until the starting material was fully consumed, warmed to ambient temperature and diluted with CH_2Cl_2 (10 mL). It washed three times with satd. aq. solution of NaHCO3 and Na2SO3 (5 mL each) and once with brine (5 mL). The organic layer was dried with $MgSO_4$, filtered and

evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **8** (89%, 10.1 mg, 0.041 mmol): colourless oil; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.67 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 15.8 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.27 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.70 (dd, J = 15.8, 7.7 Hz, 1H), 5.50 (tm, J = 6.7 Hz, 1H), 4.65 (d, J = 6.7 Hz, 2H), 3.90 (s, 3H), 1.79 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 193.4, 153.3, 151.9, 150.4, 137.8, 127.6, 127.0, 123.8, 120.2, 113.2, 110.9, 66.7, 55.6, 25.3, 17.7; IR (ATR) v 1669 (s), 1595 (m), 1507 (s), 1267 (s); HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1341

***N*-(4-(Allyloxy)phenyl)acetamide (20)**.[63,64] A suspension **20** (4.50 g, 30 mmol), K_2CO_3 (8.30 g, 60.0 mmol) and allyl bromide (3.90 mL, 45 mmol) in acetone (90 mL) was stirred at 55 °C for 12 h. After cooling to ambient temperature, the suspension was filtered through a pad of celite and washed with acetone. The filtrate was evaporated to furnish **20** (99%, 5.70 g, 30 mmol): colourless solid, mp 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.06 (ddt, J = 17.1, 10.5, 5.3 Hz, 1H), 5.42 (dd, J = 17.3, 1.5 Hz, 1H), 5.31 (s, 1H), 5.30 (dm, J = 10.5 Hz, 1H), 4.52 (d, J = 5.3 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 155.4, 133.2, 131.1, 121.9, 117.7, 115.0, 69.1, 24.3; IR (ATR) v 3285 (bm), 1658 (s), 1513 (s), 1259 (m); HRMS (EI) calcd for $C_{11}H_{13}NO_2$ $[M^+]$ 191.0946, found 191.0940.

***N*-(3-Allyl-4-(allyloxy)phenyl)acetamide (21)**.[64] A solution of **20** (1.00 g, 5.2 mmol) in *N,N*-diethylaniline (15 mL) was placed in a vessel suited for microwave irradiation and heated in a dedicated microwave reactor to 250 °C for 1 h. After cooling to ambient temperature, the solution was diluted with ethyl acetate (20 mL) and washed three times with aq. NaOH (2 M, 10 mL each). The organic layer was acidified to pH = 1 with aq. HCl (6 M) and extracted three times with ethyl acetate (20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The crude product, *N*-(3-allyl-4-hydroxyphenyl)acetamide, was used without further purification and characterization in the next step: the residue from

the previous step was dissolved in acetone (25 mL) and K_2CO_3 (1.65 g, 12.0 mmol) and allyl bromide (1.04 mL, 12.0 mmol) were added. The reaction mixture was heated to 55 °C for 12 h, filtered through a short pad of celite which was washed with acetone. The combined organic solutions were evaporated in vacuo to furnish **21** (82%, 0.80 g, 3.5 mmol) without further purification: colourless solid, mp 111-113 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.52 (dd, J = 8.8, 2.6 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 6.88, (d, J = 8.8 Hz, 1H), 6.09 (ddt, J = 17.3, 10.6, 5.0 Hz, 1H), 5.98 (ddt, J = 16.9, 10.0, 6.7 Hz, 1H), 5.43 (dq, J = 17.3, 1.8 Hz, 1H), 5.24 (dq, J = 10.6, 1.6 Hz, 1H), 5.06 (dq, J = 17.2, 1.6 Hz, 1H), 5.00 (dm, J = 10.1 Hz, 1H), 4.56 (dt, J = 4.9, 1.5 Hz, 2H), 3.37 (d, J = 6.7 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.4, 152.2, 136.9, 134.1, 132.8, 128.7, 121.0, 118.1, 115.9, 114.8, 112.0, 68.8, 34.2, 23.2; IR (ATR) ν 1521 (s), 1351 (s), 1123 (m), 736 (s); HRMS (EI) calcd for $C_{14}H_{17}NO_2$ [M^+] 231.1259, found 231.1260.

***N*-(3-(Prop-1-en-1-yl)-4-(prop-1-en-1-yloxy)phenyl)acetamide (22)**. To a solution of **21** (693 mg, 3.00 mmol) in dry and degassed toluene (30 mL) was added [$RuHCl(CO)(PPh_3)_3$] (142 mg, 5 mol%) and the solution was stirred at 65 °C for 12 h. After cooling to ambient temperature, the solvent was evaporated and the residue was purified by column chromatography on silica, using hexane/ethyl acetate mixtures as eluent, to furnish **22** (96%, 663 g, 2.90 mmol) as a mixture of isomers: colourless oil; selected NMR-data of the major *E*,*E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s(br.), 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 8.6, 2.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.66 (dm, J = 15.6 Hz, 1H), 6.35 – 6.15 (m, 2H), 4.85 (dq, J = 6.5, 6.5 Hz, 1H), 2.15 (s, 3H), 1.88 (dd, J = 6.6, 1.3 Hz, 3H), 1.74 (dd, J = 7.0, 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 150.9, 141.7, 132.8, 128.2, 127.6, 124.7, 119.9, 118.5, 116.0, 106.8, 24.3, 18.9, 9.4.

***N*-(Benzofuran-5-yl)acetamide (23)**. The isomeric mixture of **22** (622 mg, 2.70 mmol) was dissolved in dry and degassed toluene (30 mL) and second generation Grubbs' catalyst **A** (114 mg, 5 mol%) was added. The solution was stirred at 90 °C until the starting material was fully

consumed (TLC), cooled to ambient temperature and all volatiles were evaporated. The residue was purified by column chromatography on silica, using hexane/ethyl acetate mixtures as eluent to furnish **23** (quant., 486 mg, 2.70 mmol): colourless solid, mp 67-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.87 (d, J = 1.7 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.25 (dd, J = 8.8, 2.0 Hz, 1H), 6.69 – 6.64 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 151.9, 145.8, 133.2, 127.7, 118.0, 113.3, 111.3, 107.8, 24.2; IR (ATR) ν 3285 (bm), 1658 (s), 1554 (s), 1467 (s), 1199 (m); HRMS (EI) calcd for $C_{10}H_9NO_2$ [M^+] 175.0633, found 175.0632.

Benzofuran-5-amine (24a).[65] To a solution of **23** (88 mg, 0.50 mmol) in ethanol (5 mL) was added aq. HCl (6 M, 1.50 mL, 9.00 mmol), and the mixture was heated to reflux until the starting material was fully consumed (TLC). The solution was cooled to ambient temperature, the solvent was evaporated and the residue was partitioned between ethyl acetate (5 mL) and aq. NaOH (2 M, 5 mL). The aqueous layer was extracted three three times with ethyl acetate (5 mL), the combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/ethyl acetate mixtures as eluent, to furnish **24a** (59%, 39 mg, 0.30 mmol): brownish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 8.6, 1.8 Hz, 1H), 6.63 (d, J = 1.5 Hz, 1H), 3.58 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 145.4, 142.0, 128.3, 113.6, 111.6, 106.1, 106.0; IR (ATR) ν 3285 (bm), 1658 (s), 1554 (s), 1467 (s), 1199 (m); HRMS (EI) calcd for C_8H_8NO $[M+H]^+$ 134.0606, found 134.0613.

Benzofuran-5-diazonium tetrafluoroborate (25a). To a solution of **24a** (90 mg, 0.67 mmol) in ethanol (1.5 mL) was added aq. HBF_4 (48 wt-%, 177 µL, 1.35 mmol). The mixture was stirred at ambient temperature for five minutes and then cooled to 0 °C. *tert*-BuONO (179 µL, 1.35 mmol) was added and the mixture was stirred for 15 minutes at 0 °C, warmed to ambient temperature and then stirred for 1 h. Diethyl ether (20 mL) was added to precipitate the

diazonium salt, which was isolated by filtration through a Buchner funnel. The solid was washed with diethyl ether and dried in vacuo to furnish **25a** (70%, 107 mg, 0.47 mmol): red-brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (d, J = 1.8 Hz, 1H), 8.61 (dd, J = 9.1, 1.9 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2, 152.4, 129.8, 129.7, 129.6, 115.8, 109.8, 108.6; IR (ATR) ν 2279 (m), 1571 (w), 1255 (w), 1031 (s); HRMS (ESI) calcd for $C_8H_5N_2O$ [M^+] 145.0402, found 145.0417.

Methylwutaifuranate (10a).[19] To a solution of **25a** (89 mg, 0.38 mmol) in methanol (4 mL) was added $Pd(OAc)_2$ (4.2 mg, 5 mol%) and methyl acrylate (69 µL, 0,76 mmol). The reaction mixture was stirred at ambient temperature until the gas evolution had ceased, the solvent was evaporated and the residue redissolvend in MTBE (10 mL). The solution was washed with water (10 mL), the organic layer was separated and the aqueous layer was extracted three times with MTBE (10 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **10a** (87%, 68 mg, 0.33 mmol): colourless solid, mp 84-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 16.0 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.55 – 7.48 (m, 2H), 6.81 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 156.0, 146.0, 145.3, 129.5, 128.0, 124.2, 121.7, 116.6, 111.9, 106.8, 51.7; IR (ATR) ν 1707 (s), 1639 (m), 1176 (s); HRMS (EI) calcd for $C_{12}H_{10}O_3$ [M^+] 202.0630, found 202.0624.

Wutaifuranol (12a).[19] To a solution of **10a** (30 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was added DIBAl-H (1.0 M in CH_2Cl_2, 311 µL, 0.31 mmol) at −78 °C and the solution was stirred for 0.5 h. It was then warmed to ambient temperature and stirred until the starting material was fully consumed. The reaction was quenched by addition of aq. satd. solution of NH_4Cl (10 mL), the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2 (10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and

evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **12a** (92%, 24 mg, 0.14 mmol): colourless solid, mp 64-66 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.84 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.46 (dd, J = 8.6, 1.8 Hz, 1H), 6.90 (dd, J = 2.2, 0.9 Hz, 1H), 6.73 (dt, J = 15.9, 1.6 Hz, 1H), 6.41 (dt, J = 15.9, 5.4 Hz, 1H), 4.27 (ddd, J = 5.5, 5.5, 1.7 Hz, 2H), 3.88 (t, J = 5.7 Hz, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 154.5, 145.9, 132.6, 129.3, 129.2, 127.9, 122.8, 119.0, 111.1, 106.7, 62.4; IR (ATR) ν 3327 (bw), 1468 (s), 1089 (m), 972 (s); HRMS (ESI) calcd for $C_{11}H_9O_2$ [M-H$^+$] 173.0608, found 173.0645.

***(E)*-3-(Benzofuran-5-yl)acrylaldehyde (11a)**. To a solution of wutaifuranol **12a** (14.0 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin's reagent (34 mg, 0.79 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred until full conversion of the starting material. It was then diluted with CH_2Cl_2 (5 mL) and washed three times with a satd. aq. solution of $NaHCO_3$ and Na_2SO_3 (5 mL each), and once with brine. The organic layer was dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **11a** (83%, 11 mg, 0.07 mmol): colourless solid, mp 83-84 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.74 (d, J = 7.7 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 15.9 Hz, 1H), 7.76 (dd, J = 8.6, 1.8 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.01 (dd, J = 2.2, 0.9 Hz, 1H), 6.81 (dd, J = 15.9, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 193.5, 156.8, 153.5, 147.3, 130.1, 128.8, 128.2, 125.3, 122.8, 112.3, 107.3; IR (ATR) ν 1659 (s), 1617 (s), 1464 (m), 1106 (s); HRMS (ESI) calcd. for $C_{11}H_9O_2$ [M+H$^+$] 173.0603, found 173.0616.

1-(Allyloxy)-2-methoxy-4-nitrobenzene (27). A suspension of **26** (845 mg, 5.00 mmol), K_2CO_3 (1.38 g, 10.0 mmol) and allyl bromide (658 μL, 7.50 mmol) in acetone (25 mL) was stirred at 55 °C for 12 h. The resulting suspension was filtered through a pad of celite, which was washed with acetone. The combined filtrates were evaporated to furnish the title compound **27** (quant., 1.040 g, 5.00 mmol): yellow solid, mp 50-52 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.88 (dd, J = 8.9, 2.6 Hz, 1H), 7.75 (d, J = 2.6 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 6.08 (ddt, J = 17.1, 10.7, 5.4 Hz, 1H), 5.45 (dq, J = 17.3, 1.3 Hz, 1H), 5.36 (dq, J = 1.05, 1.3 Hz, 1H), 4.72 (dt, J = 4.1, 1.3 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 149.3, 141.6, 132.0, 119.2, 117.7, 111.5, 106.8, 70.2, 56.4; IR (ATR) v 1590 (m), 1505 (s), 1338 (m), 1275 (m); HRMS (EI) calcd for $C_{10}H_{11}NO_4$ [M^+] 209.0688, found 209.0676. Anal. calcd for $C_{10}H_{11}NO_4$ (209.20): C, 57.4; H, 5.3; N, 6.7. Found: C, 57.2; H, 5.4; N, 7.0.

2-Allyl-6-methoxy-4-nitrophenol (28). A solution of **27** (209 mg, 1.00 mmol) in *N,N*-diethylaniline (5 mL) was placed in a vessel suited for microwave irradiation and placed in a microwave reactor at 220 °C for 0.5 h. The solution was cooled to ambient temperature, diluted with ethyl acetate (10 mL) and washed three times with aq. HCl (2 M, 10 mL each). The organic layer was separated, and the combined washing solutions were extracted three times with ethyl acetate (15 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **28** (76%, 159 mg, 0.76 mmol): yellow solid, mp 72-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 2.5 Hz, 1H), 6.35 (s, 1H), 6.08 – 5.87 (m, 1H), 5.19 – 5.08 (m, 2H), 4.00 (s, 3H), 3.46 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 146.0, 140.7, 134.9, 126.3, 119.2, 117.1 104.5, 56.7, 33.6; IR (ATR) v 3456 (bw), 1519 (m), 1490 (m), 1337 (s); HRMS (EI) calcd for $C_{10}H_{11}NO_4$ [M^+] 209.0688, found 209.0687. Anal calcd for $C_{10}H_{11}NO_4$ (209.20): C, 57.4; H, 5.3; N, 6.7. Found: C, 57.4; H, 5.4; N, 6.8.

1-Allyl-2-allyloxy-3-methoxy-5-nitrobenzene (29). A suspension of **28** (1.26 g, 6.0 mmol), K_2CO_3 (1.65 g, 12.0 mmol) and allyl bromide (1.04 mL, 12.0 mmol) in acetone (60 mL) was heated at 55 °C for 12 h. The suspension was cooled to ambient temperature, filtered through a pad of celite and washed with acetone. All volatiles were evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **29** (94%, 1.40 g, 5.6 mmol): yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J =

2.6 Hz, 1H), 7.67 (d, *J* = 2.6 Hz, 1H), 6.06 (ddt, *J* = 16.2, 10.4, 5.9 Hz, 1H), 5.94 (ddt, *J* = 16.8, 10.3, 6.6 Hz, 1H), 5.37 (dm, *J* = 17.2 Hz, 1H), 5.25 (dm, *J* = 10.4, 1H), 5.12 (dm, *J* = 10.4 Hz, 1H), 5.10 (d, *J* = 16.9 Hz, 1H), 4.62 (d, *J* = 5.9 Hz, 2H), 3.94 (s, 3H), 3.46 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.4, 143.6, 135.6, 134.7, 133.6, 118.3, 117.9, 117.0, 105.9, 75.1, 56.2, 34.3; IR (ATR) *v* 1552 (s), 1474 (m), 1339 (s), 1289 (s); HRMS (EI) calcd for $C_{13}H_{15}NO_4$ [M^+] 249.1001, found 249.1012.

1-Methoxy-5-nitro-3-(prop-1-en-1-yl)-2-(prop-1-en-1-yloxy)benzene (30). To a solution of **29** (747 mg, 3.00 mmol) in dry and degassed toluene (15 mL) was added [$RuHCl(CO)(PPh_3)_3$] (142 mg, 5.0 mol %) and the solution was heated at 65 °C for 12 h. After cooling to ambient temperature, the solvent was evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **30** (96%, 720 g, 2.89 mmol) as a mixture of isomers: colourless, waxy solid; NMR-data of the major *E*,*E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.6 Hz, 1H), 7.63 (d, *J* = 2.6 Hz, 1H), 6.63 (dm, *J* = 16.0 Hz, 1H), 6.39 (dq, *J* = 16.0, 6.4 Hz, 1H), 6.12 (dm, *J* = 6.0 Hz, 1H), 4.70 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.91 (s, 3H), 1.93 (dd, *J* = 6.6, 1.3 Hz, 3H), 1.80 (dd, *J* = 6.9, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 148.0, 144.4, 144.2, 132.2, 130.6, 123.4, 113.9, 105.5, 103.9, 56.4, 18.9, 9.1.

7-Methoxy-5-nitrobenzofuran (31). To a solution of **30** (249 mg, 1.0 mmol) in dry and degassed toluene (10 mL) was added second generation Grubbs' catalyst A (42 mg, 5 mol %). The solution was heated to 90 °C until the starting material was fully consumed (TLC). After cooling to ambient temperature, the solvent was evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **31** (95 %, 183 mg, 0.95 mmol): colourless solid, mp 123-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.5, 145.4, 145.0, 128.6, 110.7, 108.2, 102.1, 56.7; IR (ATR) *v* 1516 (s), 1330 (s), 1299 (m); HRMS (EI) calcd for $C_9H_7NO_4$

[M^+] 193.0375, found 193.0382. Anal calcd for $C_9H_7NO_4$ (193.16): C, 56.0; H, 3.7. Found: C, 55.6; H, 3.6.

7-Methoxy-5-aminobenzofuran (24b). A suspension of **31** (48 mg, 0.25 mmol) and Pd/C (5 mg, 10 wt-%) in methanol (5 mL) was stirred under an atmosphere of hydrogen (1 bar) for 12 h. The suspension was filtered through a pad of celite and washed with methanol, all volatiles were evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **24b** (81%, 33 mg, 0.20 mmol): brownish oil; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.58 (d, J = 2.1 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 6.53 (d, J = 1.9 Hz, 1H), 6.39 (d, J = 1.7 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, methanol-d_4) δ 146.8, 146.3, 144.7, 140.5, 131.0, 107.4, 99.7, 99.1, 56.5; IR (ATR) v 3421 (bw), 1598 (s), 1478 (m); HRMS (ESI) calcd for $C_9H_{10}NO_2$ $[M+H]^+$ 164.0712, found 164.0716.

7-Methoxy-5-diazoniumbenzene tetrafluoroborate (25b). A solution of **24b** (100 mg, 0.61 mmol) and HBF_4 (aq., 48 wt-%, 160 µL, 1.22 mmol) in ethanol (2 mL) was stirred for 5 min at ambient temperature and then cooled to 0 °C. At this temperature *tert*-BuONO (163 µL, 1.22 mmol) was added and the mixture was stirred at 0°C for 0.25 h. It was warmed to ambient temperature and stirred for 1 h, followed by addition of diethyl ether (20 mL) to precipitate the diazonium salt. The precipitate was filtered through a Buchner funnel, the solid was washed with diethyl ether and dried in vacuo to furnish **25b** (78%, 123 mg, 0.48 mmol): red-brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.42 (s, 1H), 4.07 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.8, 150.4, 146.7, 130.4, 123.8, 109.9, 109.7, 109.1, 58.2; IR (ATR) v 2272 (m), 1600 (m), 1482 (m), 1029 (s); HRMS (ESI) calcd for $C_9H_7N_2O_2$ [M^+] 175.0508, found 175.0508.

Methyl-*(E)*-3-(7-methoxybenzofuran-5-yl)acrylate (10b). To a solution of **25b** (173 mg, 0.66 mmol) and $Pd(OAc)_2$ (7.4 mg, 5 mol%) in methanol (6 mL) was added methyl acrylate (110 µL, 1.32 mmol) and the reaction mixture was stirred until the gas evolution had ceased. All volatiles were evaporated, the residue was dissolved in MTBE (20 mL) and the solution

was washed with water (10 mL). The organic layer was separated and the aqueous layer was extracted three times with MTBE (20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **10b** (78%, 119 mg, 0.51 mmol): yellow solid, mp 94-97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 15.9 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 1.1 Hz, 1H), 7.00, d, J = 1.2 Hz, 1H), 6.80 (d, J = 2.1 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 4.06 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.3, 146.1, 146.0, 145.9, 130.9, 129.8, 117.0, 115.5, 107.8, 105.5, 56.5, 52.1; IR (ATR) ν 1708 (s), 1635 (m), 1470 (m), 1277 (s); HRMS (EI) calcd for $C_{13}H_{12}O_4$ [M^+] 232.0736, found 232.0741. Anal calcd for $C_{13}H_{12}O_4$ (232.24): C, 67.2; H, 5.2. Found: C, 67.2; H, 5.3.

7-Methoxywutaifuranol (12b).[19] To a solution of **10b** (48 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added DIBAl-H (1.0 M in DCM, 500 µL, 0.50 mmol) at -78 °C. After 0.5 h the reaction mixture was warmed to ambient temperature and stirred until the starting material was fully consumed (TLC). The reaction was quenched by addition of a satd. aq. solution of NH_4Cl (10 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 times 10 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **12b** (83 %, 34 mg, 0.17 mmol): colourless solid, mp 58-60 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.80 (d, J = 2.1 Hz, 1H), 7.23 (d, J = 1.2 Hz, 1H), 7.06 (d, J = 1.3 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 6.69 (dt, J = 15.9, 1.4 Hz, 1H), 6.40 (dt, J = 15.9, 5.3 Hz, 1H), 4.26 (td, J = 5.5, 1.6 Hz, 2H), 4.02 (s, 3H), 3.86 (t, J = 5.6 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 146.1, 146.0, 144.4, 134.0, 130.1, 129.8, 129.5, 112.1, 107.3, 104.5, 62.8, 55.8; IR (ATR) ν 3344 (bw), 1597 (s), 1467 (m), 1357 (m), 1146 (s); HRMS (EI) calcd for $C_{12}H_{12}O_3$ [M^+] 204.0786, found 204.0782.

7-Methoxywutaifuranal (11b).[19] To a solution of **12b** (9.4 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin's reagent (23.4 mg, 0.550 mmol). The reaction mixture was

stirred until the starting material was fully consumed (TLC) and then diluted with CH_2Cl_2 (5 mL). The solution was washed with a satd. aq. solution of $NaHCO_3/Na_2SO_3$ (3 times 5 mL) and once with brine. The organic layer was dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **11b** (97%, 9.0 mg, 0.044 mmol): colourless solid, mp 106-108 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.73 (d, J = 7.7 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 15.8 Hz, 1H), 7.45 (d, J = 1.3, Hz, 1H), 7.03 (d, J = 1.4 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 15.8, 7.7 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 193.7, 153.7, 146.2, 146.2, 146.0, 130.2, 129.6, 127.8, 111.5, 107.2, 105.3, 56.2; IR (ATR) v 1666 (s), 1591 (m), 1464 (s), 1340 (m); HRMS (EI) calcd for $C_{12}H_{10}O_3$ [M^+] 202.0630, found 202.0620.

9-Methoxy-7-nitro-2,5-dihydrobenzo[*b*]oxepine (32). To a solution of **29** (124 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added second generation Grubbs' catalyst **A** (21 mg, 5 mol %) and the reaction mixture was stirred at ambient temperature until full conversion of the starting material (TLC). The solvent was evaporated and the residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **32** (91%, 101 mg, 0.45 mmol): off-white solid, mp 105-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 2.6 Hz, 1H), 7.68 (d, J = 2.6 Hz, 1H), 5.91 (dm, J = 11.4 Hz, 1H), 5.55 (dm, J = 11.4 Hz, 1H), 4.71 – 4.66 (m, 2H), 3.96 (s, 3H), 3.59 – 3.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 152.4, 143.5, 137.7, 127.3, 125.4, 116.5, 106.0, 70.3, 56.4, 31.4; IR (ATR) v 1521 (m), 1484 (s), 1338 (s), 1272 (m), 1091 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ [M^+] 221.0688, found 221.0676.

9-Methoxy-2,5-dihydrobenzo[*b*]oxepine-7-diazonium tetrafluoroborate (34). *9-Methoxy-2,5-dihydrobenzo[b]oxepin-7-amine (**33**)*: A solution of **32** (816 mg, 3.70 mmol) in methanol/water (220 mL, 10 : 1 (v/v)) was cooled to 0 °C and NH_4Cl (3.27 g, 61.3 mmol) and Zn-dust (19.20 g, 295 mmol) were added in portions. The resulting suspension was warmed to ambient temperature und stirred until the starting material was fully consumed (TLC). The

reaction mixture was filtered through a pad of celite and washed with ethyl acetate. The filtrate was concentrated and the residue was dissolved in ethyl acetate (10 mL) and washed with brine. The organic layer was dried with $MgSO_4$, filtered and evaporated to furnish crude **33**, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, J = 2.6 Hz, 1H), 6.07 (d, J = 2.6 Hz, 1H), 5.81 (dm, J = 11.5 Hz, 1H), 5.45 (dm, J = 11.5 Hz, 1H), 4.56 – 4.51 (m, 2H), 3.82 (s, 3H), 3.66 (s (br.), 2H), 3.40 – 3.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 142.4, 139.8, 138.7, 127.8, 125.3, 107.1, 98.6, 70.8, 55.8, 31.6; IR (ATR) v 3438 (m), 3362 (m), 1598 (m), 1500 (s), 1227 (m), 1163 (m); HRMS (EI) calcd for $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1025, found 192.1015. *9-Methoxy-2,5-dihydrobenzo[b]oxepine-7-diazonium tetrafluoroborate (**34**)*: The residue from the previous step was dissolved in ethanol (7.4 mL) and cooled to 0 °C, followed by addition of aq. HBF_4 (48 wt-%, 970 µL, 7.40 mmol). *tert*-BuONO (982 µL, 7.40 mmol) was then added and the mixture was stirred at 0 °C for 0.25 h. The reaction mixture was warmed to ambient temperature, stirred for 1 h and diluted with diethyl ether (100 mL) to precipitate the diazonium salt. The resulting suspension was filtered through a Buchner funnel, the precipitate was washed with diethyl ether (10 mL) and dried in vacuo to furnish **34** (83%, 888 mg, 3.00 mmol): off-white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 – 8.16 (m, 2H), 6.15 (dt, J = 10.6, 5.9 Hz, 1H), 5.85 (dt, J = 10.6, 4.8 Hz, 1H), 4.93 (dm, J = 4.8 Hz, 2H), 3.87 (s, 3H), 3.68 (d, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.8, 152.5, 134.7, 130.1, 128.7, 127.6, 113.8, 105.6, 69.1, 57.3, 30.7; IR (ATR) v 2255 (m), 1568 (m), 1469 (m), 1273 (m), 1028 (s); HRMS (ESI) calcd for $C_{11}H_{11}N_2O_2$ $[M^+]$ 203.0821, found 203.0820.

Methyl-*(E)*-3-(9-methoxy-2,5-dihydrobenzo[*b*]oxepine-7-yl)acrylate (35). To a solution of **34** (145 mg, 0.5 mmol) in methanol (10 mL) were added $Pd(OAc)_2$ (2.8 mg, 2.5 mol %) and methyl acrylate (180 µL, 2.0 mmol) and the reaction mixture was stirred until the gas evolution had ceased. All volatiles were evaporated and the residue was dissolvend in MTBE (10 mL). The solution was washed with water (10 mL), the organic layer was separated and

the aqueous layer was extracted three times with MTBE (10 mL each). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **35** (78%, 102 mg, 0.39 mmol): colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 16.0 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 6.87 (d, J = 1.4 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 5.84 (dm, J = 11.6 Hz, 1H), 5.46 (dm, J = 11.6 Hz, 1H), 4.62 – 4.56 (m, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.49 – 3.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 152.3, 149.2, 144.7, 138.2, 130.5, 127.5, 125.6, 121.3, 117.1, 109.9, 70.5, 56.1, 51.7, 31.5; IR (ATR) ν 1709 (m), 1635 (m), 1492 (m), 1265 (s), 1149 (s); HRMS (ESI) calcd for $C_{15}H_{17}O_4$ $[M+H]^+$ 261.1127, found 261.1118.

***(E)*-3-(9-Methoxy-2,5-dihydrobenzo[*b*]oxepine-7-yl)prop-2-en-1-ol (36)**. To a solution of **35** (30 mg, 0.12 mmol) in THF (5 mL) was added DIBAl-H (1.0 M in CH_2Cl_2, 480 µL, 0.48 mmol) at -78 °C. The reaction mixture was allowed to warm to ambient temperature, stirred until the starting material was fully consumed (TLC) and then quenched by addition of a satd. aq. solution of NH_4Cl (2 mL). It was diluted with diethyl ether, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 times 5 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **36** (91%, 24 mg, 0.10 mmol): colourless oil; ^{1}H NMR (600 MHz, acetone-d_6) δ 6.97 (d, J = 1.9 Hz, 1H), 6.77 (d, J = 1.9 Hz, 1H), 6.51 (dt, J = 15.9, 1.7 Hz, 1H), 6.32 (dt, J = 15.9, 5.3 Hz, 1H), 5.81 (dtt, J = 11.6, 5.4, 2.3 Hz, 1H), 5.46 (dm, J = 11.6 Hz, 1H), 4.48 – 4.46 (m, 2H), 4.21 (ddd, J = 5.4, 5.4, 1.5 Hz, 2H), 3.98 (t, J = 5.6 Hz, 1H), 3.83 (s, 3H), 3.41 – 3.38 (m, 2H); ^{13}C NMR (150 MHz, acetone-d_6) δ 152.9, 147.2, 138.4, 133.9, 129.9, 129.4, 128.2, 125.7, 119.0, 109.3, 70.4, 62.7, 55.7, 31.4; IR (ATR) ν 3404 (bm), 1587 (m), 1498 (s), 1343 (m), 1150 (s), 1091 (s); HRMS (ESI) calcd for $C_{14}H_{16}O_3$ $[M^+]$ 232.1099, found 232.1098.

***(E)*-3-(9-Methoxy-2,5-dihydrobenzo[*b*]oxepine-7-yl)acrylaldehyde (37)**. A solution of **36** (15.4 mg, 0.066 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and Dess-Martin's reagent (33.5 mg, 0.790 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred until full conversion of the starting material (TLC). It was diluted with CH_2Cl_2 (5 mL) and washed three times with a satd. aq. solution of $NaHCO_3/Na_2SO_3$ (5 mL each) and once with brine. The organic layer was dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures as eluent, to furnish **37** (87%, 13.2 mg, 0.057 mmol): yellowish oil; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.67 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 15.9, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 6.73 (dd, J = 15.9, 7.7 Hz, 1H), 5.86 (dtt, J = 11.6, 5.4, 2.3 Hz, 1H), 5.52 (dm, J = 11.6 Hz, 1H), 4.56 – 4.53 (m, 2H), 3.90 (s, 3H), 3.49 – 3.46 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 193.4, 153.4, 152.8, 150.3, 138.9, 130.9, 128.4, 128.1, 125.7, 122.1, 111.1, 70.4, 55.9, 31.2; IR (ATR) ν 1673 (s), 1623 (m), 1588 (m), 1127 (m); HRMS (ESI) calcd for $C_{14}H_{15}O_3$ $[M+H]^+$ 231.1021, found 231.1012.

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Supporting Information Available statement

Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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