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# Feruloylbenzotriazole and Weinreb Amide as Bioinspired Building Blocks: A Reactivity Study towards O-, N-, S-, and C-Nucleophiles

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A versatile route for the conversion of ferulic acid into biologically relevant molecules is presented. The compatibility of a number of protection and activation strategies with the 1,2-addition of a variety of O-, N-, S-, and C-nucleophiles to ferulic acid is evaluated. In particular, this report contains the first systematic study of the addition of (hetero)aryllithium reagents to 3-phenylpropenoyl Weinreb amides. The relevance of this "bioinspired" method is illustrated by the synthesis of a number of natural products or analogues, such as zingerone, curcuminoids, and (heteroaryl) chalcones.

## Introduction

The feruloyl moiety is present in a vast array of natural products, and may be considered to be a "privileged fragment" (Figure 1). In nature, feruloyl-SCoA (**8**) is the precursor to curcumins (**2**),[1] chalcones (**3**),[2] pungent agents such as gingerols (**4**) and shogaols (**5**), and ferulic acid itself (**1**).[3] This biosynthetic pathway is particularly significant in the *Zingiberaceae* (ginger family). Zingerone (**6**), a compound related to the pungency of ginger, is produced during cooking by a retro-aldol reaction of gingerol. The biosynthesis of feruloyl-SCoA (**8**) starts from phenylalanine (**7**), which itself originates from the shikimate pathway (Scheme 1, i).

All of the compounds shown in Figure 1 have been found to have interesting biological activities, not in the least in the oncological domain. However, in our opinion, and that of others, their benefit–risk profiles need to be defined, and

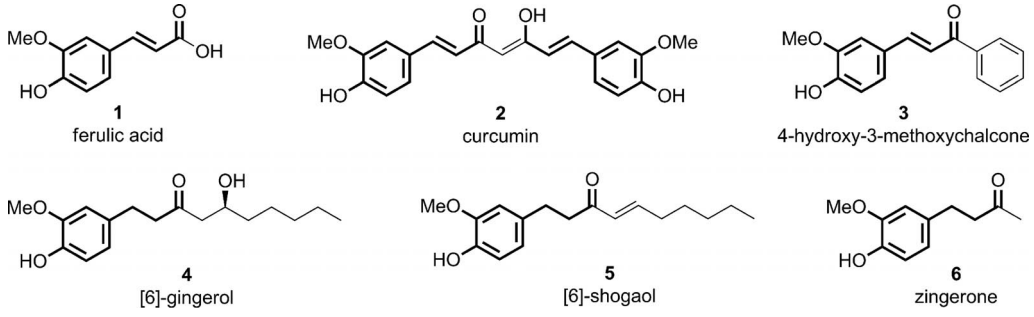


Figure 1. The feruloyl moiety is a "privileged fragment", present in a variety of biologically relevant natural products.

major issues such as their toxicities, and their poor selectivities and bioavailabilities, remain to be tackled.[4]

Therefore, we argue that there is a need for synthetic analogues of curcumins, gingerols, chalcones, etc. The study of such analogues might aid in elucidating structure–property and structure–activity relationships.[5,6] Hence, we have recently started exploring the potential of ferulic and related cinnamic acids as building blocks for the preparation of such substances. Significant work had been carried out earlier on cinnamic acid: in that context, cinnamoyl-benzotri-

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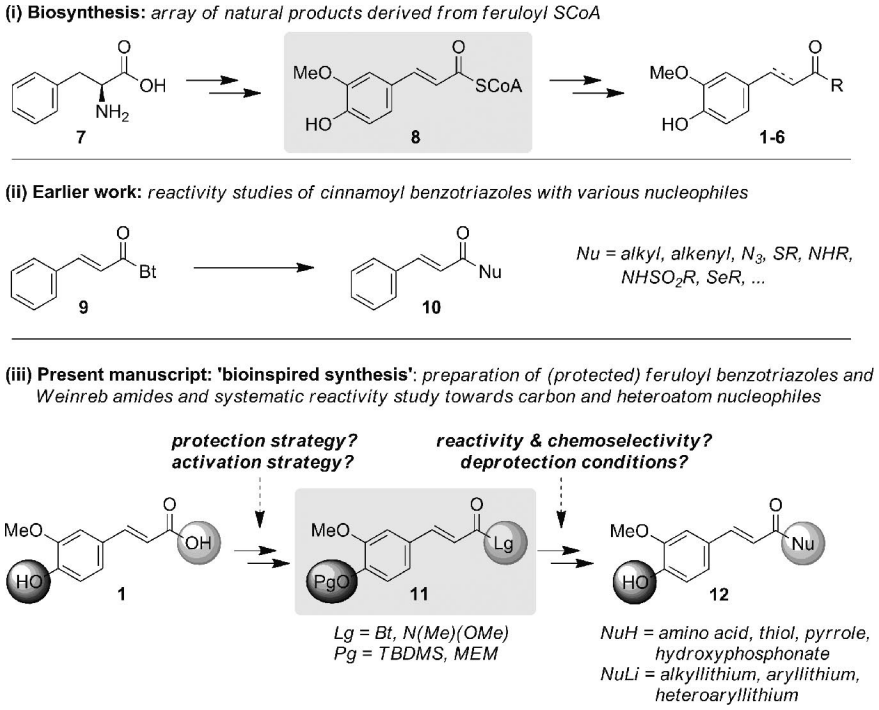



Scheme 1. Parallels between our "bioinspired" synthetic strategy, the biosynthesis of feruloylated compounds, and earlier synthetic work; TBDMS = *tert*-butyldimethylsilyl, MEM = (2-methoxyethoxy)methyl.

azole (**9**) proved to be a versatile intermediate to which a variety of nucleophiles were successfully added (Scheme 1, ii).[7–11]

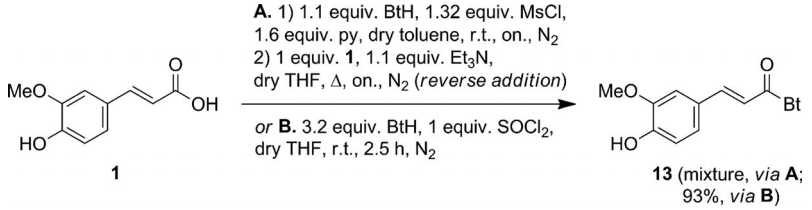
In this paper, we describe a versatile, "bioinspired" route to biologically relevant molecules, starting from ferulic acid. We have evaluated the compatibility of a number of protection and activation strategies with the 1,2-addition of a variety of carbon and heteroatomic nucleophiles to activated ferulic acid derivatives **11** (Scheme 1, iii). In particular, this report includes the first systematic study of the addition of (hetero)aryllithium reagents to activated feruloyl (or other cinnamoyl-type) Weinreb amides.

## Results and Discussion

The activation of ferulic acid by conversion into the corresponding acid chloride was considered to be unattractive, because of the difficult preparation and the limited stability of the acid chloride. Indeed, literature references to feruloyl chloride[12,13] and protocols for its preparation are scarce.[14] Taking advantage of its superior stability and versatility, *N*-feruloylbenzotriazole (**13**) was chosen as the central intermediate in the first part of our study.

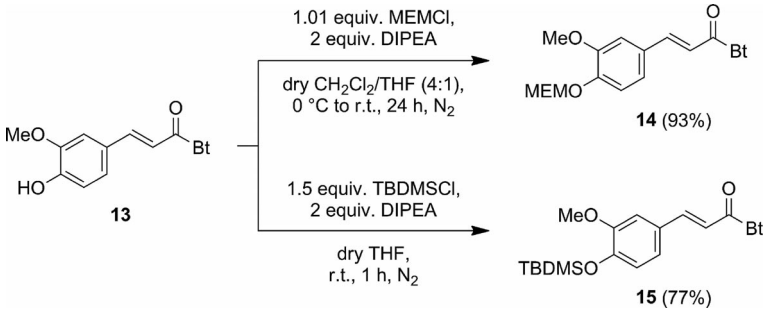
### Synthesis of *N*-Feruloyl-Substituted Benzotriazoles

In an initial attempt to synthesize *N*-feruloylbenzotriazole (**13**), previously reported conditions optimized for the activation of arene carboxylic acids were evaluated (Scheme 2).[15] However, the reaction of ferulic acid with *N*-(1-methylsulfonyl)benzotriazole, which is readily obtained by direct treatment of benzotriazole with methanesulfonyl chloride and pyridine, yielded the desired compound (i.e., **13**) in unacceptable purity and yield. An alternative approach, however, using thionyl chloride and excess 1*H*-benzotriazole,[16] rapidly gave *N*-feruloylbenzotriazole (**13**). This intermediate was obtained in excellent yield and purity after trituration of the crude reaction mixture with diethyl ether. Importantly, this activated carboxylic acid is stable when exposed to air or water at 20 °C, and it can be stored for over a year at –20 °C.




Scheme 2. Synthesis of *N*-feruloylbenzotriazole (**13**).




Scheme 3. Preparation of MEM- and TBDMS-protected *N*-feruloylbenzotriazoles **14** and **15**; DIPEA = diisopropylethylamine.

To broaden the utility of **13** as a synthetic intermediate, its phenolic hydroxy group was protected as a MEM ether (in **14**; Scheme 3). Here, the use of excess (2-methoxyethoxy)methyl chloride is to be avoided, so that the formation of 1-[(2-methoxyethoxy)methyl]-1*H*-benzotriazole as a by-product is prevented. Also, the corresponding TBDMS ether (i.e., **15**) was obtained from **13** in very good yield by a standard protocol.

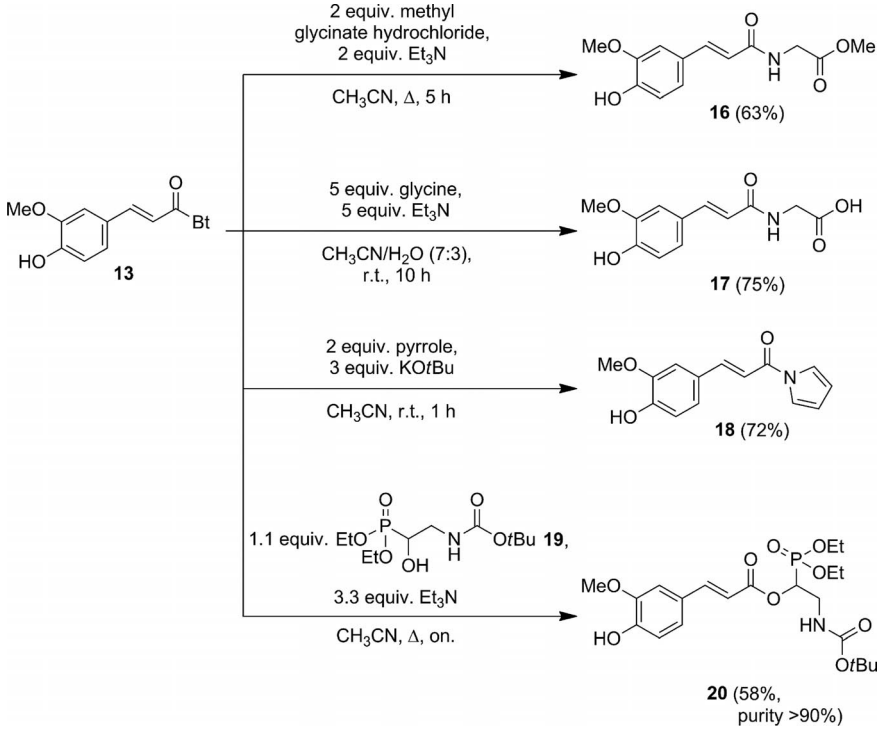
### Reactivity of *N*-Feruloylbenzotriazoles

*N*-Feruloylbenzotriazole (**13**) is a versatile intermediate that can undergo mild condensation reactions with a variety of heteroatomic nucleophiles (Scheme 4). Reaction with methyl glycinate,[17] for example, gave the corresponding feruloyl-substituted amino acid methyl ester **16** in good yield after chromatographic purification. Such ferulic acid–amino acid conjugates have been found to have enzyme-inhibitory activities,[18] and they have been used in the preparation of an investigational prodrug for delivery to the colon of 5-aminosalicylic acid.[19]

In similar fashion, *N*-feruloylglycine (**17**) was obtained in good yield without the use of protecting groups. In this case, however, the use of a larger excess of glycine was required so as to avoid reaction of the desired product (i.e., **17**) with a second molecule of the acylbenzotriazole.

This feruloylamide synthesis can also be used for the synthesis of heterocyclic aromatic amines. Reaction of **13** with pyrrole gave *N*-feruloylpyrrole (**18**) in good yield under very mild conditions. For this transformation, a number of bases were evaluated in various amounts ($Et_3N$, KO*t*Bu, NaH, $Na_2CO_3$, $CsCO_3$, and no base); the best results were obtained using 3 equiv. of KO*t*Bu.

Furthermore, *N*-feruloylbenzotriazole (**13**) is also susceptible to condensation with O-nucleophiles, such as the highly functionalized α-hydroxyphosphonate **19** (Scheme 4). For this transformation, no reaction was observed under ambient conditions in acetonitrile; overnight

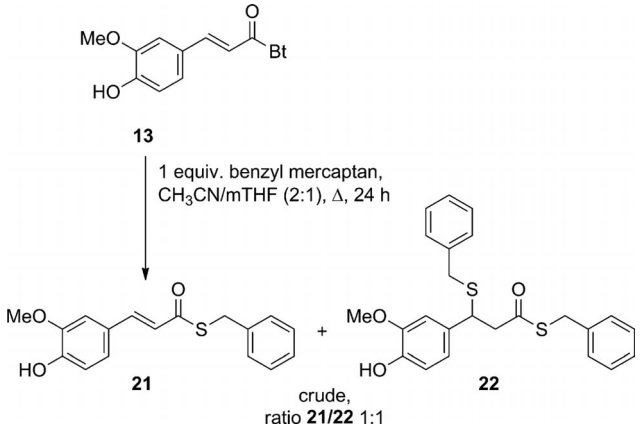



Scheme 4. Reactivity of *N*-feruloylbenzotriazole (**13**) towards N- and O-nucleophiles.

heating to reflux temperature, however, resulted in a nearly clean conversion into ferulate **20**.

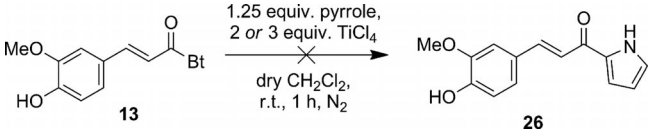
The ambident electrophilic nature of *N*-feruloylbenzotriazole is illustrated in its reaction with benzyl mercaptan, which gave a 1:1 mixture of **21** and **22**, along with remaining starting material, after prolonged heating in a mixture of acetonitrile and 2-methyltetrahydrofuran (Scheme 5). When THF was used as a solvent, reaction at room temperature gave negligible conversion (<10%). An investigation of the 1,2- or 1,4-directing effect of additives on the reactions with S-nucleophiles[20] is ongoing, and the results will be presented in due course.




Scheme 5. *N*-Feruloylbenzotriazole (**13**) behaves as an ambident electrophile towards benzyl mercaptan; mTHF = 2-methyltetrahydrofuran.

An interesting transformation of MEM-protected *N*-feruloylbenzotriazole **14** is found in its reaction with enolates.[21] As shown in Scheme 6, this approach may serve as a convenient entry to biologically relevant scaffolds such as unsymmetrical curcuminoids **24** and **25**. Evaluation of the compatibility of **14** with soft enolization approaches[22,23] is ongoing.

Various pyrroles and indoles have been shown to undergo mild Friedel–Crafts acylation with *N*-acylbenzotriazoles,[24] with a correct choice of Lewis acid[25] and solvent giving excellent regiocontrol.[26] However, in the case of *N*-feruloylbenzotriazole (**13**), an α,β-unsaturated acylbenzotriazole, acylation conditions did not give a clean conversion into 2-pyrrolyl-chalcone **26** (Scheme 7). Instead, a mixture containing the starting material, products of double addition, and other unwanted material was obtained. The desired chalcone (i.e., **26**) was, however, obtained by another route (see Scheme 17).

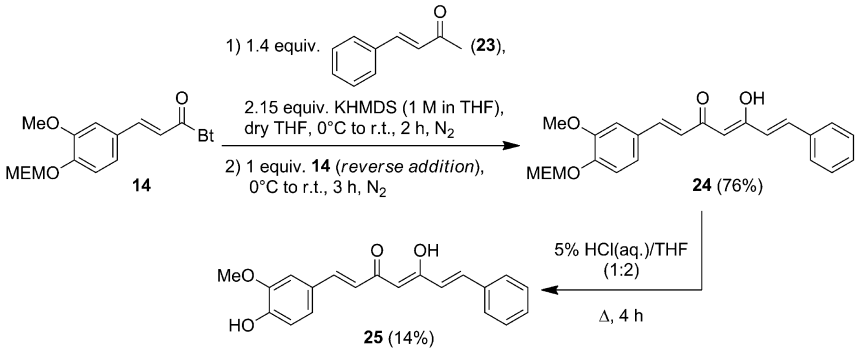



Scheme 7. *N*-Feruloylbenzotriazole (**13**) is not amenable to Friedel–Crafts-type acylations with pyrroles.

Reaction of MEM-protected *N*-feruloylbenzotriazole **14** with an alkyllithium reagent, followed by quench with water at –78 °C, gave a tertiary alcohol (**29a** or **29b**, Scheme 8). No trace of the corresponding ketone (i.e., **28**) was detected in the crude reaction mixtures. Apparently, complex **27** is non-existent or unstable, even when the reaction mixture was kept at –78 °C. Treatment of **14** with 2-lithiofuran also resulted in a complex reaction mixture, containing traces of the double addition product but not of ketone **28**.

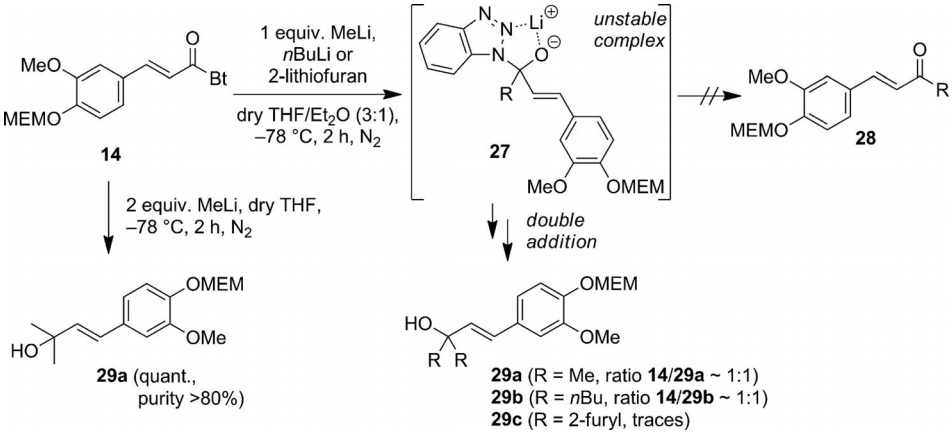
## Synthesis of *N*-Feruloyl Weinreb Amides

From the above, it follows that the preparation of ferulic-acid-derived ketones requires the use of an *N*-feruloyl Weinreb amide intermediate. Hence, the direct preparation of Weinreb amide **30** from ferulic acid **1** was attempted under Steglich conditions. Complete consumption of the starting material was observed, but numerous by-products were present. Column chromatography gave Weinreb amide **30** in poor yield and moderate purity (Scheme 9). Activation of the carboxylic acid using thionyl chloride (1 equiv., dry THF, room temperature, 2 h), or using the conditions of Sanders,[27] also yielded complex reaction mixtures; hence, no further purification efforts were made. The by-products formed in these reactions were identified as dimers and trimers of ferulic acid, formed due to the presence of the free phenolic OH group.

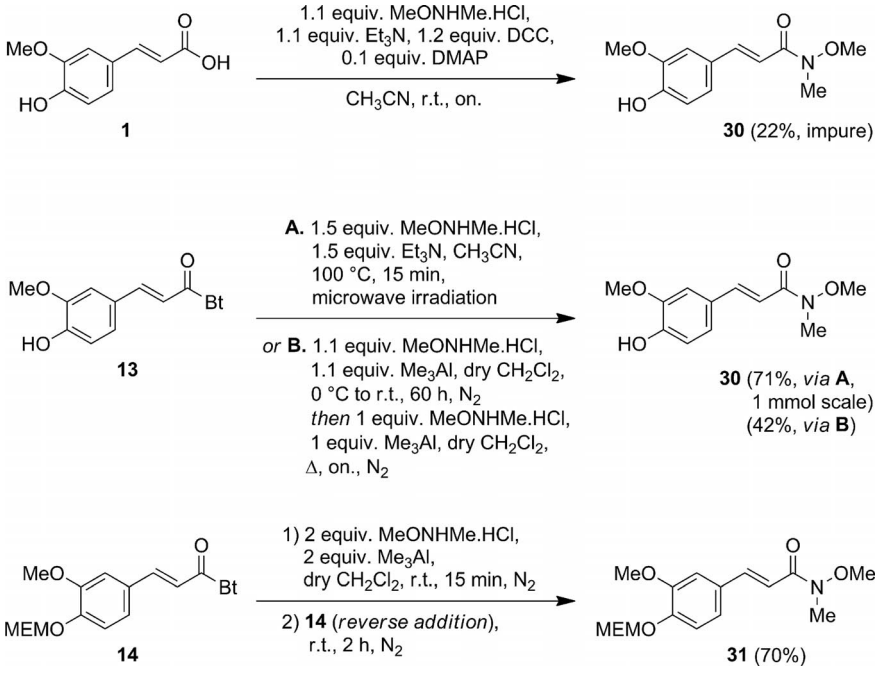



Scheme 6. Conversion of MEM-protected *N*-feruloylbenzotriazole **14** into curcuminoids **24** and **25**; KHMDS = potassium hexamethyldisilazide.




Scheme 8. Reaction of MEM-protected *N*-feruloylbenzotriazole **14** with alkyllithium reagents gave the corresponding tertiary alcohols **29a**–**29c**.




Scheme 9. Optimized conditions for the preparation of Weinreb amides **30** and **31** from different ferulic acid derivatives; DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

When *N*-feruloylbenzotriazole (**13**) was used as a substrate with *N*,*O*-DMHA·HCl (*N*,*O*-dimethylhydroxylamine hydrochloride) and triethylamine under ambient conditions, poor conversion was observed.[28] With both conventional and microwave heating, the reaction proved difficult to control: the optimal temperature for the conversion of **13** into **30** is around 100 °C, but side-reactions take place above 70 °C, and vigorous decomposition of *N*,*O*-DMHA occurs above 115 °C. Moreover, scale-up proved tedious. Nevertheless, under the strictly controlled microwave conditions shown in Scheme 9, a good yield of the desired *N*-feruloyl Weinreb amide (i.e., **30**) was obtained (71%).

In an alternative approach, 50% consumption of *N*-feruloylbenzotriazole (**13**) was obtained in a prolonged reaction with dimethylaluminium *N*-methoxy-*N*-methylamide (1.1 equiv.) at room temperature. On addition of an extra equivalent of trimethylaluminium and *N*,*O*-DMHA·HCl, and leaving the reaction overnight at reflux temperature, all of the starting material was consumed. Nevertheless, Weinreb amide **30** was isolated in a fairly low yield (42%).

The disappointing reaction outcomes observed for **1** and **13** prompted us to evaluate Weinreb amide synthesis using MEM-protected feruloylbenzotriazole **14**. An attempt using sodium hydride (2.4 equiv.) and *N*,*O*-DMHA·HCl (1.2 equiv.) gave a mixture of **31** and the bis adduct. Optimal yields of Weinreb amide **31** were obtained in the presence of trimethylaluminium at room temperature (Scheme 9). Under these mild conditions, only minor amounts of by-products were formed, and a very limited degree of deprotection was observed. Following extraction

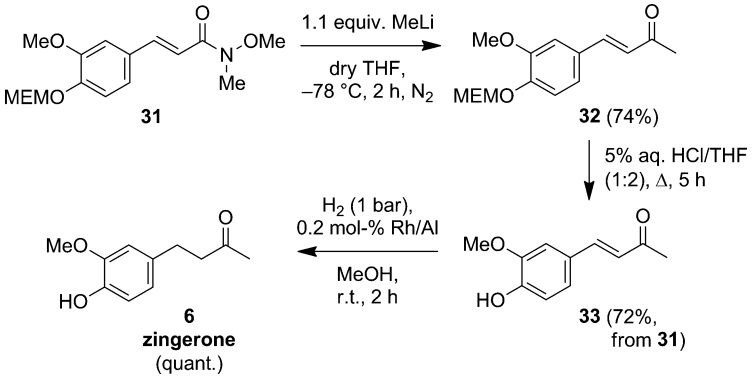
and crystallization from absolute ethanol, Weinreb amide **31** was obtained in excellent purity. When the experiment was repeated with added triethylamine, in order to suppress MEM-deprotection, more by-products were formed.

### Reactivity of MEM-Protected *N*-Feruloyl Weinreb Amide 31

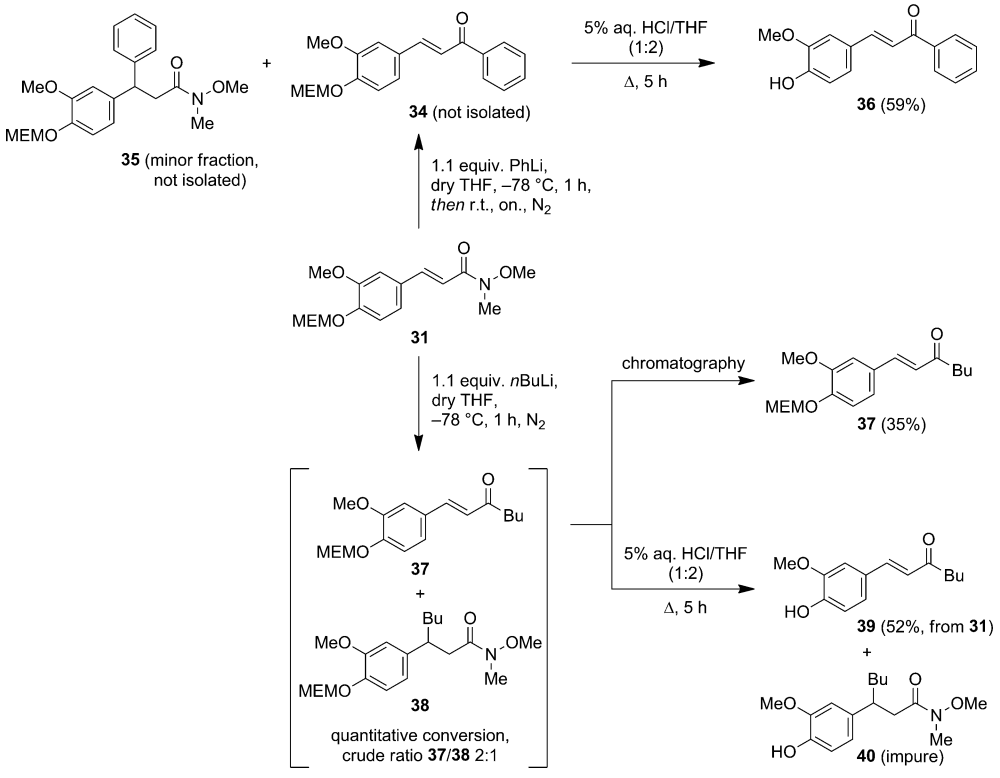
MEM-protected *N*-feruloyl Weinreb amide **31** offers a versatile approach to a variety of natural and "bioinspired" ketones with pharmacological relevance.[29,30] Treatment with methyllithium, for example, gave methyl ketone **32** in good yield and purity after simple extraction (Scheme 10). Subsequent MEM-deprotection and hydrogenation of the alkene gave the natural product zingerone (**6**) in good yield.

Similarly, reaction between MEM-protected *N*-feruloyl-substituted Weinreb amide **31** and phenyllithium (1.1 equiv.) gave the corresponding chalcone (i.e., **34**; Scheme 11). To a minor extent, formation of the 1,4-addition product (i.e., **35**) was observed. MEM-deprotection yielded 1,3-diarylpropenone **36**. This compound does not readily crystallize from ethanol, but it was obtained in high purity by column chromatography.

Addition of excess *n*-butyllithium (2 equiv.) to **31** gave an unfavourable outcome: the formation of several unidentified by-products was observed; one of them was formed in an equal amount to the desired ketone. Interestingly, reaction with 1.1 equiv. of *n*-butyllithium gave full conversion into a mixture of the expected 1,2-addition product **37** and 1,4-adduct **38** in a 2:1 ratio (Scheme 11). Compound **37** was




Scheme 10. Illustration of the use of MEM-protected *N*-feruloyl-substituted Weinreb amide **31** for the synthesis of ketones: preparation of zingerone (**6**).




Scheme 11. Ketone synthesis from Weinreb amide **31**.

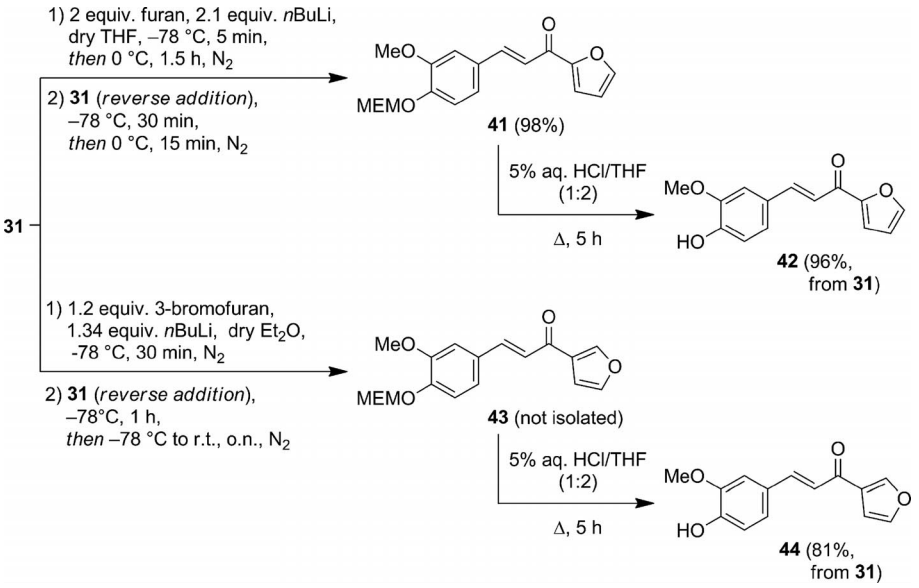
isolated in 35% yield by column chromatography. In a second, identical run, the mixture of **37** and **38** was deprotected under standard conditions, and chromatographic separation gave heptenone **39** in excellent purity. Weinreb amide **40** was obtained as an impure substance, but its structure was confirmed spectroscopically. It may be worth noting that nucleophilic attack of *n*BuLi in a less polar reaction medium (THF/$Et_2O$/hexane, 5:5:3) resulted in a small improvement in the 1,2/1,4-addition ratio. The addition of $ZnCl_2$ had the opposite effect, and led to a lower 1,2/1,4-addition ratio.

Yields similar to those of **36** and **39** were obtained by Kumar and co-workers for the addition of *n*BuLi and phenyllithium to benzoyl and cinnamoyl Weinreb amides.[31]

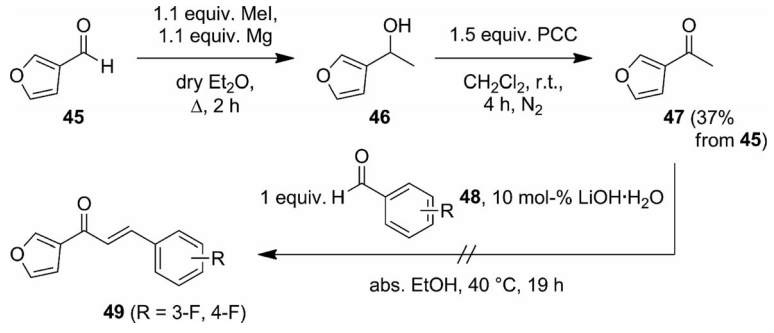
MEM-protected *N*-feruloyl-substituted Weinreb amide **31** reacted with 2-lithiofuran in a clean and almost quantitative reaction (Scheme 12). Subsequent deprotection of the phenolic hydroxy group gave furyl-chalcone **42** in excellent yield. In a similar fashion, a good yield of the pure regioisomeric ketone **44** was obtained by lithium–halogen exchange of 3-bromofuran, deprotection, and purification by column chromatography.

It should be noted that while we[32] and others[33] have shown that 1-(2-furyl)-3-phenylprop-2-en-1-ones are also accessible by a Claisen–Schmidt condensation using 2-acetylfuran, the same is not true of the 3-furyl analogues using 3-acetylfuran **47** (Scheme 13).[34,35] Indeed, literature reports of aldol reactions with 3-acetylfuran, and of 1-(3-furyl)-3-arylprop-2-en-1-ones in general, are scarce. To the best of our knowledge, only a single protocol for the preparation of such a compound has been published to date: a Pd-catalysed carbonylative coupling of 3-(tri-*n*-butylstannyl)furan and 2-phenyliodoethene gave the product in 40% yield.[36] Thus, the pathway presented here using activated cinnamoyl equivalents is a more convenient route to 3-furyl-chalcones.

Lithiated thiaheterocycles also react successfully with MEM-protected *N*-feruloyl-substituted Weinreb amide **31**. Attack of 2-lithiothiophene gave a fair yield of the pure 2-thienyl ketone (i.e., **50**) after crystallization from absolute ethanol (Scheme 14). Direct submission of the crude **50** to MEM-cleavage, and purification by column chromatography gave 1-(2-thienyl)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-en-1-one (**51**) in excellent yield (89% from **31**).

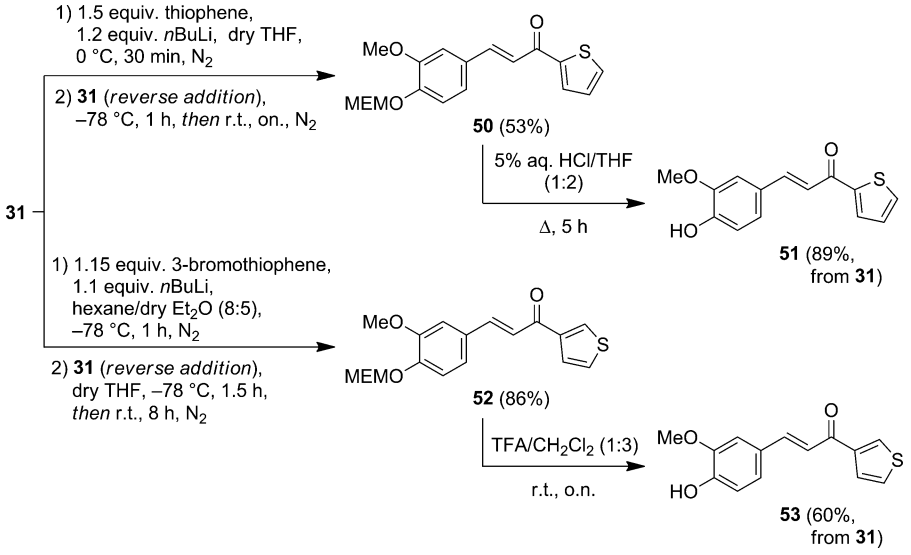



Scheme 12. Conversion of Weinreb amide **31** into furyl-chalcones.




Scheme 13. Aldol reaction of 3-acetylfuran **47** is not a straightforward route to 3-furyl-chalcones; PCC = pyridinium chlorochromate.

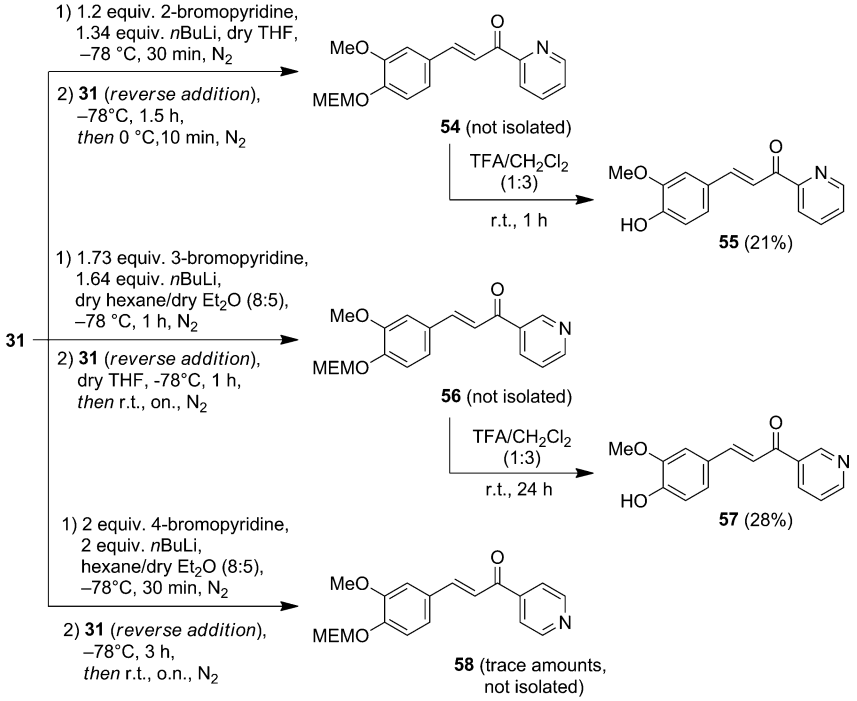
  




Scheme 14. Conversion of Weinreb amide **31** into thienyl-chalcones **50**–**53**.

For the synthesis of 3-thienyl regioisomer **53**, Weinreb amide **31** was treated with 3-lithiothiophene, prepared from 3-bromothiophene (1.2 equiv.) and *n*BuLi (1.34 equiv.). Although the desired intermediate (i.e., **52**) was obtained, the reaction was more sluggish than that with 2-lithiothiophene, and several by-products were formed in the reaction mixture. Based on LC/MS data, one of these compounds was identified as the product of butyl addition, formed due to the presence of excess *n*BuLi. Another by-product was **50**, presumably formed by halogen dance rearrangement of 3-lithiothiophene.[37,38]

In a subsequent attempt, hexane/diethyl ether was chosen as a solvent mixture in order to promote regioselective lithiation at the 3-position,[39] and a small excess of 3-bromothiophene was used (Scheme 14). Under these optimized conditions, **52** was obtained in high yield and purity, and was immediately deprotected to give **53** (combined yield of 60% over two steps). Good crystallization yields for **53** were only obtained starting from sufficiently pure **52**, as obtained using the optimized protocol. For characterization of intermediate **52**, a small product sample underwent extra purification by column chromatography over aluminium oxide.




Scheme 15. Conversion of Weinreb amide **31** into pyridyl-chalcones **54**–**58**.

These propenones are biologically relevant, as 3-thienyl-chalcones have been found to have antimicrobial and anti-cancer properties at micromolar concentrations in in vitro models.[40,41]

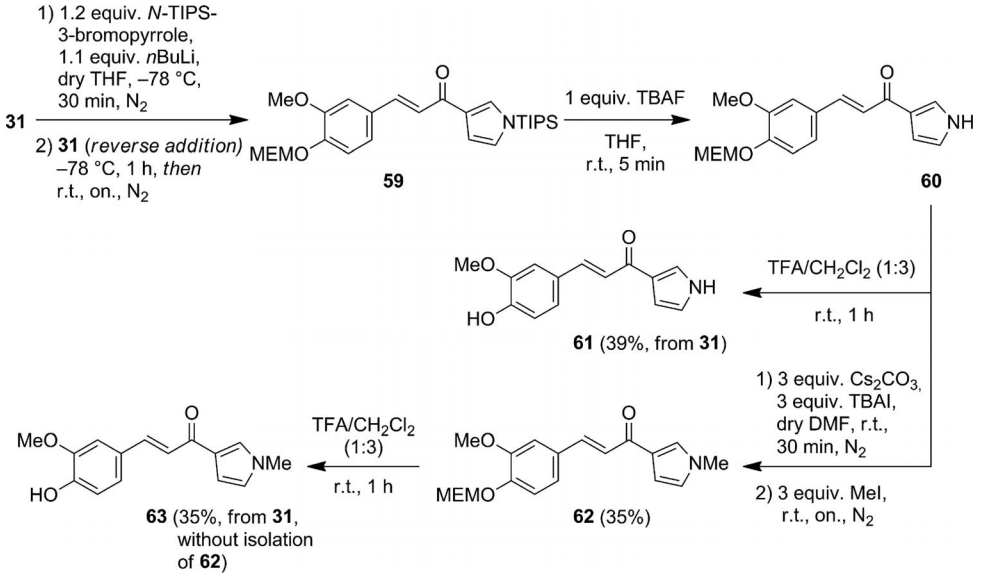
Pyridyl ketones are also accessible from Weinreb amide **31** (Scheme 15). Reaction with 2-lithiopyridine, for example, gave a fairly clean conversion into ketone **54**. A minor amount of the butyl ketone was obtained, due to the small excess of *n*BuLi used. Unfortunately, purification of the crude product proved difficult, and the pure MEM-protected ketone was therefore not isolated. Moreover, this product proved to be unstable at room temperature. Therefore, no further attempts at the isolation of **54** were made, and the crude product was immediately subjected to MEM-deprotection. Under the conditions used earlier [HCl (5% aq.)/THF, reflux], a complex reaction mixture was formed. However, treatment with TFA (trifluoroacetic acid) in dichloromethane at room temperature yielded 2-pyridyl-chalcone **55** in high purity after flash chromatography over silica and subsequent crystallization from absolute ethanol.

Reaction of **31** with 3-lithiopyridine proceeded significantly more slowly: using the procedure described above for the synthesis of 2-pyridyl ketone **54**, full conversion of the starting material was only obtained after prolonged reaction times, warming to room temperature, and addition of extra lithiopyridine reagent. When a solvent mixture of hexane and diethyl ether (8:5) was used, however, a swift conversion into feruloylpyridine **56** was observed (Scheme 15). Isolation of **56** proved difficult, and required chromatography followed by crystallization. Therefore, the crude product was submitted directly to a mild deprotection step using TFA, which gave the desired 3-pyridyl-chalcone (i.e., **57**) in high purity after crystallization from absolute ethanol. Closely related cinnamoyl pyridines were recently reported to be PAR1 antagonists with in vitro anti-aggregation properties and potent in vivo antithrombotic activity in rats.[42]

Attempts at the isolation of 4-pyridyl-chalcone **58** failed (Scheme 15). As 4-bromopyridine is prone to self-condensation, it is commercially available as its (stable) hydrochloride salt. In a first unsuccessful attempt to synthesize **58**, the optimized procedure for the preparation of **54** was used, with the addition of an extra equivalent of *n*BuLi to neutralize the HCl salt. In a second attempt, 4-bromopyridine was isolated before the reaction by neutralization of the hydrochloride salt with sodium carbonate (5% aq.) and extraction with diethyl ether.[43] The free 4-bromopyridine was immediately lithiated, and Weinreb amide **31** was added. This approach yielded a mixture containing the product of butyl addition as the major constituent, together with traces of the desired product (i.e., **58**). In a final attempt, 4-bromopyridine was converted into the corresponding Grignard reagent by reaction with isopropylmagnesium chloride. Subsequent reaction with **31** again gave traces of **58**, amongst a multitude of by-products.

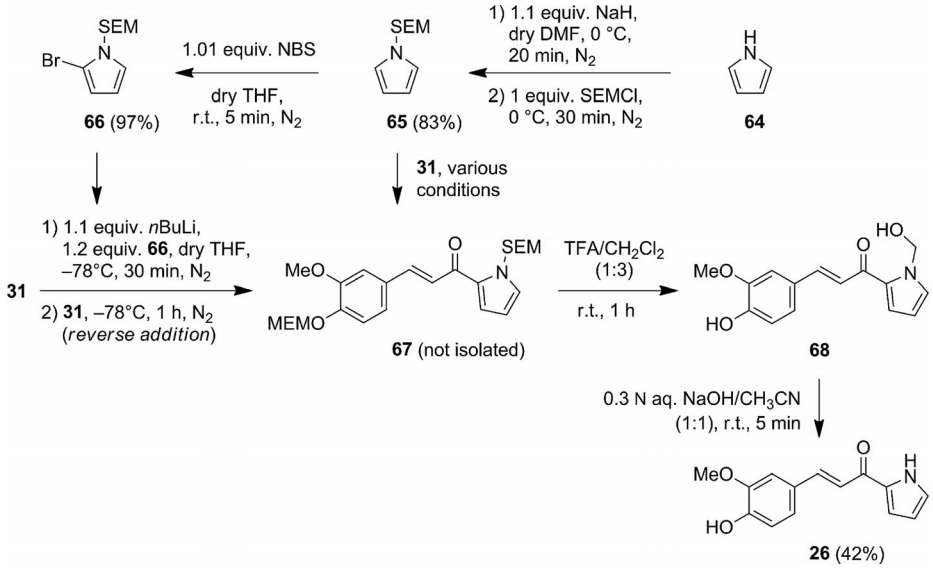
In conclusion, the preparation and deprotection of pyridyl-chalcones from Weinreb amide **31** proved more difficult than was found for the corresponding furyl and thienyl analogues. The results of our evaluation of alternative lithiation and deprotection conditions will be reported in due course.

MEM-protected *N*-feruloyl-substituted Weinreb amide **31** also provides a route to 3-pyrrolyl-chalcones (Scheme 16). Upon lithium–halogen exchange of commercially available 3-bromo-1-TIPS-pyrrole (TIPS = triisopropylsilyl),[44] and subsequent reaction with **31**, complete consumption of the Weinreb amide was observed. A mixture of **59**, **60**, and minor impurities was obtained, for which the ratio **59**/**60** varied over different runs. Complete conversion into **60** was easily obtained by treatment with TBAF (tetrabutylammonium fluoride) under mild conditions. Given the stability problems often encountered with pyrroles, subsequent removal of the MEM protecting group was performed using the milder TFA protocol. Purification by column chromatography gave 3-(4-hydroxy-3-methoxyphenyl)-




Scheme 16. Conversion of Weinreb amide **31** into 3-pyrrolyl-chalcones **59**–**63**; TBAI = tetrabutylammonium iodide.




Scheme 17. Conversion of Weinreb amide **31** into 2-pyrrolyl-chalcone **26**; NBS = *N*-bromosuccinimide.

1-(3-pyrrolyl)prop-2-en-1-one (**61**) in good purity and 39% overall yield (from **31**).

*N*-Functionalized 3-pyrrolyl-chalcones, such as *N*-methyl analogue **63**, can be obtained by alkylation and MEM cleavage (Scheme 16). Methylation of **60** proceeded well under mild conditions. Intermediate **62** was immediately subjected to MEM-cleavage conditions to give the desired *N*-methyl-3-pyrrolyl-substituted chalcone (i.e., **63**) in high purity after purification by column chromatography or preparative TLC. MEM-protected ketone intermediate **62** could also be isolated in excellent purity by crystallization from absolute ethanol. Interestingly, while free pyrrole **61** proved to be reasonably stable, its *N*-methylated analogue **63** was found to be highly photolabile.

To obtain the corresponding 2-pyrrolyl-chalcone **26**, the *ortho*-directing SEM [2-(trimethylsilyl)ethoxymethyl] group was introduced onto 1*H*-pyrrole (Scheme 17).[45] Lithiation of the resulting 1-SEM-1*H*-pyrrole (i.e., **65**) with an equimolar amount of *n*BuLi was sluggish, even when the reaction was run at room temperature. Hence, subsequent reaction with Weinreb amide **31** gave the corresponding butyl ketone as a major product. This apparent inertness of 1-SEM-1*H*-pyrrole **65** has also been observed by Muchowski et al.[46]

In an attempt to achieve higher reactivity, a bromide substituent was introduced at the 2-position of 1-SEM-pyrrole under mild conditions (Scheme 17).[47] Filtration through a silica plug gave **66**, which proved to be more susceptible to lithiation under standard conditions. 2-Pyrrolyl-chalcone **67** was obtained upon reaction with **31**, and it was immediately submitted to TFA-mediated deprotection of the SEM and MEM ether moieties. Curiously, these conditions did not give the free pyrrole (i.e., **26**), but rather its *N*-(hydroxymethyl) analogue **68**. Compound **68** proved to be surprisingly stable, and its formation was confirmed by LC/MS and $^1$H NMR spectroscopic data. After an extra hydrolysis step under basic conditions, and purification by column chromatography, pyrrole **26** was obtained in 42% overall yield (from **31**).

## Conclusions

A bioinspired route for the conversion of ferulic acid into physiologically relevant molecules is presented. A convenient preparation of (MEM-protected) feruloylbenzotriazoles **13** and **14**, and the regioselective 1,2-addition of O-, N-, and C-nucleophiles to this versatile intermediate were demonstrated. The S-nucleophile benzyl mercaptan was found to add in both a 1,2- and 1,4-fashion. Next, MEM-protected feruloyl-substituted Weinreb amide **31** was shown to allow convenient access to a wide variety of heteroaryl-substituted chalcones upon addition of (hetero)aryllithium reagents. In most cases, competing 1,4-addition and addition of *n*-butyllithium could be suppressed by choice of the correct reaction conditions, namely the use of a limited excess of the (hetero)aryllithium compound, and the use of excess heteroaryl compound with respect to *n*-butyllithium. The MEM group was found to be a stable protecting group, and its removal proved straightforward in most cases. Our method is not without its limitations: the synthesis and deprotection of pyridyl-chalcones proved tedious, and optimization remains necessary. The relevance of our "bioinspired" method was illustrated by the synthesis of a number of natural products or their analogues, such as zingerone, curcuminoids, and (heteroaryl) chalcones.

## Experimental Section

**General Remarks:** All reagents were purchased from commercial suppliers (Sigma–Aldrich, Acros, TCI), and were used without further purification. Solvents were dried with sodium (THF, diethyl

ether) or calcium hydride (dichloromethane), and distilled before use. Other solvents were purchased from commercial suppliers and used as supplied. The petroleum ether used during product purification steps had a boiling range of 40–60 °C.

Microwave reactions were carried out in a CEM Benchmate apparatus (maximum power: 300 W). Crude reaction mixtures were analysed by LC/MS/UV. Thin-layer chromatography was carried out on silica gel $60F_{254}$ plates (Merck). Preparative HPLC separations were carried out using a ZORBAX XDB-C18 column (21.2 × 150 mm, 5 μm).

High-resolution $^1H$ and $^{13}C$ magnetic resonance (NMR) spectra were recorded with Jeol Eclipse+ 300 or Bruker AVANCE III 400 FT NMR spectrometers in deuterated solvents. Chemical shifts were calibrated using tetramethylsilane, which was used as an internal reference, unless otherwise indicated. Peak assignments were obtained with the aid of DEPT, HSQC, HMBC, and COSY spectra. Attenuated total reflection (ATR) IR spectra were recorded with a Perkin–Elmer Spectrum BX spectrometer, equipped with a ZnSe crystal, at room temperature (neat). Low-resolution mass spectra were recorded with an Agilent Technologies 1100 series VL mass spectrometer (ESI, 70 eV). HRMS analyses were carried out with an HPLC coupled to an Agilent Technologies 6210 series time-of-flight mass spectrometer equipped with an ESI/APCI-multimode source. Melting points were measured with a Büchi B-540 apparatus.

**4-(4-Hydroxy-3-methoxyphenyl)butan-2-one (zingerone, 6):** (3*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (**33**; 0.120 g, 0.62 mmol, 1 equiv.) was dissolved in methanol (4 mL), and powdered Rh on alumina (0.5 wt.-%; 24 mg, 0.2 mol-%) was added. The reaction mixture was put under a hydrogen atmosphere (1 bar). The mixture was stirred at room temperature for 2 h, then it was filtered through Celite, and the filter cake was rinsed with methanol. The solvent was removed under reduced pressure to give pure 4-(4-hydroxy-3-methoxyphenyl)butan-2-one (**6**; 120 mg, quantitative). All spectroscopic data were in accordance with those reported in the literature.[48]

**(2*E*)-1-(Benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (13):** Dry THF (250 mL) was put into a flame-dried flask (500 mL) under an inert atmosphere, and then ferulic acid (10 g, 51.5 mmol, 1 equiv.) and 1*H*-benzotriazole (20 g, 167.9 mmol, 3.2 equiv.) were added. Then thionyl chloride (3.74 mL, 51.5 mmol, 1 equiv.) was added, and the reaction mixture was stirred at room temperature for 2.5 h. A yellow suspension was formed during this step. Next, the solids were removed by filtration through a glass filter, and the filter cake was rinsed with dichloromethane until the solvent came out of the filter colourless. The filtrate was concentrated in vacuo, then diethyl ether (250 mL) was added, and the suspended product was triturated intensively to dissolve any remaining 1*H*-benzotriazole. The product was collected by filtration on a glass filter, and was washed with diethyl ether (5 × 20 mL). After air-drying, compound **13** (14.14 g, 93%) was obtained as a fine yellow powder, m.p. 202–203 °C. $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 3.90 (s, 3 H, $OCH_3$), 6.89 (d, $J$ = 8.2 Hz, 1 H, 5-H), 7.34 (dd, $J$ = 8.2, $J$ = 1.5 Hz, 1 H, 6-H), 7.50 (d, $J$ = 1.5 Hz, 1 H, 2-H), 7.59 (t, $J$ = 7.6 Hz, 1 H, 5′-H), 7.76 (t, $J$ = 7.6 Hz, 1 H, 6′-H), 7.88 (d, $J$ = 15.7 Hz, 1 H, 8-H), 8.04 (d, $J$ = 15.7 Hz, 1 H, 7-H), 8.24 (d, $J$ = 8.3 Hz, 1 H, 7′-H), 8.31 (d, $J$ = 8.3 Hz, 1 H, 4′-H), 9.97 (s, 1 H, OH) ppm. $^{13}C$ NMR (100.6 MHz, [$D_6$]DMSO): $\delta$ = 56.2 ($OCH_3$), 112.3, 112.4 (C-2, C-8), 114.8 (C-4′), 116.2 (C-5), 120.5 (C-7′), 125.3 (C-6), 125.9 (C-1), 126.8 (C-5′), 131.4 (C-6′), 131.0 (C-3′a), 146.1 (C-7′a), 148.6 (C-4), 149.8 (C-7), 151.3 (C-3), 164.2 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1016, 1125, 1244, 1586 $cm^{-1}$. MS ($ESI^-$): $m/z$ (%) = 294.0 (100) $[M - H]^-$. HRMS (ESI): calcd. for $C_{16}H_{13}N_3O_3$ 295.0957; found 295.0956.

**(2*E*)-1-(Benzotriazol-1-yl)-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]propenone (14):** (2*E*)-1-(Benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 8 g, 27.09 mmol, 1 equiv.) was put into a flame-dried flask (250 mL) under an inert atmosphere, and dissolved in a mixture of dry dichloromethane and dry THF (4:1; 200 mL). The mixture was cooled to 0 °C in an ice bath, and diisopropylethylamine (9 mL, 54.18 mmol, 2 equiv.) and MEM chloride (3.12 mL, 27.36 mmol, 1.01 equiv.) were added. After the addition, the ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was washed with equal volumes of saturated sodium hydrogen carbonate solution, sodium hydroxide (1 N aq.), and brine, dried with $MgSO_4$, and evaporated in vacuo. The resulting solid was recrystallized from ethyl acetate to give **14** (9.66 g, 93%) as pale yellow crystals, m.p. 139–140 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.38 (s, 3 H, $CH_2OCH_3$), 3.55–3.60 (m, 2 H, $CH_2OCH_3$), 3.86–3.92 (m, 2 H, $CH_2CH_2OCH_3$), 3.99 (s, 3 H, $ArOCH_3$), 5.40 (s, 2 H, $OCH_2O$), 7.23–7.31 (m, 3 H, 2-H, 5-H, 6-H), 7.48–7.54 (m, 1 H, 5′-H), 7.63–7.69 (m, 1 H, 6′-H), 7.96 (d, $J$ = 15.8 Hz, 1 H, 8-H), 8.07 (d, $J$ = 15.8 Hz, 1 H, 7-H), 8.13 (d, $J$ = 8.2 Hz, 1 H, 7′-H), 8.39 (d, $J$ = 8.2 Hz, 1 H, 4′-H) ppm. $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 56.1 ($ArOCH_3$), 59.0 ($CH_2OCH_3$), 68.1 ($CH_2CH_2OCH_3$), 71.5 ($CH_2OCH_3$), 94.0 ($OCH_2O$), 110.4 (C-2), 113.9 (C-8), 114.8 (C-4′), 115.6 (C-5), 120.1 (C-7′), 124.1 (C-6), 126.1 (C-5′), 128.4 (C-1), 130.2 (C-6′), 131.5 (C-3′a), 146.3 (C-7′a), 148.6 (C-7), 149.7 (C-4), 149.8 (C-3), 164.0 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 977, 1077, 1084, 1255 $cm^{-1}$. MS ($ESI^+$): $m/z$ (%) = 406.1 (100) $[M + Na]^+$, 189.0 (40), 265.1 (38).

**(2*E*)-1-(1*H*-Benzotriazol-1-yl)-3-{4-[(*tert*-butyldimethylsilyl)-oxy]-3-methoxyphenyl}prop-2-en-1-one (15):** (2*E*)-1-(Benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 1 g, 3.39 mmol, 1 equiv.) was put into a flame-dried flask (100 mL) under a nitrogen atmosphere, and dissolved in dry THF (50 mL). The mixture was cooled to 0 °C in an ice bath, and diisopropylethylamine (1.2 mL, 6.8 mmol, 2 equiv.) and TBDMSCl (766 mg, 5.08 mmol, 1.5 equiv.) were added. After the addition, the ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated sodium hydrogen carbonate solution (50 mL), and the crude product was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized from ethyl acetate to give **15** (1.07 g, 77%) as pale yellow crystals, m.p. 117–118 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.20 [s, 6 H, $Si(CH_3)_2C(CH_3)_3$], 1.01 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 3.92 (s, 3 H, $OCH_3$), 6.91 (d, $J$ = 8.0 Hz, 1 H, 5-H), 7.22–7.26 (m, 2 H, 2-H, 6-H), 7.49–7.54 (m, 1 H, 5′-H), 7.64–7.69 (m, 1 H, 6′-H), 7.96 (d, $J$ = 15.7 Hz, 1 H, 8-H), 8.08 (d, $J$ = 15.7 Hz, 1 H, 7-H), 8.14 (d, $J$ = 8.3 Hz, 1 H, 7′-H), 8.41 (d, $J$ = 8.3 Hz, 1 H, 4′-H) ppm. $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = –4.5 [$Si(CH_3)_2C(CH_3)_3$], 18.5 [$Si(CH_3)_2C(CH_3)_3$], 25.7 [$Si(CH_3)_2C(CH_3)_3$], 55.6 ($OCH_3$), 111.1 (C-2), 113.4 (C-8), 114.9 (C-4′), 120.1 (C-7′), 121.2 (C-5), 124.1 (C-6), 126.1 (C-5′), 128.1 (C-1), 130.2 (C-6′), 131.6 (C-3′a), 146.3 (C-7′a), 148.9 (C-7), 149.1 (C-4), 151.4 (C-3), 164.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 754, 906, 985, 1282, 1514, 1594, 1618, 1707 $cm^{-1}$. MS ($ESI^+$): $m/z$ (%) = 291.1 (100) $[M - Bt]^+$.

**(2*E*)-Methyl [3-(4-Hydroxy-3-methoxyphenyl)acryloylamino]acetate (16):** Acetonitrile (50 mL) was put into a flask (100 mL), and (2*E*)-1-(benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 1 g, 3.39 mmol, 1 equiv.) and methyl glycinate hydrochloride

(0.85 g, 6.77 mmol, 2 equiv.) were added. Then triethylamine (0.95 mL, 6.77 mmol, 2 equiv.) was added, and the reaction mixture was heated at reflux for 5 h. The mixture was allowed to cool to room temperature, and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (50 mL), and this solution was washed with HCl (0.1 N aq.; 50 mL), water (50 mL), and brine (50 mL). The organic layer was dried with $MgSO_4$ and evaporated in vacuo. The residue is purified by column chromatography over silica with ethyl acetate/petroleum ether (1:2) as eluent, and then the product was recrystallized from acetonitrile to give **16** (567 mg, 63%) as pale yellow crystals, m.p. 111–112 °C. $R_f$ (EtOAc) = 0.64. $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 3.65 [s, 3 H, C(O)OCH$_3$], 3.81 (s, 3 H, ArOCH$_3$), 3.96 (d, $J$ = 5.8 Hz, 2 H, CH$_2$), 6.53 (d, $J$ = 15.7 Hz, 1 H, 8-H), 6.80 (d, $J$ = 8.1 Hz, 1 H, 5-H), 7.02 (dd, $J$ = 8.1, $J$ = 1.2 Hz, 1 H, 6-H), 7.16 (d, $J$ = 1.2 Hz, 1 H, 2-H), 7.36 (d, $J$ = 15.7 Hz, 1 H, 7-H), 8.39 (t, $J$ = 5.8 Hz, 1 H, NH), 9.48 (s, 1 H, OH) ppm. $^{13}$C NMR (100.6 MHz, [D$_6$]DMSO): $\delta$ = 41.2 (CH$_2$), 52.2 [C(O)O*C*H$_3$], 56.0 (ArOCH$_3$), 111.3 (C-2), 116.1 (C-5), 118.6 (C-8), 122.2 (C-6), 126.7 (C-1), 140.3 (C-7), 148.3 (C-3), 148.9 (C-4), 166.3 [C(O)NH], 171.0 [*C*(O)OCH$_3$] ppm. IR (ATR): $\tilde{\nu}$ = 1187, 1197, 1224, 1235, 1252, 1516, 1592 cm$^{-1}$. MS (ESI$^-$): $m/z$ (%) = 264.3 (100) [M – H]$^-$. HRMS (ESI): calcd. for $C_{13}H_{15}NO_5$ 265.0950; found 265.0955.

**(2*E*)-[3-(4-Hydroxy-3-methoxyphenyl)acryloylamino]acetic Acid (17):** A mixture of acetonitrile and water (21:9; 30 mL) was put into a flask (50 mL), and (2*E*)-1-(benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 0.5 g, 1.69 mmol, 1 equiv.) and glycine (0.635 g, 8.47 mmol, 5 equiv.) were added. Then triethylamine (1.18 mL, 8.47 mmol, 5 equiv.) was added, and the reaction mixture was stirred for 10 h at room temperature. The acetonitrile was removed in vacuo, and the remaining aqueous solution was transferred to a separation funnel, acidified with HCl (0.1 N) until the pH reached 2, and then extracted (2×) with an equal volume of ethyl acetate. The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The residue was recrystallized from acetonitrile to give **17** (318 mg, 75%) as white crystals, m.p. 217–218 °C. $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 3.82 (s, 3 H, OCH$_3$), 3.89 (d, $J$ = 5.6 Hz, 2 H, CH$_2$), 6.57 (d, $J$ = 15.7 Hz, 1 H, 8-H), 6.81 (d, $J$ = 8.1 Hz, 1 H, 5-H), 7.03 (d, $J$ = 8.1 Hz, 1 H, 6-H), 7.16 (s, 1 H, 2-H), 7.37 (d, $J$ = 15.7 Hz, 1 H, 7-H), 8.25 (t, $J$ = 5.6 Hz, 1 H, NH) ppm. $^{13}$C NMR (100.6 MHz, [D$_6$]DMSO): $\delta$ = 41.3 (CH$_2$), 56.0 (OCH$_3$), 111.3 (C-2), 116.1 (C-5), 118.9 (C-8), 122.1 (C-6), 126.7 (C-1), 140.0 (C-7), 148.3, 148.8 (C-3, C-4), 166.2 [C(O)NH], 171.9 [C(O)OH] ppm. IR (ATR): $\tilde{\nu}$ = 1020, 1153, 1170, 1196, 1216, 1241, 1514 cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 252.1 (100) [M + H]$^+$, 274.0 (78) [M + Na]$^+$.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(pyrrol-1-yl)propenone (18):** Freshly distilled pyrrole (0.14 mL, 2.02 mmol, 2 equiv.) was dissolved in acetonitrile (10 mL). Then, potassium *tert*-butoxide (342 mg, 3.05 mmol, 3 equiv.) was added to the reaction mixture, followed by (2*E*)-1-(benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 300 mg, 1.01 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 1 h, then it was quenched with HCl (0.1 N aq.; 50 mL) and extracted with ethyl acetate (3× 50 mL). The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The brown residue was recrystallized from ethanol to give **18** (177 mg, 72%) as pale yellow crystals, m.p. 164–165 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.96 (s, 3 H, OCH$_3$), 6.00 (s, 1 H, OH), 6.27–6.47 (m, 2 H, 3′-H), 6.97 (d, $J$ = 7.5 Hz, 1 H, 5-H), 6.98 (d, $J$ = 15.3 Hz, 1 H, α-H), 7.09 (s, 1 H, 2-H), 7.21 (d, $J$ = 7.5 Hz, 1 H, 6-H), 7.41–7.55 (m, 2 H, 2′-H), 7.92 (d, $J$ = 15.3 Hz, 1 H, β-H) ppm. $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 56.1 (OCH$_3$), 110.2 (C-2), 113.1 (C-α), 113.2 (C-8), 115.0 (C-5), 119.3 (C-7), 123.3 (C-6), 126.9 (C-1), 146.9 (C-3), 147.8 (C-β), 148.6 (C-4), 163.2 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 822, 1117, 1269, 1585 cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 244.0 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{13}NO_3$ 243.0895; found 243.0894.

**2-(*tert*-Butoxycarbonyl)amino-1-(diethoxyphosphoryl)ethyl (2*E*)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-enoate (20):** Acetonitrile (50 mL), diethyl (2-*tert*-butoxycarbonylamino-1-hydroxyethyl)-phosphonate (**19**; 0.5 g, 1.68 mmol, 1.1 equiv.), and *N*-feruloylbenzotriazole (**13**; 0.4514 g, 1.53 mmol, 1 equiv.) were put into a round-bottomed flask (100 mL). Et$_3$N (0.72 mL, 5.04 mmol, 3.3 equiv.) was added, and the mixture was heated to reflux temperature overnight. Next, the solvent was removed in vacuo, and the residue was dissolved in EtOAc (50 mL). The resulting mixture was washed with HCl (0.1 N; 50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (EtOAc/petroleum ether, 1:2) to give **20** (420 mg, 58%; purity >90%) as a pale yellow, viscous oil. $R_f$ (EtOAc) = 0.36. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.35 (td, $J$ = 7.2, $J$ = 5.5 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 1.42 [s, 9 H, OC(CH$_3$)$_3$], 2.00 (s, 1 H, OH), 3.47–3.65, 3.70–3.82 (m, 2 H, NHC*H*$_2$), 3.88 (s, 3 H, OCH$_3$), 4.12–4.26 (m, 4 H, 2 OCH$_2$), 5.18–5.31 (m, 1 H, NH), 5.47–5.54 (m, 1 H, OCHP), 6.28 (d, $J$ = 15.4 Hz, 1 H, α-H), 6.92 (d, $J$ = 8.3 Hz, 1 H, 5-H), 6.99 (s, 1 H, 2-H), 7.01 (d, $J$ = 8.3 Hz, 1 H, 6-H), 7.65 (d, $J$ = 15.4 Hz, 1 H, β-H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ = 14.6 (d, $J$ = 5.8 Hz, OCH$_2$*C*H$_3$), 14.7 (d, $J$ = 5.8 Hz, OCH$_2$*C*H$_3$), 26.5 [OC(*C*H$_3$)$_3$], 38.5 (NHCH$_2$), 54.1 (OCH$_3$), 61.4 (d, $J$ = 6.9 Hz, O*C*H$_2$CH$_3$), 61.7 (d, $J$ = 6.9 Hz, O*C*H$_2$CH$_3$), 64.8 (d, $J$ = 166.1 Hz, OCHP), 77.9 [O*C*(CH$_3$)$_3$], 108.2 (C-2), 111.6 (C-α), 113.4 (C-5), 121.6 (C-6), 124.4 (C-1), 145.0 (C-3), 145.6 (C-4), 147.3 (C-β), 154.1 [OC(O)NH], 164.2 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1019, 1144, 1244 cm$^{-1}$. MS (ESI$^-$): $m/z$ (%): 472.3 (100) [M – 1]$^-$.

**(1*E*,4*Z*,6*E*)-5-Hydroxy-1-{3-methoxy-4-[(2-methoxyethoxy)methoxy]phenyl}-7-phenylhepta-1,4,6-trien-3-one (24):** 4-Phenyl-3-buten-2-one (**23**; 187 mg, 1.27 mmol, 1.4 equiv.) and dry THF (10 mL) were put into a flame-dried round-bottomed flask (25 mL) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C, and KHMDS (1 M solution in THF; 2 mL, 2 mmol, 2.15 equiv.) was added. The resulting homogeneous red mixture was stirred at room temperature for 2 h. Then the solution was cooled to 0 °C, and **14** (350 mg, 0.91 mmol, 1 equiv.) was added in one portion. The mixture was stirred at room temperature for 3 h. Next, water (10 mL) was added, and the crude product was extracted with ethyl acetate (2× 15 mL). The combined organic layers were washed with saturated aqueous $Na_2CO_3$ (3× 10 mL), dried with $MgSO_4$, and concentrated in vacuo to give pure **24** (284 mg, 76%) as a viscous, orange oil. $R_f$ (EtOAc/petroleum ether, 1:1) = 0.33. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.38 (s, 3 H, OCH$_3$), 3.54–3.59 (m, 2 H, C*H*$_2$CH$_2$O), 3.86–3.90 (m, 2 H, CH$_2$C*H*$_2$O), 3.93 (s, 3 H, ArOCH$_3$), 5.37 (s, 2 H, OCH$_2$O), 5.85 (s, 1 H, OH), 6.53 (d, $J$ = 15.8 Hz, 1 H, α′-H), 6.63 (d, $J$ = 15.8 Hz, 1 H, γ-H), 7.09 (d, $J$ = 1.9 Hz, 1 H, 2′-H), 7.13 (dd, $J$ = 8.5, $J$ = 1.9 Hz, 1 H, 6′-H), 7.22 (d, $J$ = 8.5 Hz, 1 H, 5′-H), 7.32–7.46 (m, 4 H, α-H, 3-H, 4-H, 5-H), 7.56 (dd, $J$ = 7.5, $J$ = 1.9 Hz, 2 H, 2-H, 6-H), 7.62 (d, $J$ = 15.8 Hz, 1 H, β′-H), 7.66 (d, $J$ = 15.8 Hz, 1 H, δ-H) ppm. $^{13}$C NMR (100.6 MHz, [D$_6$]DMSO): $\delta$ = 56.3 (OMe), 59.1 (OMe), 68.4 (*C*H$_2$CH$_2$O), 71.9 (CH$_2$*C*H$_2$O), 94.7 (OCH$_2$O), 101.8 [*C*H=CH(OH)], 111.5 (C-5′), 116.9 (C-2′), 122.5, 123.1, 124.5 (2 *C*H=CHAr, C-6′), 128.3, 129.2 (C-2, C-4, C-3, C-5), 129.9 (C-1′), 130.2 (C-4), 135.4 (C-1), 140.9, 140.6 (2 =CHAr), 149.0, 150.5 (C-3′, C-4′), 184.2, 182.9 [C=O, =C(OH)] ppm. IR (ATR): $\tilde{\nu}$ = 699, 970, 1080, 1100, 1130, 1252, 1420, 1449, 1508, 1579, 1625, 1714,

2924 $cm^{-1}$. MS ($ESI^+$): *m/z* (%) = 411.1 (100) $[M + H]^+$, 412.2 (26). HRMS (ESI): calcd. for $C_{24}H_{26}O_6$ 410.1729; found 410.1746.

**General Procedure for the Hydrochloric-Acid-Mediated Deprotection of MEM Ethers:** In a round-bottomed flask equipped with a reflux condenser, a MEM-protected phenol (0.5 g) was dissolved in a mixture of THF (20 mL) and HCl (5% aq.; 10 mL). The mixture was heated at reflux for 5 h, then it was carefully quenched with saturated aqueous sodium hydrogen carbonate (until pH = 5), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo.

**(1*E*,4*Z*,6*E*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-phenylhepta-1,4,6-trien-3-one (25):** (1*E*,4*Z*,6*E*)-5-Hydroxy-1-{3-methoxy-4-[(2-methoxyethoxy)methoxy]phenyl}-7-phenylhepta-1,4,6-trien-3-one (**24**; 200 mg, 0.61 mmol) was deprotected following the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers to give a solid (209 mg). A sample of this crude product **25** (40.9 mg) was purified by preparative TLC (petroleum ether/EtOAc/HCOOH, 40:9:1) to give **25** (4.3 mg, 14%) as an orange powder. All spectroscopic data were in accordance with those reported in the literature.[49]

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(1*H*-pyrrol-2-yl)propenone (26):** Bromopyrrole **66** (255 mg, 0.92 mmol, 1.2 equiv.) and dry THF (10 mL) were put into a flame-dried flask (25 mL) under an inert atmosphere. The solution was cooled to –78 °C in a dry ice/acetone bath. Then, *n*-butyllithium (2.12 N solution in hexanes; 0.4 mL, 0.85 mmol, 1.1 equiv.) was added dropwise to the reaction mixture. The reaction mixture was stirred for 30 min at –78 °C, and then (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)-phenyl]-*N*-methylacrylamide (**31**; 0.25 g, 0.77 mmol, 1 equiv.) was added. The reaction mixture was stirred at –78 °C for 1 h, and the temperature was then allowed to gradually rise to room temperature, after which the reaction mixture was stirred at room temperature overnight. The reaction was carefully quenched with saturated sodium hydrogen carbonate (10 mL), and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and evaporated in vacuo.

The residue was dissolved in dry dichloromethane (9 mL), and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and then it was carefully neutralized with saturated sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and evaporated in vacuo.

The residue was dissolved in a mixture of acetonitrile (10 mL) and NaOH (0.3 N aq.; 10 mL). The mixture was stirred for 5 min at room temperature, then it was neutralized with dilute aqueous HCl and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with magnesium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:3) as an eluent ($R_f$ = 0.1) to give **26** (79 mg, 42%) as a yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.93 (s, 3 H, $OCH_3$), 6.27 (br. s, 1 H, NH), 6.33–6.35 (m, 1 H, 4′-H), 6.95 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.08–7.10 (m, 1 H, 5′-H), 7.11–7.13 (m, 2 H, 2-H, 3′-H), 7.20 (dd, *J* = 8.2, *J* = 1.6 Hz, 1 H, 6-H), 7.22 (d, *J* = 15.6 Hz, 1 H, α-H), 7.79 (d, *J* = 15.6 Hz, 1 H, β-H), 10.25 (br. s, 1 H, OH) ppm. $^{13}C$ NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 56.0 ($OCH_3$), 110.2 (C-2), 110.9 (C-4′), 115.0 (C-5), 116.4 (C-5′), 119.6 (C-α), 123.1 (C-6), 125.5 (C-3′), 127.6 (C-1), 133.2 (C-1′), 142.7 (C-β), 146.9 (C-4), 148.1 (C-3), 179.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 721, 735, 748, 1031, 1051, 1107, 1205, 1276, 1402, 1425, 1509, 1542, 1563 (C=C), 1637 (C=O), 3260 (OH) $cm^{-1}$. MS ($ESI^+$): *m/z* (%) = 244.0 (100) $[M + H]^+$, 509.2.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (30):** Acetonitrile (4 mL) was put into a a microwave vial (10 mL), and (2*E*)-1-(benzotriazol-1-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**13**; 0.2953 g, 1 mmol, 1 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (0.1463 g, 1.5 mmol, 1.5 equiv.) were added. Then, triethylamine (0.21 mL, 1.5 mmol, 1.5 equiv.) was added, and the reaction mixture was heated in a microwave reactor at 100 °C for 15 min. Next, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (25 mL), and this solution was washed with equal volumes of HCl (0.1 N) and brine. The organic layer was dried with $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:2) as eluent, and the product was recrystallized from absolute ethanol to give **30** (168 mg, 71%) as white crystals, m.p. 99–100 °C. $R_f$ (EtOAc/petroleum ether, 1:1) = 0.52. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.31 (s, 3 H, $NCH_3$), 3.77 (s, 3 H, $NOCH_3$), 3.93 (s, 3 H, $ArOCH_3$), 6.13 (s, 1 H, OH), 6.88 (d, *J* = 15.7 Hz, 1 H, 8-H), 6.93 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.04 (d, *J* = 1.9 Hz, 1 H, 2-H), 7.15 (dd, *J* = 8.2, *J* = 1.9 Hz, 1 H, 6-H), 7.67 (d, *J* = 15.7 Hz, 1 H, 7-H) ppm. $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 32.6 ($NCH_3$), 56.0 ($ArOCH_3$), 61.9 ($NOCH_3$), 110.1 (C-2), 113.1 (C-8), 114.8 (C-5), 122.4 (C-6), 127.7 (C-1), 143.7 (C-7), 146.7 (C-4), 147.6 (C-3), 167.3 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 990, 1269, 1509, 1597, 1584 $cm^{-1}$. MS ($ESI^+$): *m/z* (%) = 238.1 (100) $[M + H]^+$.

**(2*E*)-*N*-Methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (31):** Dry dichloromethane (50 mL) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.55 g, 26.2 mmol, 2 equiv.) were put into a flame-dried flask (500 mL) under an inert atmosphere. Next, $Me_3Al$ (2 N solution in toluene; 13.1 mL, 26.2 mmol, 2 equiv.) was slowly added to the reaction mixture. The mixture was stirred at room temperature for 15 min, then a solution of (2*E*)-1-(benzotriazol-1-yl)-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]propenone (**14**; 5.03 g, 13.1 mmol, 1 equiv.) in dry dichloromethane (200 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 2 h, then it was quenched carefully with saturated sodium hydrogen carbonate (250 mL). The resulting emulsion was filtered through Celite, and the filter cake was rinsed with dichloromethane (2 × 25 mL). The layers were separated, and the organic layer was washed with equal volumes of sodium hydroxide (1 N aq.; 2 ×) and brine, dried with $MgSO_4$, and evaporated in vacuo. The residue was recrystallized from absolute ethanol to give **31** (2.98 g, 70%) as white crystals, m.p. 58–59 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.31 (s, 3 H, $NCH_3$), 3.37 (s, 3 H, $CH_2OCH_3$), 3.53–3.59 (m, 2 H, $CH_2OCH_3$), 3.78 (s, 3 H, $NOCH_3$), 3.84–3.90 (m, 2 H, $CH_2CH_2OCH_3$), 3.92 (s, 3 H, $ArOCH_3$), 5.36 (s, 2 H, $OCH_2O$), 6.92 (d, *J* = 15.7 Hz, 1 H, 8-H), 7.08 (d, *J* = 1.8 Hz, 1 H, 2-H), 7.15 (dd, *J* = 8.4, *J* = 1.8 Hz, 1 H, 6-H), 7.21 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.68 (d, *J* = 15.7 Hz, 1 H, 7-H) ppm. $^{13}C$ NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 32.5 ($NCH_3$), 56.0 ($ArOCH_3$), 59.0 ($CH_2OCH_3$), 61.9 ($NOCH_3$), 67.9 ($CH_2CH_2OCH_3$), 71.5 ($CH_2OCH_3$), 94.2 ($OCH_2O$), 110.9 (C-2), 114.1 (C-8), 115.9 (C-5), 121.7 (C-6), 129.6 (C-1), 143.3 (C-7), 148.1 (C-3), 149.6 (C-4), 167.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 972, 1098, 1256, 1598 $cm^{-1}$. MS ($ESI^+$): *m/z* (%) = 326.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{23}NO_6$ 325.1525; found 325.1534.

**(3*E*)-4-[3-Methoxy-4-(2-methoxyethoxymethoxy)phenyl]but-3-en-2-one (32):** Dry THF (5 mL) and (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.178 g,

0.545 mmol, 1 equiv.) were put into a flame-dried flask (10 mL) under an inert atmosphere. The reaction mixture was cooled to –78 °C in a dry ice/acetone bath, and methyllithium (1.6 N solution in THF; 0.375 mL, 0.6 mmol, 1.1 equiv.) was added dropwise to the reaction mixture. The mixture was stirred at –78 °C for 2 h, then it was carefully quenched with water (2 mL), and warmed up to room temperature. Water (40 mL) was added, and the pH was adjusted to pH = 7 by the addition of HCl (0.1 N). Next, the mixture was extracted with dichloromethane (40 mL). The organic layer was washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo to give **32** (113 mg, 74%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.38 [s, 3 H, C(O)-$CH_3$], 3.37 (s, 3 H, $CH_2OCH_3$), 3.52–3.60 (m, 2 H, $CH_2OCH_3$), 3.83–3.91 (m, 2 H, $CH_2CH_2OCH_3$), 3.92 (s, 3 H, $ArOCH_3$), 5.37 (s, 2 H, $OCH_2O$), 6.62 (d, $J$ = 16.2 Hz, 1 H, 8-H), 7.09 (br. s, 1 H, 2-H), 7.11 (dd, $J$ = 8.5, $J$ = 2.2 Hz, 1 H, 6-H), 7.22 (d, $J$ = 8.5 Hz, 1 H, 5-H), 7.47 (d, $J$ = 16.2 Hz, 1 H, 7-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 27.4 [C(O)$CH_3$], 55.9 ($ArOCH_3$), 59.0 ($CH_2OCH_3$), 68.0 ($CH_2CH_2OCH_3$), 71.5 ($CH_2OCH_3$), 94.1 ($OCH_2O$), 110.2 (C-2), 115.8 (C-5), 122.7 (C-6), 125.7 (C-8), 128.7 (C-1), 143.4 (C-7), 148.8 (C-4), 149.8 (C-3), 198.4 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 974, 1100, 1242, 1509 cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 281.3 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{20}O_5$ 280.1311; found 280.1318.

**(3*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (33):** (3*E*)-4-[3-Methoxy-4-(2-methoxyethoxymethoxy)phenyl]but-3-en-2-one (**32**; 113 mg, 0.4 mmol) was deprotected following the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The crude product was recrystallized from absolute ethanol to give **33** (75 mg, 72% from **31**) as yellow crystals. All spectroscopic data were in accordance with those reported in the literature.[50]

**(2*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-phenylprop-2-en-1-one (36):** (2*E*)-*N*-Methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy) phenyl]-*N*-methylacrylamide (**31**; 0.25 g, 0.77 mmol, 1 equiv.) was dissolved in dry THF (10 mL) in a flame-dried flask (25 mL) under a nitrogen atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and phenyllithium (2.0 N solution in dibutyl ether; 0.43 mL, 0.85 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred at –78 °C for 1 h, then the reaction temperature was allowed to rise gradually to room temperature, and the reaction mixture was stirred overnight. Next, the mixture was carefully quenched with water and extracted with ethyl acetate (3×). The organic layers were combined, washed with brine, dried with $MgSO_4$, and evaporated in vacuo. The crude product **35** was deprotected following the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The crude product obtained after deprotection was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:5) as an eluent to give **36** (116 mg, 59% from **31**) as a yellow oil. $R_f$ (EtOAc/petroleum ether, 1:5) = 0.13. All spectroscopic data were in accordance with those reported in the literature.[51]

**(1*E*)-1-[3-Methoxy-4-(2-methoxyethoxymethoxy)phenyl]hept-1-en-3-one (37):** (2*E*)-*N*-Methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.25 g, 0.77 mmol, 1 equiv.) was dissolved in dry THF (10 mL) in a flame-dried flask (25 mL) under a nitrogen atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and *n*-butyllithium (2.5 N solution in hexanes; 0.34 mL 0.85 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred at –78 °C for 1 h, then the reaction was carefully quenched with saturated sodium hydrogen carbonate (10 mL), and the mixture was warmed up to room temperature. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:4) as an eluent to give **37** (87 mg, 35%) as white crystals, m.p. 53–54 °C. $R_f$ (EtOAc) = 0.86. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.95 (t, $J$ = 7.4 Hz, 3 H, 12-H), 1.31–1.46 (m, 2 H, 11-H), 1.57–1.73 (m, 2 H, 10-H), 2.66 (t, $J$ = 7.4 Hz, 2 H, 9-H), 3.37 (s, 3 H, $CH_2OCH_3$), 3.52–3.59 (m, 2 H, $CH_2CH_2OCH_3$), 3.83–3.90 (m, 2 H, $CH_2CH_2OCH_3$), 3.92 (s, 3 H, $ArOCH_3$), 5.37 (s, 2 H, $OCH_2O$), 6.64 (d, $J$ = 15.9 Hz, 1 H, 8-H), 7.11 (m, 2 H, 2-H, 6-H), 7.22 (d, $J$ = 7.7 Hz, 1 H, 5-H), 7.49 (d, $J$ = 15.9 Hz, 1 H, 7-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 13.9 (C-12), 22.5 (C-11), 26.6 (C-10), 40.5 (C-9), 55.9 ($ArOCH_3$), 59.0 ($CH_2OCH_3$), 68.0 ($CH_2CH_2OCH_3$), 71.5 ($CH_2OCH_3$), 94.2 ($OCH_2O$), 110.3 (C-2), 115.9 (C-5), 122.5 (C-6), 124.9 (C-8), 128.9 (C-1), 142.2 (C-7), 148.7, 149.8 (C-3, C-4), 200.7 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 975, 1082, 1099, 1256, 1510, 1652 cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 323.3 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{18}H_{26}O_5$ 322.1780; found 322.1788.

**(1*E*)-1-(4-Hydroxy-3-methoxyphenyl)hept-1-en-3-one (39):** Compound **37** was synthesized as described above, but it was not purified by column chromatography. Instead, crude **37** was deprotected following the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The crude product obtained after deprotection was purified by column chromatography using ethyl acetate/petroleum ether (1:5) as an eluent ($R_f$ = 0.23) to give **39** (129 mg, 52% from **31**) as a yellow oil. All spectroscopic data were in accordance with those reported in the literature.[50]

**(2*E*)-1-(Furan-2-yl)-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]prop-2-en-1-one (41):** *n*-Butyllithium (2.33 N solution in hexanes; 2.77 mL 6.45 mmol, 2.1 equiv.) and dry THF (40 mL) were put into a flame-dried flask (100 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and then furan (0.45 mL, 6.15 mmol, 2 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 5 min, then it was warmed up to 0 °C with an ice bath, and stirred at 0 °C for 1.5 h. The mixture was cooled to –78 °C again, and (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 1 g, 3.08 mmol, 1 equiv.) was added. The reaction mixture was stirred at –78 °C for 30 min and then at 0 °C for 15 min. Next, the reaction mixture was carefully quenched with saturated sodium hydrogen carbonate solution (10 mL), and extracted with diethyl ether (10 mL). The aqueous layer was extracted (2×) with an equal volume of diethyl ether, and the combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo to give compound **41** (1 g, 98%) as a yellow-orange oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.38 (s, 3 H, $CH_2OCH_3$), 3.54–3.59 (m, 2 H, $CH_2CH_2OCH_3$), 3.85–3.91 (m, 2 H, $CH_2OCH_3$), 3.95 (s, 3 H, $ArOCH_3$), 5.38 (s, 2 H, $OCH_2O$), 6.60 (dd, $J$ = 3.9, $J$ = 1.4 Hz, 1 H, 4′-H), 7.17 (s, 1 H, 2-H), 7.22–7.25 (m, 2 H, 5-H, 6-H), 7.33 (d, $J$ = 3.9 Hz, 1 H, 5′-H), 7.34 (d, $J$ = 15.7 Hz, 1 H, α-H), 7.66 (d, $J$ = 1.4 Hz, 1 H, 3′-H), 7.84 (d, $J$ = 15.7 Hz, 1 H, β-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.0 ($OCH_3$), 59.0 ($ArOCH_3$), 68.0 ($CH_2CH_2OCH_3$), 71.5 ($CH_2CH_2OCH_3$), 94.1 ($OCH_2O$), 111.0 (C-4′), 112.5 (C-2), 115.7 (C-5), 117.3 (C-6), 119.6 (C-5′), 122.8 (C-α), 129.1 (C-1), 144.0 (C-β), 146.4 (C-3′), 148.9, 149.8 (C-3, C-4), 154.0 (C-1′), 178.0 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1286, 1464, 1508, 1580, 1590 (C=C), 1654 (C=O) cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 332.8 (100) [M + H]$^+$, 354.7 (50) [M + Na]$^+$.

**(2*E*)-1-(Furan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (42):** (2*E*)-1-(Furan-2-yl)-3-[3-methoxy-4-(2-methoxyethoxy-

methoxy)phenyl]prop-2-en-1-one (**41**; 1 g, 3.01 mmol, 1 equiv.) was MEM-deprotected according to the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The resulting oil was recrystallized from absolute ethanol to give compound **42** (720 mg, 98%) as green crystals, m.p. 128.5–129.5 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.98 (s, 3 H, $OCH_3$), 5.93 (s, 1 H, OH), 6.60 (dd, $J$ = 1.4, $J$ = 3.6 Hz, 1 H, 4′-H), 6.96 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.14 (d, $J$ = 2.2 Hz, 1 H, 2-H), 7.24 (dd, $J$ = 2.2, $J$ = 8.3 Hz, 1 H, 6-H), 7.32 (d, $J$ = 16.0 Hz, 1 H, α-H), 7.33 (dd, $J$ = 3.6 Hz, 1 H, 5′-H), 7.65 (dd, $J$ = 1.4 Hz, 1 H, 3′-H), 7.83 (d, $J$ = 16.0 Hz, 1 H, β-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.0 ($OCH_3$), 110.2 (C-4′), 112.5 (C-2), 115.0 (C-5), 117.3 (C-6), 118.6 (C-5′), 123.6 (C-α), 127.3 (C-1), 144.5 (C-β), 146.4 (C-3′), 146.9 (C-4), 148.6 (C-3), 153.8 (C-1′), 178.2 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1123, 1280, 1422, 1460, 1527, 1552, 1569 (C=C), 1651 (C=O), 2358, 3288 (OH) cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 245.1 (100) [M + H]$^+$.

**(2*E*)-1-(Furan-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propenone (44):** 3-Bromofuran (0.20 mL, 2.23 mmol, 1.2 equiv.) was dissolved in dry diethyl ether (20 mL) in a flame-dried flask (50 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, then *n*-butyllithium (1.9 N solution in hexanes; 1.3 mL, 2.47 mmol, 1.34 equiv.) was added dropwise. The mixture was stirred at –78 °C for 30 min, then (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.6 g, 1.84 mmol, 1 equiv.) was added. The reaction mixture was stirred at –78 °C for 1 h, and then stirred at room temperature overnight. Next, the reaction mixture was poured in a mixture of HCl (2 N; 25 mL), ethanol (50 mL), and ice (25 g). Water (170 mL) was then added, and the mixture was extracted with dichloromethane (150 mL). The aqueous layer was extracted again with dichloromethane (100 mL), and the combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo.

The crude product **43** was immediately MEM-deprotected according to the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The product was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:2) as eluent and finally recrystallized from absolute ethanol to give compound **44** (364 mg, 81%) as yellow crystals, m.p. 115–116 °C. $R_f$ (EtOAc) = 0.64. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.94 (s, 3 H, $OCH_3$), 6.18 (s, 1 H, OH), 6.90 (dd, $J$ = 1.7, $J$ = 0.8 Hz, 1 H, 10-H), 6.95 (d, $J$ = 8.2 Hz, 1 H, 5-H), 7.03 (d, $J$ = 15.6 Hz, 1 H, 8-H), 7.09 (d, $J$ = 1.8 Hz, 1 H, 2-H), 7.19 (dd, $J$ = 8.2, $J$ = 1.8 Hz, 1 H, 6-H), 7.48 (t, $J$ = 1.7 Hz, 1 H, 11-H), 7.74 (d, $J$ = 15.6 Hz, 1 H, 7-H), 8.13–8.18 (m, 1 H, 12-H) ppm. $^{13}$C NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 56.0 ($OCH_3$), 109.2 (C-10), 110.2 (C-2), 115.0 (C-5), 120.6 (C-8), 123.2 (C-6), 127.1, 128.6 (C-1, C-9), 144.0 (C-7), 144.3 (C-11), 146.9 (C-4), 147.1 (C-12), 148.4 (C-3), 184.3 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1154, 1268, 1283, 1510, 1579 cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 245.1 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{12}O_4$ 244.0736; found 244.0743.

**(2*E*)-3-[3-Methoxy-4-(2-methoxyethoxymethoxy)phenyl]-1-(thiophen-2-yl)prop-2-en-1-one (50):** Thiophene (0.09 mL, 1.16 mmol, 1.5 equiv.) and dry THF (10 mL) were put into a flame-dried flask (25 mL) under an inert atmosphere. The mixture was cooled to 0 °C in an ice bath, then *n*-butyllithium (2.12 N solution in hexanes; 0.44 mL, 0.93 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C, then it was cooled to –78 °C in a dry ice/acetone bath. Then, (2*E*) *N* methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.25 g, 0.77 mmol, 1 equiv.) was added in one portion, and the reaction mixture was stirred at –78 °C for 1 h. The reaction temperature was allowed to rise gradually to room temperature, and the reaction mixture was stirred overnight. The reaction was carefully quenched with saturated sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to give a yellow oil. Recrystallization from absolute ethanol gave compound **50** (142 mg, 53%) as yellow crystals, m.p. 69.5–70.5 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.38 (s, 3 H, $OCH_3$), 3.54–3.59 (m, 2 H, $CH_2CH_2OCH_3$), 3.85–3.90 (m, 2 H, $CH_2OCH_3$), 3.95 (s, 3 H, $ArOCH_3$), 5.38 (s, 2 H, $OCH_2O$), 7.15 (br. s, 1 H, 2-H), 7.19 (dd, $J$ = 5.0, $J$ = 3.9 Hz, 1 H, 4′-H), 7.23–7.26 (m, 2 H, 5-H, 6-H), 7.31 (d, $J$ = 15.4 Hz, 1 H, α-H), 7.68 (dd, $J$ = 5.0, $J$ = 1.1 Hz, 1 H, 3′-H), 7.81 (d, $J$ = 15.4 Hz, 1 H, β-H), 7.87 (dd, $J$ = 3.9, $J$ = 1.1 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.0 ($OCH_3$), 59.0 ($ArOCH_3$), 68.0 ($CH_2CH_2OCH_3$), 71.5 ($CH_2CH_2OCH_3$), 94.1 ($OCH_2O$), 111.1 (C-2), 115.9 (C-5), 120.0 (C-6), 122.5 (C-α), 128.2 (C-4′), 129.0 (C-1), 131.6 (C-3′), 133.7 (C-5′), 144.0 (C-β), 145.7, 148.9, 149.7 (C-1′, C-3, C-4), 182.0 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1260, 1415, 1513, 1584, 1599 (C=C), 1643 (C=O) cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 348.7 (100) [M + H]$^+$, 370.7 (64) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{20}O_5S$ 348.1031; found 348.1039.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (51):** 2-Thienyl-chalcone **50** was synthesized as described above, but it was not purified by recrystallization. Instead, the crude product **50** was deprotected following the general procedure for the hydrochloric-acid-mediated deprotection of MEM ethers. The crude solid product was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:3) as an eluent to give **51** (178 mg, 89%) as yellow crystals, m.p. 122.5–123.5 °C. $R_f$ (EtOAc/petroleum ether, 1:3) = 0.21. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.97 (s, 3 H, $OCH_3$), 5.95 (s, 1 H, OH), 6.97 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.12 (d, $J$ = 2.0 Hz, 1 H, 2-H), 7.18 (dd, $J$ = 4.7, $J$ = 3.9 Hz, 1 H, 4′-H), 7.24 (dd, $J$ = 8.3, $J$ = 2.0 Hz, 1 H, 6-H), 7.28 (d, $J$ = 15.4 Hz, 1 H, α-H), 7.67 (dd, $J$ = 4.7, $J$ = 1.1 Hz, 1 H, 3′-H), 7.80 (d, $J$ = 15.4 Hz, 1 H, β-H), 7.87 (dd, $J$ = 3.9, $J$ = 1.1 Hz, 1 H, 5′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.0 ($OCH_3$), 110.3 (C-2), 115.0 (C-5), 119.2 (C-6), 123.3 (C-α), 127.2 (C-1), 128.2 (C-4′), 131.6 (C-3′), 133.6 (C-5′), 144.5 (C-β), 145.7, 146.9 (C-1′, C-4), 148.4 (C-3), 182.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1122, 1210, 1408, 1420, 1509, 1525, 1556, 1594 (C=C), 1641 (C=O), 3318 (OH) cm$^{-1}$. MS (ESI$^+$): $m/z$ (%) = 261.0 (100) [M + H]$^+$, 283.0 (36) [M + Na]$^+$.

**(2*E*)-3-[3-Methoxy-4-(2-methoxyethoxymethoxy)phenyl]-1-(thiophen-3-yl)prop-2-en-1-one (52):** 3-Bromothiophene (0.18 mL, 1.9 mmol, 1.15 equiv.) was dissolved in a mixture of hexane (8 mL) and diethyl ether (5 mL) under an inert atmosphere, and the solution was cooled to –78 °C in a dry ice/acetone bath. Then, *n*-butyllithium (2.38 N solution in hexanes; 0.77 mL, 1.8 mmol, 1.1 equiv.) was added dropwise, and the reaction mixture was stirred at –78 °C for 1 h. Next, (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.543 g, 1.67 mmol, 1 equiv.) was dissolved in dry THF (10 mL), and this solution was cooled to –78 °C and then added to the reaction mixture. The reaction mixture was stirred at –78 °C for 1.5 h, and then at room temperature for 8 h. The reaction mixture was quenched with saturated sodium hydrogen carbonate (20 mL), and extracted with dichloromethane (2× 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography over neutral $Al_2O_3$ with ethyl acetate/petroleum ether (1:3) as eluent to give compound **52** (500 mg, 86%) as a yellow oil. $R_f$ (EtOAc/petroleum ether, 1:3) = 0.12. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.38 (s, 3 H, $OCH_3$), 3.55–3.58 (m, 2 H, $CH_2CH_2OCH_3$), 3.87–3.90 (m, 2 H,

$CH_2OCH_3$), 3.95 (s, 3 H, $ArOCH_3$), 5.38 (s, 2 H, $OCH_2O$), 7.15 (br. s, 1 H, 2-H), 7.22–7.24 (m, 2 H, 5-H, 6-H), 7.28 (d, $J$ = 15.7 Hz, 1 H, α-H), 7.37 (dd, $J$ = 5.0, $J$ = 2.8 Hz, 1 H, 4′-H), 7.67 (dd, $J$ = 5.0, $J$ = 1.1 Hz, 1 H, 5′-H), 7.77 (d, $J$ = 15.7 Hz, 1 H, β-H), 8.17 (dd, $J$ = 2.8, $J$ = 1.1 Hz, 1 H, 2′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.0 ($OCH_3$), 59.0 ($ArOCH_3$), 68.0 ($CH_2CH_2OCH_3$), 71.5 ($CH_2CH_2OCH_3$), 94.1 ($OCH_2O$), 111.0 (C-2), 115.9 (C-5), 121.2 (C-6), 122.5 (C-α), 126.4 (C-2′), 127.5 (C-3′), 129.2 (C-1), 131.8 (C-5′), 143.2 (C-1′), 144.1, 148.8, 149.8 (C-β, C-3, C-4), 184.0 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1253, 1417, 1513, 1589, 1653 (C=O) $cm^{-1}$. MS ($ESI^+$): $m/z$ (%) = 349.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{18}H_{20}O_5S$ 348.1031; found 348.1041.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(thiophen-3-yl)prop-2-en-1-one (53):** 3-Thienyl-chalcone **52** was synthesized as described above, but it was not purified by column chromatography. Instead, the crude product **52** was MEM-deprotected. To remove the MEM protecting group, the residue was dissolved in dichloromethane (9 mL) and trifluoroacetic acid (3 mL), and this solution was stirred at room temperature overnight. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (20 mL), and this solution was washed with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:4) as eluent to give a yellow solid. Recrystallization from methanol gave **53** (261 mg, 60% from **31**) as yellow crystals, m.p. 137.5–138.5 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.97 (s, 3 H, $OCH_3$), 5.92 (s, 1 H, OH), 6.96 (d, $J$ = 8.2 Hz, 1 H, 5-H), 7.12 (d, $J$ = 1.8 Hz, 1 H, 2-H), 7.23 (dd, $J$ = 8.2, $J$ = 1.8 Hz, 1 H, 6-H), 7.26 (d, $J$ = 15.5 Hz, 1 H, α-H), 7.37 (dd, $J$ = 5.1, $J$ = 2.9 Hz, 1 H, 4′-H), 7.67 (dd, $J$ = 5.1, $J$ = 1.2 Hz, 1 H, 5′-H), 7.76 (d, $J$ = 15.5 Hz, 1 H, β-H), 8.16 (dd, $J$ = 2.9, $J$ = 1.2 Hz, 1 H, 2′-H) ppm. $^{13}$C NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 56.0 ($OCH_3$), 110.1 (C-2), 114.9 (C-5), 120.4 (C-6), 123.2 (C-α), 126.4 (C-5′), 127.5 (C-1), 127.6 (C-4′), 131.7 (C-2′), 143.3 (C-1′), 144.5 (C-β), 146.8 (C-4), 148.3 (C-3), 184.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1033, 1121, 1246, 1511, 1562, 1591 (C=C), 1648 (C=O), 3262 (OH) $cm^{-1}$. MS ($ESI^+$): $m/z$ (%) = 261.0 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{14}H_{12}O_3S$ 260.0507; found 260.0514.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (55):** 2-Bromopyridine (0.146 g, 0.92 mmol, 1.2 equiv.) was dissolved in dry THF (13 mL) in a flame-dried flask (25 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and *n*-butyllithium (1.8 N solution in hexanes; 0.57 mL, 1.03 mmol, 1.34 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, and then (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.250 g, 0.77 mmol, 1 equiv.) was added. The mixture was stirred at –78 °C for 1.5 h, and then at 0 °C for 10 min. The reaction was carefully quenched with saturated sodium hydrogen carbonate solution (10 mL). Next, the mixture was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo.

To remove the MEM protecting group, the residue was dissolved in dichloromethane (9 mL) and trifluoroacetic acid (3 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized by adding saturated sodium hydrogen carbonate solution, and then it was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo. The resulting oil was purified by column chromatography over silica with ethyl acetate/petroleum ether (5:6) as eluent, and the product was recrystallized from ethanol to give compound **55** (41 mg, 21%) as green crystals, m.p. 101.5–102.5 °C. $R_f$ (EtOAc/petroleum ether, 5:6) = 0.22. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.97 (s, 3 H, $OCH_3$), 6.07 (br. s, 1 H, OH), 6.95 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.22–7.33 (m, 2 H, 2-H, 6-H), 7.45–7.54 (m, 1 H, 4′-H), 7.84–7.97 (m, 2 H, 5′-H, α-H), 8.14 (d, $J$ = 16.0 Hz, 1 H, β-H), 8.20 (d, $J$ = 7.7 Hz, 1 H, 6′-H), 8.75 (d, $J$ = 4.4 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 56.1 ($OCH_3$), 109.9 (C-2), 114.8 (C-5), 118.2 (C-α), 123.0 (C-6′), 124.5 (C-6), 126.8 (C-4′), 127.8 (C-1), 137.1 (C-5′), 145.3 (C-β), 146.8 (C-4), 148.5 (C-3), 148.8 (C-3′), 154.5 (C-1′), 189.3 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1227, 1306, 1573, 1584, 1616, 1683, 3344, 3445 $cm^{-1}$. MS ($ESI^+$): $m/z$ (%) = 256.3 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{13}NO_3$ 255.0895; found 255.0902. IR data and m.p. were in accordance with literature values.[51]

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(pyridin-3-yl)prop-2-en-1-one (57):** 3-Bromopyridine (0.27 g, 2.8 mmol, 1.73 equiv.), dry diethyl ether (5 mL), and hexane (8 mL) were put into a flame-dried flask (50 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and *n*-butyllithium (2.38 N solution in hexanes; 1.12 mL, 2.67 mmol, 1.64 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h. Next, a solution of (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.53 g, 1.62 mmol, 1 equiv.) in dry THF (10 mL), cooled to –78 °C, was added. The mixture was stirred at –78 °C for 1 h, then it was warmed to room temperature, and stirred at room temperature overnight. Next, the mixture was carefully quenched with a saturated sodium hydrogen carbonate solution (15 mL), and extracted with dichloromethane (2 × 40 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo.

To remove the MEM protecting group, the residue was dissolved in dichloromethane (9 mL) and trifluoroacetic acid (3 mL), and the mixture was stirred at room temperature for 24 h. The reaction mixture was neutralized by carefully adding a saturated sodium hydrogen carbonate solution, and extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo. The crude product was purified by silica column chromatography with ethyl acetate/petroleum ether (1:1) as an eluent to give pure **57** (115 mg, 28%) as a yellow solid, m.p. 185–186 °C. $R_f$ (EtOAc/petroleum ether, 1:1) = 0.25. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.98 (s, 3 H, $OCH_3$), 6.32 (br. s, 1 H, OH), 6.98 (d, $J$ = 8.2 Hz, 1 H, 5-H), 7.15 (d, $J$ = 1.8 Hz, 1 H, 2-H), 7.24 (dd, $J$ = 8.2, $J$ = 1.8 Hz, 1 H, 6-H), 7.34 (d, $J$ = 15.6 Hz, 1 H, α-H), 7.48 (dd, $J$ = 7.8, $J$ = 4.9 Hz, 1 H, 5′-H), 7.79 (d, $J$ = 15.6 Hz, 1 H, β-H), 8.30 (d, $J$ = 7.8 Hz, 1 H, 6′-H), 8.72–8.91 (m, 1 H, 4′-H), 9.15–9.34 (m, 1 H, 2′-H) ppm. $^{13}$C NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 56.0 ($OCH_3$), 110.1 (C-2), 115.1 (C-5), 119.0 (C-α), 123.8 (C-5′), 124.0 (C-6), 127.0 (C-1), 133.9 (C-1′), 136.0 (C-6′), 146.5 (C-β), 147.0 (C-4), 149.0 (C-3), 149.6 (C-2′), 152.8 (C-4′), 189.1 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 982, 1018, 1591 (C=C), 1656 (C=O). MS ($ESI^+$): $m/z$ (%) = 256.0 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{13}NO_3$ 255.0895; found 255.0903. IR data[52] and m.p.[53] were in accordance with literature references.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one (61):** 3-Bromo-1-(triisopropylsilyl)pyrrole (0.169 g, 0.65 mmol, 1.2 equiv.) was dissolved in dry THF (13 mL) in a flame-dried flask (25 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and *n*-butyllithium

(2.17 N solution in hexanes; 0.24 mL, 0.65 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, and then (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.150 g, 0.46 mmol, 1 equiv.) was added. The mixture was stirred at –78 °C for 1 h, and at room temperature overnight. The reaction was carefully quenched with saturated sodium hydrogen carbonate solution (10 mL). Next, the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo.

To remove the TIPS protecting group, the crude product was dissolved in THF (10 mL), TBAF (1 N solution in THF; 0.46 mL, 0.46 mmol, 1 equiv.) was added, and the reaction mixture was stirred at room temperature for 5 min. Next, the volatiles were removed in vacuo.

To remove the MEM protecting group, the residue was dissolved in dichloromethane (9 mL) and trifluoroacetic acid (3 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized by adding saturated sodium hydrogen carbonate solution, and then it was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo. The resulting oil was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:1) as eluent to give compound **61** (44 mg, 39%) as an orange powder, m.p. 205.5–206.5 °C. $R_f$ (EtOAc/petroleum ether, 1:1) = 0.15. $^1$H NMR ([D$_6$]DMSO, 400 MHz): $\delta$ = 2.51 (s, DMSO), 3.38 (s, $H_2O$), 3.87 (s, 3 H, $OCH_3$), 6.63 (br. s, 1 H, 5′-H), 6.82 (d, $J$ = 8.1 Hz, 1 H, 5-H), 6.89 (d, $J$ = 1.4 Hz, 1 H, 4′-H), 7.22 (dd, $J$ = 8.1, $J$ = 1.2 Hz, 1 H, 6-H), 7.43 (d, $J$ = 1.2 Hz, 1 H, 2-H), 7.46 (d, $J$ = 15.6 Hz, 1 H, α-H), 7.53 (d, $J$ = 15.6 Hz, 1 H, β-H), 7.91 (br. s, 1 H, 2′-H), 9.52 (s, 1 H, OH), 11.53 (br. s, 1 H, NH) ppm. $^{13}$C NMR ([D$_6$]DMSO, 100.6 MHz): $\delta$ = 56.3 ($OCH_3$), 108.5 (C-5′), 112.0 (C-2), 116.0 (C-5), 120.5 (C-4′), 121.7 (C-α), 123.5 (C-6), 125.4 (C-2′), 126.9, 127.1 (C-1, C-1′), 141.3 (C-β), 148.4 (C-4), 149.3 (C-3), 183.9 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1102, 1280, 1417, 1568 (C=C), 1645 (C=O), 2349, 3144 (OH), 3340 (NH) cm$^{-1}$. MS (ESI$^+$): *m*/*z* (%) = 244.3 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{13}NO_3$ 243.0895; found 243.0902.

**(2*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(1-methylpyrrol-3-yl)prop-2-en-1-one (63):** 3-Bromo-1-(triisopropylsilyl)pyrrole (0.169 g, 0.65 mmol, 1.2 equiv.) was dissolved in dry THF (13 mL) in a flame-dried flask (25 mL) under an inert atmosphere. The mixture was cooled to –78 °C in a dry ice/acetone bath, and *n*-butyllithium (2.17 N solution in hexanes; 0.24 mL, 0.65 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, and then (2*E*)-*N*-methoxy-3-[3-methoxy-4-(2-methoxyethoxymethoxy)phenyl]-*N*-methylacrylamide (**31**; 0.150 g, 0.46 mmol, 1 equiv.) was added. The mixture was stirred at –78 °C for 1 h, and then at room temperature overnight. The reaction was carefully quenched with saturated sodium hydrogen carbonate solution (10 mL). Next, the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo.

To remove the TIPS protecting group, the crude product was dissolved in THF (10 mL), TBAF (1 N solution in THF; 0.46 mL, 0.46 mmol, 1 equiv.) was added, and the reaction mixture was stirred at room temperature for 5 min. Next, the volatiles were removed in vacuo.

Methylation of the pyrrole nitrogen was achieved as follows. The crude product was dissolved in dry DMF (10 mL) under an inert atmosphere. Next, cesium carbonate (0.45 g, 1.38 mmol, 3 equiv.) and TBAI (0.51 g, 1.38 mmol, 3 equiv.) were added, and the reaction mixture was stirred at room temperature for 30 min. Then, methyl iodide (0.086 mL, 1.38 mmol, 3 equiv.) was added, and the reaction mixture was stirred at room temperature overnight. Ethyl acetate(20 mL) was added, and the mixture was washed with brine (3 × 20 mL). The organic layer was dried with $MgSO_4$ and evaporated in vacuo.

To remove the MEM protecting group, the crude product was dissolved in dichloromethane (30 mL) and trifluoroacetic acid (10 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized by adding saturated sodium hydrogen carbonate solution, and then it was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with an equal volume of brine, dried with $MgSO_4$, and evaporated in vacuo. The resulting oil was purified by column chromatography over silica with ethyl acetate/petroleum ether (1:1) as an eluent to give compound **63** (42 mg, 35%) as orange crystals. A sample of extra high purity was obtained by preparative HPLC (water/$CH_3CN$; 0–20 min, 65:35; 20–35 min, 0:100; 35–45 min, 65:35), m.p. 64.5–65.5 °C. $R_f$ (EtOAc/petroleum ether, 1:1) = 0.09. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 3.72 (s, 3 H, $NCH_3$), 3.95 (s, 3 H, $OCH_3$), 5.99 (br. s, 1 H, OH), 6.62 (br. t, $J$ = 2.7 Hz, 1 H, 4′-H), 6.72 (dd, $J$ = 2.7, $J$ = 1.8 Hz, 1 H, 5′-H), 6.94 (d, $J$ = 8.3 Hz, 1 H, 5-H), 7.09 (d, $J$ = 1.9 Hz, 1 H, 2-H), 7.12 (d, $J$ = 15.6 Hz, 1 H, α-H), 7.19 (dd, $J$ = 8.3, $J$ = 1.9 Hz, 1 H, 6-H), 7.38 (t, $J$ = 1.8 Hz, 1 H, 2′-H), 7.70 (d, $J$ = 15.6 Hz, 1 H, β-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 36.7 ($NCH_3$), 56.0 ($OCH_3$), 109.7 (C-5′), 110.1 (C-2), 114.8 (C-5), 121.4 (C-α), 122.6 (C-6), 123.4 (C-4′), 126.8 (C-1 or C-1′), 126.9 (C-2′), 127.9 (C-1 or C-1′), 142.0 (C-β), 146.7 (C-4), 147.7 (C-3), 184.6 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 1182, 1266, 1423, 1509, 1560 (C=C), 1639 (C=O), 2348, 2928, 3119 (OH) cm$^{-1}$. MS (ESI$^+$): *m*/*z* (%) = 258.3 (100) [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{15}NO_3$ 257.1052; found 257.1056.

**{[2-(Trimethylsilyl)ethoxy]methyl}pyrrole (65):** This product was synthesized according to the procedure of Muchowski et al.[46] Compound **65** (187 mg, 83%) was obtained as a colourless oil. NMR spectroscopic data were in accordance with the data reported by Muchowski et al.[46]

**2-Bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrole (66):** This product was synthesized from **65** according to the procedure of Garg et al.[47] Compound **66** (255 mg, 97%) was obtained as a pale yellow oil. NMR spectroscopic data were in accordance with those reported by Garg et al.[47]

**Supporting Information** (see footnote on the first page of this article): copies of the $^1$H and $^{13}$C NMR spectra of key intermediates and final products.

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