Synthesis of natural and non-natural diarylheptanoids and evaluation of their neuroprotective activity

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List of abbreviations

1D	one-dimensional
2D	two-dimensional
Aβ	amyloid beta
AD	Alzheimer's disease
APCI	atmospheric pressure chemical ionization
aq.	aqueous
$B_2(pin)_2$	pinacolato diboron
CAPE	caffeic acid phenethyl ester
CC	column chromatography
γ-GCS	gamma-glutamoylcysteine synthase
cGMP	cyclic guanosine monophosphate
CoA	coenzyme A
COSY	correlation spectroscopy
COX-2	cyclooxygenase-2
DIBAl-H	diisobutyl aluminum hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron-impact ionization
eq.	equivalent
ERα	estrogen receptor alpha
ERK	extracellular-signal regulated kinase
ESI	electro-spray ionisation
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron volt
FCS	fetal calf serum
GC	gas chromatography
Glc	*β*-D-glucose
Glu	glutamate
GSH	glutathione
GTP	guanosine triphosphate
HCl	hydrochloric acid

HMBC	heteronuclear multiple-bond correlation
HMEC	human microvascular endothelial cells
HO-1	heme oxygenase 1
HPLC	high-performance liquid chromatography
HR	high resolution
HSQC	heteronuclear single-quantum correlation
IC_{50}	half maximal inhibitory concentration
IFN	interferone
IκBα	inhibitor of kappa B, alpha
IKK	IκB kinase
IL	interleukin
JNK	c-Jun N-terminal kinase
iNOS	inducible nitric oxide synthase
KOAc	potassium acetate
12-LOX	arachidonate 12-lipoxygenase
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
MAXIM.	(Karl) Maximowicz
MeOD	methanol-d_4
MeOH	methanol
Me_2SO_4	dimethyl sulfate
MOM	methoxymethyl
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	microwave irradiation
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
n-BuLi	*n*-butyl lithium
N-Cbz	*N*-carboxybenzyl
NF-κB	nuclear factor-kappa B
NMDA	*N*-methyl-D-aspartat
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NP	normal phase
Nrf2	nuclear factor-erythroid-2-related factor 2
p53	protein 53
PD	Parkinson’s disease

Pd/C	palladium on charcoal
PE	petroleum ether (boiling point: 40-60 °C)
Ph_2S	diphenyl sulfide
PI3K/Akt	phosphatidylinositol-4,5-phosphate 3-kinase/Akt
PPh_3	triphenylphosphine
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
R^2	coefficient of determination
R_f	retardation factor
ROS	reactive oxygen species
RP	reversed phase
r.t.	room temperature
s-GC	soluble guanylyl cyclase
SDS	sodium dodecyl sulfate
S_N2	bi-molecular substitution
SOD	superoxide dismutase
t-BuOOH	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TNF	tumor necrosis factor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
t_R	retention time
UV	ultraviolet

Content

1 Introduction

1.1 General classification of diarylheptanoids

Diarylheptanoids are a class of secondary plant metabolites with a structure generally consisting of two aromatic rings connected by a seven membered aliphatic chain. They can be further subdivided into linear and cyclic diarylheptanoids where the latter are represented by *meta,para*-bridged diphenyl ether type and *meta,meta*-bridged biphenyls.[1] A special group represent compounds with an additional cycle in the connecting chain,[2] e.g. cyclocurcumin (**4**). Typical examples of all four types are depicted in Fig. 1.

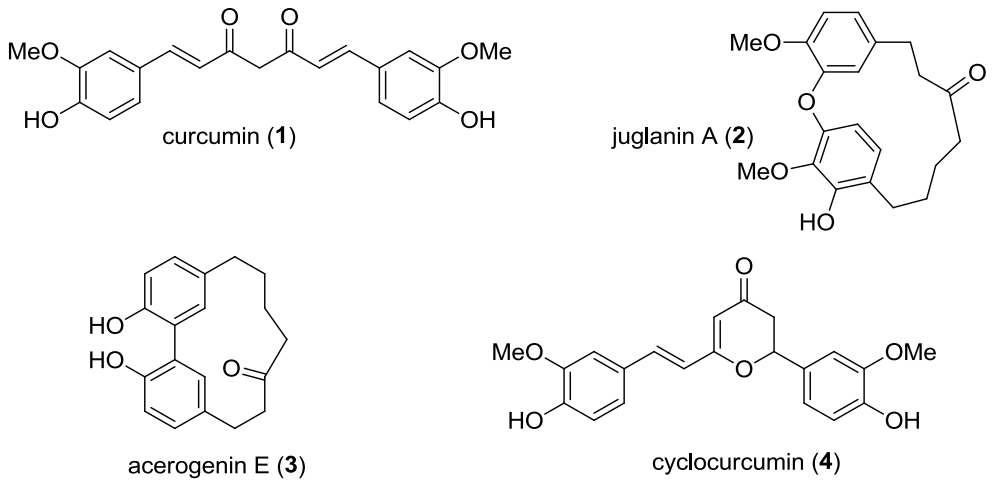


Fig. 1: Characteristic representatives of diarylheptanoid classes: linear (curcumin, **1**), cyclic of diphenyl ether type (juglanin A, **2**), biphenyl cyclic type (acerogenin E, **3**) and diarylheptanoids with cyclized C_7-chain (cyclocurcumin, **4**).

1.2 Occurrence and structure of diarylheptanoids

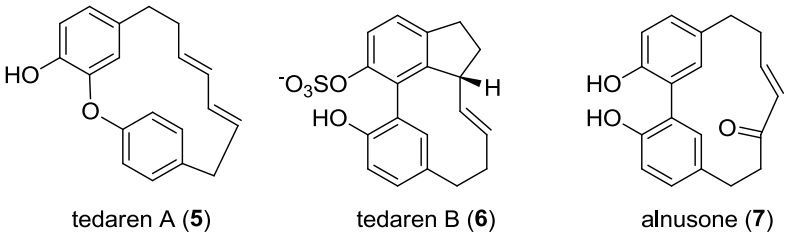
Compounds of the diarylheptanoid family can be typically found in the (inner) stem and the root bark of parent trees and shrubs, in the rhizomes of herbs,[3] but also in extracts of leaves and twigs.[4] Juglanin A (**2**) and B (**17**), two cyclic compounds from *Juglans regia* L., were isolated from the green pericarps of walnuts.[5] Due to the phenolic nature of diarylheptanoids, MeOH, MeOH/CH_2Cl_2 mixtures[6] or EtOH are normally used for their extraction. In some cases, e.g. for the extraction of *Betula platyphylla* leaves, acetone was used as solvent.[7]

Table 1: Occurrence of diarylheptanoids in plants based on Keserü et al.,[1] Claeson et al.[2] and Lv et al.[3, 8]

Family	Genus	Diarylheptanoids			
		linear	diphenyl ethers	biphenyls	with cyclized C_7 chain
Aceraceae	*Acer*	+	+	+	-
Betulaceae	*Alnus*	+	+	+	+
	Betula	+	+	+	-
	Corylus	-	-	+	-
	Carpinus	-	-	+	-
	Ostrya	-	-	+	-
Burseraceae	*Garuga*	-	+	+	-
	Boswellia	-	+	-	-
Casuarinaceae	*Casuarina*	-	-	+	-
Dioscoreaceae	*Dioscorea*	+	-	-	+
	Tacca	+	-	-	+
Juglandaceae	*Juglans*	+	+	+	+
	Platycarya	-	+	+	-
	Rhoiptelea	+	+	+	-
Leguminosae	*Centrolobium*	+	-	-	+
Myricaceae	*Myrica*	-	+	+	-
Santalaceae	*Viscum*	+	-	-	-
Zingiberaceae	*Alpinia*	+	-	-	+
	Curcuma	+	-	-	+
	Zingiber	+	-	-	+
	Amomum	+	-	-	+
	Aframomum	+	-	-	-
	Etlingera	+	-	-	-

There is evidence on approximately 400 compounds of this kind (state 2011) which were discovered among several plant families.[8] Interestingly, not all of the plant families, in which diarylheptanoids occur, are taxonomically relative and thus similar derivatives can be found in Zingiberaceae (order Zingiberales, clade monocots) as well as in Betulaceae (order Fagales, clade eudicots). Table 1 provides a summary of the distribution in nature for all four types.

Besides terrestrial plants, two cyclic diarylheptanoids named tedaren A (**5**) and tedaren B (**6**) were isolated from the marine sponge *Tedania ignis*. The second one was identified as the smallest natural product with planar, central and axial chirality.[9] Another example of unusual appearance was the extraction of alnusone (**7**) and its five congeners from *Nidus vespae*, the nest of paper wasp (*Polistes*), which is commonly used in Traditional Chinese Medicine. Since animals normally do not produce such secondary metabolites, the isolated compounds have to originate from plant material processed by the insects (Fig. 2).[10]



tedaren A (**5**) tedaren B (**6**) alnusone (**7**)

Fig. 2: Examples of diarylheptanoids which were not isolated from terrestrial plants.

Concerning the structural motifs, linear diarylheptanoids typically exhibit hydroxyl and methoxy substituents on one or both aromatic rings, mostly in positions 3', 3'', 4', 4'', 5' and 5'', rarely in positions 2' and 2'' (Fig. 3).[8] Compounds without aromatic OH-groups were discovered only in few cases in *Curcuma*, *Alpinia* and *Alnus* species.[2] Phenolic glycosylation was observed, comprising mainly mono- and diglycosides with e.g. glucose or apiose.[11] The substitution of the tethered chain is more distinct. Since phenylpropanoids are their biosynthetic precursors, oxygenation prevails in position 3 and 5, however, examples of natural products, oxygenated at carbon(s) 1, 2, 6 or 7, were described.[8] The hydroxyl derivatives can be acylated, glycosylated or sulfated.[8] The aliphatic chain is either fully saturated or contains up to three double bonds.[2, 8] Conjugations with other units, such as chalcones,[12] flavonoids[12] or phenethyl,[13] are rare but possible (Fig. 3).

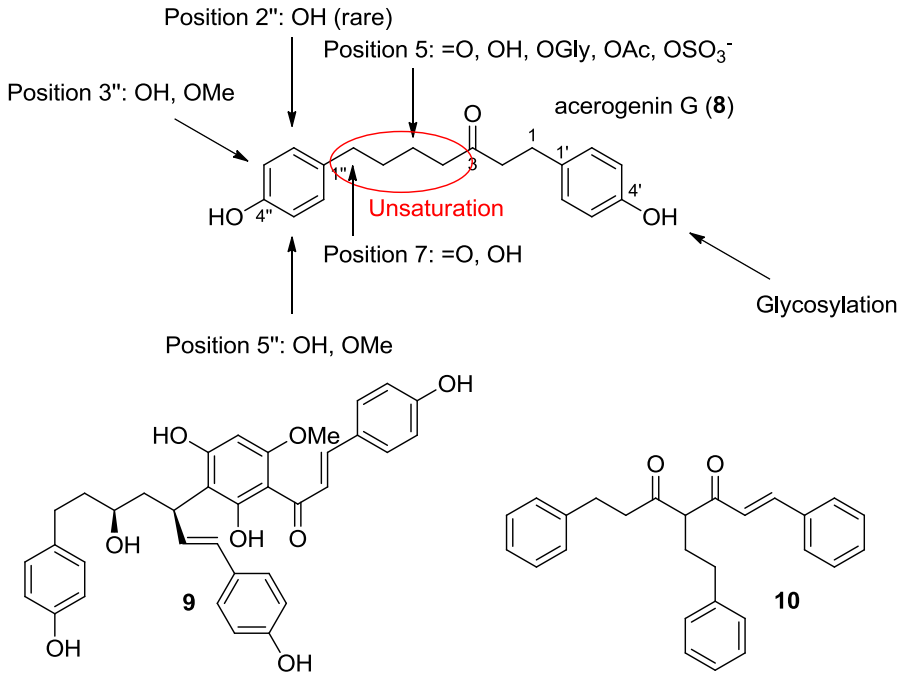


Fig. 3: Common substitutions of linear diarylheptanoids on the example of acerogenin G (**8**) and two examples of unusual conjugations with other phenolic compounds (**9**, **10**)

The structural diversity among the diphenyl ether type is high, nevertheless, certain structural similarities in terms of phenolic substitution can be found within botanical families (Fig. 4). In the Aceraceae family, mono-hydroxylation in position 2 can typically be seen (e.g. acerogenin C, **11**), whereas *Garuga* species (Burseraceae) exhibit multiple methoxylations and hydroxylations in positions 2, 3 or 4 (garuganin I (**12**), garuganin IV (**13**)) (Fig. 4).[14] Myricaceae are more known for their biphenyl type diarylheptanoids, although even here exceptions exist like galeon (**14**) with 2-hydroxyl-16-methoxy substitution.[15] Finally, the diaryl ethers are represented in the Juglandaceae family by compounds like juglanin A (**2**)[5] or pterocarine (**15**), isolated from trees of the genus *Pterocarya* (Fig. 4).[16] As for their linear congeners, a glycosylation of phenolic and aliphatic OH-groups was observed.[2]

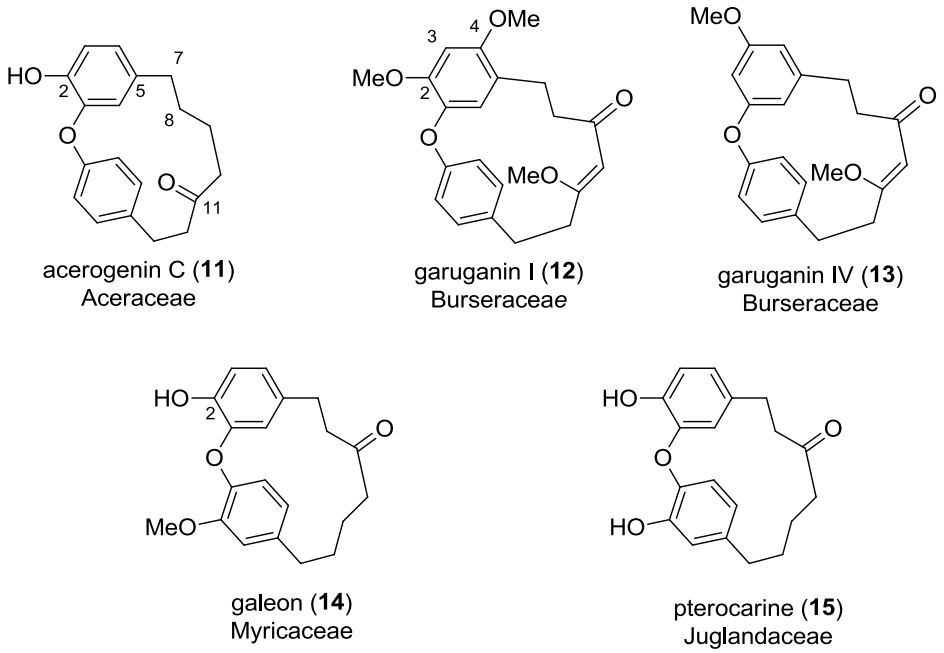


Fig. 4: Typical representatives of the diphenyl ether type diarylheptanoids

In analogy to the diphenyl ether cyclic diarylheptanoids, the biphenyl compounds exhibit a limited diversity of aryl substituents (Fig. 5). Natural products isolated from Aceraceae, Casuarinaceae, Burseraceae and the majority of the biphenyls from Betulaceae are characteristic due to their 3,17-dihydroxyl substitution, e.g. acerogenin K (**16**). Additional methoxy group in position 4 occurs in walnut (Juglandaceae, juglanin B (**17**))[5] and in a few derivatives from *Myrica* (e.g. myricananin C (**18**)).[17] The highest variety of aryl substituent patterns shows the genus *Myrica* with typical 17-hydroxy-3,4-dimethoxy motifs, supplemented by either a methoxy, hydroxyl or *O*-sugar moieties in position 5.[18] The tethered chain is mostly, but not exclusively, oxygenated in position 11. A double bond occurs mostly in conjugation with a keto functionality affording an enone, e.g. in alnusone (**7**) or myricananin D (**20**) (Fig. 5).

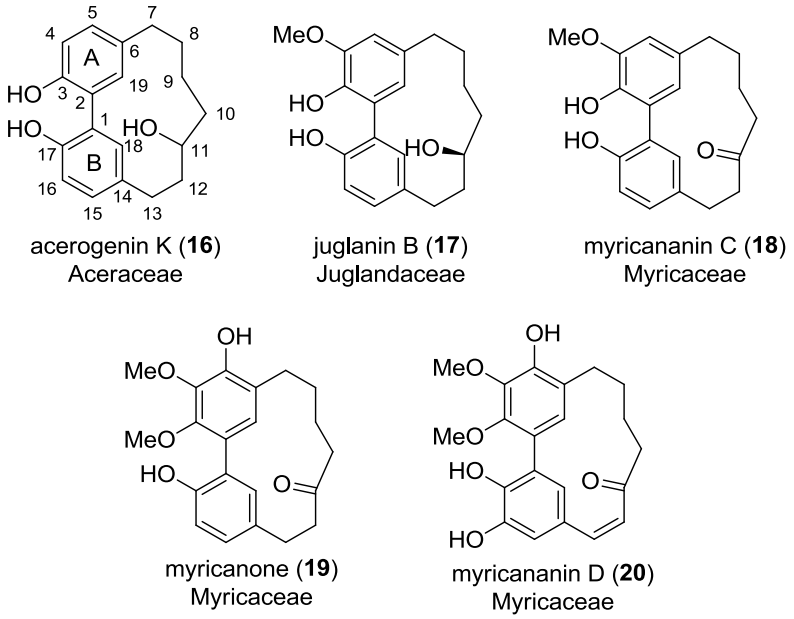


Fig. 5: Examples of biphenyl type cyclic diarylheptanoids

The last group of diarylheptanois consists of compounds employing extra rings within the seven carbon connecting chain (Fig. 6). These compounds show an interesting variability regarding the aliphatic part. A typical example is the *Curcuma longa* diarylheptanoid cyclocurcumin (**4**), i.e. derivative of curcumin (**1**) with a 2,3-dihydro-4*H*-pyran-4-one ring formed by a intramolecular cyclization. *Alpinia blepharocalyx* contains numerous substances with a tetrahydropyran ring, of which some are conjugated with chalcones or flavonoids. Another source of diarylheptanoids with cyclized C_7-chain is ginger (*Zingiber officinale*), a close relative of the above mentioned plants. Diarylheptanoids with a tetrahydrofuran ring in the tethered chain were discovered in *Renealmia exaltata*, a Brazilian medicinal plant of the ginger family.[19] A completely different structure shows bicyclic diarylheptanoid **22** from the fruits of *Musa* × *paradisiaca*, a cultivated sort of banana tree. This compound was accompanied by three 9-phenylphenalenones,[20] emphasizing the biosynthetic relation of diarylheptanoids and the latter.[1] Finally, the compound **24** (Fig. 6) with a tetrahydro-5*H*-benzo[7]annulen moiety was found in greater cardamom (*Amomum subulatum* Roxb.)[21] and is so far the only isolated representative of this kind.

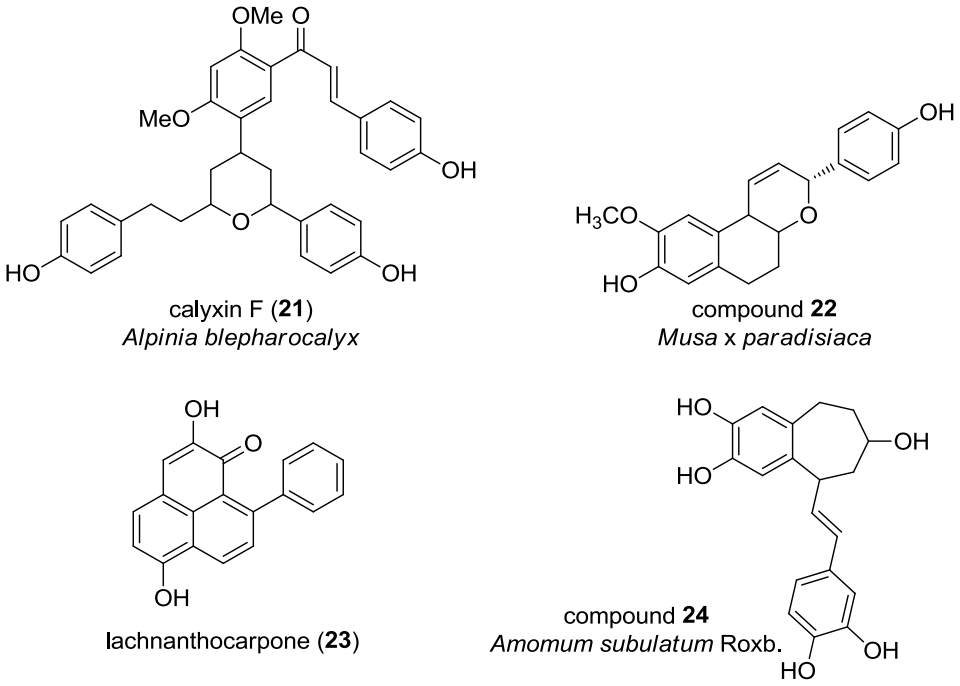
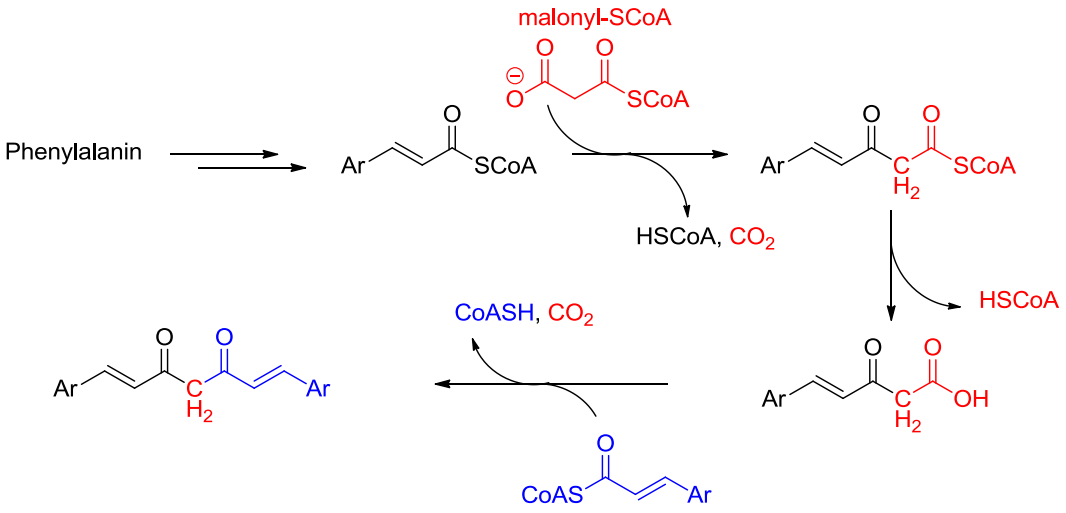


Fig. 6: Representatives of diarylheptanoids with cyclized C_7-chain

1.3 Biosynthesis of diarylheptanoids

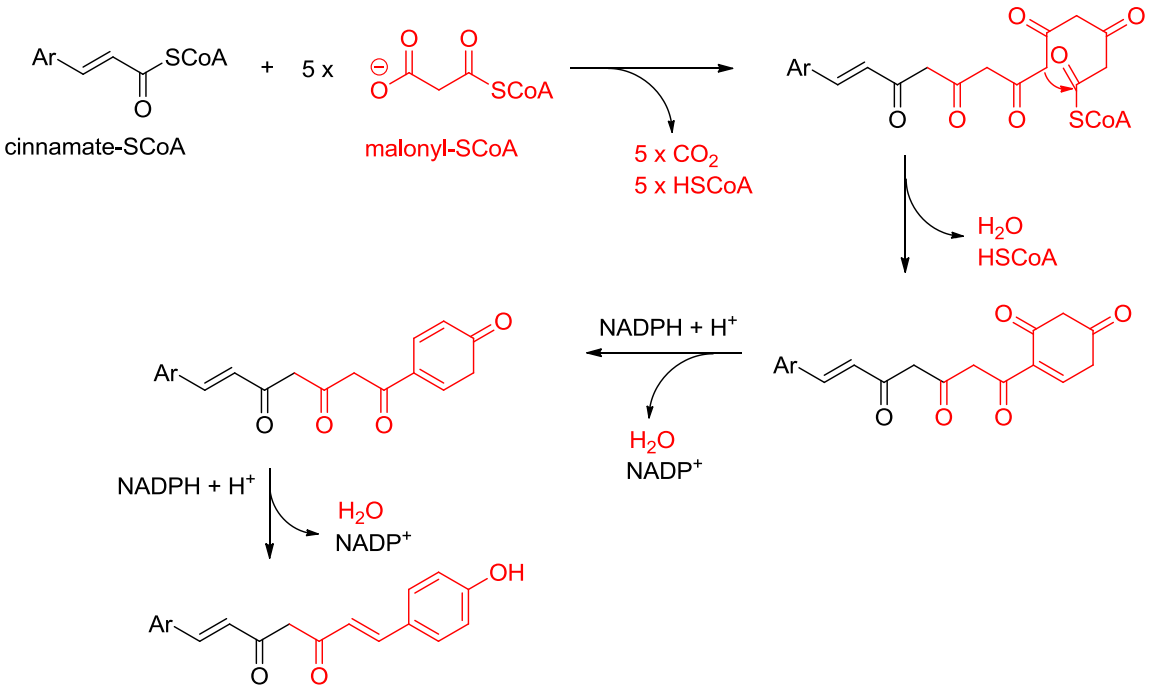
Curcumin (**1**), the most prominent linear diarylheptanoid, is often referred to as diferuloyl methane. This name indicates its biosynthetic origin from two cinnamate (ferulate) units (C_6-C_3) with a central methylene group provided by a malonate unit (Scheme 1).[22]



Scheme 1: Biosynthesis of linear diarylheptanoids - Route 1

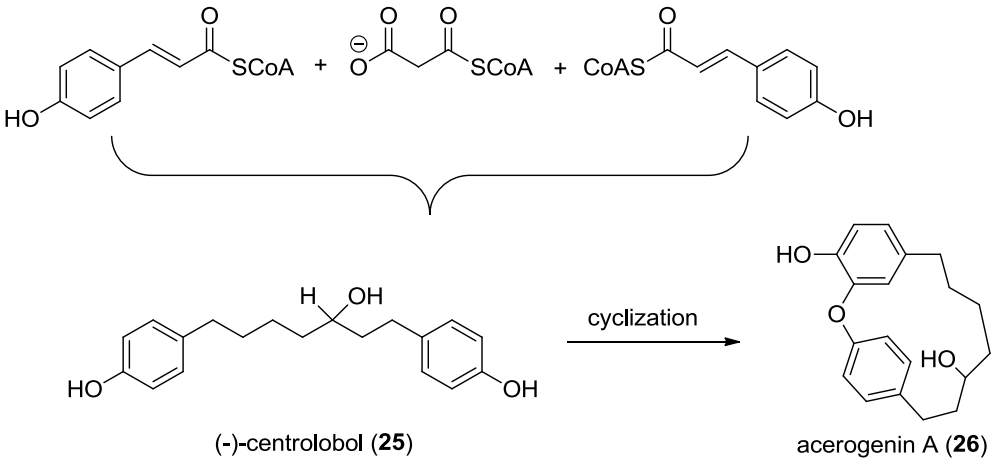
However, investigations carried out by Roughley and Whiting using radioisotope labeled acetate and malonate revealed that an alternative pathway has to be involved in the biosynthesis of curcumin since the radioactivity was distributed among other carbons of the heptane chain and the aryl ring.[23] This discovery led to the postulation of a competing

mechanism which incorporates polyketide extension of a cinnamate unit with five acetate (or malonate) units followed by a cyclization (Scheme 2).[22-23]



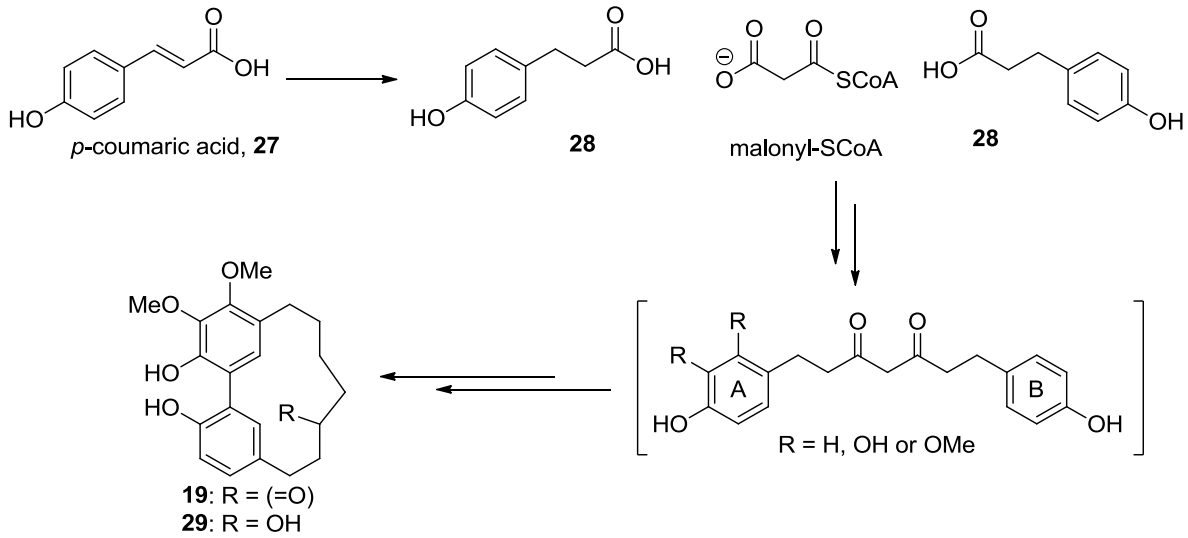
Scheme 2: Alternative biosynthetic pathway incorporating a polyketide synthase proposed by Roughley and Whiting – Route 2

Mechanistic studies were performed for the diphenyl ether type compound acerogenin A (**26**) from the bark of *Acer nikoense* (Scheme 3). Feeding of young shoots of this tree with ^{14}C-labeled phenylalanine, cinnamic acid, sodium acetate and malonic acid showed that two cinnamate units are combined with a C_1-unit from malonate to form (-)-centrolobol (**25**) which is then further cyclized to acerogenin A (**26**) (Scheme 3).[24] This mechanism agrees with the pathway described in Scheme 1 and is in contrast to the route proposed by Roughley and Whiting for the biosynthesis of curcumin (**1**).[22] The cyclization step was not discussed by the authors.[24]



Scheme 3: Biosynthesis of acerogenin A (**26**) according to Inoue et al. [24]

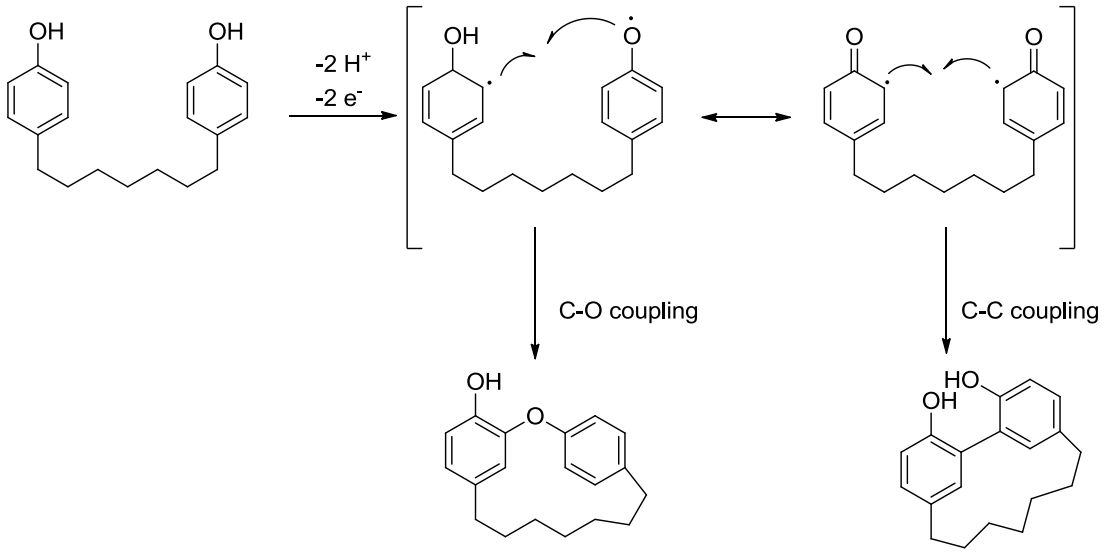
The biosynthesis of the biphenyl type cyclic diarylheptanoids was investigated using the example of myricanone (**19**) and myricanole (**29**) (Scheme 4). ^{13}C-labeled *p*-coumaric acid (**27**) was administrated to young shoots of *Myrica rubra* and its extract was analyzed with GC-MS. The results were consistent with those obtained for acerogenin A (**26**), namely that two molecules of the C_6-C_3 acid are involved in the formation of the linear precursor (Route 1, Scheme 1).[25] Further investigation by the same group with the aid of NMR spectroscopy and MS revealed that 3-(4-hydroxy)-propionic acid (**28**), the reduced equivalent of *p*-coumaric acid (**27**), was preferably incorporated in myricanol (**29**) and thus the mechanism was modified to the pathway described in Scheme 4.



Scheme 4: Biosynthesis of the biphenyl type cyclic diarylheptanoids myricanone (**19**) and myricanol (**29**) in *Myrica rubra*

Altogether, the biosynthesis of diarylheptanoids most likely differs from plant to plant, following one of the two routes described above (Scheme 1 and Scheme 2). The actual

cyclization mechanism towards both types of cyclic derivatives is not completely known yet, but a phenolic oxidative coupling, as in the case of the lignan biosynthesis,[26] is possibly involved. According to this theory, a phenolic oxidative C-C coupling would lead to *meta*,*meta*-bridged biphenyls whereas the corresponding C-O coupling would preferably result in the formation of *meta*,*para*-bridged diphenyl ethers (Scheme 5). This indeed corresponds with the isolated natural products.[27]

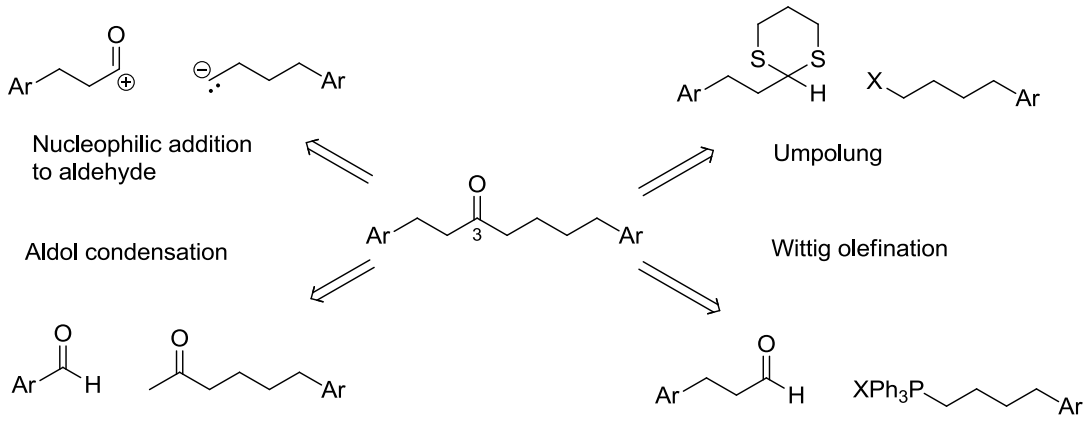


Scheme 5: Proposed mechanism for the cyclization of diarylheptanoids

1.4 Synthesis of diarylheptanoids

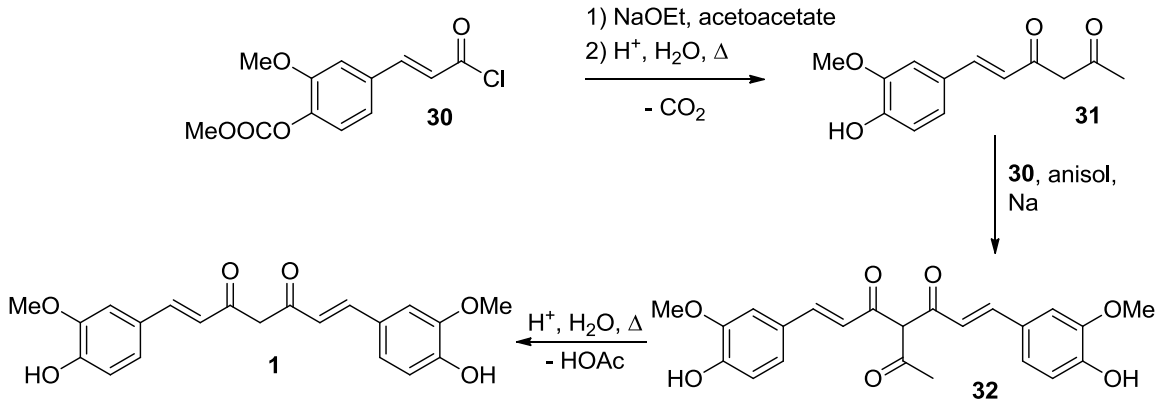
Due to the relatively simple nature of opened chain diarylheptanoids, many synthetic strategies were developed over the years. Different approaches have to be applied depending on the number of oxygenated carbons in the tethered chain. Typically, the aliphatic part bears either one (e.g. centrolobol, **25**), two (e.g. curcumin, **1**) or three (e.g. yashabushiketodiol A), extremely rarely four, oxygen atoms.[27]

Mono-oxygenated acyclic diarylheptanoids exhibit the oxygenation in position 3 due to their biosynthetic origin from phenylpropanoids. This can be synthetically achieved, for instance, by nucleophilic additions to aldehydes,[28] by aldol condensations,[29] by the incorporation of *Umpolung* strategy with dithians[28] or by Wittig-type reactions (Scheme 6).[29]



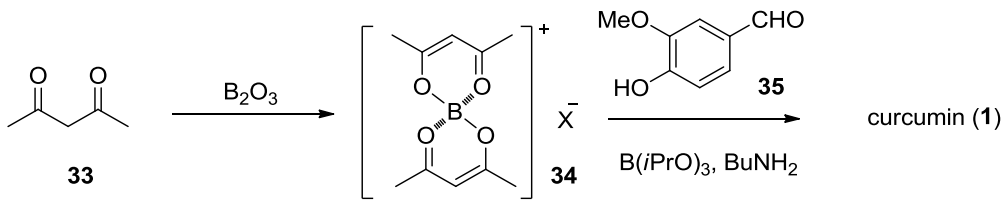
Scheme 6: Retrosynthetic considerations towards mono-oxygenated linear diarylheptanoids

Double-oxygenated diarylheptanoids can be considered as the closest relatives of curcumin (**1**). Such curcuminoids are usually substituted with hydroxyl or keto groups in positions 3 and 5. The first synthesis of curcumin (**1**) was accomplished in 1918 by V. Lampe using carbomethoxyferuloyl chloride (**30**) and acetoacetate. This reaction yielded a diketone **31**, which upon a treatment with another carbomethoxyferuloyl chloride (**30**) and a loss of acetic acid gave the desired natural product **1** (Scheme 7).[30]



Scheme 7: The first synthesis of curcumin (**1**) by V. Lampe in 1918[30]

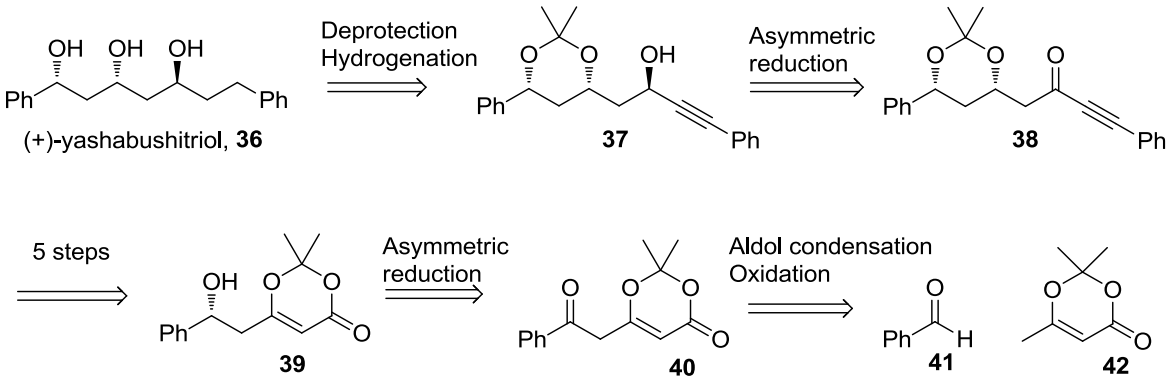
The first industrial synthesis was later developed by Pavolini (1937) and improved by Pabon[31] in 1964 (Scheme 8). This method incorporates acetylacetone **33** and two equivalents of vanillin **35**. To avoid an undesired Knoevenagel condensation, the carbon 3 of the acetylacetone has to be protected as a complex **34** with boric anhydride. The formation of curcumin (**1**) is then carried out in the presence of triisopropylborate and butylamine to afford the product in 80% yield.



Scheme 8: Industrial synthesis of curcumin (**1**) according to Pavolini and Pabon

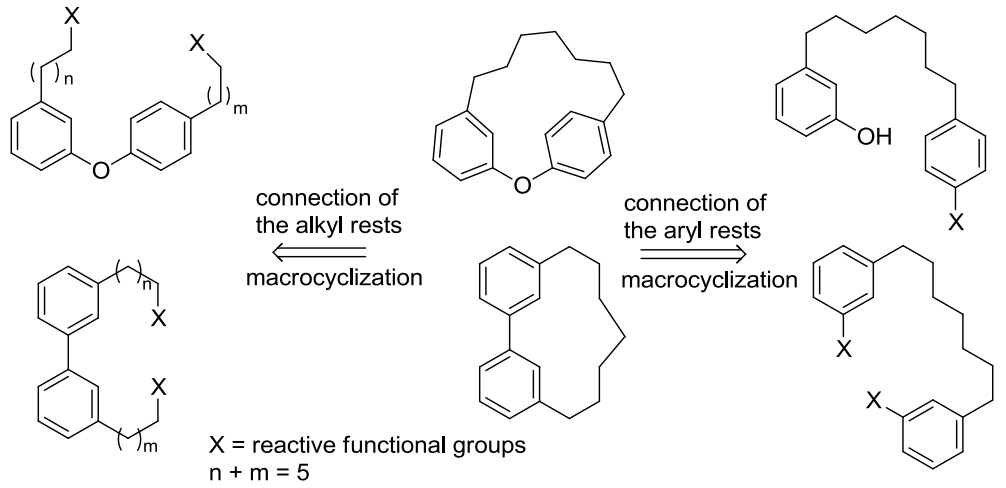
This method offers a unified strategy towards symmetric curcuminoids and was applied for the synthesis of electron rich curcumin derivatives[32] as well as for a library of compounds with various linkers and heteroaryl rings.[33]

The last group of linear diarylheptanoids is represented by compounds with three oxygenations in the tethered chain. As an example for the preparation of this relatively rare derivatives might be used the asymmetric synthesis of (+)-yashabushitriol (**36**),[34] a natural product from *Alnus sieboldiana* (Scheme 9).[35] The core reactions were the asymmetric reductions of synthons **40** and **38** with the aid of ruthenium catalysis, providing enantiomerically pure **36** and its 5-epimer in 11 steps.[34]



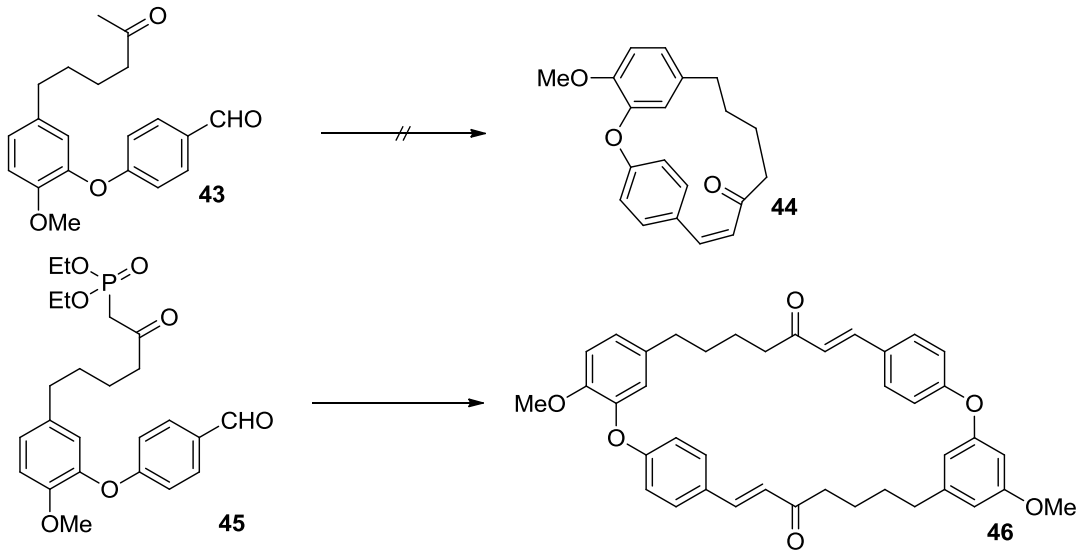
Scheme 9: The retrosynthesis of (+)-yashabushitriol (**36**), a linear diarylheptanoid with 3 oxygenations

A bigger challenge than the synthesis of the opened chain diarylheptanoids offers the preparation of their cyclic derivatives (Scheme 10). The key step in the formation of the latter is the ring closing reaction. This can be performed either by a connection of two alkyl or two aryl rests, yielding both aryl ethers and biphenyls. Both strategies were investigated and with more or less success applied in the synthesis of different cyclic natural products of the diarylheptanoid family.[27]



Scheme 10: General approaches towards cyclic diarylheptanoids

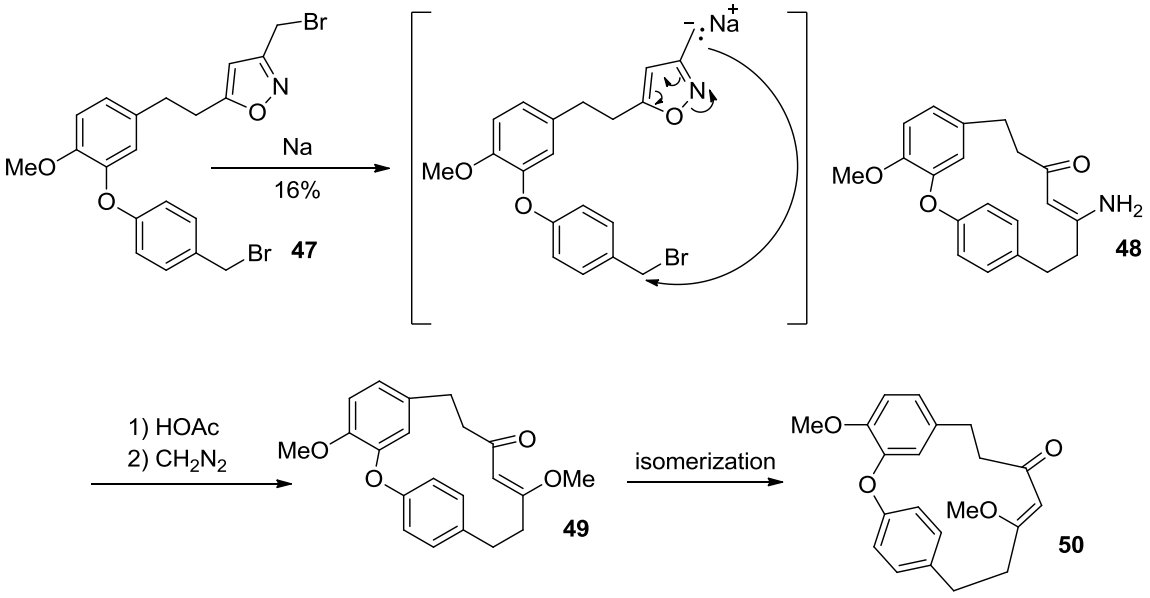
The first macrocyclization strategy, incorporating the connection of the aliphatic rests, was explored mostly in the synthesis of the diphenyl ether type diarylheptanoids. Especially the groups of Nógrádi and Keserü contributed important findings to this field. On the way to acerogenin A (**26**), an attempted intramolecular Claisen-Schmidt condensation of **43** afforded no product **44**, whereas a Wittig-Horner olefination of the aldehyde-phosphonate **45** resulted in the cyclic dimer **46** (Scheme 11).



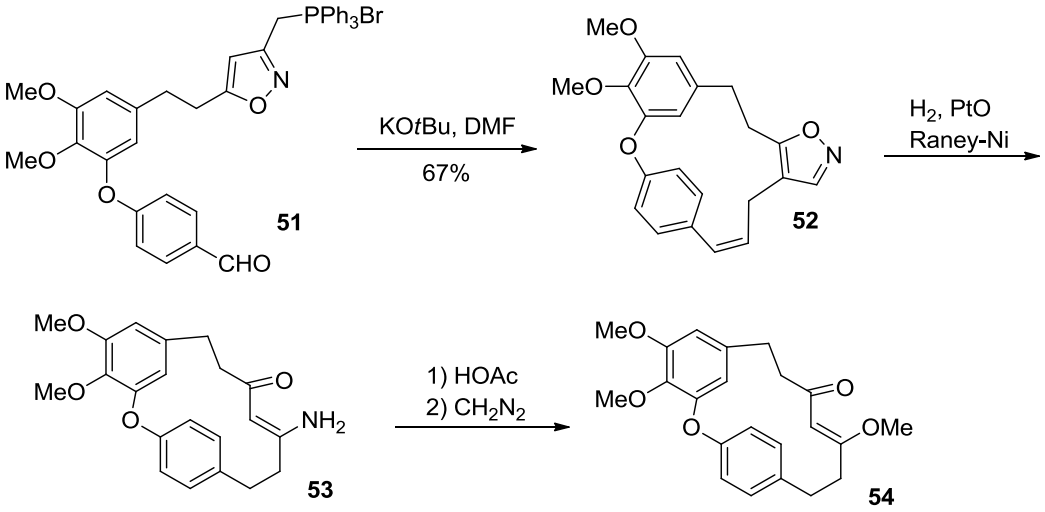
Scheme 11: Failed aldol condensation and Wittig-Horner reaction towards acerogenin A precursors

An elegant alternative to the linear substrates **43** and **45** was the incorporation of isoxazole **47**, a surrogate of a 1,3-diketone unit, which upon the use of a Wurtz (Scheme 12) or a Wittig (Scheme 13) reaction led to garugamblin-1 (**50**)[36] or garuganin III (**54**),[37]

respectively. Although the presence of the isoxazole moiety helped to preorganize the molecule for the intramolecular reaction in these actual cases, the application of this method for other substrates failed, clearly showing its limited scope.



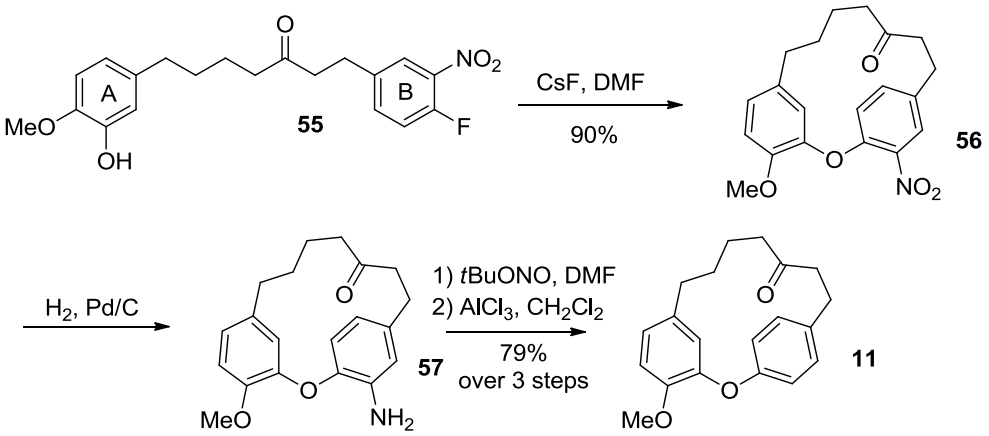
Scheme 12: Wurtz reaction applied in the synthesis of garugamblin-1 (**50**)



Scheme 13: Intramolecular Wittig reaction of isoxazole **51**, a precursor of garuganin III (**54**)

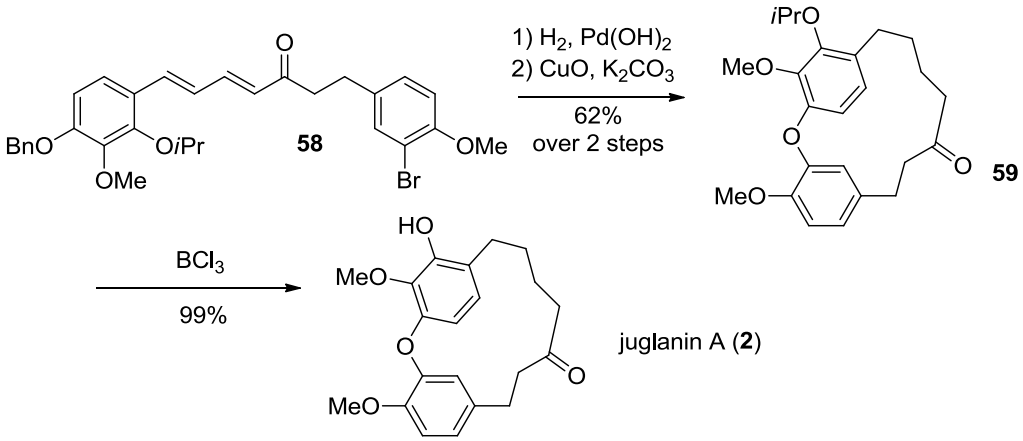
More examples can be found in the literature for the macrocyclization via an aryl-ether bond formation. Zhu et al. developed a strategy based on a nucleophilic aromatic substitution (Scheme 14). Acerogenins A (**26**)[38] and C (**11**)[39] were obtained by this method, using linear compound with a hydroxylated A-ring and a B-ring with 4-fluoro-3-nitro substitution (**55**). The cyclization reaction was promoted by CsF or potassium

carbonate and provided the nitrated product **56** in almost quantitative yield. The conversion was then finished by the reduction of the nitro group to the corresponding amine (**57**), followed by a deamination (Scheme 14).[39]



Scheme 14: Synthesis of acerogenin C (**11**) by an intramolecular nucleophilic aromatic substitution

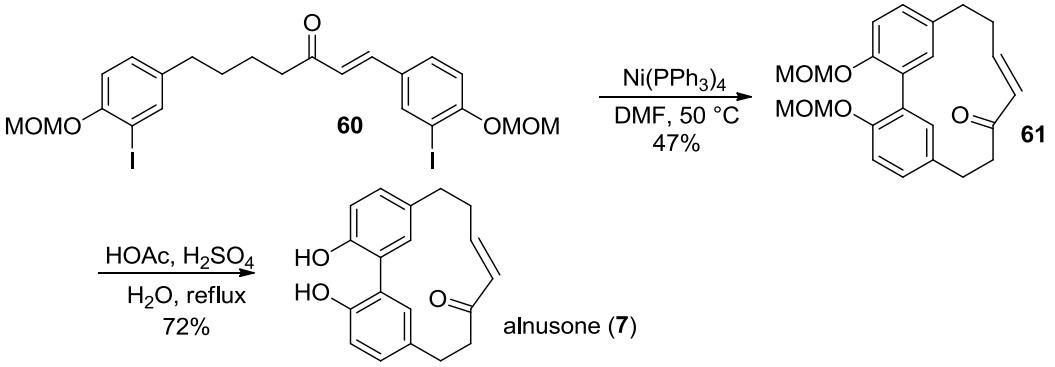
Another method widely used for the formation of the diphenyl ether type cyclic diarylheptanoids provides an intramolecular Ullmann reaction (Scheme 15). This protocol, originally applied by Nógrádi et al. for the synthesis of acerogenins A (**26**) and C (**11**),[40] was later optimized and extended by more working groups[16, 41] and represents a state of the art methodology for this class of compounds. The synthesis of juglanin A (**2**) by Salih and Beaudry[16] depicted in Scheme 15 illustrates the versatility of this strategy.



Scheme 15: Synthesis of juglanin A (**2**) via an intramolecular Ullmann reaction

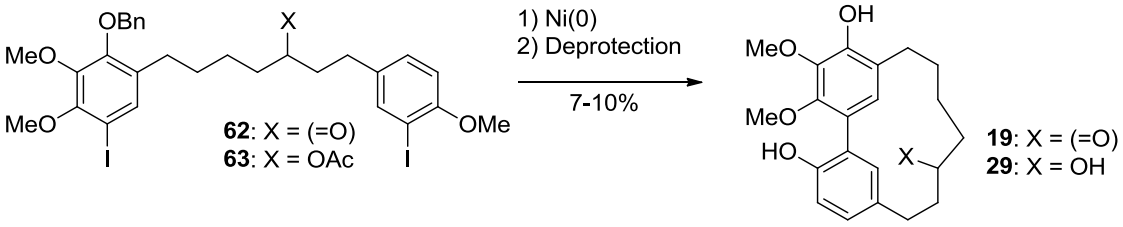
In contrast to the 15-membered *meta*,*para*-cyclophane ring of the diphenyl ethers, the *meta*,*meta*-bridged biphenyl diarylheptanoids exhibit merely a 13-membred ring. The higher ring-strain of such system might be the reason for relatively limited literature evidence for the synthesis of latter. The first example was the synthesis of alnusone (**7**) by

Semmelhack et al., where a biphenyl coupling via a zerovalent nickel catalyzed Ullmann reaction was applied.[42] A diiodinated linear precursor acted as a substrate and the cyclization step proceeded in 47% yield (Scheme 16).



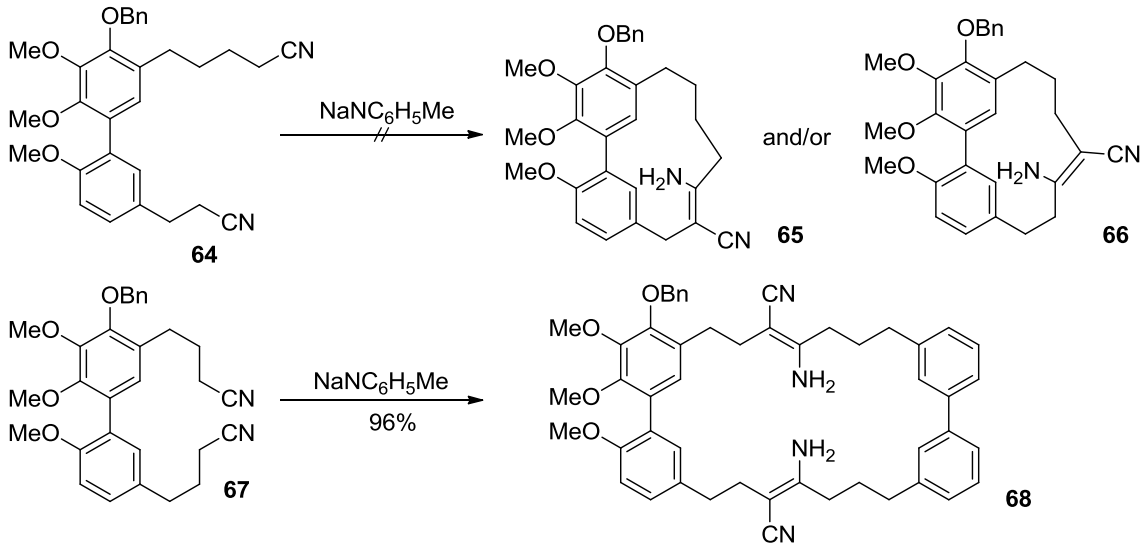
Scheme 16: Synthesis of alnusone (**7**) by a Ni(0) catalyzed Ullmann reaction

Semmelhack's protocol, developed in the early 1980s, was at the same time employed by Whiting and Wood for the synthesis of myricanone (**19**) and myricanol (**29**) reaching, however, only 7-10% yields. The authors pointed out lower ring strain of alnusone (**7**) in contrast to myricanone (**19**) due to the presence of three sp^2 carbons in the heptane linkage of **7** and higher steric hindrance adjacent to the biphenyl in case of **19** (Scheme 17).[43]



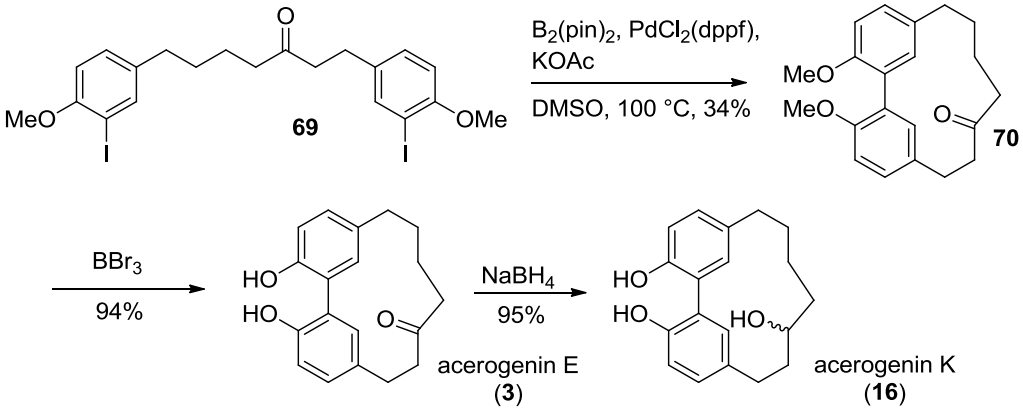
Scheme 17: Key steps in the synthesis of myricanone (**19**) and myricanol (**29**)

To avoid the drawbacks of Semmelhack's and Whiting's method, an alternative approach via an intramolecular Thorpe-Ziegler condensation was examined by Dansou et al (Scheme 18). This strategy employed a biphenyl coupling using a Suzuki reaction at the early stage of the synthetic pathway and dinitriles **64** and **67** as cyclization substrates. Unfortunately, the attempted ring-closure afforded a dimeric compound **68** instead of the envisioned diarylheptanoid.[44]



Scheme 18: Attempted synthesis of myricanone (**19**) via a Thorpe-Ziegler condensation

The last contribution to this topic was the synthesis of acerogenin E (**3**) and K (**16**) by Ogura and Usuki in 2013 (Scheme 19).[29] Herein, the Ni(0)-catalyzed Ullmann coupling was replaced by a more recent methodology, namely by a domino sequence of a Miyaura arylborylation and an intramolecular Suzuki reaction.[45] Using this concept, the first total synthesis of the two biphenyl type cyclic diarylheptanoids from *Acer nikoense* was accomplished, using diiodinated linear precursors **69** as a substrate for the macrocyclization.[29]



Scheme 19: Total synthesis of acerogenin E (**3**) and K (**16**) by Ogura and Usuki[29]

All in all, the linear diarylheptanoids have become accessible by many of methods over the decades[27] but in particular new asymmetric strategies for the synthesis of chiral compounds attract currently the focus of the scientific community.[46] The number of publications on the synthesis of diaryl ether type cyclic compounds is rising due to their

accesibility by CuO-catalyzed Ullmann reaction.[16, 47] More attention is being dedicated to the unique properties of this cyclophanes such as the ring strain and axial chirality.[47] Within the class of diarylheptanoids with a cyclized C_7-chain, in particular compounds of the cyclocurcumin type[48] and natural products from *Alpinia blepharocalyx*[49] have gained interest since their discovery in the early 1990s. The last group of the biphenyl type cyclic compounds remains, besides very few exceptions,[29, 42, 43b] synthetically unexplored, most likely because of the difficulties in the formation of the extremely strained cycle.

1.5 Biological activity of diarylheptanoids

The parent plants of diarylheptanoids find a broad use in traditional medicines of Asia, South America and Africa. For example, the rhizome of turmeric (*Curcuma longa* L.) is known in Indian (Ayurvedic) and Traditional Chinese Medicine for the treatment of biliary, skin or stomach diseases,[50] as well as for hepatoprotective[51] and anticarcinogenic[52] activity. Multiple review articles cover this field, above all publications by the group of B. Aggarwal.[53] Another plant of the Zingiberaceae family, *Alpinia blepharocalyx*, is traditionally used in southwest of China against stomach disorders. Calyxins, diarylheptanoids with cyclized C_7-chain, were isolated from the seeds of this plant and might thus contribute to the beneficial health effects of *Alpina*.[12] Roots of Korean walnut *Juglans sinensis*, which contain cyclic diarylheptanoids of the juglanin class, are traditionally applied in the folk medicine of Korea as a remedy for inflammatory diseases.[4] Another example is the use of the stem bark of *Acer nikoense*, rich on acerogenin-type cyclic diarylheptanoids, for the treatment of hepatic disorders and as eyewash.[54]

Herein, an overview on published pharmacological effects of various diarylheptanoids is presented, with a special focus on cyclic compounds of both types.

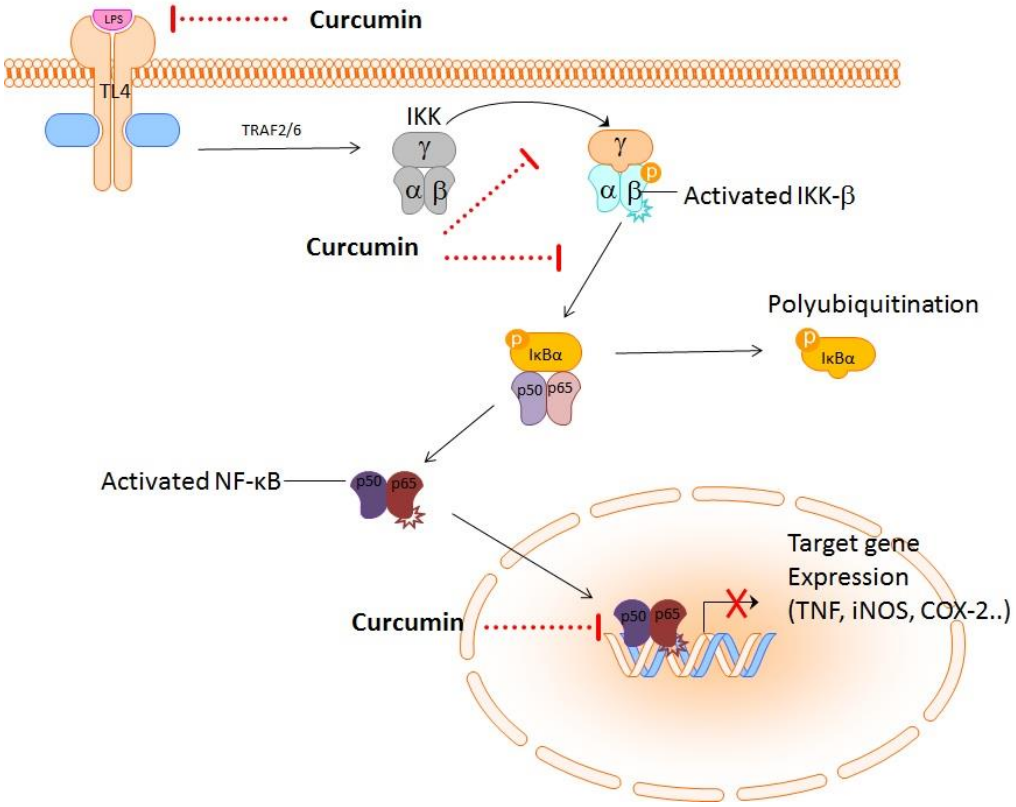
1.5.1 Anticarcinogenic and anticancer effects

The anticarcinogenic activity of curcumin was shown in many publications. An influence on the cell cycle and the tumor suppressor protein p53,[55] as well as effects on pro- and anti-inflammatory signaling pathways (NF-κB[56], Nrf2[57]) were described. Further relative compounds of curcumin exhibited cytotoxicity against different cancer cell lines. Linear diarylheptanoid glycosides from the inner bark of *Betula papyrifera* suppressed the proliferation of human colorectal cancer cells (DLD-1) with IC_{50}-values of 10.3 – 13.8 μM.[58] Another open chained derivative from *Viscum cruciatum* showed cytotoxic activity against melanoma (UACC-62), renal (TK-10) and breast (MCF-7) cancer cell lines.[59] Moreover, blepharocalyxins D and E, i.e. compounds with cyclized tethered chain included in *Alpinia blepharocalys*, had an strong antiproliferative effect against colon carcinoma (26-L5) and fibrosarcoma (HT-1080) cells, respectively.

Chemopreventive properties of cyclic diarylheptanoids were studied by Ishida and co-workers, pointing out a high antitumor-promoting potential of myricanone (**19**) and 13-oxomyricanol. These two compounds exerted the same inhibitory effect as curcumin. A structure-activity comparison among 11 compounds revealed that the oxo-functionality in position 11 as well as the 5,17-dihydroxy substitution were important for the suppression of the tumor promotion.[60] Furthermore, the diphenyl ether type cyclic diarylheptanoid galeon (**14**) from the roots of *Juglans mandshurica* was significantly cytotoxic when exposed to human colon carcinoma (HT29) and human lung carcinoma (A-549) cell lines.[61] Finally, juglanin A (**2**) and B (**17**), isolated from pericarps of walnut, exhibited a cytotoxic activity against human hepatoma (HepG2) cells.[5]

1.5.2 Anti-inflammatory activity

The use of turmeric as a remedy of inflammatory diseases was mentioned above, as well as the interactions of curcumin (**1**) with the transcription factor NF-κB. The signaling pathway of NF-κB can be affected by **1** at various points. On the one hand, **1** can prevent the binding of pro-inflammatory stimuli such as LPS to the cellular receptors. In the intracellular space, it attenuates the activation of kinase IKK which cannot phosphorylate its substrate, the IκBα protein. This protein is the inhibitory unit of NF-κB. When the IKK phosphorylates IκBα, the p50/p65 dimer is released and can translocate to the nucleus where it triggers the transcription of pro-inflammatory genes. Curcumin (**1**) can block the p50/p65-DNA binding and thus reduce the levels of pro-inflammatory cytokines, such as TNF, IL-8 and IFNγ, as well as the expression of COX-2 or iNOS (Scheme 20).[62]



Scheme 20: A simplified illustration of the NF-κB signaling pathway and interactions with curcumin, modified according to Rimbach et al.[62]

Even other diarylheptanoids besides curcumin were shown to inhibit inflammatory processes. For instance, acyclic derivative hirsutenone (**71**) (Fig. 7), ubiquitous in different *Alnus* species, reduced the LPS-stimulated inflammation by suppressing the Toll-like receptor 4 (TL4) mediated NF-κB activation that is regulated by the ERK pathway.[63] The same effect exhibited this compound against TNF-induced activation of the pro-inflammatory signaling pathway NF-κB.[64] Another linear compound from *Alnus formosana*, namely oregonin (**72**), possessed anti-inflammatory activity by the reduction of LPS-induced, NF-κB-mediated expression of iNOS. At the same time, **71** appeared to the induce production of the anti-inflammatory enzyme heme oxygenase 1 (HO-1).[65]

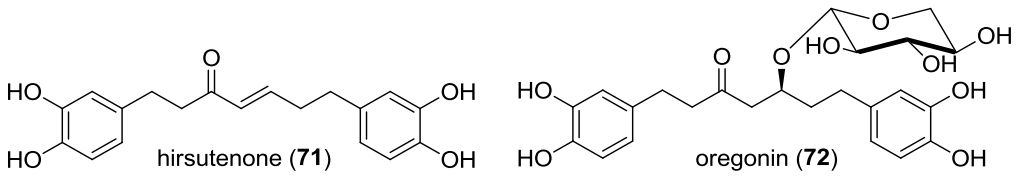


Fig. 7: Anti-inflammatory linear diarylheptanoids hirsutenone (**71**) and oregonin (**72**)

Among the cyclic compounds, biphenyl and diphenyl ether type diarylheptanoids from *Acer nikoense* MAXIM. could reduce the TPA-induced inflammation in mice,[66] as well as the production of nitric oxide (NO), a known pro-inflammatory mediator, in macrophages stimulated by LPS.[67] The suppression of the NO production was additionally observed for cyclic biphenyls from *Myrica rubra*[68] and *Myrica nana*.[17]

1.5.3 Antioxidant activity

Free radicals cause cellular damage by peroxidation of lipid membranes and DNA. The effects triggered by free radicals, commonly referred to as oxidative stress, can be attenuated by phenolic compounds such as flavonoids or diarylheptanoids. The literature on this topic often distinguishes between direct and indirect antioxidants. The first are small molecules which undergo direct redox reactions with reactive oxygen and nitrogen species. Upon this interaction, they are being consumed or modified and thus have to be regenerated. The indirect antioxidants exert their effects by upregulation of cytoprotective proteins, such as HO-1 or γ-GCS (γ-glutamylcysteine synthetase), which catalyze detoxification reactions.[69]

Curcumin, the molecule with the best explored pharmacological properties, exhibits both direct and indirect antioxidant effects. Its radical-scavenging capacity can be assigned to the presence of phenolic hydroxyl and methoxy groups, as well as the β-diketone moiety.[70] The indirect antioxidant activity is mediated by the activation of the Nrf2 cascade, which leads to the induction of HO-1 and γ-GCS, i.e. the key enzyme in the biosynthesis of the cytosolic antioxidant glutathione (GSH).[62]

Other linear diarylheptanoids isolated from *Alnus japonica*, i.a. hirsutenone (**71**) and oregonin (**72**) (Fig. 7), showed a good direct antioxidant potential in the TOSC (total oxidant scavenging capacity) assay.[71] In a different study, the capability of scavenging superoxide radicals was described for derivatives with a cyclized heptane chain from rhizomes of *Zingiber officinale*.[72] Finally, antioxidant activity within the group of cyclic diarylheptanoids possessed, e.g., myricanol (**29**),[18] myricanone (**19**)[18] or acerogenin M.[73]

1.5.4 Antimicrobial activity

Numerous disorders, which are traditionally treated by turmeric in the Indian folk medicine, are caused by microbial infections. Hence, the antimicrobial effects of **1** were investigated in various studies. Curcumin (**1**) displayed antifungal properties against 14 *Candida* strains,[74] as well as antiviral activity against coxsackievirus.[75] Furthermore, antimalarial,[76] antiparasitic[77] and nematocidal[78] effects of **1** were described.

In another study, the activity of linear diarylheptanoids from *Alnus japonica* against the papain-like protease (PL^{pro}) was examined. This protein represents a promising target in

the treatment of corona-virus induced severe acute respiratory syndrome (SARS). A structure-activity relationship for nine diarylheptanoids was determined revealing that the enone and the catechol moiety of hirsutenone (**71**) were essential for the biological effect.[79] Moreover, hirsutenone could effectively inhibit methicillin-resistant *Staphylococcus aureus*.[80]

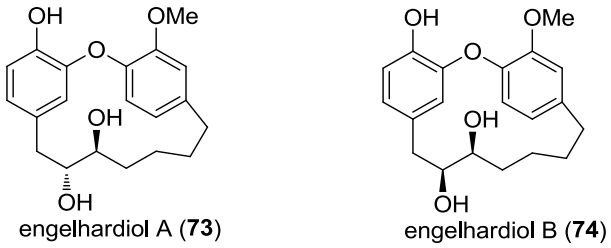


Fig. 8: Antitubercular diarylheptanoids from *Engelhardia roxburghiana*

Among the cyclic diarylheptanoids, diphenyl ether type compounds engelhardiols A (**73**) and B (**74**) (Fig. 8) from the stem of *Engelhardia roxburghiana* (Juglandaceae) displayed antitubercular properties,[80] whereas biphenyl type compounds from various *Betula* species exhibited antileishmanial activity.[81]

1.5.5 Estrogenic activity

Phytoestrogens are natural product with estrogen-like activity, which is mainly exerted by a specific binding to estrogen receptors. These effects could be shown for several secondary plant metabolites, e.g genistein, 8-prenylnaringenin (Fig. 9) or some diarylheptanoids.

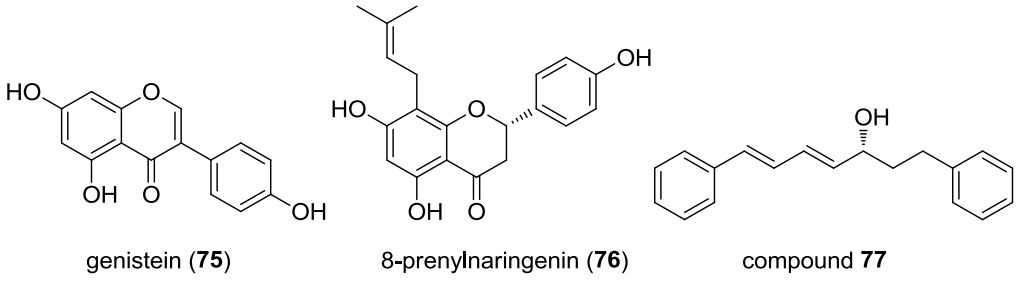


Fig. 9: Natural occurring phytoestrogens

For instance, open chained compounds from *Curcuma comosa* induced Bcl-xL and estrogen receptor β (ERβ) gene expression, which are genes closely associated with an estrogenic activity.[82] Further investigations on these diarylheptanoids resulted in the identification of compound **77** as a potent, ERα selective phytoestrogen *in vitro* and *in vivo*.[83]

1.5.6 Hepatoprotective activity

Hepatoprotective activity refers to the ability of some substances to prevent liver damage. This effect could be demonstrated for curcumin (**1**) when acting against different inducers of liver injuries, such as heavy metals,[84] chronic alcohol intake[85] and carbon tetrachloride.[86] The activity can be attributed to its general antioxidant[87] and anti-inflammatory properties, especially the Nrf2-mediated induction of the HO-1 expression[88] and the attenuation of the pro-inflammatory NF-κB pathway.[89]

Besides **1**, a 50% aqueous methanolic extract from the bark of *Betula platyphylla* showed inhibitory effects against CCl_4-induced liver injury *in vivo*. It was identified upon further isolation and *in vitro* testing that three linear diarylheptanoids from this extract significantly contributed to the hepatoprotective activity.[90] Additionally, open chained compounds from *Alnus hirsuta* exhibited a protective activity against *t*-BuOOH-induced hepatotoxicity in HepG2 cells.[91]

1.5.7 Neuroprotective activity

Neuroinflammation can be triggered by several stimuli, such as bacterial and viral infections, hypoxia/ischemia or neurodegenerative diseases. Upon activation by these stimuli, primary immune cells in the brain (microglia) start to produce pro-inflammatory cytokines, like TNF or IL-1β.[62] Long term stimulation of the immune system, accompanied by an astrogliosis,[92] leads to permanent changes in the neuronal balance and finally to neurodegeneration.[62]

In Alzheimer's disease (AD), the chronic inflammation goes along with an extracellular accumulation of amyloid β peptide (Aβ plaque) and a neurofibrillary tangle. In addition, overstimulation of *N*-methyl-D-aspartat (NMDA) receptors by the neurotransmitter glutamate followed by a massive increase of the intracellular Ca^{2+} concentration, also referred to as excitotoxicity, is often associated with AD. In response to the excitotoxicity, mitochondrial damage and oxidative stress occur which, all together, result in neuronal loss.[62]

The treatment of AD is only symptomatic and incorporates acetylcholinesterase inhibitors and antagonists of NMDA receptors. Since the impact of this treatment is only limited and new therapeutic agents are being searched, natural antioxidants like the polyphenols resveratrol or curcumin (**1**) are getting in the focus. The limiting factor is, however, the bioavailability of these compounds. Especially **1** undergoes a high first-pass effect and a rapid metabolization, therefore, it has to be administrated over a long period of time in large doses to reach the therapeutically effective concentrations in the brain tissue.[93] Once in the brain, **1** inhibits the extracellular aggregation of Aβ plaque,[94] supports the integrity

of mitochondrial membranes,[95] prevents the expression of pro-inflammatory stimuli (e.g. IL-1β)[94] and alleviates the effects of excitotoxicity.[96] Altogether, due to the promising neuroprotective effects in animal models and *in vitro* **1** remains a good lead compound for further development of optimized structures.[97]

Although the most attention in terms of neuroprotection was dedicated to **1**, a few diarylheptanoids from other sources were investigated too. Hirsutenone (**71**) from *Alnus japonica* protected retinal ganglion cells, neurons from the inner surface of the eye, against oxidative stress induced by L-buthionine-(S,R)-sulfoximine/glutamate.[98] Standardized extract from *Betula platyphylla* bark ameliorated the scopolamine-induced amnesia in rodents, as well as the glutamate-induced neurotoxicity in HT22 cells.[99] Moreover, an extract of *Alpinia katsumadai*, which consisted predominantly of flavonoids, stilbens, chalcones and diarylheptanoids, was able to protecte hippocampal neurons from ischemic damage.[100] Finally, biphenyl type cyclic diarylheptanoid juglanin C and diphenyl ether type compound juglanin A, both from the leaves of *Juglans sinensis*, effectively diminished neuronal cell death of HT22 cells stressed by glutamate. The glutathione level, significantly reduced after the glutamate exposure, was restored by the compounds, but not the level of antioxidant enzyme superoxide dismutase (SOD).[4]

2 Aim of the project

Diarylheptanoids attract ambiguous attention in both synthesis and pharmacology. Whereas literature concerning curcuminoids is of an enormous size (6745 hits for search term "curcumin" in PubMed, state 2014-07-01), the cyclic diarylheptanoids appear to be rather neglected. The reason might be the limited availability of these compounds. The isolation of the cyclic diarylheptanoids from the stem bark of selected trees requires a big amount of plant material and multiple extraction and chromatographic steps, eventually affording the desired substances in a lower milligram range. Convenient synthetic methods were established for the diphenyl ether type diarylheptanoids[16, 41] but not for the cyclic compounds of the biphenyl type.

Due to this, the aim of the presented work was to explore and develop a synthetic strategy towards linear and biphenyl type cyclic diarylheptanoids. The synthesis of linear derivatives was focused on monocarbonyl analogues of curcumin (MACs) with a natural product-like aromatic substitution, such as (±)-centrolobol (**25**), in order to obtain a library of compounds for structure-activity relationship investigations. Upon the cyclic diarylheptanoids, special attention was given to the natural products of acerogenin and myricananin type (acerogenin E (**3**), acerogenin K (**16**) and myricananin C (**18**), Fig. 10). The challenging aspect of their synthesis was the formation of the strained 13-membered ring with the *meta*,*meta*-bridged biphenyl moiety.

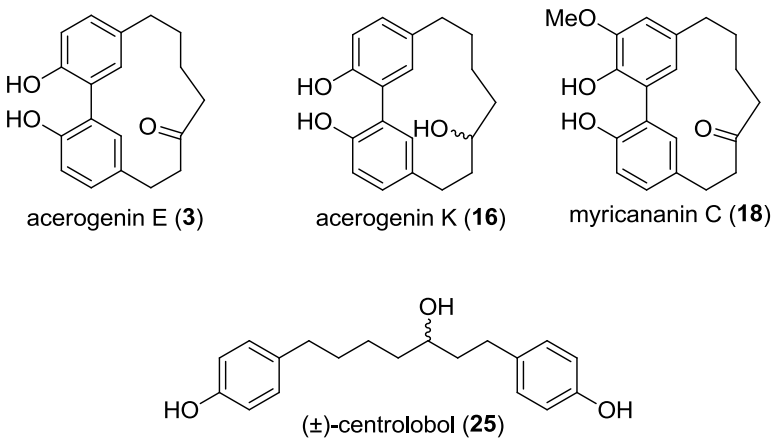


Fig. 10: Natural products synthesized for the evaluation of their potential neuroprotective activity.

Focus of the pharmacological testing was dedicated to potential neuroprotective effects of the synthetized compounds. Yang et al. observed attenuation of the glutamate-induced toxicity by cyclic diarylheptanoids isolated from *Juglans sinensis*.[4] Hence, protective

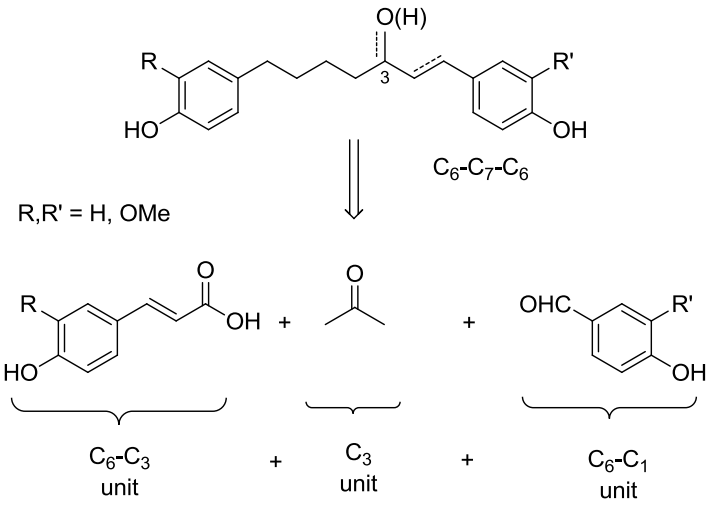
activity of the prepared linear and cyclic diarylheptanoids against oxidative stress was tested in the murine hippocampal cells HT22 to compare and evaluate biological effects of both substance classes.

3 Results and discussion

3.1 Synthesis of linear diarylheptanoids

3.1.1 Retrosynthetic approach towards linear diarylheptanoids

The linear diarylheptanoids are biosynthetic precursors of their cyclic counterparts.[25] A general synthetic strategy towards monocarbonyl analogues of curcumin (MACs) was therefore developed (Scheme 21) to eventually allow for a comparison of pharmacological properties of both classes.

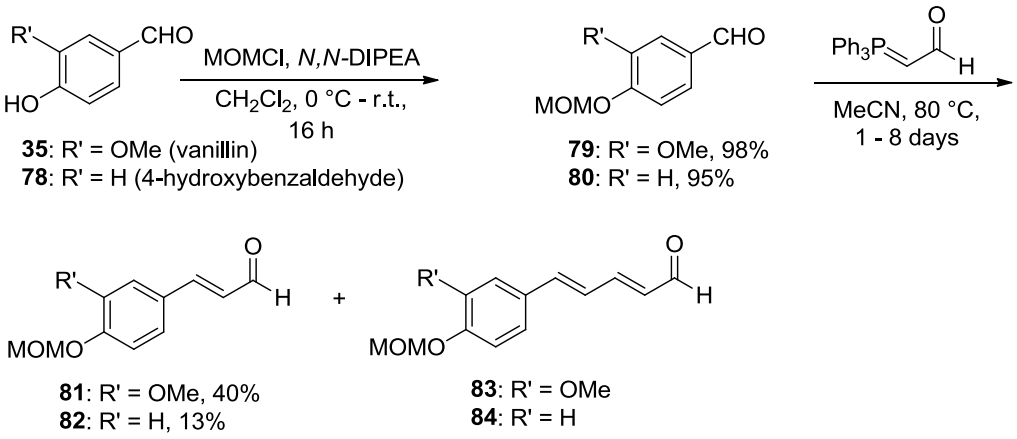


Scheme 21: Retrosynthetic strategy towards linear diarylheptanoids

For the synthesis of linear diarylheptanoids, several methods can be taken in account depending on the desired substitution of the tethered chain. A common feature for the cyclic diarylheptanoids of interest was an oxygen in position 11, corresponding to the position 3 in the acyclic compounds. The linear molecules are, in comparison to curcumin (**1**), asymmetric and hence, the classical curcumin synthesis combining two molecules of vanillin with acetylacetone[31] cannot be applied. Different approaches were prospected, leading eventually to a modification of strategy used in the synthesis of engelhardione by Shen and Sun,[101] combining phenylpropanoid units (C_6-C_3) from hydroxycinnamic acids with three carbons provided by acetone (C_3) and vanillin or 4-hydroxybenzaldehyde (C_6-C_1 unit) (Scheme 21).

3.1.2 Formation of the C_6-C_3 building block

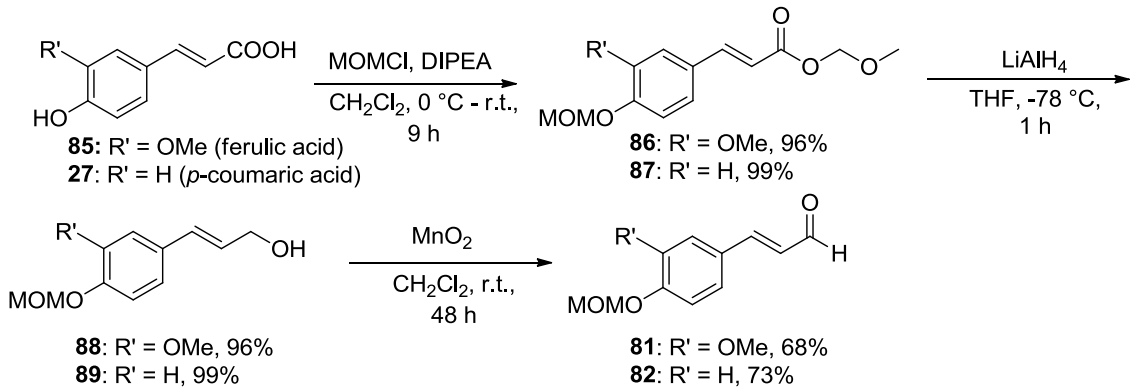
In order to prepare hydroxy- and methoxylated cinnamic aldehydes as C_6-C_3 building blocks, two different reaction sequences were carried out. Common for both strategies was the protection of phenolic OH-groups as base stable methoxymethyl ethers. The unprotected hydroxyl group in the *para*-position of the benzaldehyde increases the electron density of the aromatic system under basic conditions and lowers thus the ability of aldol condensation with ketones in further stages of the synthesis. The protection of vanillin (**35**) and 4-hydroxybenzaldehyde (**78**) proceeded quantitatively using MOM chloride in presence of Hunig's base (DIPEA) (Scheme 22).[102]



Scheme 22: Synthesis of hydroxycinnamic aldehyds via Wittig olefination

The first elongations towards desired C_6-C_3 aldehydes were performed via a Wittig olefination of aldehydes **79** and **80** with commercially available ylidens,[103] affording the aldehydes **81** and **82** in 40% and 13% yield, respectively (Scheme 22). This strategy suffered from low selectivity since the obtained aldehydes could react with the olefination reagent towards side product **83** and **84**. Therefore, the purification of the reaction mixtures was slightly complicated and the resulting yields unsatisfactory.

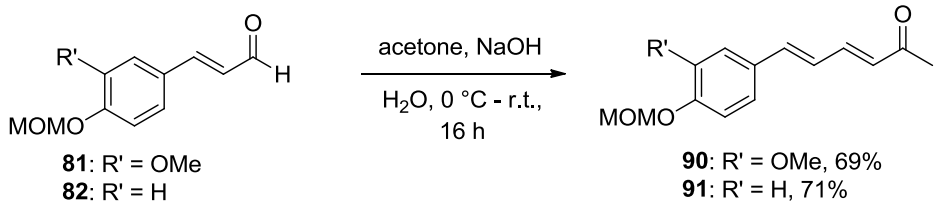
The second synthetic route used *p*-coumaric (**27**) or ferulic (**85**) acid as starting material (Scheme 23). These phenylpropanoids already contain the desired C_6-C_3 unit, only in a different oxidative state. Even though a selective reduction of esters to corresponding aldehydes with diisobutylaluminium hydride (DIBAl-H)[104] and lithium aluminium hydride ($LiAlH_4$)[55] is known, more common conversion is the reduction of the acid to the alcohol followed by a mild oxidation towards the desired aldehyde.



Scheme 23: Optimized synthetic route towards hydroxycinnamic aldehydes

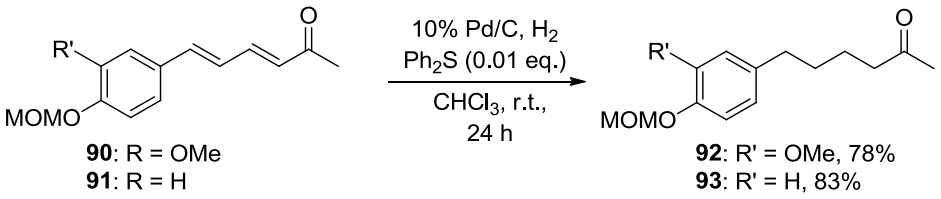
Firstly, the OH-group of the ferulic (**85**) and *p*-coumaric (**27**) acid was protected as a MOM-ether,[102] whilst an esterification of the carboxylic group occurred. These methoxymethyl esters (**86** and **87**), obtained in almost quantitative yields, were reduced with lithium aluminium hydride[105] to the allylic alcohols **88** (96%) and **89** (99%), which were subsequently oxidized with manganese dioxide[105] to aldehydes **81** and **82** in 68% and 73% yields, respectively (Scheme 23). Although this synthetic strategy towards the hydroxycinnamic aldehydes **81** and **82** requires three instead of two steps compared with the first method, the higher overall yield (62 - 72% over 3 steps vs. 13 - 38% over 2 steps) and easier product purification due to the absence of "over-olefination" side products justified its use.

3.1.3 Construction of the C_6-C_6 ketones



Scheme 24: Formation of the C_6-C_6 unit via Claisen-Schmidt condensation

With the C_6-C_3 aldehydes in hand, elongation of their aliphatic chains towards C_6-C_6 ketones **90** and **91** was envisioned (Scheme 24). This was achieved by a Claisen-Schmidt condensation with acetone in presence of NaOH as base[101] in reasonable yields (69% and 71%, respectively).

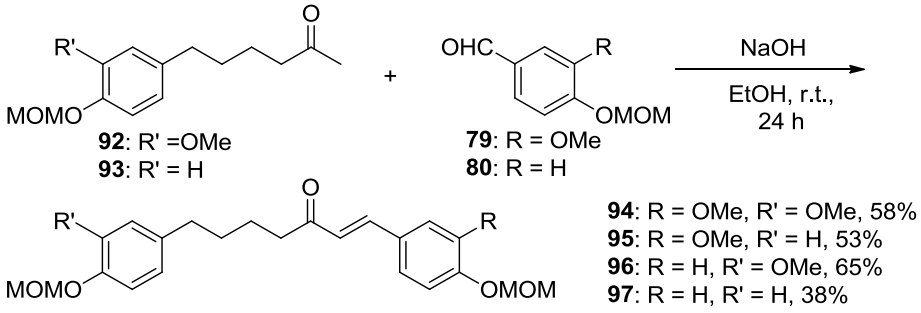


Scheme 25: Hydrogenation of the unsaturated ketones **90** and **91**

The next step was the hydrogenation of the two double bonds (Scheme 25). To prevent reduction of the oxo-group, a reaction protocol developed by Mori et al. was applied. In this method, the reactivity of the Pd/C hydrogenation catalyst is lowered by diphenylsulfide as catalyst poison. This allows for selective reductions of olefins in presence of carbonyls, aromatic halogens or *N*-Cbz groups.[106] Interestingly, when methanol was used as solvent, a partial cleavage of the MOM-protecting group was observed. However, using chloroform instead of MeOH led to a clean reaction towards the desired products with high yields (78% for **92**, 83% for **93**, Scheme 25).

3.1.4 Synthesis of linear diarylheptanoids via Claisen-Schmidt condensation

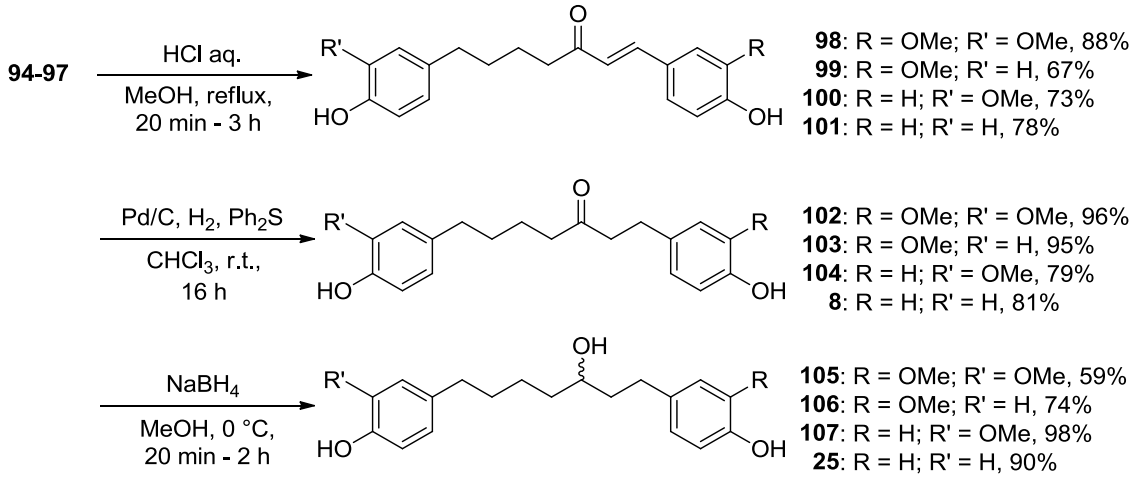
The final step of the planned synthesis was the reaction of the C_6-C_6 ketones **92** and **93** with C_6-C_1 units, represented by the MOM-protected aromatic aldehydes **79** and **80** (Scheme 26). The combination of the two ketones (**92**, **93**) with the two aldehydes (**79**, **80**) afforded four differently substituted, MOM-protected, diarylheptanoids. The reactions were carried out in the presence of sodium hydroxide as base, using a small excess of aldehydes (1.8 eq.) compared to ketones,[101] yielding the products in moderate to reasonable yields (38 – 65%, Scheme 26).



Scheme 26: Formation of the linear diarylheptanoids **94**-**97**

3.1.5 Modifications of the aliphatic chain

The acidic hydrolysis of the MOM-protecting groups, performed in methanol and HCl (aq.) at reflux temperature,[107] resulted in four diarylheptanoids (**98**-**101**) with an enone moiety in the aliphatic chain in good yields (67 - 88%, Scheme 27). Such compounds, also known as monocarbonyl analogues of curcumin (MACs), [108] can further be modified on the aliphatic chain in regard to its oxidation state. Hence, the double bond of the α,β-unsaturated carbonyl system was reduced using Pd/C-catalyzed hydrogenation with diphenyl sulfide as a catalyst poison.[106] This reaction afforded four ketones **102**, **103**, **104** and **8** (acerogenin G) in good to excellent yields (Scheme 27). Furthermore, reduction of the oxo-group of these compounds with sodium borohydride[109] led to four linear diarylheptanoids with an alcohol moiety in position 3 (**105**, **106**, **107** and **25**, Scheme 27). No asymmetric reduction method was applied because the biological activity of the compounds was expected to be predominantly associated with the phenolic groups or the Michael system.[97]

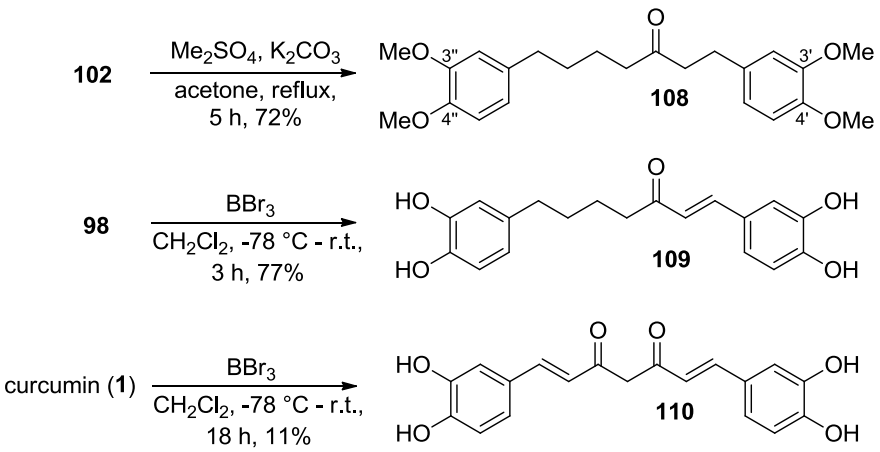


Scheme 27: Three types of acyclic diarylheptanoids with enone, ketone and alcohol structure

Altogether, 12 linear diarylheptanoids (Scheme 27) with four various substitution patterns of the aromatic rings and three different oxidation states of the tethered chain were prepared in course of 8-10 steps with overall minimum yield of 7% for (±)-centrolobol (**25**) and maximum 12% for alcohol **107**. Among these 12 compounds, curcuminoids **103**, **104**, **106** and **107** were identified before as *in vivo* metabolites of demethoxycurcumin in rat feces[110] and compound **25** as a metabolite of bisdemethoxycurcumin.[111] Ketone **103** was isolated from *Curcuma kwangsinensis*[112] and compound **102** was previously prepared by Lee et al.[113] and found in *Zingiber officinale*.[114] Ketone **8** is also known as acerogenin G and occurs in various *Acer* species,[11] as well as its reduced form centrolobol (**25**).[115] Enones **98**-**101** have not been described so far.

3.1.6 Synthesis of further curcumin analogues

To enlarge the scope of the synthesized curcuminoids, analogues with minor modifications were prepared. The common feature for above described open chained diarylheptanoids was the 4-hydroxy or 4-hydroxy-3-methoxy substitution of the aromatic rings. Hence, three new curcuminoids with 3,4-dimethoxy **108** and 3,4-dihydroxy (caffeoyl) motifs **109** and **110** were prepared (Scheme 28).

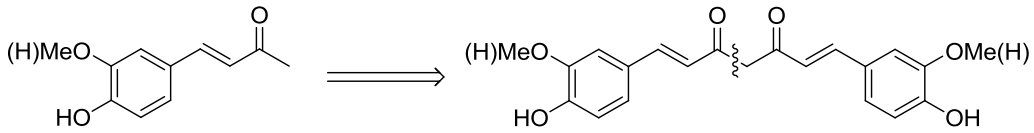


Scheme 28: Analogues of curcumin with modified aromatic rings

The synthesis of the 3',3'',4',4''-tetramethoxy substituted derivative **108** was performed by methylation of ketone **102** with dimethyl sulfate as methylating agent and potassium carbonate as base (Scheme 28).[116] The demethylation of enone **98** and curcumin (**1**) towards 3',3'',4',4''-tertahydroxy curcuminoids **109** and **110** (also di-*O*-demethylcurcumin) was carried out under the same conditions, namely with 6.0 eq. of boron tribromide (Scheme 28).[117] Sousa and Silva computationally proposed a mechanism involving a bimolecular reaction between two ether-BBr_3 adducts,[118] therefore the use of a BBr_3 extent might be beneficial for the reaction outcome. Nevertheless, the conversion of **1** into di-*O*-demethylcurcumin proceeded only in 11% yield, probably due to a possible photo-instability of the product.

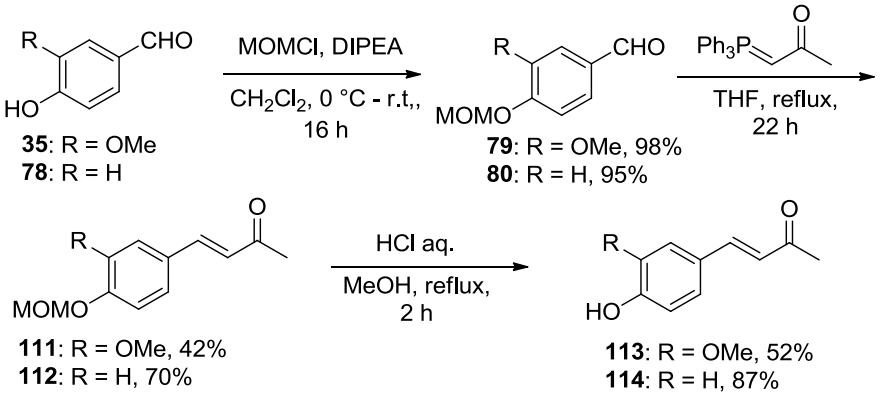
3.1.7 Synthesis of single ring analogues of curcumin

To investigate, whether the diarylheptanoid scaffold or only its part was important for the biological activity, two 'half-molecules' consisting of a C_6-C_4 scaffold with a conjugated enone motif and 4-hydroxy-(3-methoxy) aromatic substitutions were prepared (Scheme 29).



Scheme 29: Single ring analogues derived from natural curcuminoids

The synthesis started, similar as in the case of the linear diarylheptanoids, with the protection of the hydroxyl group of vanillin (**35**) and 4-hydroxybenzaldehyde (**78**) under the conditions described in 3.1.2. Wittig olefination strategy was then applied for the formation of the 4-phenyl-but-3-en-2-one moiety, affording MOM-protected compounds **111** and **112** in 42% and 70% yield, respectively. After the acidic hydrolysis of the methoxy-methyl ether groups, the desired single ring analogues **113** and **114** were obtained (Scheme 30). Ketone **113** is known in the literature under the name dehydrozingerone and naturally occurs in ginger (*Zingiber officinale*).[119] Compound **114**, first synthesized by Buck and Heilbron,[120] is a biosynthetic precursor of raspberry ketone which can be found in raspberries and other fruits.[121]



Scheme 30: Synthesis of single ring analogues **113** and **114**

3.2 Synthesis of linear diarylheptanoids with cyclized C_7-chain

The term diarylheptanoids with cyclized C_7-chain was introduced by Claeson et al.[2] and was described in 1.1. Although the focus of this project was dedicated to linear and cyclic diarylheptanoids with a *meta*,*meta*-bridged biphenyl structure, two novel compounds with an unusual cyclization of the aliphatic chain (**115** and **116**) were serendipitously produced and fully characterized by means of 2D NMR spectroscopy. The formation of those compounds could be reproduced and a reaction mechanism was proposed. A literature review revealed that a similar tricyclic compound **24** was discovered before in the fruits of greater cardamom (*Amomum subulatum* Roxb.) (Fig. 11).[21]

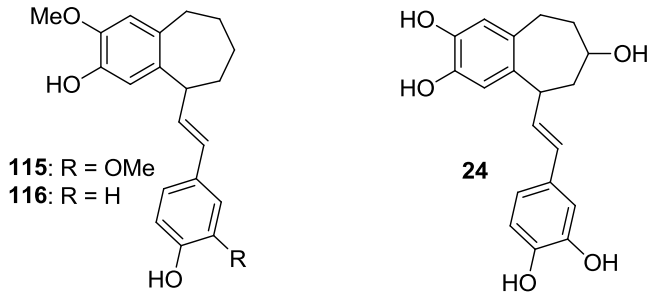
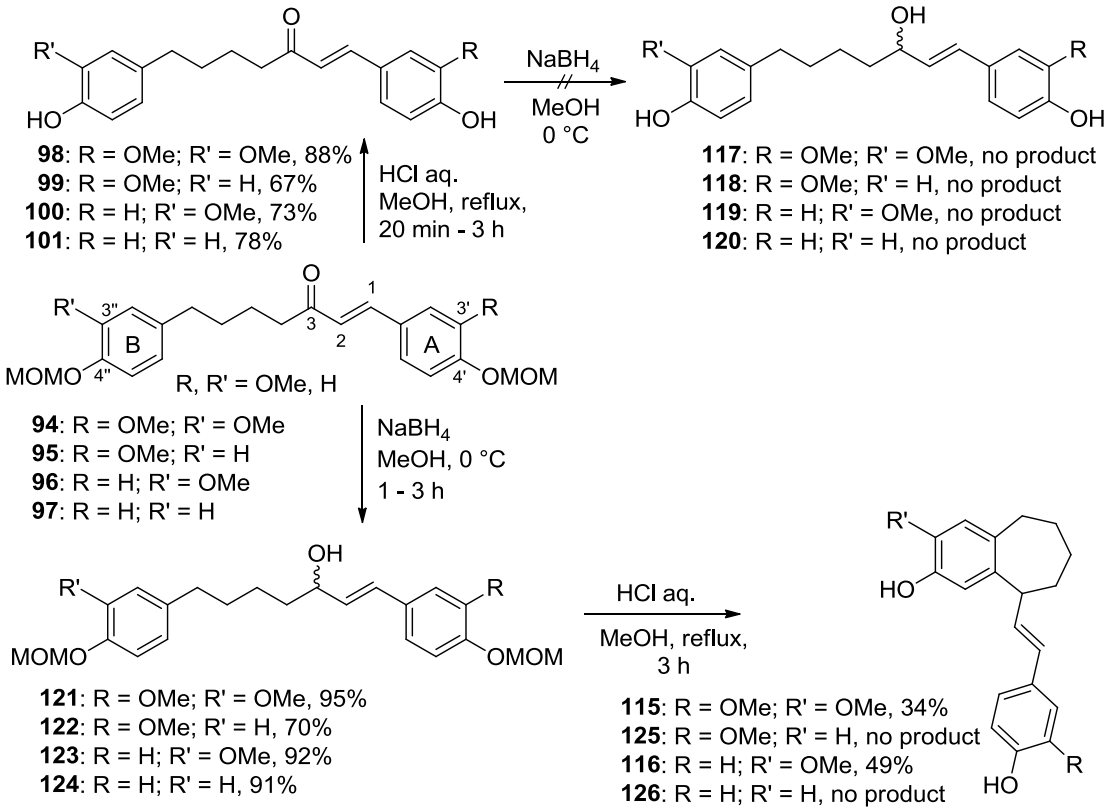


Fig. 11: Synthetic (**115**, **116**) and natural (**24**) diarylheptanoids with cyclized C_7-chain

Originally, a synthesis of linear diarylheptanoids with an allylic alcohol moiety was aimed to obtain the fourth substitution type of the tethered chain (additionally to enone, ketone and alcohol). Two different approaches were tested, both of them starting from the MOM-protected enones **94-97** (Scheme 31). At first, cleavage of the methoxymethyl ether groups was performed under acidic conditions gaining the unprotected enones **98**-**101**. The subsequent reduction of the oxo group of the enone with sodium borohydride, however, afforded not the corresponding allylic alcohols **117**-**120** but instead a mixture of multiple products (Scheme 31). One possible explanation for this observation could be a low stability of diarylheptanoids with the allylic alcohol motif.



Scheme 31: Attempted synthesis of linear diarylheptanoids with allylic alcohol motif which led to compounds with cyclized C7-chain

In the second pathway, the sequence of the steps was switched whereby the reduction of the oxo group was carried out at first using the MOM-protected diarylheptanoids **94**-**97** as substrates. This proceeded at 0 °C in the presence of sodium borohydride[109] in good to excellent yields (70 - 95%). In contrast to their unprotected counterparts **117**-**120**, allylic alcohols **121**-**124** exhibited sufficient stability and could be submitted to the following deprotection step (Scheme 31).

The general procedure used for the MOM-ether cleavage incorporates aqueous HCl solution (30 eq. of H^+) in methanol.[107] It was observed in the deprotection reactions towards **98**-**101** (3.1.5) that the hydrolysis occurred in reasonable reaction rates only at elevated temperature. Allylic alcohols **122** and **124**, bearing a 4''-hydroxy substitution on the B-ring, reacted under a complete conversion of the starting material to a complex mixture of products. This was in accordance with the observations made in the first synthetic route towards **117** and **119** and confirmed the assumption of low stability of compounds with the 1-en-3-ol moiety (Scheme 31).

Surprisingly, substrate **121** with the 4''-hydroxy-3''-methoxy substitution of the B-ring reacted even at r.t. towards a single product (based on TLC analysis) with a higher R_f value

(0.43 vs. 0.09 compared to the starting material, SiO_2; *n*-hexane/EtOAc 3:1) (Scheme 31). When the reaction was stopped and worked up at this stage, proton signals of the O-CH_2-O-groups were detected in the ^{1}H-NMR indicating a change in the structure of the substrate but no hydrolysis of the MOM-groups. The same reaction, carried out at reflux temperature of methanol, resulted into a single product with a R_f value of 0.34 (TLC, SiO_2; *n*-hexane/EtOAc 3:1) after 2 h. After aqueous work-up and CC and HPLC purification, compound **115** with unpredicted structure, elucidated in chapter 3.2.1, was obtained in 34% yield (Scheme 31). The MOM-deprotection of the other 4''-hydroxy-3''-methoxy substituted diarylheptanoid **123** under the same conditions afforded the analogues product **116** in 49% yield (Scheme 31).

3.2.1 Structure elucidation of diarylheptanoids with cyclized C_7-chain

The structure elucidation of compounds **115** and **116** was performed with the aid of mass spectrometry and NMR spectroscopy.

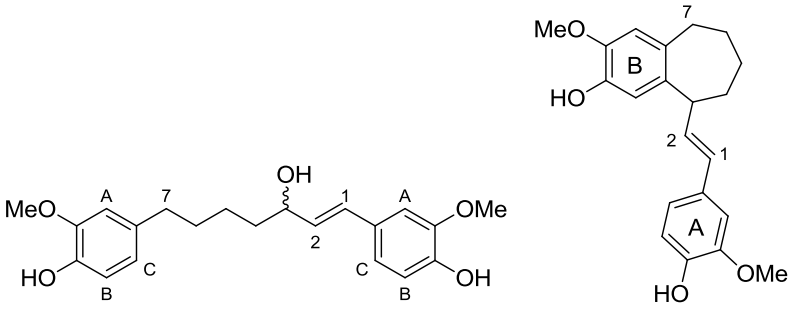


Fig. 12: The expected **117** and the actual product **115** of the reduction-deprotection sequence of compound **94**

Compound **115** showed in HR ESI-MS the $[MH]^+$ ion peak at m/z 341.1745 corresponding to the molecular formula $C_{21}H_{25}O_4$. Further ion peaks in LR ESI-MS were identified as follows: m/z (%) 341 $[MH]^+$ (100), 340 $[M]^{+\cdot}$ (71) and 363 $[MNa]^+$ (36). These results pointed at loss of m/z 18 [H_2O] in comparison to expected allylic alcohol **117** (Fig. 12). The ^{13}C-NMR spectrum exhibited 21 carbon signals with four methylene carbons (δ 29.7, 30.1, 35.5 and 36.8 ppm), three oxygenated aliphatic carbons (δ 49.1 overlapped with MeOD, 56.4 and 56.6 ppm) and fourteen olefinic or aromatic carbons (δ 110.3, 115.2, 116.2 117.3, 120.3, 130.7, 131.5, 131.8, 135.3, 138.4, 144.9, 146.5, 147.0 and 149.1 ppm). This was in agreement with expected double methoxylated diarylheptanoid without carbonyl functionality.

In contrast to expectations for the linear compound **117**, the ^{1}H-NMR showed only one ABC system at δ 6.96 ppm (d, J = 1.7 Hz, 1H), 6.81 ppm (dd, J = 8.1, 1.8 Hz, 1H) and 6.72 ppm (d, J = 8.1 Hz, 1H) (Fig. 13). The protons at δ 6.13 ppm (d, J = 15.9 Hz, 1 H) and 6.35 ppm (dd, J = 15.9, 6.7 Hz, 1H) were assigned to the *trans* substituted double bond in positions 1 and 2, respectively. However, only two more singlets remained in the aromatic region with δ 6.66 and 6.69 indicating a tetrasubstituted benzene ring which countered the structure of **117** with two ABC systems (Fig. 12). The aliphatic region consisted of two signals for the methoxy groups (δ 3.82 and 3.86 ppm), a triplett at δ 3.61 ppm (assigned to H-3), and further methylene groups at δ 2.75 (m, 2H), 1.74 - 1.95 (m, 4H) and 1.62 ppm (m, 2H). Striking was the difference to the MOM-protected precursor **121** (Scheme 31), where the multiplet of the proton in position 3 (geminal to the OH-group) showed a chemical shift of 4.20 - 4.37 ppm, hereby being more deshielded than the H-3 in the examined spectrum (3.61 ppm). The badly resolved multiplet of the benzylic methylene group (H-7, 2.76) (Fig. 13) was in contrast to the signals of typical linear diarylheptanoids, where the protons at C-7 usually exhibited a clear triplett. This could be explained by a restricted rotation of the system and gave a hint to the presence of additional ring.

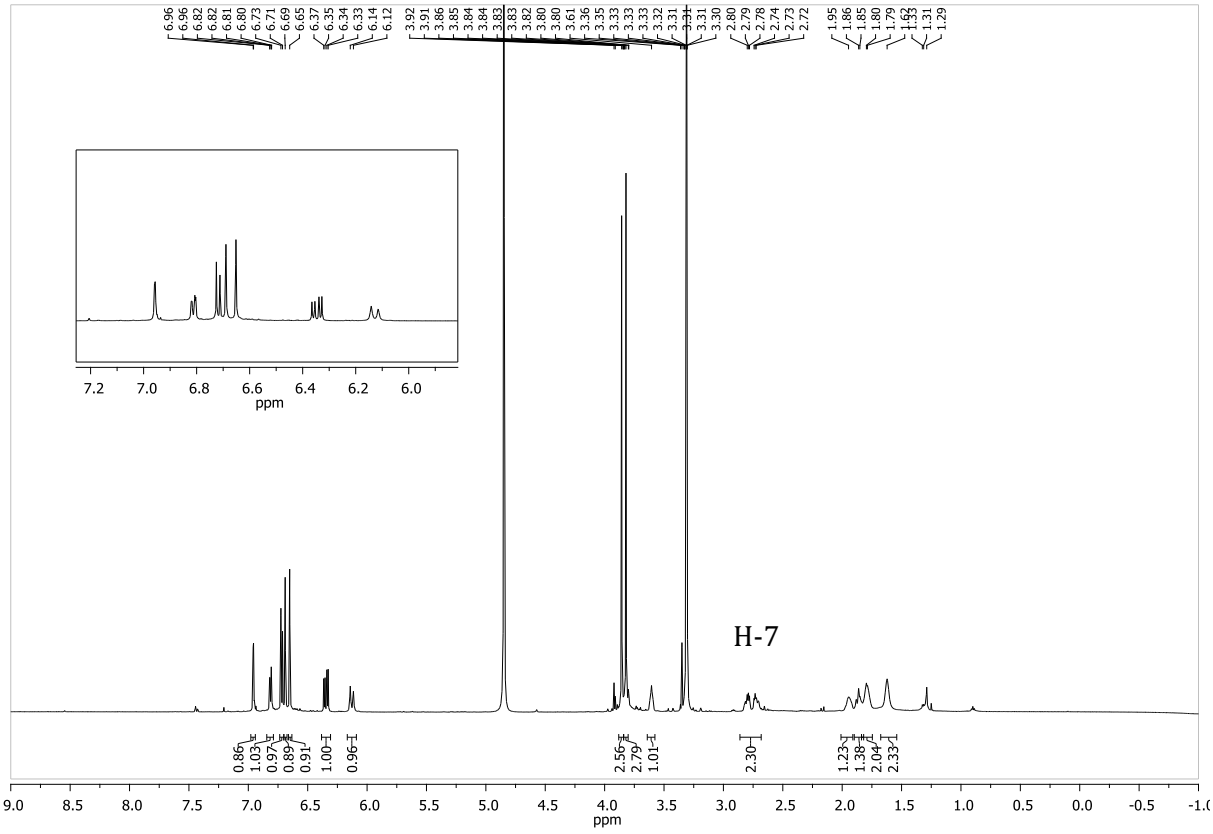


Fig. 13: ^{1}H-NMR spectrum of compound **115**. (MeOD, 600 MHz, 298 K)

The final assignment of all carbons and protons was performed on the basis of HSQC and HMBC measurements, supported by NOESY and is summed up in Table 2. The best evidence for the attachment of the third ring was the HMBC correlations between H-5'' (δ 6.66 ppm) and C-3 (δ 49.1 ppm), as well as the NOE between H-2 and H-5'' of the B-ring.

Table 2: ^{1}H- and ^{13}C-NMR data for **115**. (MeOD, 600 MHz for ^{1}H, 150 MHz for ^{13}C, 298 K, δ in ppm, *J* in Hz)

Position	δH	δC
1	6.13 (d, 15.9, 1H)	130.7
2	6.35 (dd, 15.9, 6.7, 1H)	131.8
3	3.61 (t, 6.2, 1H)	49.1
4	1.78, 1.85 (m, m, 2H)	35.5
5	1.78, 1.93 (m, m, 2H)	30.1
6	1.62 (m, 2H)	29.7
7	2.76 (m, 2H)	36.8
1’		131.5
2’	6.96 (d, 1.7, 1H)	110.3
3’		149.1
3’-OCH_3	3.86 (s, 3H)	56.4
4’		147.0
5’	6.71 (d, 8.1, 1H)	116.2
6’	6.81 (dd, 8.1, 1.8, 1H)	120.3
1’’		135.3
2’’	6.69 (s, 1H)	115.2
3’’		146.5
3’’-OCH_3	3.82 (s, 3H)	56.6
4’’		144.9
5’’	6.66 (s, 1H)	117.3
6’’		138.4

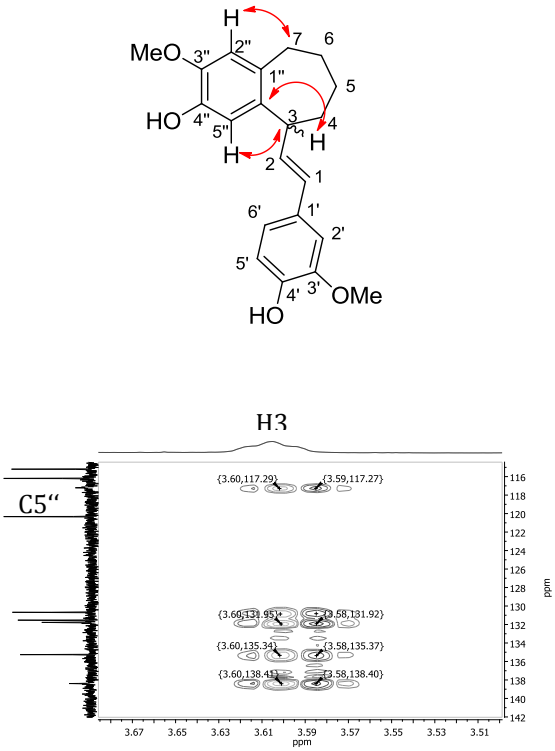


Fig. 14: Key HMBC correlations for **115**

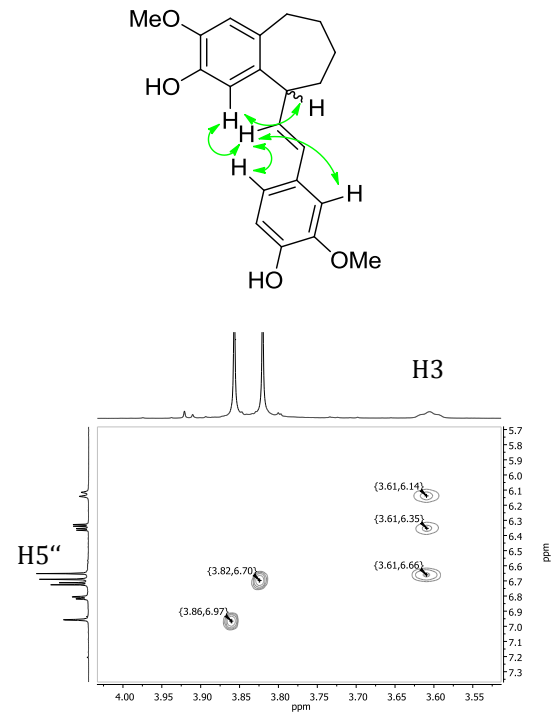


Fig. 15: Key NOESY correlations for **115**

The same elucidation approach was performed for compound **116** (Fig. 16). The ESI-MS showed an ion peak m/z (%) 311 $[MH]^+$ (98) in the positive mode and m/z (%) 309 $[M - H]^-$ (15) in the negative mode. This result was confirmed by EI-MS (70 eV) wherein only the mass peak with m/z (%) 310 $[M]^{+\cdot}$(100) but not with m/z 326, expected for **119** (Scheme 31), was detected. The ^{13}C-NMR revealed twenty carbons with one at δ 49.0 interfering with the solvent peak of MeOD (confirmed by HSQC). In contrast to the MOM-protected precursor **122**, the signal at δ 73.0 ppm, belonging to the secondary allylic alcohol, vanished while a new peak at δ 49.0 ppm was observed (Fig. 16).

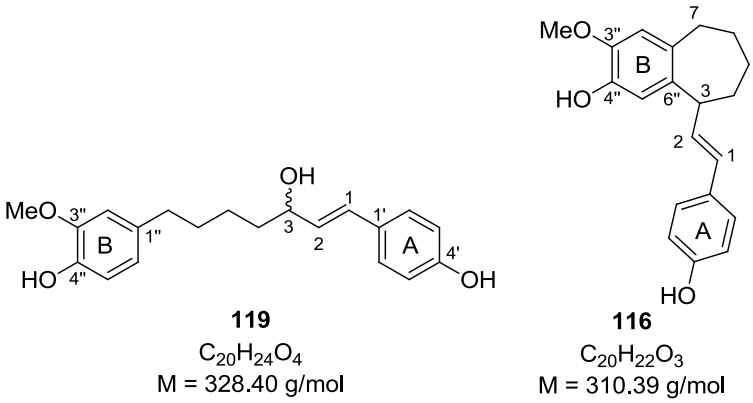


Fig. 16: The expected **119** and the actual product **116** of reduction-deprotection sequence of compound **96**

Similar to above described compound **115**, no 1,3,4-trisubstituted benzene ring was detected in the ^{1}H-NMR. Instead, a tetrasubstituted B-ring with δ 6.69 (s, 1H) and 6.65 ppm (s, 1H) and AA'BB' 1,4-disubstituted A-ring (δ 7.21 (d, J = 8.6 Hz, 2H) and 6.71 ppm (d, J = 8.6 Hz, 2H)) were observed. The signal of proton H-3 attached to the allylic carbon, with a chemical shift of δ 4.24 ppm in the MOM-protected substrate **123**, moved upfield to 3.60 ppm in case of the deprotected product **116** (Fig. 16). This was an evidence for a new bond between position 6'' of the B-ring and the position 3 of the aliphatic chain. The final proof provided the homonuclear (NOESY) and heteronuclear (HMBC) 2D NMR analysis, revealing long range correlations between C-6'' and H-3 (Fig. 17) and NOE between H-5'' and H-2 (Fig. 18). The assignment of all proton and carbon signals was supported by HSQC and COSY and is summed up in Table 3.

Table 3: ^{1}H- and ^{13}C-NMR data for **116**. (MeOD, 600 MHz for ^{1}H, 150 MHz for ^{13}C, 298 K, δ in ppm, *J* in Hz)

Position	δH	δC
1	6.13 (d, 15.9, 1H)	130.3
2	6.33 (dd, 6.7, 15.9, 1H)	131.5
3	3.60 (t, 6.0, 1H)	49.0
4	1.78, 1.85 (m, m, 2H)	35.5
5	1.78, 1.92 (m, m, 2H)	30.7
6	1.61 (m, 2H)	29.7
7	2.71, 2.78 (m, m, 2H)	36.8
1’		130.9
2’	7.21 (d, 8.6, 1H)	128.2
3’	6.71 (d, 8.6, 1H)	116.3
4’		157.7
5’	6.71 (d, 8.6, 1H)	116.3
6’	7.21 (d, 8.6, 1H)	128.2
1’’		135.3
2’’	6.69 (s, 1H)	115.2
3’’		146.6
3’’-OCH_3	3.82 (s, 3H)	56.6
4’’		144.9
5’’	6.65 (s, 1H)	117.2
6’’		138.5

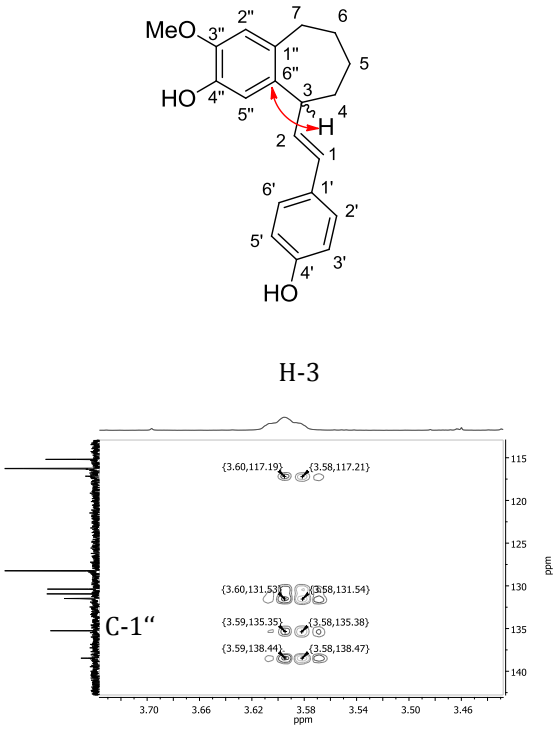


Fig. 17: Key HMBC correlations for **116**

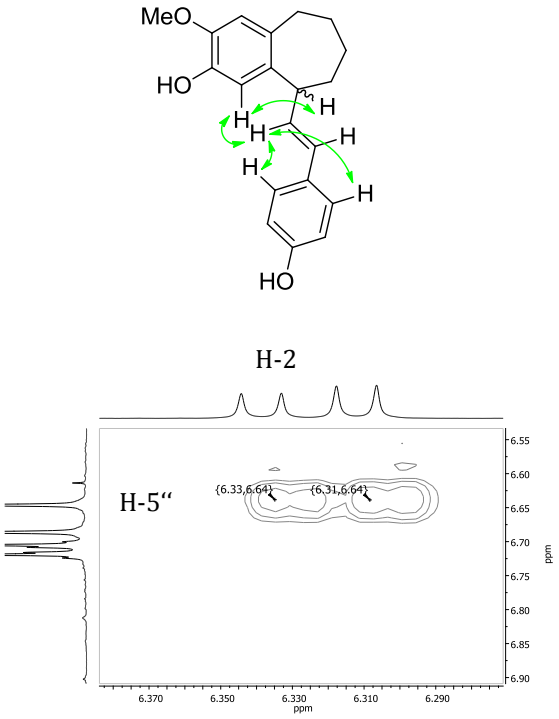
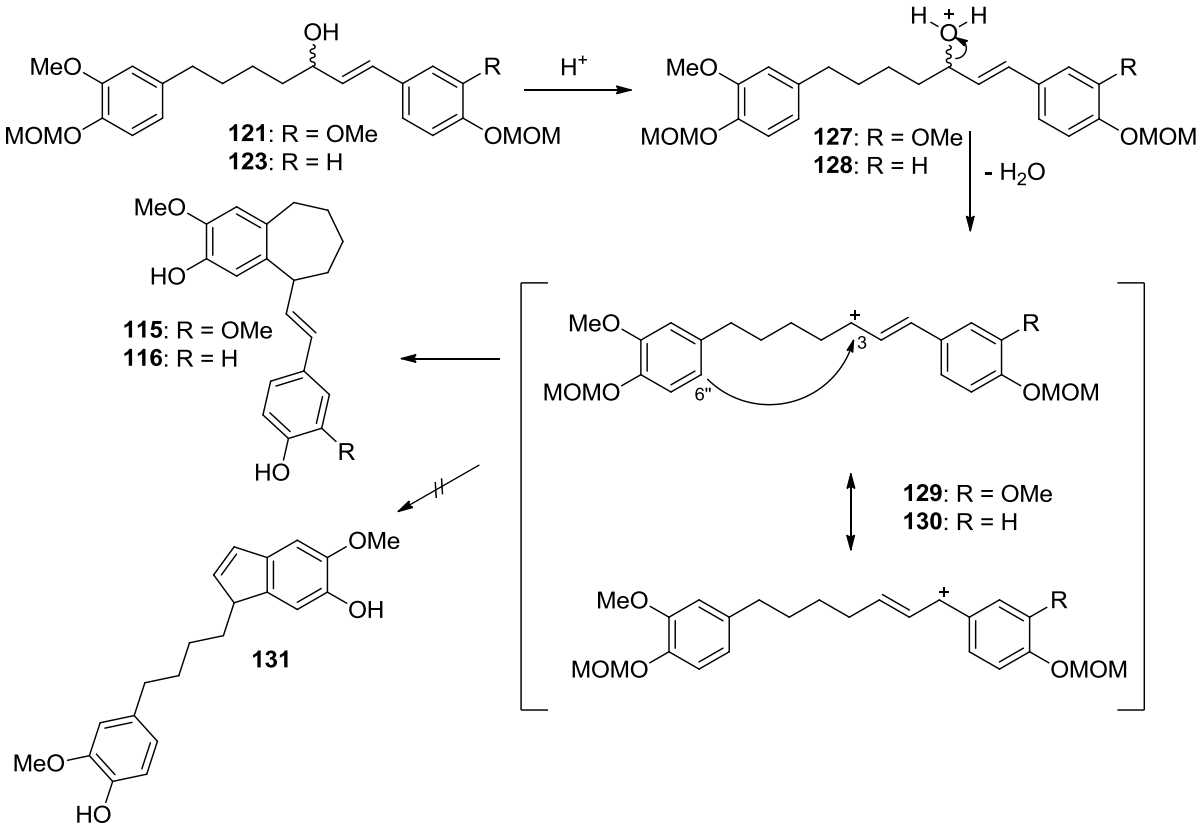


Fig. 18: Key NOESY correlation for **116**

3.2.2 Proposed mechanism for the formation of diarylheptanoids with cyclized C_7-chain

The unexpected outcome of the reactions described in 3.2 can be rationalized in consideration of the reaction conditions of the MOM-deprotection step and the nature of the substrates. The MOM-ether cleavage of compounds **121** and **123** takes place in presence of 30 eq. HCl. This leads to a protonation of the OH-group in position 3, making it a better leaving group. The carbocation in the allylic position resulting from the H_2O-cleavage is well stabilized in both resonance structures of **129** and **130**. Each of them can undergo an electrophilic aromatic substitution on one of the rings. Position 6'' of the B-ring with the *para* methoxy group is the most activated one, thus allowing a 7-exo-trig cyclization (Scheme 32). Alternatively, a 5-exo-trig cyclization at the activated position 6' of the A-ring in **115** can occur, nevertheless, no such indene product **131** could be identified probably due to a higher ring strain of such a molecule (Scheme 32). This type of reactions, involving acid-promoted carbocation formation, is also known as cyclodehydration.[122]



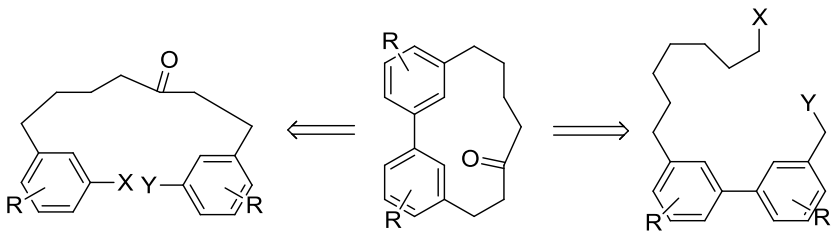
Scheme 32: Proposed cyclization mechanism for compounds **115** and **116**

3.3 Synthesis of cyclic diarylheptanoids

The formation of cyclophane natural products represents a challenge in most cases, especially in small rigid 13-membred rings of biphenyl type cyclic diarylheptanoids.[123] Only a few methods for the synthesis of the latter have been described up to date in the literature[27, 123] prompting for a new convenient synthetic strategy.

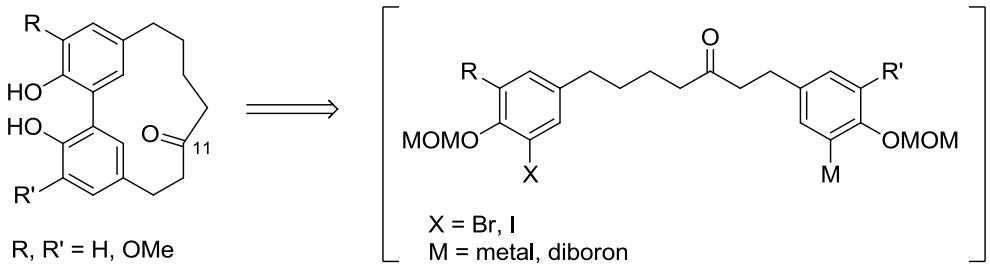
3.3.1 Retrosynthetic approach towards cyclic diarylheptanoids

In general, there are two possibilities to assess the targeted macrocycles. On one side, a precursor with the biphenyl structure within the aliphatic chain can be introduced and the cyclization takes place via the connection of the alkyl residues. According to literature, this strategy worked well in a few specific diphenyl-ether type cases,[36] but there is no literature evidence for a synthesis of biphenyl diarylheptanoids (1.4).[1] Therefore, it has been decided to prepare linear diarylheptanoids with suitable substituents which would allow for the macrocyclization via the biaryl-bond formation (Scheme 33).



Scheme 33: General retrosynthetic analysis for the formation of *meta*,*meta*-bridged biphenyl macrocycles

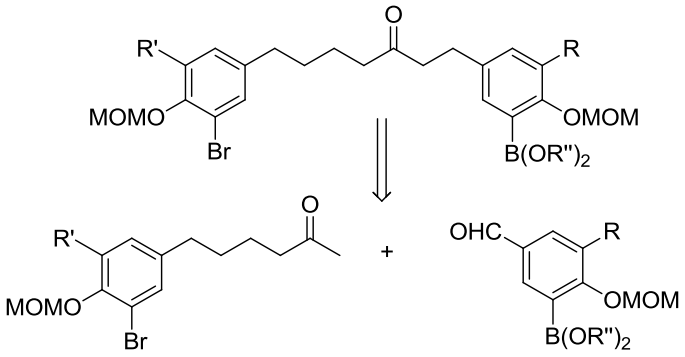
The cyclization approach (Scheme 34) was inspired by a pioneer publication from Semmelhack et al., who used a Ni(0) catalyzed Ullmann reaction of iodinated precursors for the first synthesis of alnusone (**7**) (Scheme 16).[42] This strategy was then further modified by Zhu et al., replacing the zerovalent nickel catalyzed Ullmann coupling with a palladium-catalyzed domino sequence of Miyaura arylborylation and Suzuki reaction, which was used for a synthesis of cyclic tripeptide containing such a biphenyl moiety.[45] Finally in 2013, Ogura and Usuki applied Zhu's strategy for the first total synthesis of acerogenins E and K (Scheme 19).[29]



Scheme 34: Cyclization strategy for the synthesis of cyclic diarylheptanoids

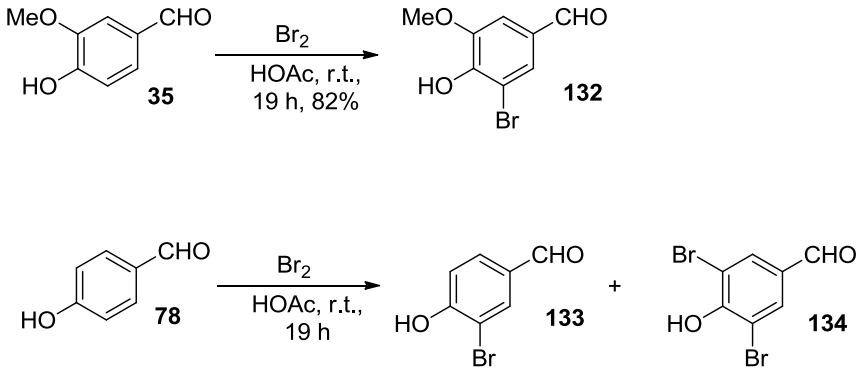
3.3.2 Attempted synthesis via brominated precursors

The Suzuki reaction, a palladium catalyzed coupling reaction between boronic acids and halides established in 1979 by Akira Suzuki,[124] emerged to a method of the first choice for biaryl formations.[125] Although there are a few examples for the use of aryl chlorides,[126] the most applications incorporate aryl bromides and iodides due to their better reactivity in the oxidative addition step.[125a] Hence, the initial idea was to prepare brominated and borylated segments and assemble them to linear diarylheptanoids functionalized for the intramolecular Suzuki cross-coupling (Scheme 35).



Scheme 35: Planned synthesis of functionalized precursors for the intramolecular cyclization

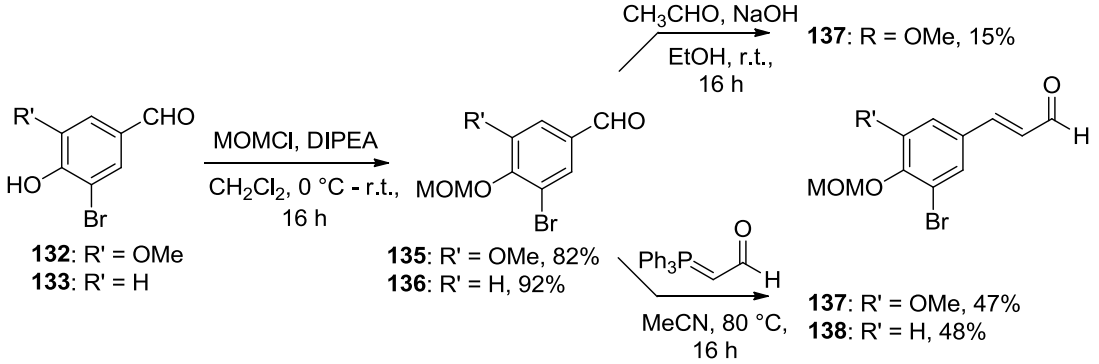
In accordance to the strategy applied for the synthesis of linear diarylheptanoids, the reaction sequence started from brominated vanillin **132** and brominated 4-hydroxybenzaldehyde **133**. Whereas the first one was obtained in excellent yield out of vanillin (**35**) via bromination in presence of Br_2/HOAc,[127] the synthesis of the latter suffered from poor selectivity and mostly the dibrominated side product **134** was isolated (Scheme 36). Therefore, commercially available 3-bromo-4-hydroxybenzaldehyde **133** was used in further reactions.



Scheme 36: Bromination of vanillin (**35**) and 4-hydroxybenzaldehyde (**78**)

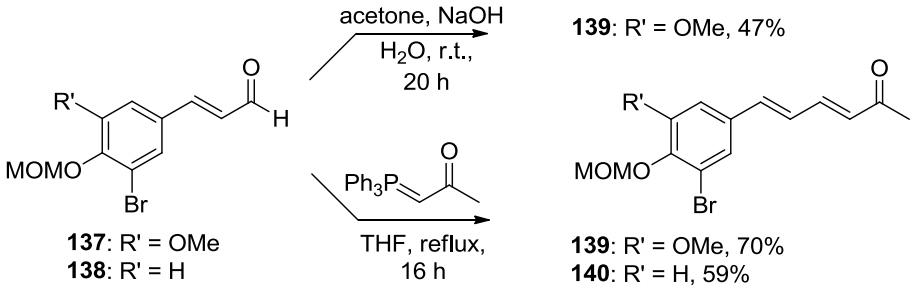
After the protection of the phenolic OH-group as methoxymethylether,[102] the next step on the planned synthetic route was the elongation of the aliphatic chain. Claisen-Schmidt

condensation and Wittig olefination were examined as methods for building of C_6-C_3 aldehydes. Because of low yields (15%) and poor selectivity by the Claisen-Schmidt condensation between 5-bromovanillin **135** and acetaldehyde,[33] olefination with 2-(tristriphenylphosphoranylidene)-acetaldehyde[103] was preferred and gave the desired products **137** and **138** in 47 and 48% yield, respectively (Scheme 37).



Scheme 37: Synthesis of brominated C_6-C_3 aldehydes **137** and **138**

With the C_6-C_3 aldehydes **137** and **138** in hands, further extension of the aliphatic chain towards C_6-C_6 ketones **139** and **140** was aimed. Claisen-Schmidt condensation of substrate **137** with acetone catalyzed with NaOH[101] gave the desired product **139** in 47% yield. A better yield (70%) was achieved with Wittig reaction, using 1-(triphenylphosphoranylidene)-2-propanone as olefinating agent.[103] Therefore, this strategy was used for the brominated cinnamaldehyde **138** affording ketone **140** in 59% yield (Scheme 38).

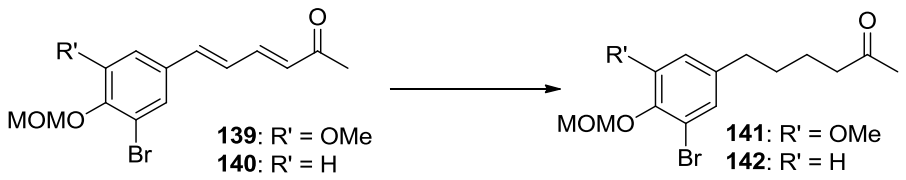


Scheme 38: Formation of the brominated C_6-C_6 ketones **139** and **140**

The brominated C_6-C_6 ketones **139** and **140** were subsequently submitted to a hydrogenation reaction in order to reduce the two double bonds. Several methods had to be screened before reasonable yields were achieved. Hydrogenation catalyzed with Pd/C was tested, revealing a crucial role of the solvent and the catalyst type (Table 4). First experiments performed in $CHCl_3$ at 1 bar hydrogen pressure with 10% (w/w) Pd/C[41]

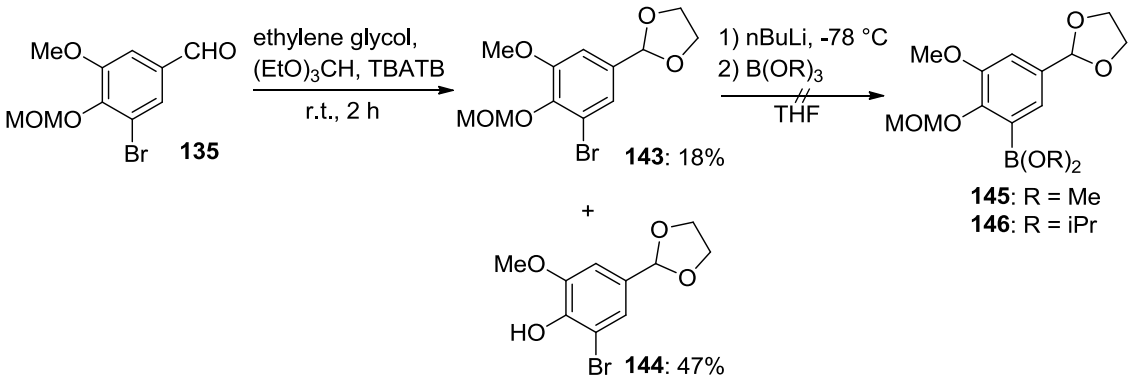
resulted in moderate yield of 50% for **141** and 56% for **142**. An improvement of the yields was targeted and so the reaction was repeated in EtOAc at elevated hydrogen pressure (5 bar). This resulted, however, to a cleavage of the MOM-protecting group, as did the reaction in MeOH even at atmospheric pressure. Finally, the use of Ph_2S (0.05 eq.) as a mild catalyst poison[106] in $CHCl_3$ allowed for the fine tuning of the catalyst activity, so that the saturated ketone **142** was obtained in excellent yield (91%) (Table 4).

Table 4: Hydrogenation of brominated ketones **139** and **140**



Substrate	Catalyst	Additive	Solvent	H_2 pressure [bar]	Time [h]	Yield [%] /comment
139	10% Pd/C	-	$CHCl_3$	1	24	50
140	10% Pd/C	-	$CHCl_3$	1	21	56
139	10% Pd/C	-	EtOAc	5	17	MOM-deprotection
139	10% Pd/C	-	MeOH	1	1.5	MOM-deprotection
140	10% Pd/C	Ph_2S 0.05 eq.	$CHCl_3$	1	3	91

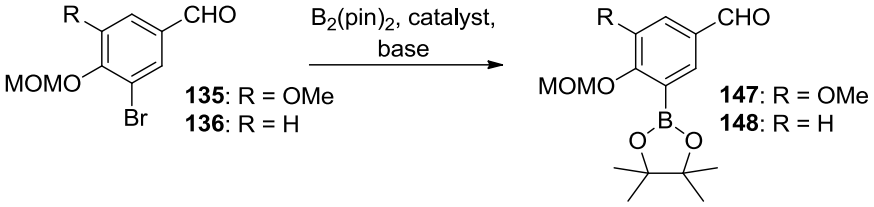
Parallel to the synthesis of brominated ketones **141** and **142**, an effort was made towards a synthesis of benzaldehydes with arylboronic acid moiety as the second part of the final diarylheptanoids. The aromatic aldehyde **135** with bromide in position 5 was used as substrates and numerous borylation methods were screened. The first strategy was to perform a lithium-bromine exchange, followed by a reaction with suitable boronic acid ester. For this reaction, the aldehyde had to be protected as an acetal to avoid side reactions of the lithiating agent nBuLi with the carbonyl functionality. The aldehyde was acetalized with ethylene glycol in presence of triethyl orthoformate and tetrabutylammonium tribromide[128] in 18% yield to give **143** and the MOM-deprotected acetal **144** as the major side product (47% yield). Compound **143** was then submitted to several borylation reactions with nBuLi and trimethyl-[128] or triisopropylborate, which all failed to afford the desired product (Scheme 39).



Scheme 39: Protection of aldehyde **135** and attempted arylborylation of compound **143**

Instead of the unsuccessful lithiation/transmetalation sequence with nBuLi and the trialkyl borates (Scheme 39), an alternative approach using a palladium-catalyzed Miyaura aryl-borylation[129] was applied. This method tolerates various functionalities such as carbonyls[129] and thus allowed to avoid the acetalization-deacetalization steps. Furthermore, the use of bis(pinacolato)diboron as borylating agent gives directly the arylboronic acid pinacolates which are common substrates for Suzuki reactions.[130] Different reaction conditions, like the use of a proper catalyst, solvent and base, had to be tried to reach satisfactory yields. In most cases, debromination occurred as the major side reaction. All the methods required elevated temperatures whereby the best result was achieved when microwave irradiation (140 °C) was applied. In the end, borylated compound **147** was obtained in 26% and compound **148** in 44% yield (Table 5).

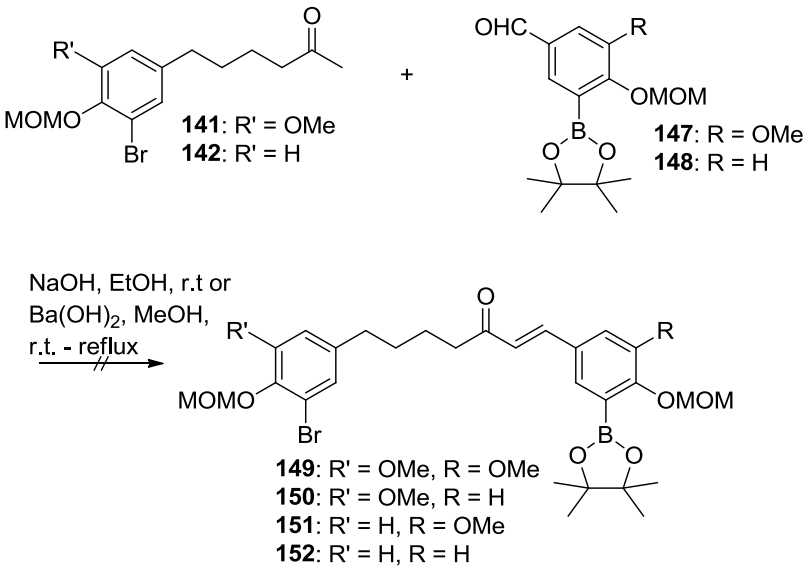
Table 5: Miyaura arylborylation of aldehydes **135** and **136**



Substrate	Catalyst (mol. eq.)	Reaction conditions [Lit.]	Yield [%]
135	$PdCl_2(dppf)$ (0.05), $Pd(OAc)_2$ (0.12)	$B_2(pin)_2$, KOAc, dioxane, 4 h, 100 °C[131]	26
135	$PdCl_2(dppf)$ (0.05), $Pd(OAc)_2$ (0.05)	$B_2(pin)_2$, KOAc, dioxane, 5 h, 100 °C[131]	0
135	$PdCl_2(PPh_3)_2$ (0.05)	$B_2(pin)_2$, NaOAc, PEG400, 1.5 h, 90 °C[132]	0
136	$PdCl_2(dppf)$ (0.05)	$B_2(pin)_2$, KOAc, dioxane, 40 min, MW[a] 140 °C[102]	44

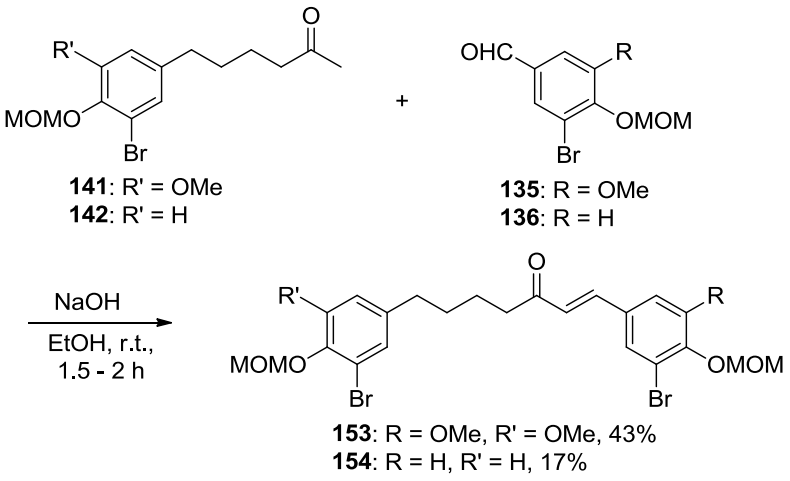
[a]MW, microwave

With the both halfs of the desired precursors in hand, a Claisen-Schmidt condensation of the borylated benzaldehydes **147** or **148** and brominated C_6-C_6 ketones **141** or **142** was attempted. However, this reaction gave multiple side products but no linear diarylheptanoid under basic conditions (Scheme 40).



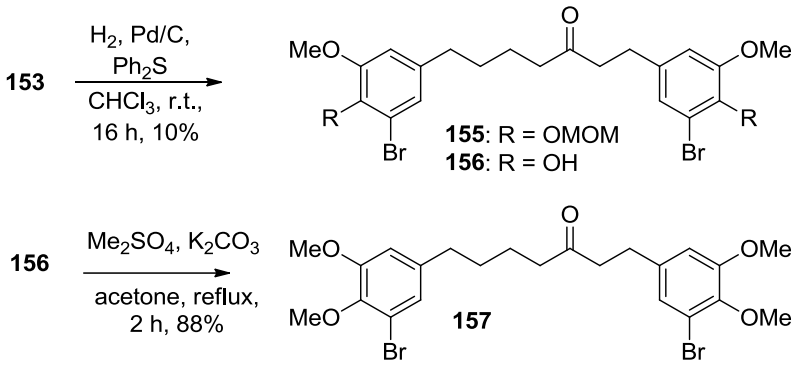
Scheme 40: Attempted Claisen-Schmidt condensation of the borylated aldehydes **147**, **148** and brominated ketones **141**, **142**

The failure of the aldol condensation towards brominated and borylated linear diarylheptanoids prompted a need for a new synthetic strategy for the macrocyclization precursors. Since the reaction conditions used in the arylborylation are identical with the conditions of Suzuki-Miyaura reaction (Pd catalyst, base, elevated temperature), a new idea was to combine the borylating and the coupling steps in one domino reaction, as Zhu et al[45] did in the synthesis of peptide macrocycles. Dibrominated diarylheptanoids were supposed to act as a substrate and so the brominated ketones **141** and **142** were reacted with brominated aldehydes **135** and **136** in a Claisen-Schmidt condensation under basic conditions[101] to afford the brominated diarylheptanoids **153** in 43% and **154** in 17% yield (Scheme 41).



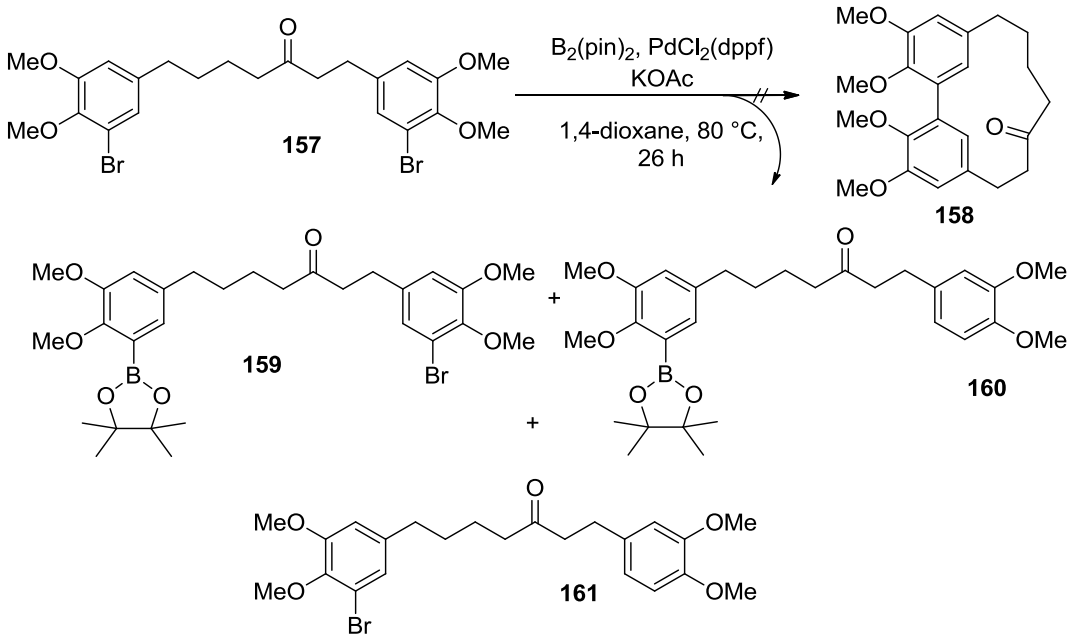
Scheme 41: Brominated linear diarylheptanoids **153** and **154**

The unsaturated aliphatic chain was expected to be too rigid for a successful cyclization. Therefore, a reduction of the double bond was performed using Pd/C catalyzed hydrogenation in presence of Ph_2S. Even though the sulfide was used to diminish the catalytic activity of the Pd/C, only low yield (10%) was achieved for **155** whilst the MOM-deprotected compound **156** could be isolated (38% yield) as the major side product. The cleaved MOM-groups were not reinstalled, instead, a methylation of **156** was performed using Me_2SO_4/K_2CO_3[116] to gain tetramethoxylated dibromide **157** in 88% yield (Scheme 42).



Scheme 42: Hydrogenation of compound **153** afforded saturated diarylheptanoid **155** and MOM-deprotected substance **156**, which was immediately methylated towards **157**.

After all the optimizations, only a small amount of dibrominated substrate **155** was obtained, so that the tetramethoxylated substance **157** was submitted for the arylborylation/biaryl formation sequence. This was carried out in presence of $B_2(pin)_2$, $PdCl_2(dppf)$ and KOAc as base, using 1,4-dioxane as solvent.[45] Conventional heating, gradually increasing from r.t. to 80 °C, as well as microwave irradiation (120 °C) were tested but in both cases no product **155** could be isolated. A mass spectrometric investigation revealed molecular ion peaks of a brominated/borylated linear diarylheptanoid (**156**, m/z 608 $[MNH_4]^+$), borylated/debrominated linear diarylheptanoid (**157**, m/z 530 $[MNH_4]^+$) and mono-debrominated linear diarylheptanoid (**158**, m/z 482 $[MNH_4]^+$) (Scheme 43).



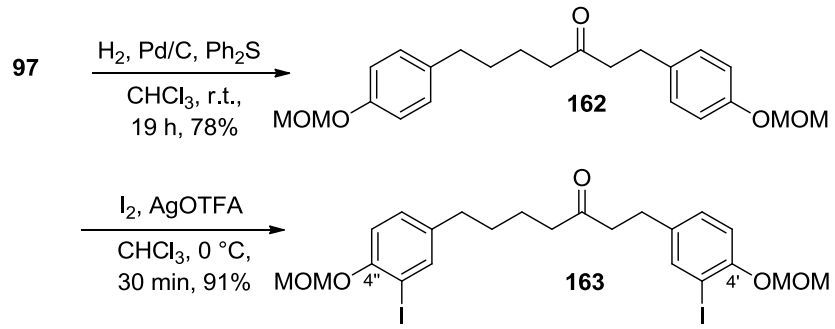
Scheme 43: Attempted cyclization of dibrominated linear compound **157** yielded only side products **159**-**161** (proposed structures based on LC-MS)

The identified side products indicate that the Miyaura borylation takes place, but it competes with a debromination reaction. The reactivity of the aryl-bromides is apparently not high enough to complete the ring closure and consequently the faster cleavage of the carbon-bromine bond occurs. While working on this project, Ogura and Usuki published their synthesis of acerogenin E (**3**) and K (**16**) where the same issues with brominated precursors are described.[29] Therefore, attention was placed towards similar strategy using aryl-iodides instead of the bromides.

3.3.3 Synthesis of cyclic diarylheptanoids from linear aryl-iodides

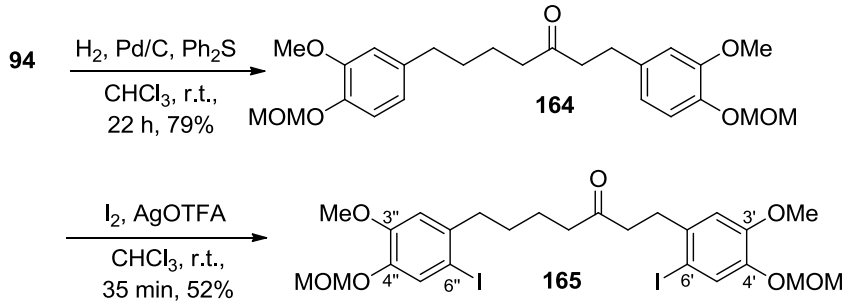
Since the cyclization of the brominated linear precursors failed, the synthesis of linear aryl-iodide analogues was envisioned. Plenty of methods for iodination of aromatic compounds are known in the literature[133] and the number is growing since aryl-iodides are useful substrates for metal-catalyzed C-C couplings.[134] Some of the methods require harsh acidic conditions, e.g. I_2 in H_2SO_4/HNO_3,[133] but there are also mild methods incorporating silver(I) salts.[133]

Inspired by Semmelhacks synthesis of alnusone (**7**) (Scheme 16) and by the synthesis of acerogenin E (**3**) (Scheme 19), the iodination of already synthesized linear diarylheptanoids was investigated. The most attractive strategy was to directly iodinate the MOM-protected linear diarylheptanoids, which would lead to the actual substrates for the cyclization. Electrophilic aromatic substitution with I_2/AgOTFA system according to Ogura and Usuki was applied (Scheme 44).[29]



Scheme 44: Hydrogenation and iodination of 4',4''-disubstituted linear diayrlheptanoid **97**

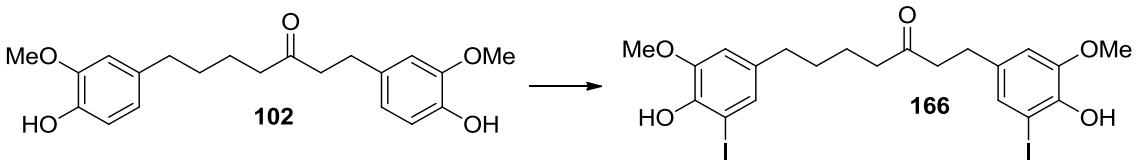
Unfortunately, this method worked only for 4',4''-di(methoxymethoxy) substituted compound **162** (Scheme 44) while the attempted iodination of compound **164**, bearing additional methoxy groups in positions 3 and 3', yielded substance **165** with iodide groups in positions 6' and 6'' (Scheme 45). This can be explained by a steric hindrance due to the methoxymethoxy substituent in position 4, directing the electrophilic attack in position 6, i.e. *para* to the 3-OMe group.



Scheme 45: Iodination of 3-methoxy-4-methoxymethoxy-substituted substrates

To overcome the selectivity problem during the iodination of **164**, the MOM-groups were cleaved and the 4',4''-dihydroxy-3',3''-dimethoxy diarylheptanoid **102** was used as substrate for iodination experiments under various conditions. However, methods incorporating iodine with silver(I) salts (Ag_2SO_4,[135] AgOTFA[29]) or N-iodosuccinimide as "I^+"-donor[136] as well as KI/I_2 protocols, known from the iodination of vanillin[137] or electron-poor phenols,[138] failed to afford any iodinated product **166** (Table 6).

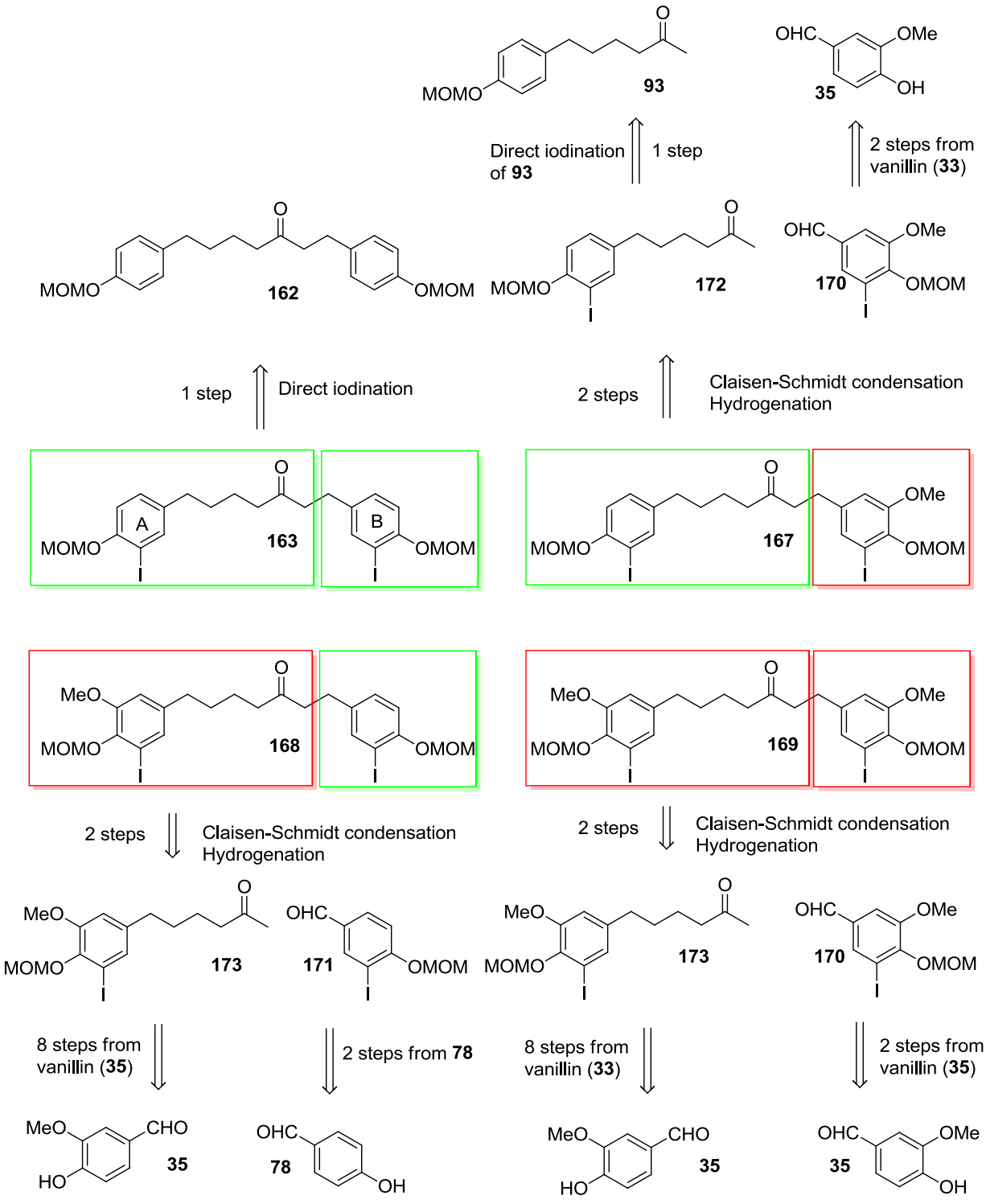
Table 6: Iodination of compound **102**



Reaction conditions[a]	Yield [%]
I_2 (4.0 eq.) AgOTFA, $CHCl_3$	0
I_2 (2.5 eq.), Ag_2SO_4, EtOH	0
NIS (2.0 eq.), TFA (solv.)	24 (mono-iodo)[b]
NIS (2.2 eq.), TFA (cat.), MeCN	0
NIS (2.0 eq.), *p*-TsOH (2.0 eq.), MeCN	0
I_2 (2.1 eq.), KI, NaOH, MeOH/H_2O	0

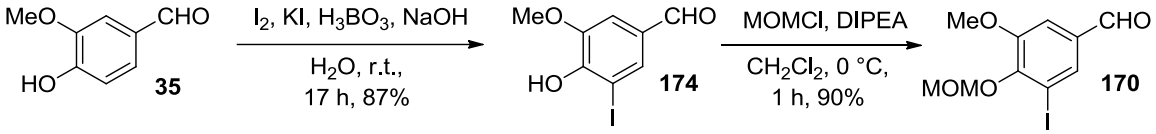
[a]solv., solvent; [b] calculated yield, detected by ESI-MS

The fact that only 4',4''-dihydroxy substituted linear diarylheptanoids could be iodinated, whereas compounds with 4-hydroxy-3-methoxy motif could not, prompted a need for a new strategy for the formation of the latter. 5-Iodovanillin (**174**) was selected as a common starting material for substances with 4-hydroxy-3-methoxy substitution, since the iodination of vanillin was known. This provided a quick access to the iodinated future B-ring via compound **170** which, combined with easily feasible iodinated ketone **172**, allowed for the preparation of the linear precursor **167**. On the other hand, compounds with the iodinated subsequent A-ring had to be prepared in 9 steps starting from 5-iodovanillin **174**. General approaches towards all the iodinated precursors of cyclic diarylheptanoids are summed up in the Scheme 46.



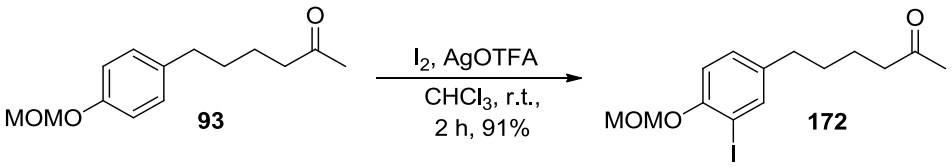
Scheme 46: General synthetic strategies towards iodinated linear precursors of cyclic diarylheptanoids

Whereas the iodination of 4-hydroxy-3-methoxy substituted diarylheptanoids was an insurmountable challenge, the iodination of vanillin is well established.[137, 139] However, the first iodination experiments towards 5-iodovanillin **174** using iodine in presence of Ag_2SO_4 according to Nair et al.[139] did not lead to any of the desired product. A successful method was the iodination with I_2/KI in aqueous solution buffered with H_3BO_3/NaOH to pH ≥ 8.5,[137] affording **174** in 87% yield (Scheme 47). The 4-hydroxy group of this compound was subsequently protected as a MOM-ether **170** using MOM chloride and DIPEA[102] as a base in a clean reaction with 90% yield (Scheme 47).



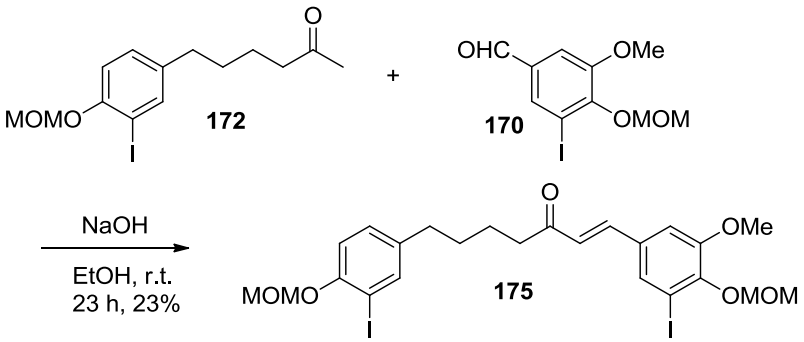
Scheme 47: Iodination and MOM-protection of vanillin (**35**)

The MOM-protected 5-iodovanillin **170** represented the B-ring of iodinated linear diarylheptanoids **167** and **169**. Whilst the formation of the A-ring of **169** required whole new reaction sequence, the future A-ring moiety **172** of the open chained precursor **167** was readily available by iodination of C_6-C_6 ketone **93** (prepared in 3.1.3). This was performed under the same conditions as the iodination of linear diarylheptanoid **162**, namely with I_2 and AgOTFA in chloroform (Scheme 48).[29]



Scheme 48: Iodination of ketone **93** to form the A-ring precursor **172** for acyclic diarylheptanoid **167**

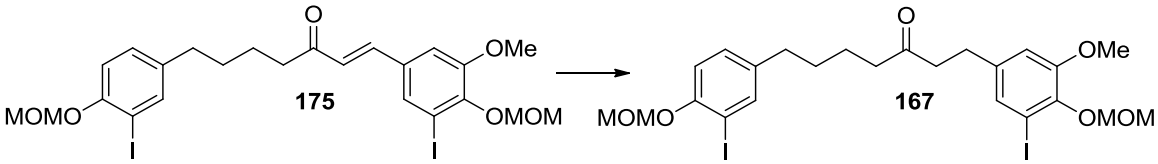
The iodinated C_6-C_6 ketone **172** and the aldehyde **170** were then used as starting materials to assemble the iodinated linear diarylheptanoid **175** via Claisen-Schmidt condensation in presence of NaOH.[101] This afforded the objected compound with an enone motif in 23% yield (Scheme 49). The product was accompanied by multiple side products with yellow fluorescence on TLC, which could not be exactly identified.



Scheme 49: Claisen-Schmidt condensation towards iodinated diarylheptanoid **175**

The double bond of enone **175** had to be hydrogenated to make the linear chain more flexible for the envisioned cyclization (Table 7). However, the standard hydrogenation protocol using the 10% Pd/C catalyst with Ph_2S as a catalyst poison, readily applied in hydrogenation of linear diarylheptanoids **98**-**101** in 3.1.5, yielded no saturated product **167**. No reaction was observed even in absence of Ph_2S, at elevated pressure (10 bar) or with methanol as solvent. Other hydrogenation systems were tested, for instance transfer hydrogenation methods with cyclohexene,[140] Hantzsch ester (Fig. 19)[141] or ammonium formate as hydrogen-donors, homogenous catalysis with Wilkinson's catalyst ($Rh(PPh_3)Cl$), hydrogenation with *in situ* formed indium hydride[142] or a cationic reduction with hydrosilane,[143] but none of the methods resulted in the saturated compound **167** (Table 7). The literature generally lacks examples for hydrogenations of iodinated substrates. Therefore, a promising method seemed to be the one by Xing et al. where a double bond of an *ortho*-iodinated cinnamic ketone was reduced by tellurium and $NaBH_4$.[144] Such a sodium hydrogen telluride promoted reduction, originally developed by Derek Barton,[145] failed when applied on the substrate **175**. The final breakthrough was achieved by homogenous iridium(I)-catalyzed hydrogenation, inspired by a publication of Bennie et al.[146] The use of Crabtree's catalyst, a highly active iridium(I) complex with 1,5-cyclooctadiene, tris-cyclohexylphosphine and pyridine, gave the desired saturated product **167** in excellent yield (98%) (Table 7).

Table 7: Hydrogenation of iodinated diarylheptanoid **175**



Reaction conditions	Result[a]
H_2 (1 bar), Pd/C, Ph_2S, $CHCl_3$, r.t., 28 h[106]	n.r.
H_2 (1 bar), Pd/C, $CHCl_3$, r.t., 4 days	n.r.
H_2 (10 bar), Pd/C, $CHCl_3$, r.t., 3 h	partial deiodination
H_2 (1 bar), Pd/C, MeOH, reflux, 16 h	MOM-deprotection
$Pd(OH)_2$, cyclohexene, r.t., 24 h[140]	n.r.
Pd/C, Hantzsch ester (Fig. 19), EtOH, r.t. – reflux, 24 h[141]	n.r.
Pd/C, NH_4HCO_2, 100 °C, 2 h	complete deiodination
$InCl_3$, $NaBH_4$, MeCN, r.t., 2.5 h[142]	MOM-deprotection
H_2 (1 bar), $Rh(PPh_3)_3Cl$, $CHCl_3$, 60 °C, 24 h	n.r.
TFA, Et_3SiH, $CHCl_3$, r.t., 19 h[143]	ketone reduction
$NaBH_4$, Te, EtOH, reflux, 3 h[144-145]	n.r.
H_2 (1 bar), Crabtree's catalyst (Fig. 19), CH_2Cl_2, 2 h[146]	**167** (98% yield)

[a]n.r., no reaction

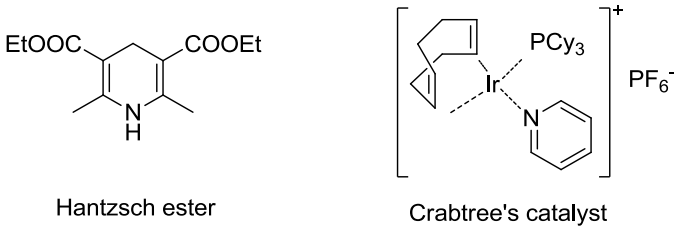
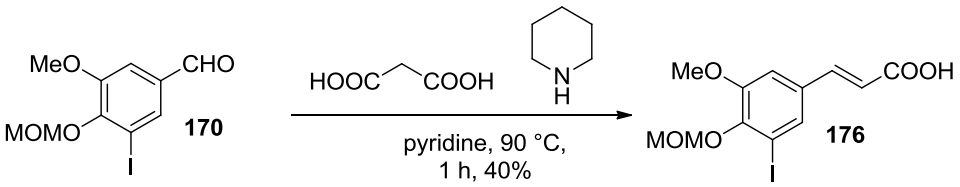


Fig. 19: Structures of Hantzsch ester and Crabtree's catalyst applied in the hydrogenation of **175**

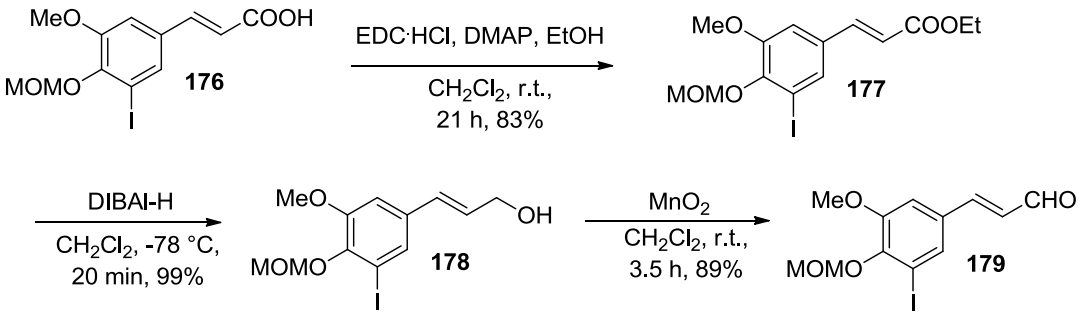
Whereas the iodinated linear diarylheptanoids with a 4-hydroxy substituted A-ring **163** and **167** were obtained by established methods (Scheme 46), the remaining two compounds **168** and **169** required a new synthetic strategy for the formation of a 4-hydroxy-5-iodo-3-methoxy substituted A-ring. Hence, the iodinated C_6-C_6 ketone **173** had to be build up from MOM-protected 5-iodovanillin **170** (Scheme 46). The first step

towards this ketone was the elongation of its alkyl chain. Instead of using low yielding aldol condensation or Wittig olefination, as described in chapter 3.3.2, a Knoevenagel-Doebner condensation was incorporated (Scheme 50). This condensation reaction of aldehyde **170** with malonic acid, catalyzed with piperidine, was carried out in pyridine and resulted in the desired C_6-C_3 acid **176**. The isolation of the product was rather difficult due to its high polarity and sensibility of the MOM-group towards acidification, hence only a moderate yield of 40% was achieved.



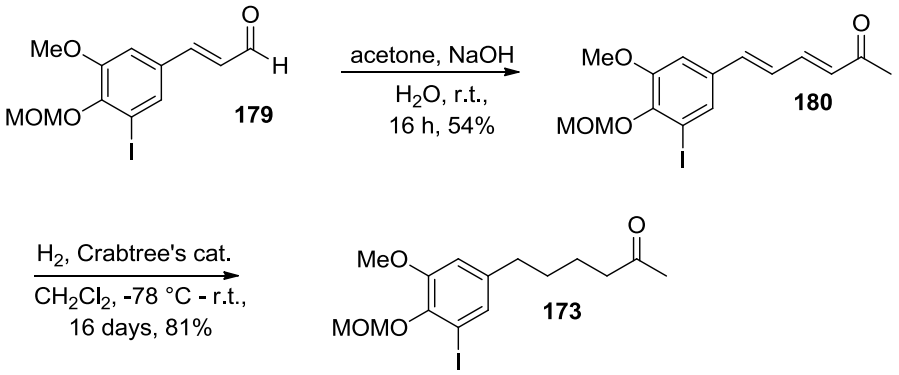
Scheme 50: Knoevenagel-Doebner condensation towards C_6-C_3 acid **176**

To enable further extension of the aliphatic rest, the acid moiety had to be converted into an aldehyde (Scheme 51). This was achieved by a sequence of esterification to form **177**, reduction to the alcohol **178** and oxidation to the aldehyde **179**. The esterification to the ethyl ester of carboxylic acid **176** could not be performed under standard EtOH/H_2SO_4 conditions due to the acid-labile MOM-protecting group. A valuable alternative offered a Steglich esterification, comprising activation by a carbodiimide and DMAP to form the active ester and subsequent substitution reaction with EtOH.[147] This transformation proceeded cleanly without any undesired side products in 83% yield to get the ester **177**. The following reduction was performed by diisobutylaluminium hydride (DIBAl-H)[147] in practically quantitative yield (99% of **178**). Finally, the allylic alcohol **178** was oxidized with an excess of MnO_2 (18 mol eq.) to form the iodinated C_6-C_3 aldehyde **179** in 89% yield.[105]



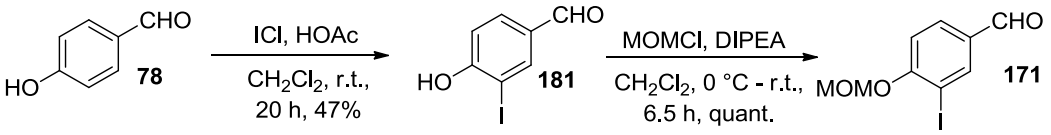
Scheme 51: The transformation of carboxylic acid **176** into aldehyde **179** in three steps

The reaction sequence continued in analogy to the synthesis described in 3.1.3 with the preparation of iodinated C_6-C_6 ketone **180** (Scheme 52). This was achieved by a Claisen-Schmidt condensation with acetone in presence of sodium hydroxide.[101] The unsaturated enone **180** was obtained in 54% yield and was subsequently submitted to hydrogenation. The reaction was accomplished using Crabtree's catalyst (10 mol%) and 1 bar of hydrogen gas.[146] The reaction rate was much lower compared to the reduction of **175**, but a complete conversion was achieved after 16 days.



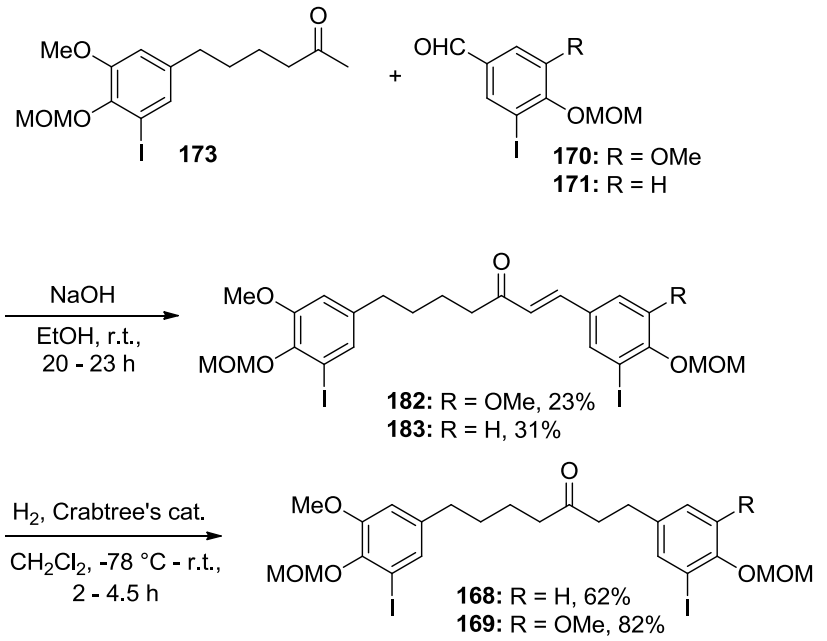
Scheme 52: Transformation of aldehyde **179** to ketone **180**, followed by a hydrogenation towards iodinated C_6-C_6 ketone **173**

The ketone **173**, synthesized in eight steps from vanillin (**35**), represents the A-ring part of desired cyclic diarylheptanoids. The only missing part was the iodoaldehyde **171** (Scheme 46), which was prepared in two steps, starting with the iodination of 4-hydroxybenzaldehyde **78** with the aid of iodine monochloride and acetic acid,[148] followed by a MOM-protection with MOM chloride and Hunig's base (Scheme 53).[102]



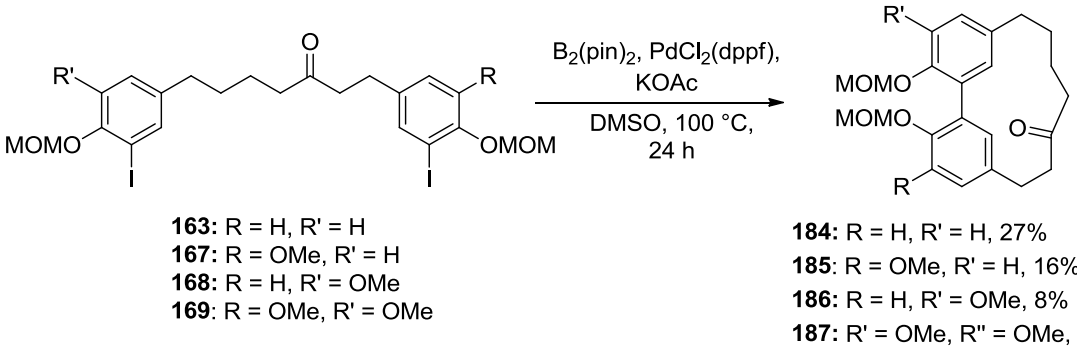
Scheme 53: Iodinated aldehyde **171** as the future B-ring of **168**

With the ketone **173** and the aldehydes **170** and **171** in hands, the remaining two linear precursors **168** and **169** could be formed (Scheme 54). The Claisen-Schmidt condensation, carried out in presence of sodium hydroxide,[101] afforded enone **182** in 23% yield and enone **183** in 31% yield. These compounds were further hydrogenated under the iridium(I) homogenous catalysis (Crabtree's catalyst)[146] in good to excellent yields (62% and 82%, respectively).



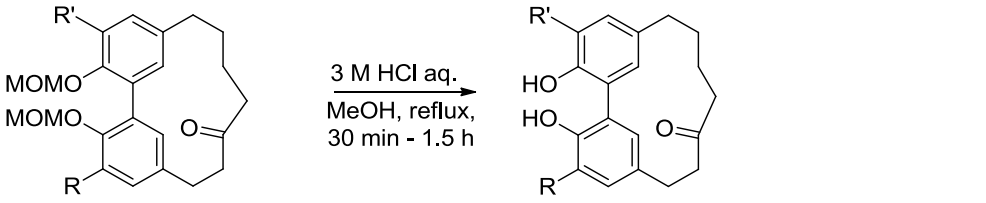
Scheme 54: Synthesis of iodinated linear diarylheptanoids **168** and **169**

After all the iodinated linear diarylheptanoids **163, 167, 168** and **169** were prepared, the cyclization towards biphenyl type cyclic diarylheptanoids could be performed (Scheme 55). The conditions were applied in accordance with the method of Ogura and Usaki, using pinacolato diboron (1.2 eq.) as borylating agent, $PdCl_2$(dppf) as catalyst (0.1 eq.) and potassium acetate as base (10 eq.).[29] The reaction took place in degassed DMSO under inert atmosphere (N_2) at 100 °C. Three of four aimed cyclic diarylheptanoids were obtained, namely **184** in 27%, **185** in 16% and **186** in 8% yield. The last compound **187** could be detected by LC-MS (ESI-MS m/z 467 $[MNa]^+$) but due to a small batch size (64.0 mg, 91.6 µmol of starting material **169**) and generally low yields of the cyclization reactions, not enough product for further characterization and transformation could be isolated (Scheme 55).



Scheme 55: Formation of cyclic diarylheptanoids **184**-**187**; [a]n.p., no product

The protecting groups of compounds **184**-**187** were subsequently cleaved under acidic conditions providing three cyclic diarylheptanoids, among them two natural products (acerogenin E (**3**) and myricananin C (**18**)) and one new compound **188** (Scheme 56).

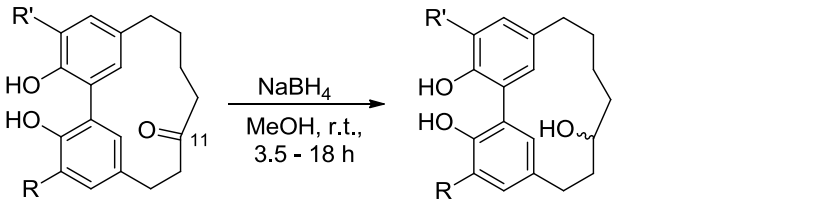


184: R = H, R' = H
185: R = OMe, R' = H
186: R = H, R' = OMe

3 (acerogenin E): R = H, R' = H, 98%
188: R = OMe, R' = H, 89%
18 (myricananin C)**:** R = H, R' = OMe, 73%

Scheme 56: MOM group cleavage to obtain cyclic diarylheptanoids **188**, **18** (myricananin C) and **3** (acerogenin E)

The last conversion was the reduction of the oxo group to form alcohol analogues of **3**, **18** and **188** (Scheme 57). This reaction was performed with acerogenin E and compound **188**, since the amount of myricananain C was only sufficient for its biological testing. The reduction was performed in analogy to the linear compounds with sodium borohydride. Interestingly, much more hydride equivalents were needed for the conversion of the cyclic compounds in comparison to their open chained counterparts. Using this method, acerogenin K (**16**) and alcohol **189** were obtained in 41% and 73% yield, respectively (Scheme 57).



188: R = OMe, R' = H
3: R = H, R' = H

189: R = OMe, R' = H, 73%
16 (acerogenin K): R = H, R' = H, 41%

Scheme 57: Reduction of the cyclic ketones to alcohols **16** and **189**

All in all, five biphenyl type cyclic diarylheptanoids were synthetically prepared. Among these compounds, **3** and **16** are known natural products with published synthesis, myricananin C (**18**) is a natural product prepared for the first time and so were the two novel non-natural cyclic diarylheptanoids **182** and **183**.

3.3.3.1 Structure elucidation of cyclic diarylheptanoids

The precise assignment of all carbons and protons of the final products was performed with the help of 1D (^{1}H, ^{13}C) and 2D (HSQC, HMBC, COSY, NOESY) NMR methods and is

summed up bellow. The difference between aliphatic signals of compounds with oxo-group in position 11 (acerogenin E (**3**), **188**, myricananin C (**18**)) and the derivatives with hydroxyl group at carbon 11 is worth mentioning. The first three compounds exhibit clearly resolved signals in the aliphatic region with chemically equivalent geminal protons whereas the second group of compounds shows multiplets with partially high geminal couplings for the protons of the connecting chain. These observations are in accordance to spectra presented in the literature and might be explained by the differences in the ring strain and rotation barriers. The strain of the compounds bearing a sp^2 hybridized oxo-group in the tethered chain is lower since the angle of such bond is 120° and thus the ring is less rigid and enables a movement of the geminal protons. On the other hand, due to the presence of sp^3 hybridized carbon 11 with angle of approximately 109° the ring strain and rotation barrier are higher for acerogenin K and compound **189** and therefore the geminal protons of the latter appear with inequivalent chemical shifts.

Acerogenin E (**3**) and the cyclic ketone **188** were crystallized from EtOH and crystals were submitted to X-ray analysis. The resulting structures revealed that both compounds are present in the crystal lattice as a mixture of two atropoisomers (Fig. 20, Fig. 21). Torsion angels of the biaryl units of **3** and **188** were 31.78° and 36.58°, respectively.

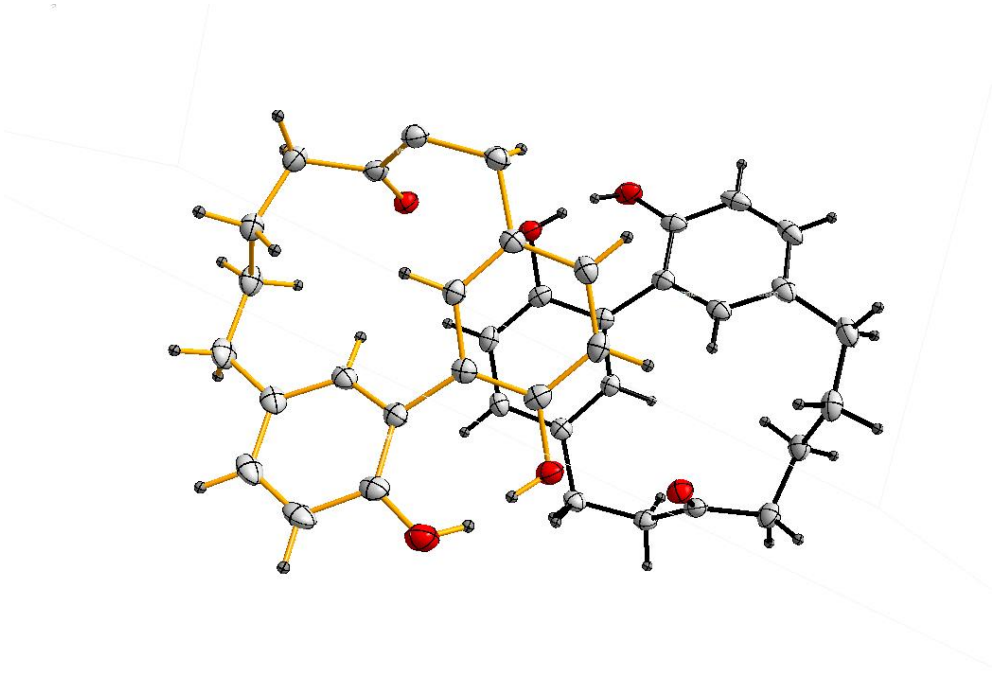


Fig. 20: X-ray structure of acerogenin E (**3**) showing the two atropoisomers; ellipsoids are shown at the 50% probability level (Diamond 3.2 software)

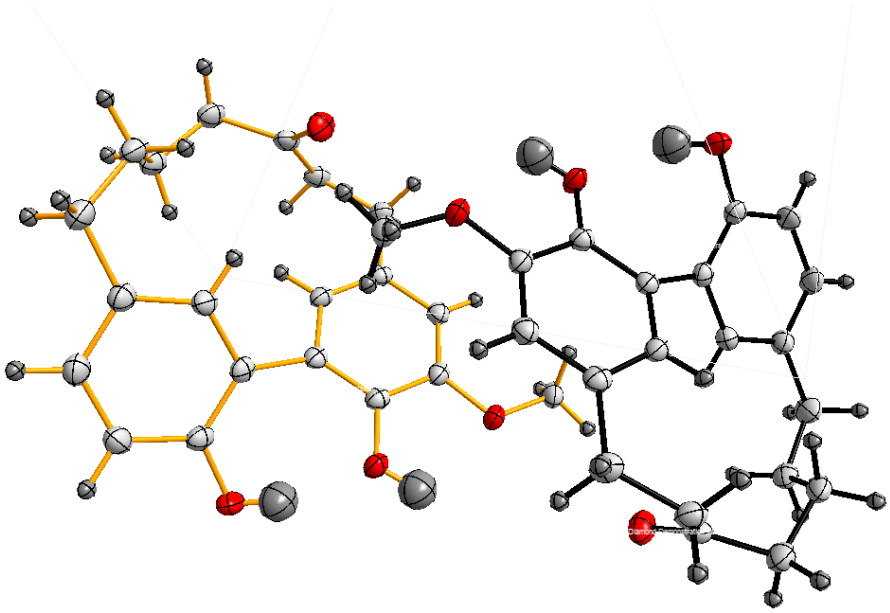
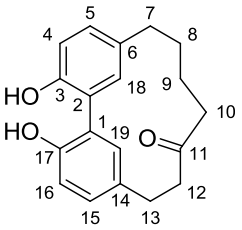


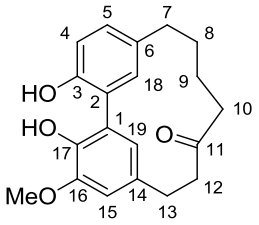
Fig. 21: X-ray structure of diarylheptanoid **188** showing the two atropoisomers; ellipsoids are shown at the 50% probability level (Diamond 3.2 software)

Table 8: NMR spectral data of acerogenin E (**3**) (acetone-d_6, ^{1}H 400 MHz, ^{13}C 101 MHz, 298 K, δ in ppm, J in Hz)



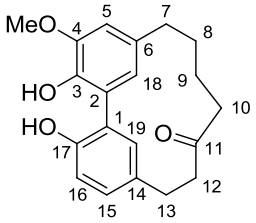
Position	δH	δC
1, 2		126.8, 127.2
3, 17		152.1, 152.2
4, 16	6.86 (m, 2H)	116.8, 117.0
5, 15	7.05 (m, 2H)	129.4, 130.4
6		132.5
7	2.75 (m, 2H)	32.0
8	1.94 (m, 2H)	26.5
9	1.76 (m, 2H)	22.9
10	2.75 (m, 2H)	45.0
11		212.7
12	2.87 (m, 2H)	42.5
13	2.96 (m, 2H)	28.4
14		133.4
18	6.96 (d, 1.9, 1H)	134.5
19	6.76 (d, 1.8, 1H)	134.5

Table 9: NMR spectral data of compound **188** (acetone-d_6, ^{1}H 600 MHz, ^{13}C 151 MHz, 298 K, δ in ppm, J in Hz)



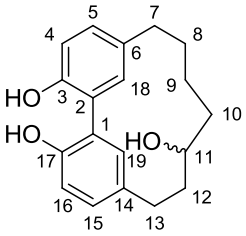
Position	δH	δC
1		125.9
2		125.6
3		152.2
4	6.80 (d, 8.2)	116.7
5	7.02 (dd, 2.4, 8.2)	129.6
6		131.2
7	2.74 (m, 2H)	31.1
8	1.94 (m, 2H)	25.7
9	1.75 (dt, 7.2, 14.4, 2H)	22.0
10	2.74 (m, 2H)	44.2
11		211.6
12	2.87 (m, 2H)	41.5
13	2.97 (m, 2H)	28.0
14		132.3
15	6.84 (d, 2.0)	110.7
16		147.7
16-OMe	3.89 (s, 3H)	55.8
17		140.2
18	6.97 (d, 1.9)	133.2
19	6.36 (d, 1.9)	125.4

Table 10: NMR spectral data of myricananin C (**18**) (acetone-d_6, ^{1}H 600 MHz, ^{13}C 151 MHz, 298 K, δ in ppm, J in Hz)



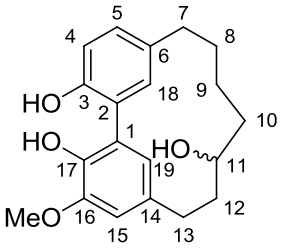
Position	δH	δC
1		126.9
2		126.3
3		141.3
4		148.8
4-OMe	3.85 (s, 3H)	56.7
5	6.79 (m, 1H)	112.1
6		132.3
7	2.74 (m, 2H)	32.7
8	1.91 (m, 2H)	26.4
9	1.78 (m, 2H)	22.7
10	2.74 (m, 2H)	45.3
11		212.7
12	2.86 (m, 2H)	42.6
13	2.95 (m, 2H)	28.6
14		132.9
15	7.03 (dd, 2.2, 8.2, 1H)	129.5
16	6.79 (m, 1H)	117.4
17		153.0
18	6.54 (br s, 1H)	126.1
19	6.77 (m, 1H)	134.0

Table 11: NMR spectral data of acerogenin K (**16**) (acetone-d_6, ^{1}H 600 MHz, ^{13}C 151 MHz, 298 K, δ in ppm, J in Hz). [a]Signals assigned according to published data.[54]



Position	δH	δC
1[a]		127.1
2[a]		126.9
3, 17		152.17, 152.18
4, 16	6.86 (2 × d, 8.1, 2H)	116.95, 116.97
5, 15	7.04 (2 × dd, 2.2, 8.2, 2H)	130.16, 130.26
6[a]		131.9
7	2.49, 2.92 (m, m, 2H)	30.6
8	1.84, 2.01 (m, m, 2H)	27.4
9	1.46, 1.66 (m, m, 2H)	23.8
10	1.58, 1.84 (m, m, 2H)	40.6
11	4.04 (t, 9.7, 1H)	68.4
12	1.66, 2.27 (m, m, 2H)	35.6
13	2.83, 2.95 (m, m, 2H)	27.4
14[a]		132.3
18	7.24 (br s, 1H)	135.0
19	7.21 (br s, 1H)	134.6

Table 12: NMR spectral data of compound **189** ($CDCl_3$, ^1H 600 MHz, ^{13}C 151 MHz, 298 K, δ in ppm, J in Hz)

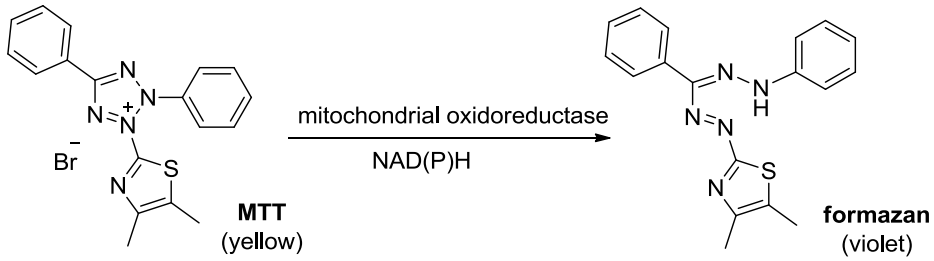


Position	δH	δC
1		124.5
2		124.8
3	7.12 (s, OH)	151.6
4	6.90 (d, 8.2, 1H)	117.0
5	7.06 (dd, 2.3, 8.2, 1H)	130.0
6		130.9
7	2.53, 2.96 (m, m, 2H)	30.0
8	1.89, 2.01 (m, m, 2H)	26.7
9	1.51, 1.67 (m, m, 2H)	22.7
10	1.55, 1.93 (m, m, 2H)	39.7
11	4.17 (t, 9.6, 1H)	69.0
12	1.68, 2.31 (m, m, 2H)	34.9
13	2.91 (m, 2H)	27.4
14		131.4
15	6.72 (d, 1.9, 1H)	110.2
16		146.7
16-OMe	3.94 (s, 3H)	56.3
17	6.31 (s, OH)	139.1
18	7.18 (br s, 1H)	133.4
19	6.85 (br s, 1H)	126.4

3.4 Biological properties of synthesized diarylheptanoids - cytotoxicity

The assessment of the biological properties of the diarylheptanoids was performed with the aid of cell based cytotoxicity assays. By this means, the toxicity of the compounds against immortalized mouse hippocampal neuronal cell line HT22 was determined, as well as the ability of the compounds to protect the cells against oxidative stress induced by high extent of glutamate.

To determine the cytotoxicity of the synthesized diarylheptanoids, a quantitative colorimetric cell viability assay using the tetrazolium dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) was applied. In course of this assay, the HT22 cells were treated with the tested compounds at different concentrations, followed by addition of the water soluble MTT after 24 h of incubation. The yellow tetrazolium dye MTT is reduced only by viable cells due to the presence of mitochondrial NAD(P)H-dependent oxidoreductase enzymes, forming the insoluble violet formazan (Scheme 58). This reaction was finished after 3 h of incubation by a SDS-lysis and the intensity of the purple color was spectrophotometrically measured. The formazan absorbance, determined at 560 nm, is direct proportional to the number of living cells and so the cell viability of the treated cells can be expressed in a relation to the untreated cells.



Scheme 58: The principle of the MTT colorimetric cytotoxicity assay

3.4.1 Cytotoxicity of linear diarylheptanoids

The cytotoxicity of all compounds against the HT22 cell line was determined at four different concentrations (1, 5, 10 and 25 µM) by the MTT assay. The linear diarylheptanoids could be grouped either according to the oxidation state of their aliphatic chain (enone, alcohol, ketone) or with regard to the substituent pattern of their aromatic rings (derivatives of curcumin, demethoxycurcumin and bisdemethoxycurcumin). The comparison of the cytotoxicity and the neuroprotection data indicated a relationship between the substitution of the phenyl rings and the biological activity. Hence the substances were grouped and discussed with respect to this feature.

Diarylheptanoids with 4',4''-dihydroxy-3',3''-dimethoxy substitution of the aromatic rings (**98**, **102** and **105**) could be considered as derivatives of curcumin (**1**). These compounds showed certain toxicity only at the highest 25 μM concentration (cell viability of 57% for **98** and 53% for **105**) but did not significantly affect the cell viability in the range from 1 to 10 μM (65–89%) (Fig. 22).

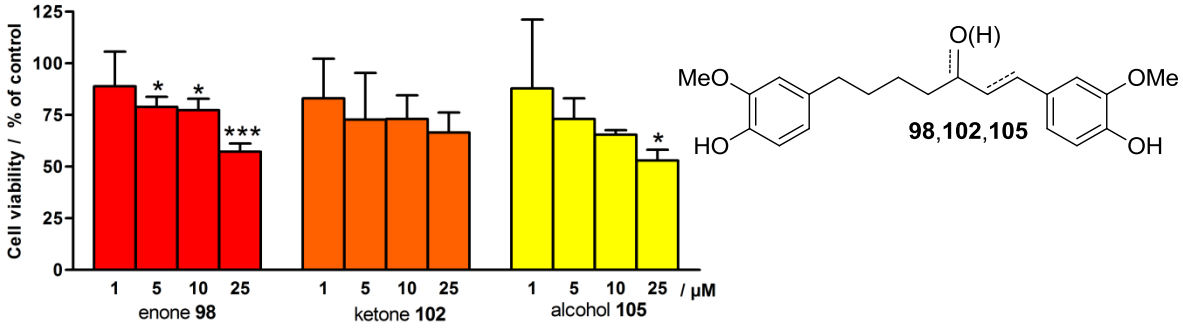


Fig. 22: Cytotoxicity of compounds **98**, **102** and **105** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

Curcuminoids **99**, **103** and **106** lack the methoxy group at the B-ring in position 3'' and could thus be seen as derivatives of demethoxycurcumin of type B. Among these compounds, ketone **103** significantly lowered the cell viability at all tested concentrations (67% at 1 μM, 37% at 25 μM) whereas alcohol **106** was toxic only at 25 μM (61%) and enone **99** showed a minor effect on the viability of the cells at 10 μM (73%) and a moderate effect at 25 μM (51%) (Fig. 23).

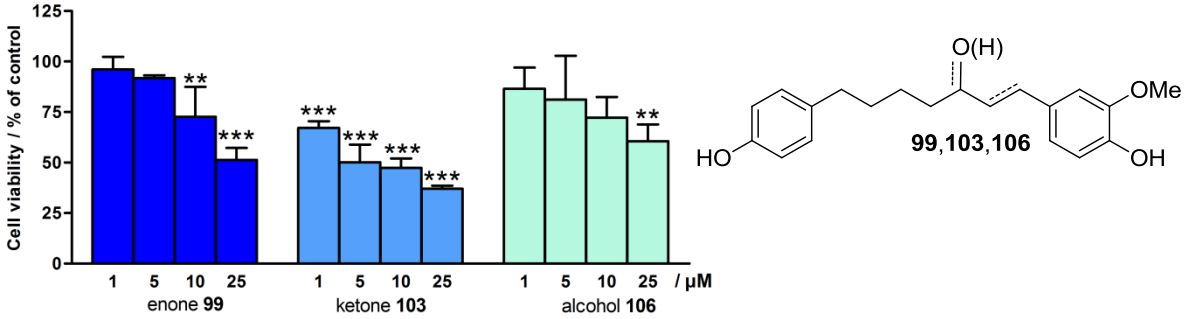


Fig. 23: Cytotoxicity of demethoxycurcumin derivatives - type B **99**, **103** and **106** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

Demethoxycurcumin derivatives of type A were compounds without methoxy group at position 3' of their A-ring. This group of compounds included enone **100**, ketone **104** and

alcohol **107**. Similar to the above discussed curcuminoids, these compounds exhibited no or only minor toxicity at lower concentrations. Significant effects on the cell viability were observed at higher concentrations of 10 and 25 µM (54% cell viability for enone **100** and alcohol **107**, 66% for ketone **104**) (Fig. 24).

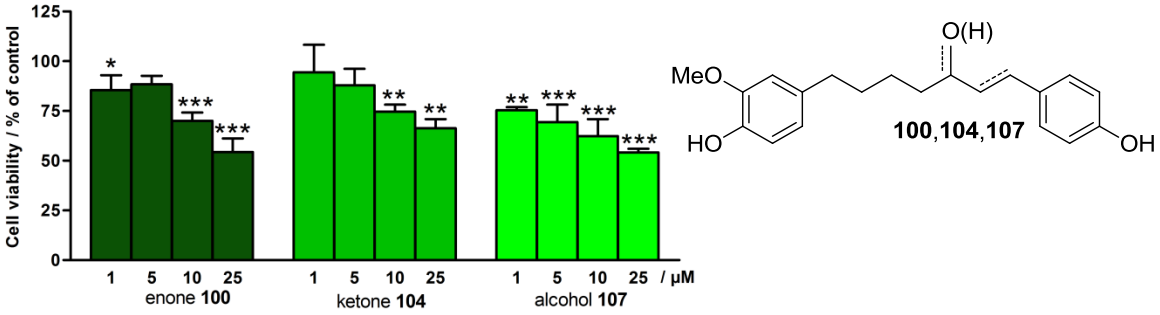


Fig. 24: Cytotoxicity of demethoxycurcuminoids - type A **100**, **104** and **107** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

Finally, diarylheptanoids **101**, **8** and **25** which were lacking both methoxy groups in positions 3' and 3'', could be referred to as derivatives of bisdemethoxycurcumin. These compounds showed remarkable influence on the cell viability in a concentration dependent manner. Whereas the lowest concentrations of 1 and 5 µM had no or only small toxic effects, a concentration of 10 µM reduced the cell viability to approximately 50% and 25 µM to 25% (Fig. 25). This was the highest toxicity observed within all tested diarylheptanoids, with the exception of compound **110**. Interestingly, alcohol **25** was identified by Li et al. as a phase-1 metabolite of bisdemetoxycurcumin in rat feces.[111]

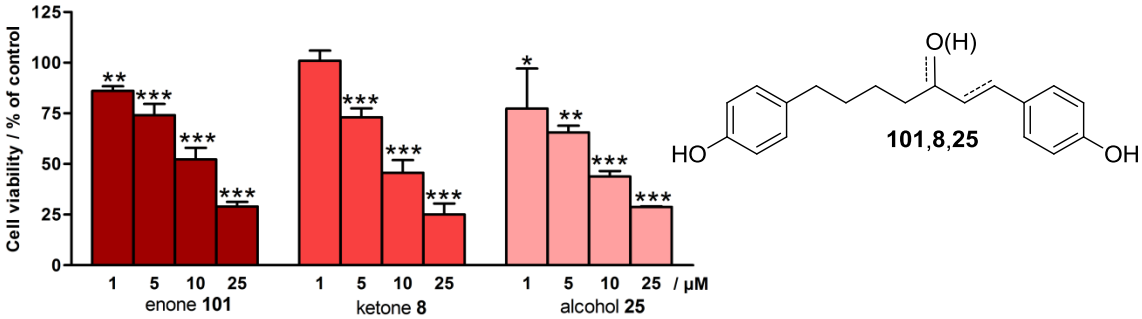


Fig. 25: Cytotoxicity of bisdemethoxcurcuminoids **101**, **8** and **25** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

Curcumin (**1**), demethoxycurcumin (**190**) and bisdemethoxycurcumin (**191**), as well as the natural-product like 3',3'',4',4''-tetrahydroxy derivative of curcumin **110**, were tested to obtain information about biological properties of the model compounds for the synthesized curcuminoids. Curcumin (**1**) is generally considered as a non-toxic natural product which can be administrated at high doses.[62] In the presented test system, 1 - 10 µM concentration of **1** slightly reduced the viability of HT22 cells to 84-82% with a more significant effect at 25 µM (36% less viability in comparison to untreated cells). Compounds **110**, **190** and **191** exerted higher toxicity in contrast to **1**. Di-*O*-demethylcurcumin **110** lowered the viability by 36-84% at 5 to 25 µM, while demethoxycurcumin (**190**) and bisdemethoxycurcumin (**191**) significantly influenced the cells from 10 µM (73% for **190**, and 55% for **191**) to 25 µM (53% for **190** and 32% for **191**) (Fig. 26).

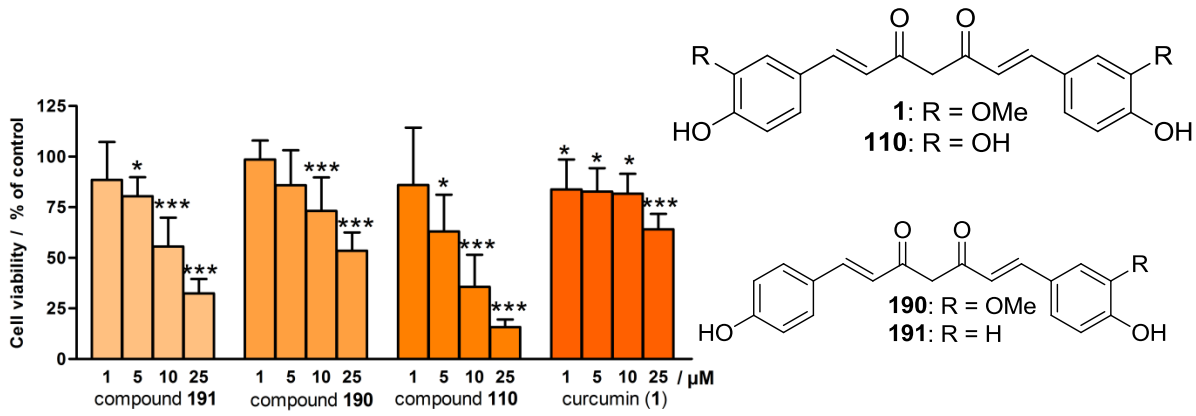


Fig. 26: Cytotoxicity of natural curcuminoids **1**, **110**, **190** and **191** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

The last linear compounds to be tested were the non-natural curcuminoids **108** and **109**, together with the single ring analogues of curcumin **113** and **114**. Tetrahydroxylated enone **109** exhibited lower toxicity (98-72% cell viability) compared to tetramethoxylated ketone **108** (77-50%), while among the single ring compounds, the 3-methoxy-4-hydroxy substituted enone **113** was less toxic then its 4-hydroxy substituted counterpart **114** (Fig. 27).

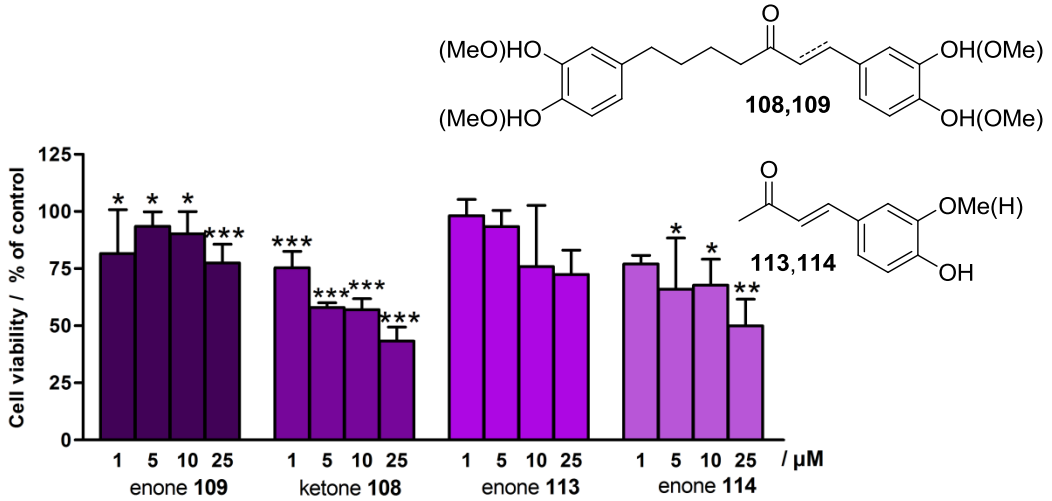


Fig. 27: Cytotoxicity of non-natural curcuminoids **108**, **109** and single ring analogues **113**, **114** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

3.4.2 Cytotoxicity of diarylheptanoids with cyclized C_7-chain

Compounds **115** and **116** were the only two representatives of this class of diarylheptanoids. Formally they derived from enones **98** and **100** by a formation of the additional seven-membered ring. In contrast to their precursors, diarylheptanoids **115** and **116** showed no toxicity up to 10 µM and at 25 µM lowered the cell viability only to 79-80% (Fig. 28).

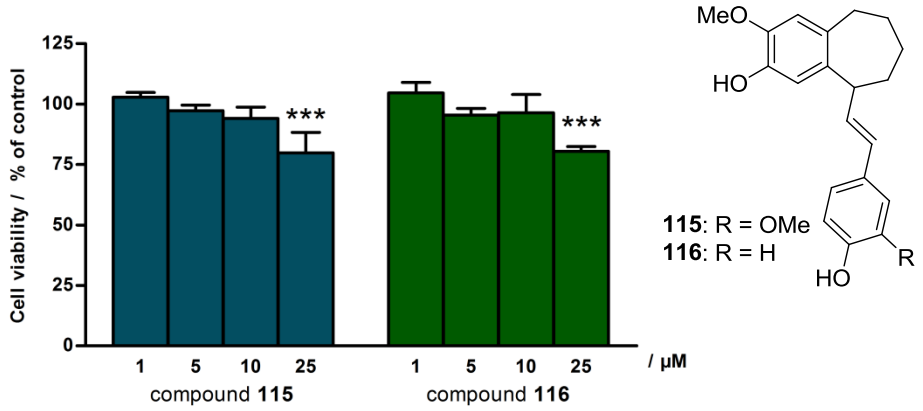


Fig. 28: Cytotoxicity of compounds **115** and **116** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

3.4.3 Cytotoxicity of cyclic diarylheptanoids

Biphenyl type cyclic diarylheptanoids **3** (acerogenin E), **18** (myricananin C) and **188** were formal derivatives of linear ketones **8**, **104** and **102**, respectively. In contrast to the open chained compounds, the cyclic derivatives exhibited no or only low (76% cell viability for **3** at 25 µM, 77% for **188** at 25 µM) cytotoxicity against HT22 neuronal cells (Fig. 29). This

result indicates that the cyclization removes or significantly reduces the toxicity of the diarylheptanoids.

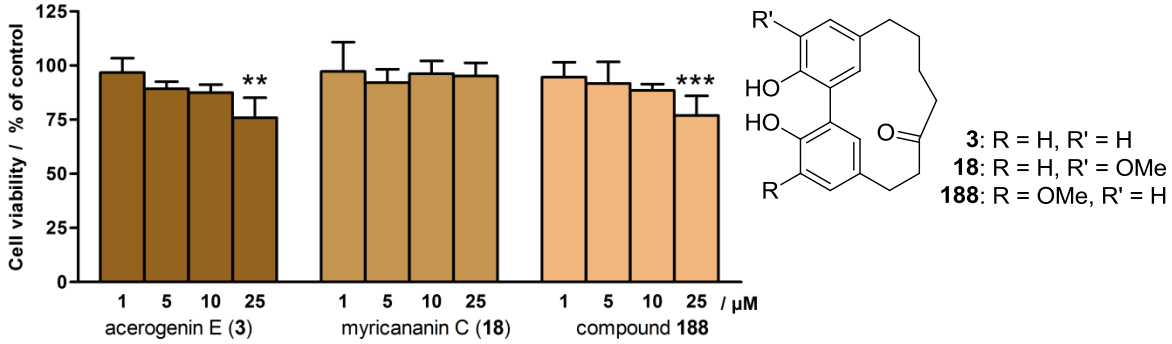


Fig. 29: Cytotoxicity of biphenyl type cyclic ketones **3**, **18** and **188** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

The last two compounds tested were the cyclic biphenyls with the 11-hydroxyl moiety, namely **16** (acerogenin K) and **189**. Similar to the 11-oxo analogues, derivative **189** possessed no significant toxic properties and compound **16** exerted only a minor effect at 25 µM concentration (Fig. 30).

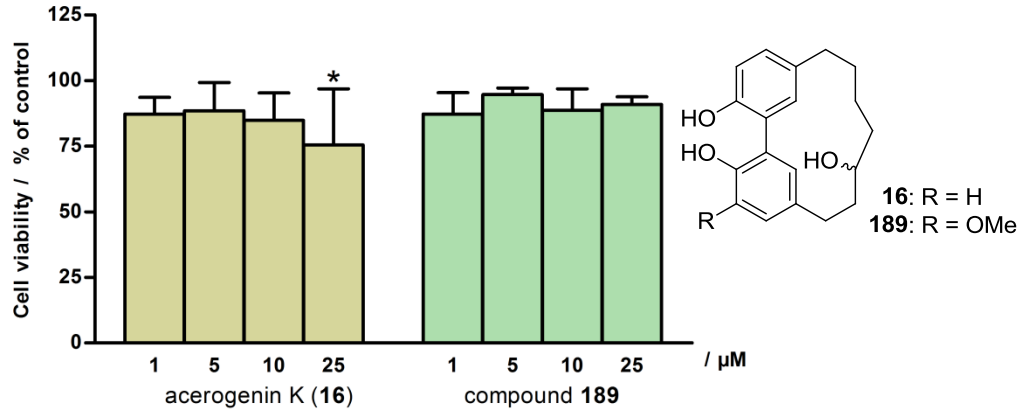


Fig. 30: Cytotoxicity of biphenyl type cyclic alcohols **16** and **189** on HT22 cells determined by MTT assay. Values are expressed as mean ± SD, n = 3. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

3.5 Biological properties of synthesized diarylheptanoids - neuroprotective activity

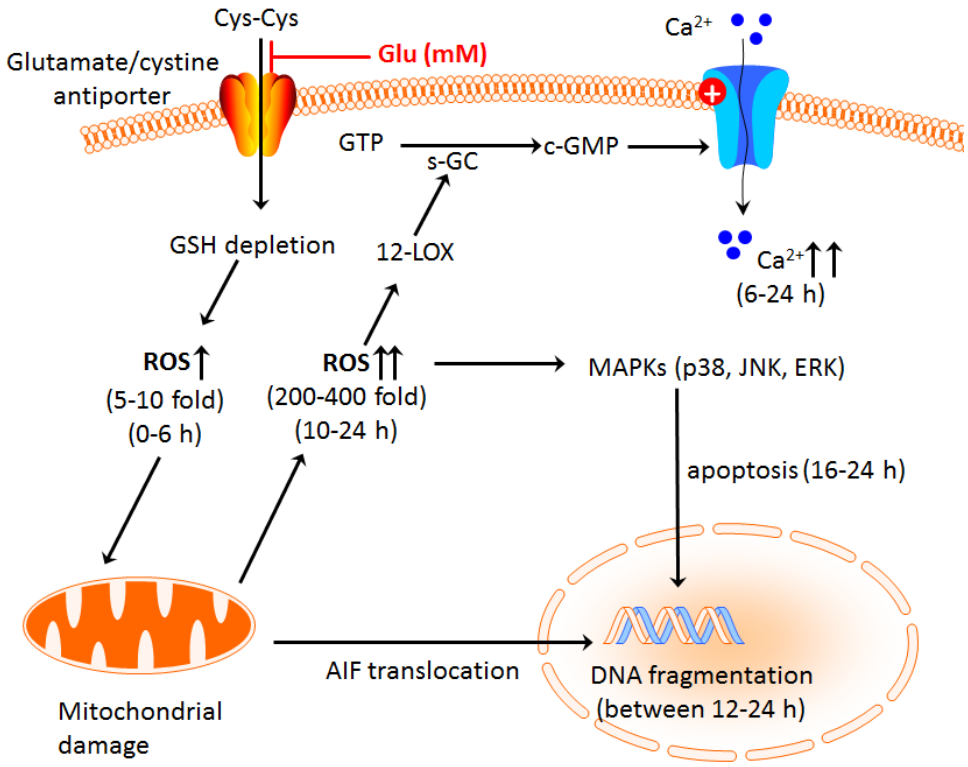
In course of the further pharmacological characterization of the diarylheptanoids, the protective activity of the synthesized compounds against glutamate-induced neurotoxicity

was measured. Glutamate (Glu) is an endogenous excitatory neurotransmitter, ubiquitous in the spinal cord and brain. High concentrations of glutamate in the central nervous system are, however, toxic and thus thought to be involved in the development of neurodegenerative diseases, such as Parkinson's diseases (PD) and Alzheimer's diseases (AD).[149]

The toxicity of glutamate is on one hand mediate by ionotropic receptors, most notably by the NMDA receptor, where glutamate acts as an agonist. In response to the activation by Glu, Na^+ and Ca^{2+} ions can flow in the cell while K^+ ions efflux outwards. In particular the increased concentration of the Ca^{2+} causes phospholipase A_2 catalyzed initiation of the arachidonic acid cascade, stimulates the NO production and the formation of $O_2^{\cdot-}$ radical through xanthine metabolism. This Glu-induced, NMDA-mediated neurotoxicity is commonly referred to as excitotoxicity.[149]

The neuronal cell line HT22 is a cloned sub-line from the HT4 cell line which was derived from primary mouse hippocampal neurons and immortalized by a temperature-sensitive small virus-40 T antigen.[150] The HT22 cells lack the ionotropic NMDA receptors but upon exposure to high concentrations of glutamate, the glutamate/cystine antiporter is blocked and so is the uptake of cystine by the cell (Scheme 59). The lowered intracellular concentration of the amino acid cysteine, i.e. the oxidized form of cystine, leads to a depletion of glutathione (GSH) level and causes oxidative stress.[151] The resulting cellular death shows morphological characteristics of both necrosis and apoptosis[152] and is thus in some publications called oxytosis. At early stages (8 – 12 h), necrosis characteristics like the mitochondrial oxidative stress and dysfunction prevail, whereas at later time points (16 – 24 h), apoptosis is induced due to the release of apoptosis-inducing factor (AIF) from damaged mitochondria and the activation of MAPK cascades.[153]

Tan et al. studied the relationship between the GSH depletion and the ROS production. The Glu-induced decrease of the GSH level causes only 5-10 fold increase of ROS at early stage. However, an explosive burst to 200-400 fold of ROS concentration above control values followed at later time point. This ROS burst originated from mitochondria and was accompanied by influx of extracellular Ca^{2+}.[154] The ROS mediated activation of 12-lipoxygenase (12-LOX) led to the activation of soluble guanylylcyclase (s-GC), which catalyzed the conversion of GTP into c-GMP.[155] The latter is responsible for the Ca^{2+}-influx via opening of Ca^{2+}-channels. The mechanism of glutamate-triggered cell death in HT22 cells is summed up in Scheme 59, based on Fukui et al.[153] and Tan et al.[154]



Scheme 59: Glutamate-induced toxicity in HT22 cells proposed by Fukui et al. and Tan et al.

The actually proposed protective mechanism of some antioxidant natural products against Glu-induced oxytosis is rather debatable. Curcumin (**1**) attenuated HT22 cell death by suppression of MAP kinases JNK and p38 in nanomolar concentrations.[156] Ishige and co-workers screened a battery of flavonoids and could demonstrate that, depending on their structure, the flavonoids exerted the protective activity by three distinct mechanisms. Quercetin and related compounds increased basal GSH levels possibly due electrophile responsive element-mediated up-regulation of γ-GCS. The compounds of the galangin group (galangin, kaempferol etc.) did not affect the GSH level but reduced directly the ROS concentration. Finally, neat flavonol and its derivatives with hydroxyl groups in position 6 or 7 neither maintained the GSH level nor did they act as antioxidants. Instead, these compounds inhibited the Ca^{2+} influx and thus protected the cells despite of elevated intracellular ROS levels.[157] Resveratrol, investigated by Fukui et al. on neuroprotection in the HT22 cell model, exhibited its indirect antioxidant activity through the activation of PI3K/Akt signaling pathway which led to elevated expression of superoxide dismutase SOD2 within 1 h. This enzyme can catalyze the conversion of mitochondrial superoxide to hydrogen peroxide, which is then further detoxified by HO-1.[158] Fukui's findings are not completely in accordance with data collected by Yang et al. for cyclic diarylheptanoids juglanin A (**2**) and C. These compounds attenuated the Glu-induced neurotoxicity and restored the activity of glutathione reductase (GR) and glutathione peroxidase (GSH-Px), however, did not affect the activity of SOD (without specification of the enzyme type).[4]

3.5.1 Protective activity of the linear diarylheptanoids against Glu-induced neurotoxicity

HT22 cells were exposed to glutamate (5 mM) in presence of tested diarylheptanoids at four concentrations (1, 5, 10 and 25 μM). The cell viability was subsequently (after 24 h) determined by a MTT assay and was expressed as percentage of the untreated cells. Cells treated merely with glutamate (5 mM) underwent major morphological changes (Fig. 31 B) and exhibited viability of about 13%. Importantly, some of the synthesized diarylheptanoids were able to increase the survival rate of the cells in a concentration dependent manner.

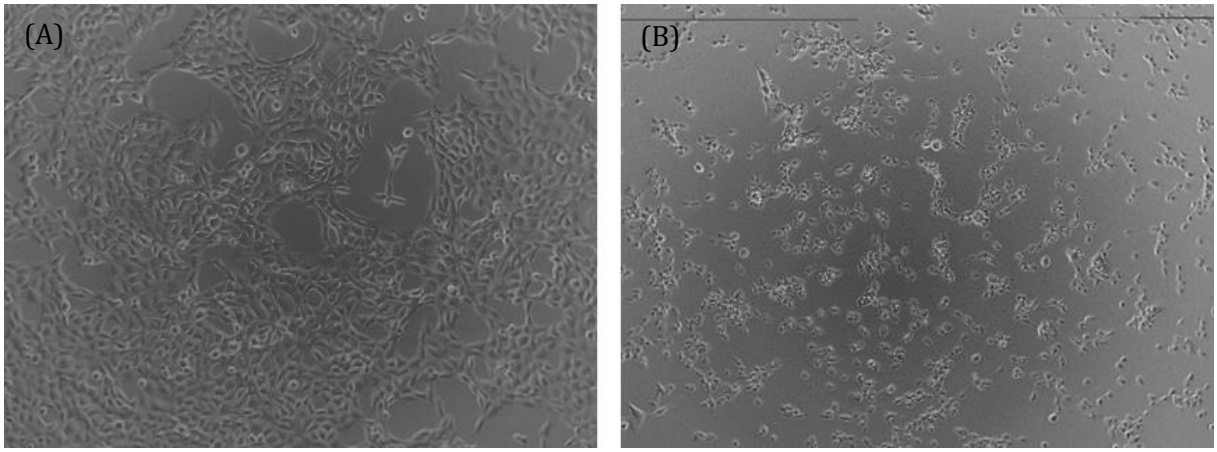


Fig. 31: (A) HT22 neuronal cells; (B) HT22 neuronal cells 24 h after treatment with Glu (5 mM)

Compounds derived from bisdemethoxycurcumin (enone **101**, ketone **8** and alcohol **25**) and demethoxycurcuminoids of type A (enone **100**, ketone **104** and alcohol **107**) showed no or only negligible protective properties within the tested concentration range (Fig. 32). The lack of activity was observed regardless weather the enone, the ketone or the alcohol moiety was present in the aliphatic chain. Common feature for both groups of compounds was the 4'-hydroxyl substitution of the A-ring (Fig. 32).

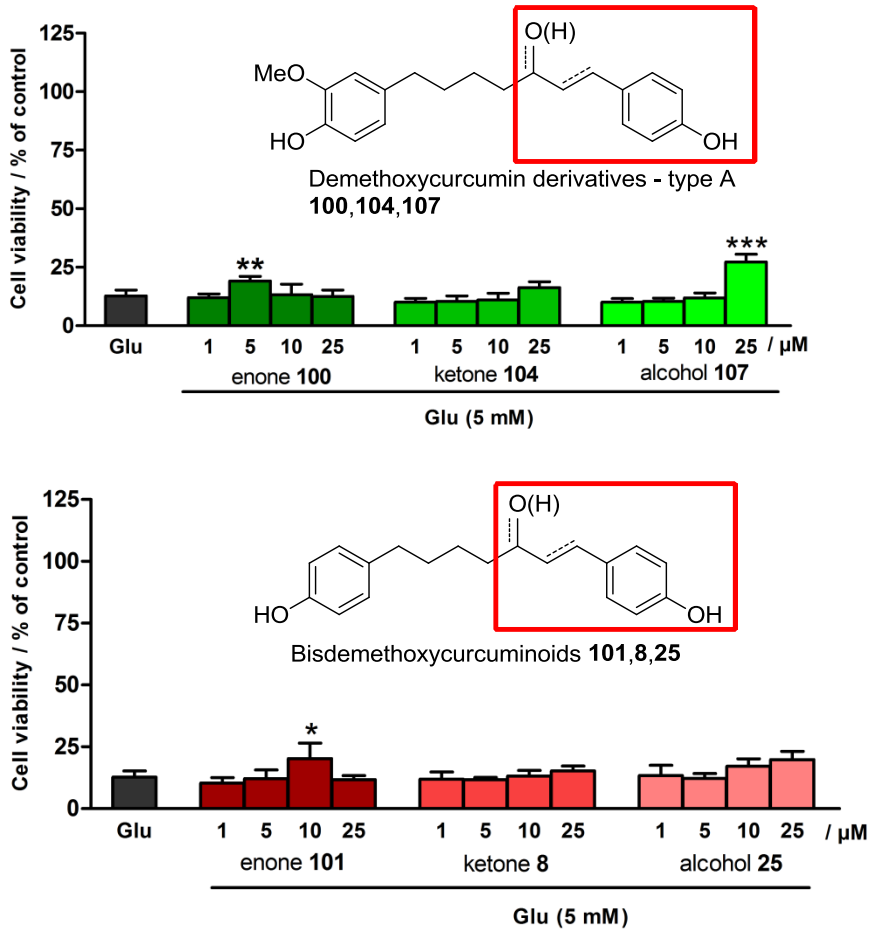


Fig. 32: Bisdemethoxycurcuminoids (**101**, **8** and **25**) and derivatives of demethoxycurcumin of type A (**100**, **104** and **107**) could not protect HT22 cells from Glu-induced toxicity. Values represent means ± SD, n ≥ 3. Significance levels: ***, $p < 0.001$, **, $p < 0.01$, *, $p < 0.05$ vs. Glu control.

On the other side, diarylheptanoids derived from curcumin and desmethoxycurcumin of type B reduced, in some cases, the toxicity triggered by glutamate (Fig. 33). These compounds share the 4'-hydrox-3'-methoxy substitution of the A-ring. Most potent was enone **98** which increased the HT22 viability up to 44% at 5 µM and 63% at 10 µM. Ketone **102** and alcohol **105** showed positive effect on the viability only at 25 µM (55-52%).

Analogue to the described curcuminoids, the enone **99** was the most potent compound among demethoxycurcumin derivatives of type B with significant elevation of the viability to 28% at 10 µM and 47% at 25 µM. However, these concentrations of **99** were already considered as toxic for the HT22 cells (Fig. 23). The reduced forms of compound **99**, namely the ketone **103** and the alcohol **106**, showed comparably lower effect (Fig. 33). All in all, the results of the glutamate assay for these two kinds of diarylheptanoids indicated the importance of a Michael system in proximity of a 4-hydroxy-3-methoxy substituted aromatic ring (ferulic acid-like motif).

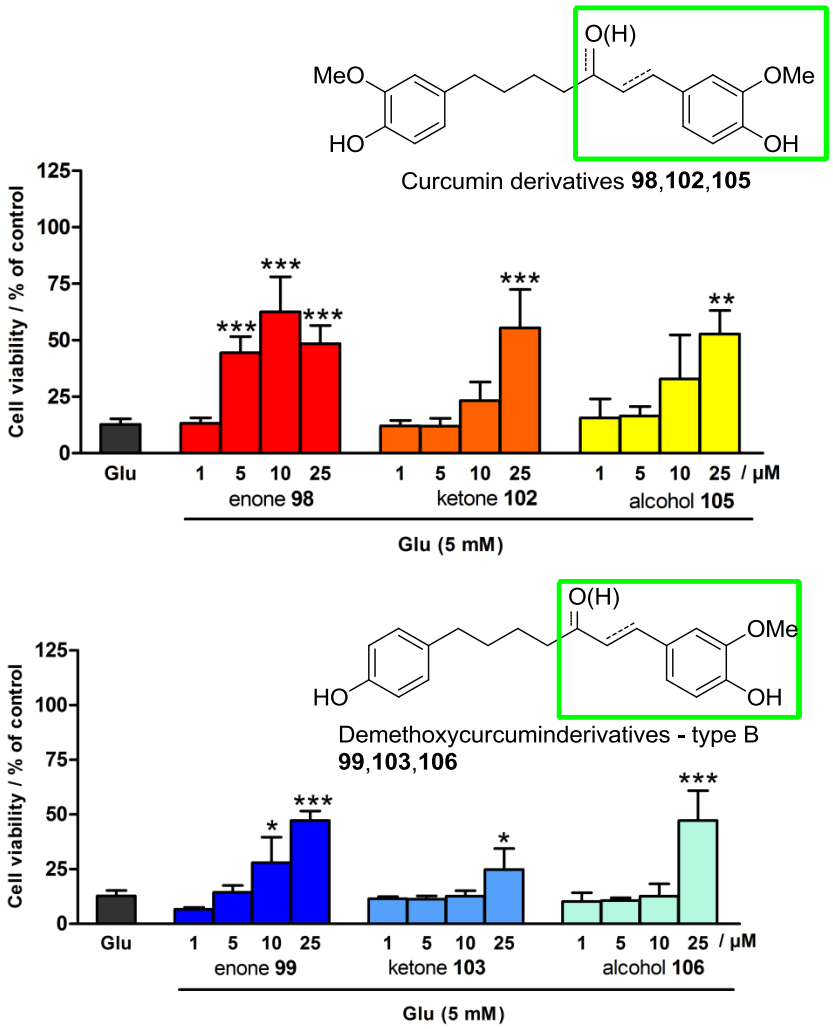


Fig. 33: Protective activity of diarylheptanoids derived from curcumin (**98**, **102**, **105**) and demethoxycurcuminoids of type B (**99**, **103**, **106**) against Glu-induced toxicity. Values represent means ± SD, n ≥ 3. Significance levels: ***, $p < 0.001$, **, $p < 0.01$, *, $p < 0.05$ vs. Glu control.

Furthermore, the non-natural curcuminoids **108** and **109** as well as the single ring analogues **113** and **114** were examined on the neuroprotective activity against Glu-induced oxidative damage (Fig. 34). Whereas the "half"-curcuminoids **113** and **114** and the tetramethoxylated ketone **108** showed no significant attenuation of the toxicity, the enone **109** increased the HT22 viability to 68% at non-toxic 25 µM concentration. Therefore, the α,β-unsaturated carbonyl unit conjugated with the 3',4'-dihyroxyl substituted A-ring (caffeoyl moiety) was considered as an additional structural motif with beneficial properties against Glu-induced neurotoxicity. Moreover, since the single ring molecules **113** and **114** were inactive, the complete diarylheptanoid scaffold was essential for the neuroprotection (Fig. 34).

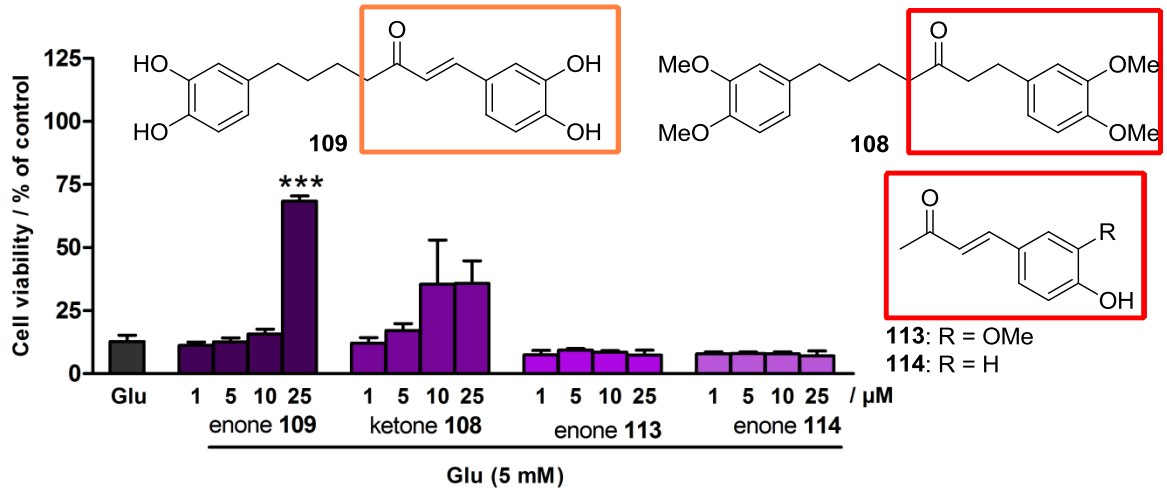


Fig. 34: Non-natural curcuminoids **108**, **109** and the single ring analogues **113**, **114** tested on protective activity against Glu-induced toxicity in HT22 cells. Values represent means ± SD, n ≥ 3. Significance levels: ***, p < 0.001, **, p < 0.01, *, p < 0.05 vs. Glu control.

In addition, parent compounds of the synthesized curcuminoids, namely curcumin (**1**), demethoxycurcumin (**190**) and bisdemethoxycurcumin (**191**), were purchased from commercial sources and assayed on potential neuroprotectivity (Fig. 35). As expected, **1** could reduce the toxicity within the complete concentration range, increasing the cell viability to 37% 1 µM and to 68% at 25 µM concentration. The remaining two natural curcuminoids **190** and **191** showed as well certain protective activity which was, however, at higher concentration (10, 25 µM) diminished by their own toxicity. This effect was observed in the case of di-*O*-demethylcurcumin **110** too, where the high toxicity of the compound was superior to the neuroprotection.

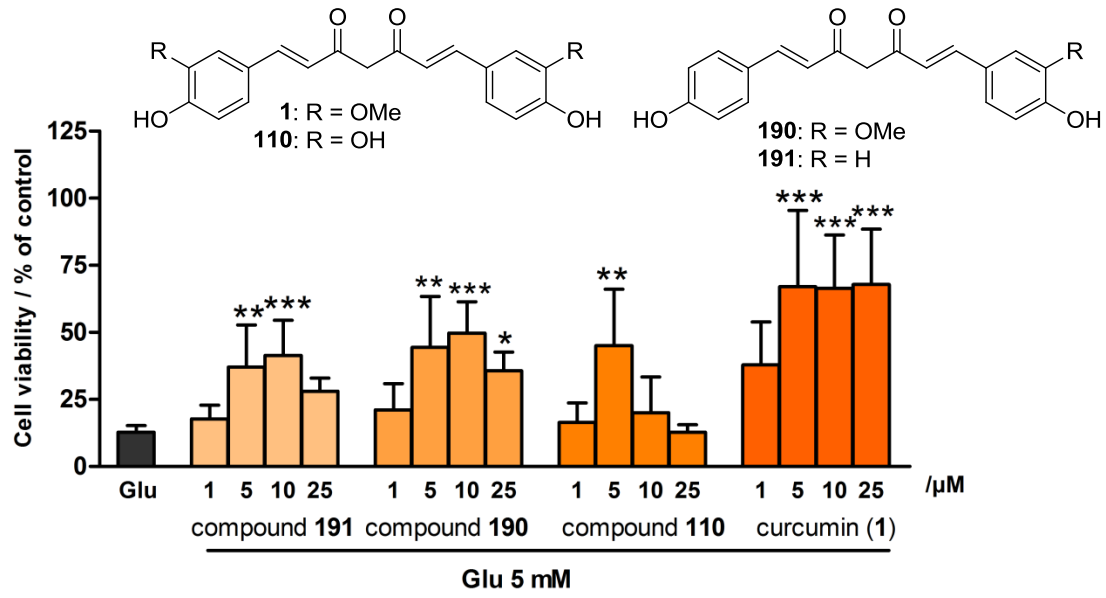


Fig. 35: Protective activity of natural curcuminoids **1**, **110**, **190** and **191** against Glu-induced toxicity in HT22 cells. Values represent means ± SD, n ≥ 3. Significance levels: ***, p < 0.001, **, p < 0.01, *, p < 0.05 vs. Glu control.

Altogether, the screening of twenty curcuminoids on potential protective activity against glutamate-induced toxicity in HT22 neuronal cells revealed the following findings:

1. The complete diarylheptanoid scaffold is required for the neuroprotection
2. A 4'-hydroxy substitution of the A-ring (*p*-cumaroyl motif) does not contribute to the protective activity
3. The combination of a Michael system with the 4'-hydroxy-3'-methoxy substituted A-ring (feruloyl motif) is essential for the reduction of the cell viability by Glu
4. The caffeoyl motif, i.e. a 3',4'-dihydroxy substituted A-ring adjacent to the enone moiety, exhibits protective effects at higher concentrations

3.5.2 Protective activity of curcuminoid 98 and 109 against *t*-BuOOH-induced toxicity

The neurotoxicity triggered by glutamate involves depletion of GSH-level, accumulation of ROS, increase of intracellular Ca^{2+} concentration and activation of MAPK cascades (Scheme 59). To obtain more information about the actual protective mechanism of the curcuminoid **98** (ferulic acid-like substitution) and compound **109** (caffeic acid-like substitution), *tert*-butyl hydroperoxide (*t*-BuOOH) was utilized as toxic agent for the HT22 cells instead of glutamate. *t*-BuOOH is a lipophilic radical donor which directly elevates ROS-level in the cells.[159]

During this experiment, 50,000 cells/well were seeded in 96-well plates pre-coated with gelatin. This setup was optimized by Beata Kling[160] in order to get confluent cell layers which were needed for the robustness of this assay. The cells were then treated with the tested compounds 3 h prior to the *t*-BuOOH addition to avoid direct reaction of the stressor with the potential radical scavengers in the supernatant. Substances were tested in the concentration range of 1 – 100 µM, while the *t*-BuOOH was used in excess (300 µM).

Remarkably, enone **98** with two 4-hydroxy-3-methoxy substituted rings (feruloyl-like)**,** which was the most potent synthetic compound in the reduction of the glutamate toxicity, was completely inactive against *t*-BuOOH-induced oxidative cell damage. On the other hand, enone **109** with two 3,4-dihyroxy aromatic rings (caffeoyl-like), which was active only at 25 µM against Glu, showed decent activity against *t*-BuOOH in a concentration dependent manner. This observation pointed to direct radical scavenging potential by the catechol units of **109** and to involvement of more complex pathways in case of feruloyl-analogue **98** (Fig. 36).

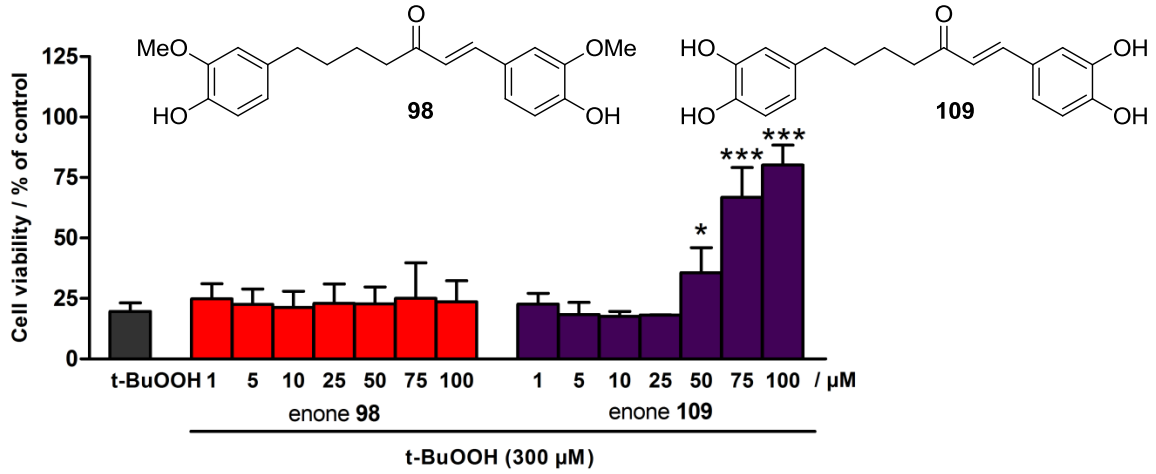


Fig. 36: Protection of HT22 cells against *t*-BuOOH by compound **109** in contrast to inactive compound **98**; Values are means ± SD of at least three independent experiments. Levels of significance: ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$ vs. *t*-BuOOH control. Experiments performed by F. S. Kücükoktay.

Kling et al. examined different phenolic compounds on their neuroprotective effects against *t* BuOOH-induced toxicity in HT22 cells. Their MTT- and ECIS-based studies were in a good agreement with the results described in Fig. 36, showing an essential role of the catechol (caffeoyl) unit for the scavenging of ROS.[160]

3.5.3 Stability of curcumin and its synthetic analogue 98 in cell culture medium

The stability of curcumin (**1**) and its monocarbonyl analogue **98** in cell culture medium was the object of an HPLC-based test. Despite of the number of remarkable biological effects *in vitro*, curcumin (**1**) finds only a limited clinical application due to its poor water solubility and bioavailability.[62] Curcumin (**1**) stability in buffer solutions and cell culture medium was investigated by Wang et al. Their study revealed that **1** decomposed fast under neutral and basic conditions as well as in culture medium. Addition of fetal calf serum was beneficial, nonetheless, more than 50% of **1** decomposed within 8 h of incubation.[161]

Curcumin (**1**), incubated at 37 °C and 5% CO_2 in cell culture medium, continuously decomposed while new peaks appeared in the HPLC chromatogram. The area of the curcumin peak decreased to 63% after 4 h and after 8 h down to 44%. No **1** was detected after 24 h of incubation (Fig. 37). On the other hand, curcuminoid **98** exhibited an outstanding stability in the cell culture medium, showing no decay during the tested period of time (24 h) (Fig. 38).

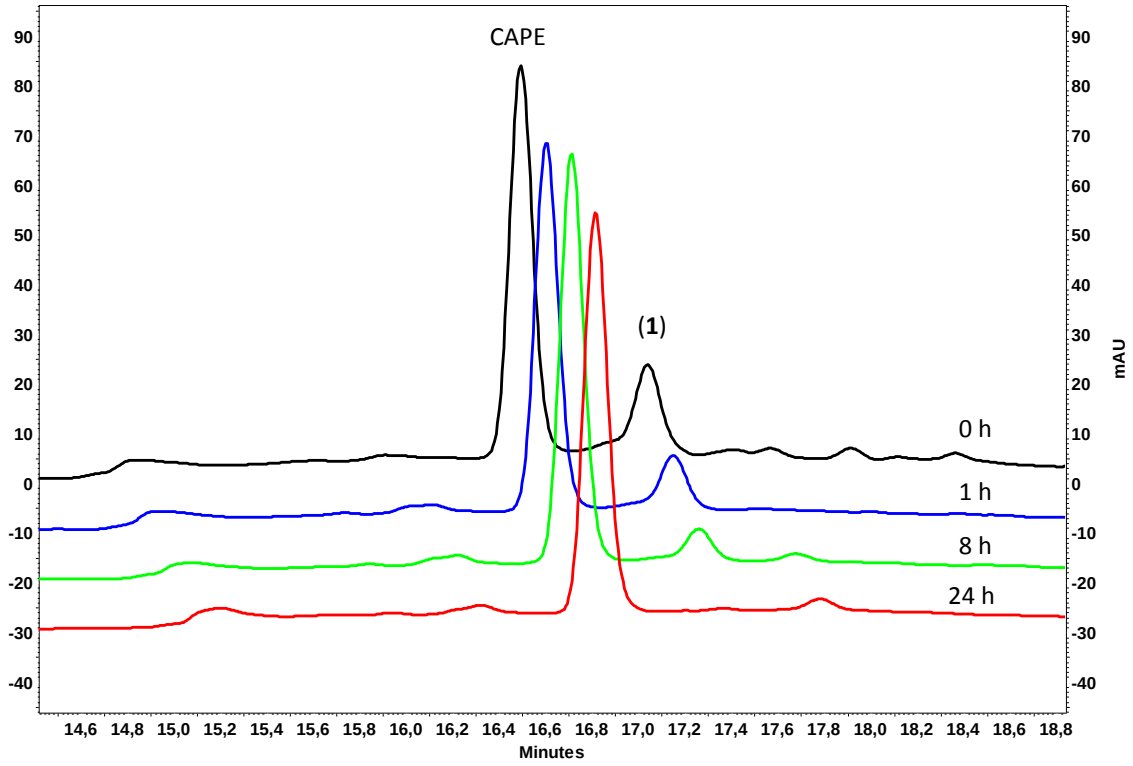


Fig. 37: Stability of curcumin (**1**) in DMEM cell culture medium determined by HPLC; CAPE used as an internal standard; complete data depicted in the Appendix

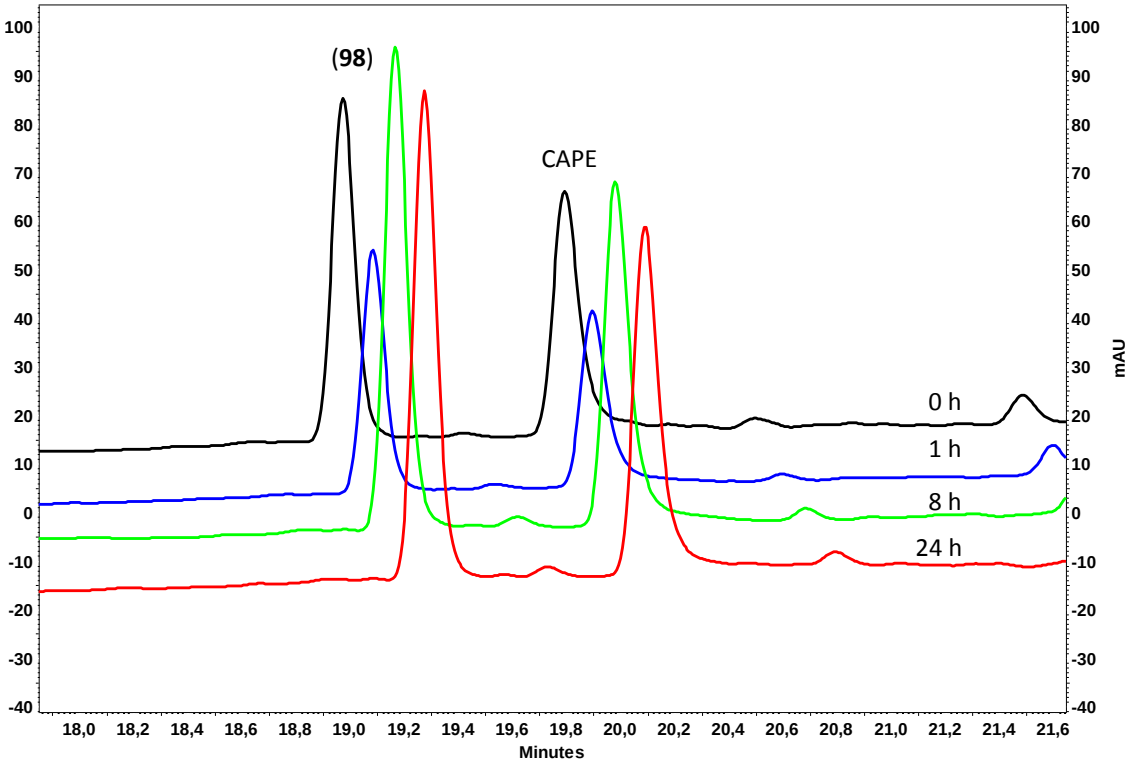
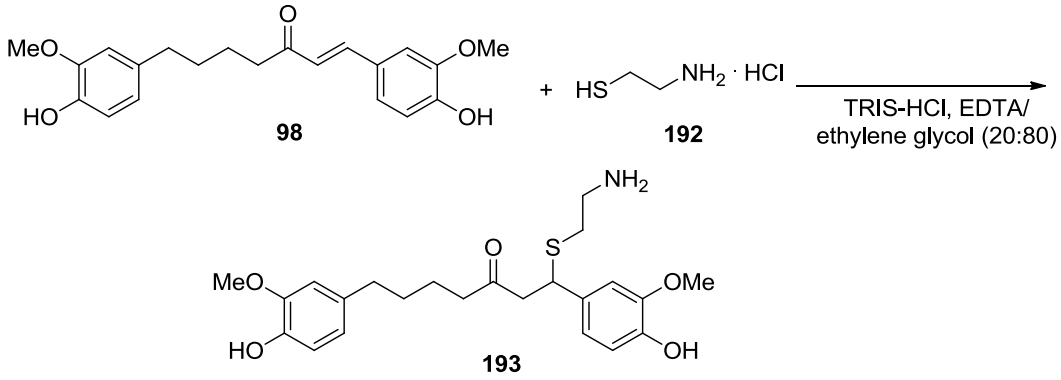


Fig. 38: Stability of the synthetic curcuminoid **98** in DMEM cell culture medium determined by HPLC; CAPE used as an internal standard; complete data shown in the Appendix

3.5.4 Michael acceptor activity of curcumin and its analogue 98

Curcumin (**1**) and its synthetic derivative **98** posses α,β-unsaturated carbonyl units and can be thus considered as Michael acceptors. The ability to react with cysteine residues of signal transduction proteins like Keap1 (an adaptor of Nrf2) and NF-κB in thia-Michael addition reactions is responsible for biological activity of different naturally occurring electrophiles.[162] Such reactivity can be determined by a spectrophotometric screening assay developed by Sabine Amslinger and Nafisah Al-Rifai,[163] providing information about electrophilicity of compounds **1** and **98**.



Scheme 60: Michael addition of cysteamine **192** on curcuminoid **98**

The optimized thiol assay measures the decay of the absorbtion band of the α,β-unsaturated carbonyl during the reaction with cysteamine (**192**) in ethylene glycol/EDTA-TRIS buffer (80:20).[163] A general reactivity screening of curcumin (**1**) and curcuminoid **98** was performed in presence of 300 fold of cysteamine, showing a comparable Michael acceptor activity of both enones (Fig. 39). The product of the Michael reaction between compound **98** and the thiol was confirmed by mass spectrometry (compound **193**, m/z 434 $[MH]^+$) (Scheme 60).

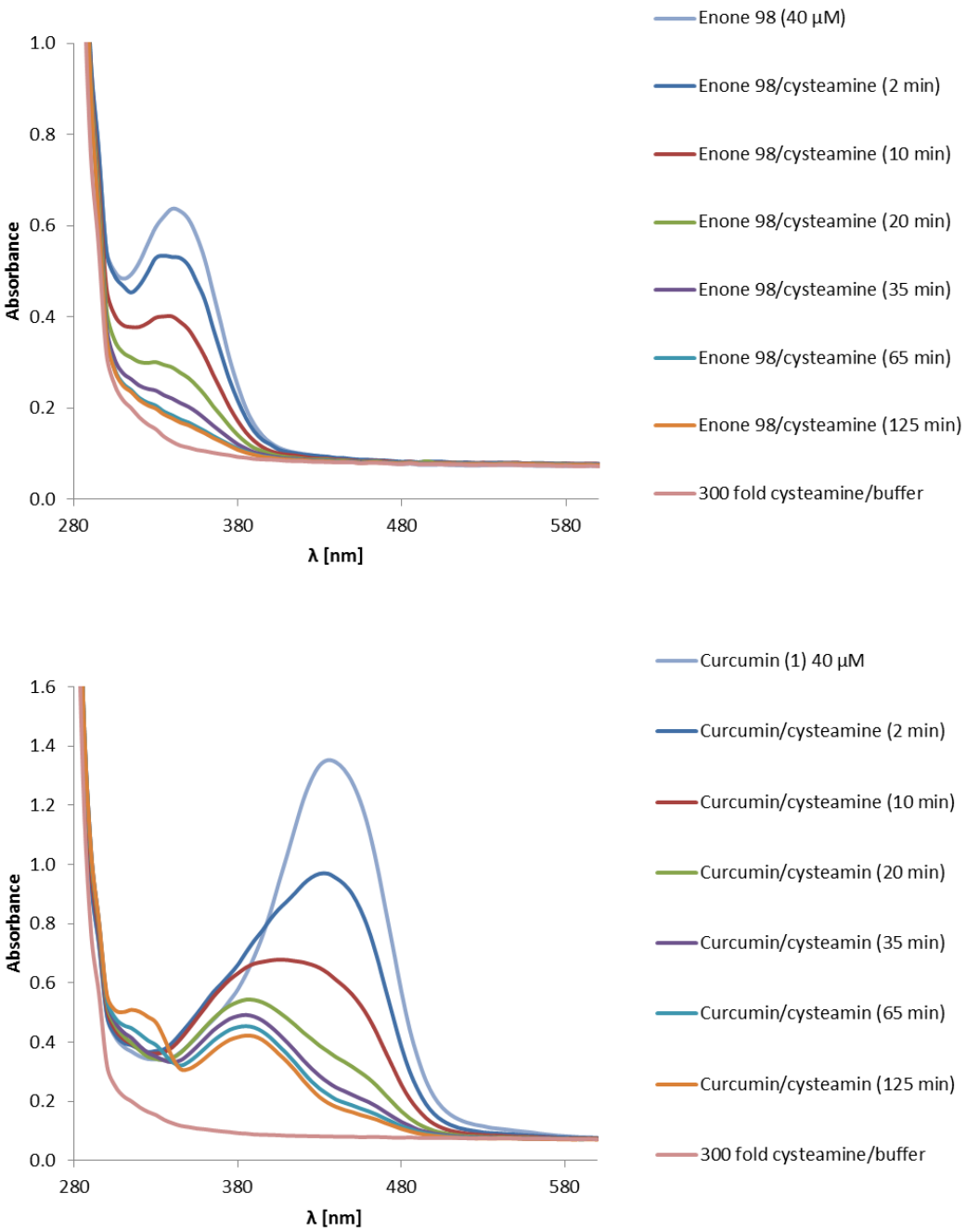


Fig. 39: UV-Vis spectra of curcuminoid **98** and curcumin (**1**) (40 µM) in presence and absence of 300 fold excess of cysteamine; 100 mM TRIS-HCl pH 7.4, 2 mM EDTA/ethylene glycole (20:80) at 25 °C

3.5.5 Protective activity of diarylheptanoids with cyclized C_7-chain against glutamate-induced toxicity

Synthetic diarylheptanoids **115** and **116**, possessing a seven-membered ring adjacent to the B-ring, were tested in HT22 cells at four different concentrations (1-25 µM) on protective activity against glutamate-induced oxidative damage (Fig. 40). These compounds showed no activity at 1 µM, however, both substances exerted remarkable protective effects at 5-25 µM. The derivative **115** reassembled the cell viability up to 84%

at 5 µM and 67% at 25 µM, whereas diarylheptanoid **116** exhibited slightly lower activity at 5 µM with the cell viability of 59% but with 85% at 10 µM concentration. The slight decrease in the cell viability observed at 25 µM can be explained by some toxic effects of **115** and **116** (Fig. 28) themselves.

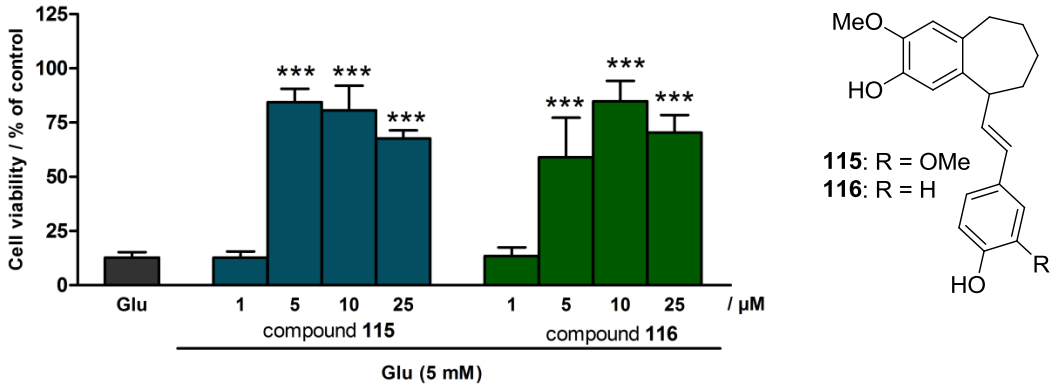


Fig. 40: Neuroprotective activity of diarylheptanoids **115** and **116** against Glu-induced toxicity in HT22 cells. Values represent means ± SD, n ≥ 3. Significance levels: ***, $p < 0.001$, **, $p < 0.01$, *, $p < 0.05$ vs. Glu control.

3.5.6 Protective activity of cyclic diarylheptanoids against glutamate-induced toxicity

Interesting structure-activity relationships were observed for the synthesized biphenyl type cyclic diarylheptanoids (Fig. 41). Acerogenin E (**3**) was inactive over the complete tested concentration range (1-25 µM). Its reduced derivative acerogenin K (**16**), bearing in position 11 a hydroxyl instead of oxo group, exhibited a moderate increase of cell viability (38%) at 25 µM but no effect at 1-10 µM. An almost identical result (39% at 25 µM) was obtained for myricananin C (**18**). However, the non-natural cyclic compound **188** enhanced the cell viability to 44% at 5 µM and to 67-71% at 10 and 25 µM, whereas its 11-hydroxyl derivative was potent first at 25 µM concentration (58% cell viability, Fig. 41).

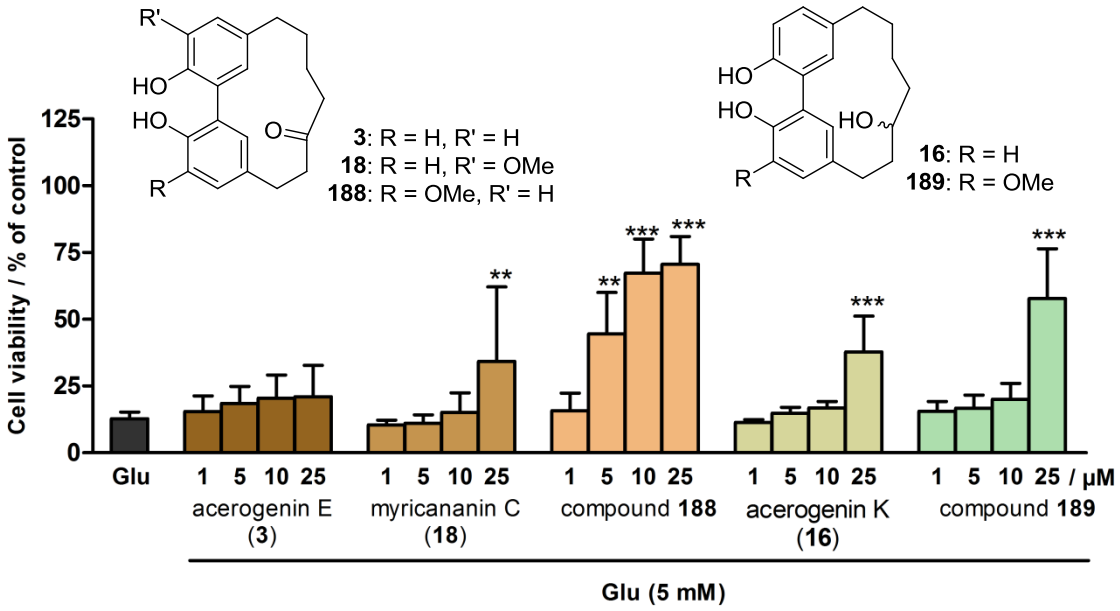


Fig. 41: Neuroprotectiv activity of the cyclic diarylheptanoids against Glu-induced toxicity in HT22 cells. Values represent means ± SD, n ≥ 3. Significance levels: ***, $p < 0.001$, **, $p < 0.01$, *, $p < 0.05$ vs. Glu control.

Although the group of examined derivatives is rather small, the combination of the 11-oxo group with the 17-hydroxy-16-methoxy substitution of the B-ring appears to be important for the protective activity. This observation is in partial agreement with the effects of linear diarylheptanoids, in which this type of substitution in combination with a Michael system was crucial for the neuroprotectivity. Interstingly, compound **188** exerted its biological effect despite of missing such a Michael system.

4 Summary

Diarylheptanoids are natural products consisting of two aromatic rings connected by a seven carbon aliphatic chain which can be found in certain parts of various trees and shrubs as well as in rhizomes of some medicinal herbs. The most prominent representative of the diarylheptanoid class is curcumin (**1**), a linear diferuloyl methane from *Curcuma longa* L. with a broad spectrum of pharmacological effects. However, cyclic derivatives with a biphenyl or a diphenyl ether moiety, which were discovered in trees of Aceraceae, Juglandaceae and Myricaceae family, also exhibit promising anti-inflammatory and cytoprotective activity.

This thesis was focused on the synthesis of linear diarylheptanoids along with their biphenyl type cyclic derivatives and compounds with cyclized C_7-chain. A straight forward synthetic strategy towards monocarbonyl analogues of curcumin was developed and used for the synthesis of fourteen curcuminoids with four different substitution patterns of aromatic rings and three types of connecting chains. Additionally, two 4-phenylbut-3-en-2-ones were prepared as single ring curcuminoids and di-(*O*)-demethylcurcumin was obtained from **1** to extend the structural variety of the compounds prior their biological testing.

Moreover, five biphenyl type cyclic diarylheptanoids were prepared via a novel synthetic route which comprised formation of iodinated acyclic precursors followed by an intramolecular cyclization. The ring closing step was accomplished by a domino sequence of a Miyaura aryl borylation and a Suzuki reaction. Among the cyclic diarylheptanoids, three known natural products (acerogenin E (**3**), acerogenin K (**16**) and myricananin C (**18**)) were prepared, together with two non-natural derivatives **188** and **189**. Myricananin C, a natural product from *Myrica nana*, was synthesized for the first time.

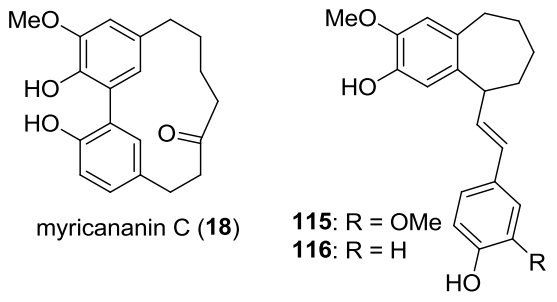


Fig. 42: Novel diarylheptanoids synthesized in the course of this work

Finally, two diarylheptanoids with cyclized aliphatic chain (**115**, **116**) were prepared by an unpredicted intramolecular electrophilic aromatic substitution and were fully characterized. Their structure showed a high analogy to a natural product **24** from greater cardamom (*Amomum subulatum* Roxb.), hence, the herein described methodology might serve to a total synthesis of the latter.

The pharmacological testing of the synthesized diarylheptanoids was focused on their potential neuroprotective activity. Accordingly, the ability to attenuate glutamate-induced toxicity in HT22 neuronal cells was evaluated and revealed interesting structure-activity relationships for different classes of the diarylheptanoids (Fig. 43).

In case of the linear compounds, the presence of an α,β-unsaturated carbonyl system conjugated with a 4-hydroxy-3-methoxy substituted aromatic ring (ferulic acid-like motif) was essential for the protective activity. Especially the compound **98** exhibited effects comparable with its parent compound curcumin (**1**) with significantly improved stability in the cell culture medium and comparable Michael acceptor activity. Furthermore, the radical scavenging properties of compound **98** and its di-(*O*)-demethyl derivative **109** were tested in HT22 cells injured by *t*-BuOOH. Whereas the caffeic acid-like substituted diarylheptanoid **109** showed a protective effect in a concentration dependent manner, substance **98** was inactive. This fact indicates that the protective activity of the ferulic acid-like substituted diarylheptanoids against glutamate-induced toxicity in HT22 neuronal cells is mediated by a different molecular mechanism than a simple ROS-scavenging.

Besides, the investigation of the cyclic diarylheptanoids showed an interesting analogy to the above described findings. The non-natural compound **188**, bearing a 4-hydroxy-3-methoxy substituted aromatic ring in proximity of the oxo functionality, exerted a protective activity from 5 μM concentration against oxidative damage triggered by glutamate. The other congeners showed no or only minor effects at 25 μM, thus, the presence of the (reduced) feruloyl motif appears to be important even in case of the cyclic diarylheptanoids.

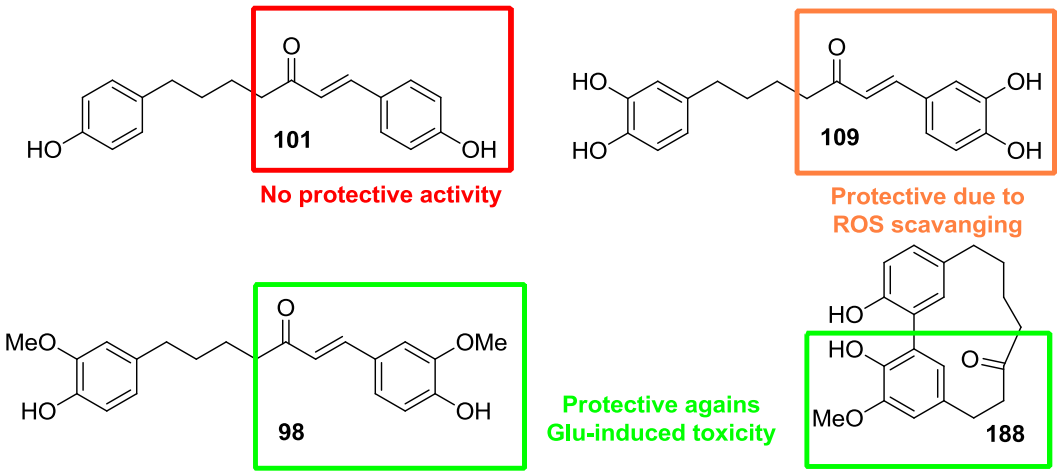


Fig. 43: Structural requirements for the neuroprotective activity

Lastly, the most potent diarylheptanoids among the synthesized compounds were the tricyclic derivatives **115** and **116**. These substances could restore the cell viability of the HT22 cells injured by glutamate up to 85% at 5 μM concentration without showing any toxic effects towards the cells at this concentration.

5 Experimental part

5.1 General synthetic methods and materials

5.1.1 Chemicals and reagents

All chemicals were purchased from commercial sources, namely:

Vanillin, 4-hydroxybenzaldehyde, lithium aluminum hydride, manganese dioxide, Pd/C (10% palladium on charcoal), diphenyl sulfide, sodium borohydride, dimethylsulfate, potassium iodide, boric acid, iodine monochloride, malonic acid and potassium acetate from Merck (Darmstadt, Germany); chloromethyl methyl ether (MOM chloride), boron tribromide, iodine, diisobutylaluminum hydride, silver trifluoroacetate, TFA, (triphenylphosphoraneylidene)-2-propanone, pinacolato diboron and $PdCl_2$(dppf) from Sigma Aldrich (Taufkirchen, Germany); *p*-coumaric acid and piperidine from Fluka (Neu-Ulm, Germany); (formylmethylene)triphenylphosphoran and Crabtree's catalyst from ABCR (Karlsruhe, Germany); diisopropylethylamine and DMAP from Acros/Fisher (Geel, Belgium), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimid (EDC·HCl) from Novabiochem (Merck group, Darmstadt, Germany) and ferulic acid from Carl Roth (Karlsruhe, Germany).

Solvents were purchased in high quality from commercial sources or distilled before use when obtained in technical quality. Reactions were conducted under nitrogen atmosphere in oven-dried glassware (110 °C) and dry solvents when dry conditions were needed.

5.1.2 Chromatography

The reaction progress was monitored by TLC, using aluminum plates coated with silica 60 F_{254} from Merck (Darmstadt, Germany) and detected by UV light (254 and 366 nm) or vanillin/H_2SO_4 staining reagent (15 g of vanillin in 250 ml EtOH + 2.5 ml conc. H_2SO_4). Column and flash chromatography was performed on silica gel 60 (0.063 – 0.200 mm pore size), the flash chromatography with the aid of Armen Spot instrument (VWR, Vannes, France) equipped with UV detector. All final products were purified with preparative HPLC before submission for biological testing. For that reason, a Varian Prostar instrument with DAD detector and Galaxie HPLC software was used, with following characteristics:

Column: HPLC Knauer RP-18, Eurosphere 100 (7 µm; 16 × 250 nm)

Solvents: MeOH (degassed, HPLC grade, Merck), H_2O (degassed, Millipore)

Application: liquid injection in 100% MeOH, injection volume 500 µl, concentration 20 mg/ml

Method 1: gradient H_2O/MeOH; 50% MeOH at t = 0 min, 100% MeOH at t = 20 min, 100% MeOH at t = 25 min; flow 10 ml/min

Method 2: gradient H_2O/MeOH; 50% MeOH at t = 0 min, 100% MeOH at t = 30 min, 100% MeOH at t = 35 min; flow 10 ml/min

The stability test of **1** and curcuminoid **98** was performed on a Hitachi DAD L2455 instrument with L2200 autosampler, L2130 pump, L2350 column oven, equipped with EZChrom Elite 3.1.7 software.

Column: Hilbar®RT 250-4 cartridge with Purosphere®Star RP-18e (5 µm) (Merck, Darmstadt, Germany)

Internal standard: CAPE, ≥99%, Carl Roth, Karlsruhe, Germany

Method for curcumin (**1**): oven temperature: 40 °C; injection volume: 20 µl; flow: 1 ml/min; solvent A: MeOH (35%) in H_2O + 0.1% TFA; solvent B: H_2O

time (min)	solvent A (%)	solvent B (%)
0	100	0
20	0	100
25	0	100
27	100	0
35	100	0

Method for compound **98**: oven temperature: 40 °C; injection volume: 20 µl; flow: 1 ml/min; solvent A: MeOH; solvent B: H_2O

time (min)	solvent A (%)	solvent B (%)
0	100	0
20	0	100
25	0	100
27	100	0
35	100	0

5.1.3 Mass spectrometry

Low resolution (LR) ESI-MS and APCI-MS spectra were measured on a TSQ 7000 (ThermoQuest Finnigan, Bremen, Germany), high resolution (HR) ESI-MS and APCI-MS on a Q-TOF 6540 UHD (Agilent, Santa Clara, USA), LR EI-MS on a MAT SSQ 710 (Finnigan) and HR EI-MS on MAT95 (Finnigan).

5.1.4 NMR spectroscopy

All ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 (measurement frequency 300.13 MHz for ^{1}H, 75.47 MHz for ^{13}C, temperature 296.1 K), Bruker Avance 400 (400.13 MHz for 1H, 101 MHz for ^{13}C, 296.1 K) and Bruker Avance III 600 (600.25 MHz for ^{1}H, 150.95 MHz for ^{13}C, 298.0 K), all instruments supplied by Bruker Corporation (Billerica, USA). Samples were dissolved in deuterated solvents (MeOD, acetone-d_6 from Deutero GmbH, Kastellaun, Germany and $CDCl_3$ from Sigma Aldrich, Steinheim, Germany) and submitted for measurement in NMR tubes (507-HP, 203 mm) from Norell, Landisville, USA.

^{1}H-NMR spectra are referenced to residual non-deuterated solvent peaks (7.26 ppm for $CDCl_3$, 3.31 ppm for MeOD and 2.05 ppm for acetone-d_6). ^{13}C-NMR spectra are referenced to solvent peaks: 77.0 ppm for $CDCl_3$, 49.0 ppm for MeOD and 29.9 ppm for acetone-d_6. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; sept, septet; m, multiplet. Coupling constants (*J*) are given in Hz.

5.1.5 UV/Vis spectroscopy

The UV spectra were recorded on a Varian Cary 300 in MeOH (>99.9%, Uvasol, Merck, Darmstadt, Germany).

5.1.6 Melting points

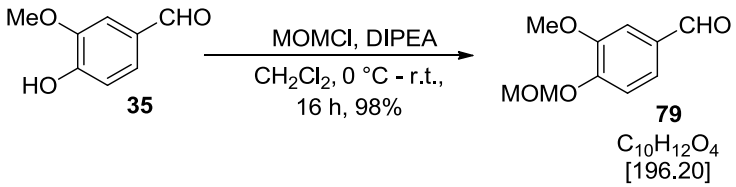
Melting points were determined using a Büchi Melting Point B-545 apparatus and are uncorrected.

5.1.7 X-ray analysis

The X-ray data were collected with SuperNova, Single source at offset, Atlas difractometer (Agilent, USA). The graphics were processed with Diamond 3.0 software.

5.1.8 Experimental procedures

5.1.8.1 4-(Methoxymethyl)-3-methoxy-benzaldehyd (79)[102]

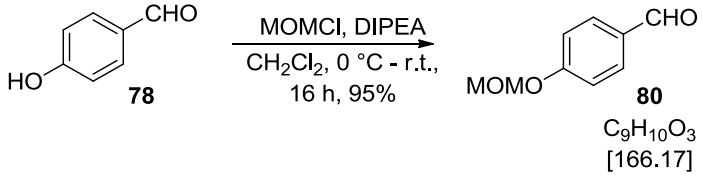


Vanillin (**35**) (10.0 g, 65.7 mmol, 1.0 eq.) was dissolved in 100 ml CH_2Cl_2 and cooled to 0 °C. Hunig's base (DIPEA) (13.6 g, 18.3 ml, 105 mmol, 1.6 eq.) and MOM chloride (6.88 g, 6.49 ml, 85.4 mmol, 1.3 eq.) were dropwise added and the solution was stirred at room temperature overnight. The reaction was then quenched with sat. aq. NH_4Cl (45 ml) and the aqueous layer was extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with brine (2 × 100 ml) and dried over $MgSO_4$. After concentrating *in vacuo*, the residue was passed through a pad of silica to yield a white solid (**79**, 12.6 g, 64.2 mmol, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.49 – 7.34 (m, 2H), 7.25 (d, J = 8.7 Hz, 1H), 5.31 (s, 2H), 3.93 (s, 3H), 3.50 (s, 3H).

The ^{1}H-NMR spectrum agrees with the literature.[164]

5.1.8.2 4-(Methoxymethoxy)benzaldehyde (80)[102]

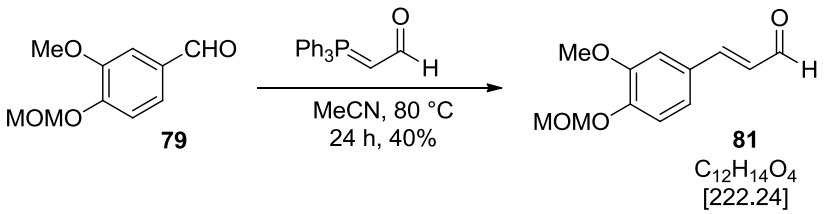


4-Hydroxybenzaldehyde (**78**) (10.0 g, 81.9 mmol, 1.0 eq.) was dissolved in 100 ml CH_2Cl_2 and cooled to 0 °C. Hunig's base (22.8 ml, 16.9 g, 131 mmol, 1.6 eq.) was dropwise added, followed by dropwise addition of MOM chloride (8.09 ml, 8.57 g, 107 mmol, 1.3 eq.). The mixture was allowed to warm to room temperature and stirred under nitrogen. After 16 h, the reaction was quenched with 45 ml NH_4Cl aq. solution (sat.) and the aqueous layer was extracted with EtOAc (2 × 75 ml). The combined organic layers were washed with brine (100 ml), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was passed through a pad of silica (eluted by PE/EtOAc 2:1) to yield 12.9 g (77.8 mmol, 95%) of pure **80** as yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.87 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 5.22 (s, 2H), 3.46 (s, 3H).

The ^{1}H-NMR spectrum agrees with the literature.[165]

5.1.8.3 3-(3-Methoxy-4-(methoxymethoxy)phenyl)acrylaldehyde (81)[103]



The MOM-protected vanillin **79** (8.00 g, 40.8 mmol, 1.0 eq.) was dissolved in 200 ml acetonitrile, followed by the addition of (formylmetylen)triphenylphosphorane (15.0 g, 48.9 mmol, 1.2 eq.). The red mixture was stirred at 80 °C for 24 h, while the progress of the reaction was monitored by TLC analysis. The solvent was then removed *in vacuo* to yield a red solid, which was passed through a pad of silica. The resulting yellow oil was purified by flash chromatography (SiO_2; PE/EtOAc 4:1), yielding 3.65 g (16.4 mmol, 40%) of the product **81** as yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.59 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 15.8 Hz, 1H), 7.18 – 6.97 (m, 3H), 6.55 (dd, J = 15.8, 7.7 Hz, 1H), 5.21 (s, 2H), 3.85 (s, 3H), 3.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 193.5, 152.6, 149.9, 149.4, 128.3, 127.1, 123.0, 115.7, 110.5, 95.1, 56.4, 55.9.

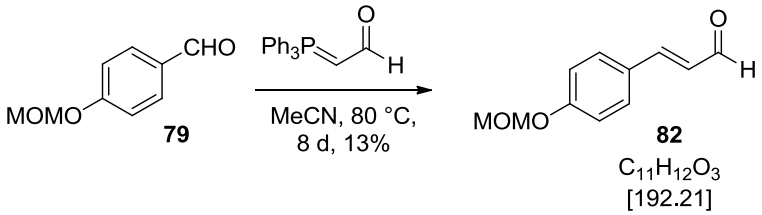
EI-MS m/z (%) 222 $[M]^{+\cdot}$ (23), 192 (6), 161 (7)

HR EI-MS m/z 222.0889 $[M]^{+\cdot}$ (calcd. for $C_{12}H_{14}O_4$, 222.0892)

mp: 67-69 °C

UV λ_{max} 236, 330 nm.

5.1.8.4 (*E*)-3-(4-(Methoxymethoxy)phenyl)acrylaldehyde (82)[103]



4-(Methoxymethoxy)-benzaldehyde **79** (5.16 g, 31.0 mmol, 1.0 eq.) and (formylmethylen)tri-phenylphosphine (13.2 g, 43.3 mmol, 1.4 eq.) were dissolved in 100 ml acetonitrile and stirred at 80 °C for 8 days. Subsequently, the solvent was removed *in vacuo* and the red solid was passed through a pad of silica in order to remove triphenylphosphine oxide. The residue was purified by column chromatography (SiO_2; PE/EtOAc 3:1) and preparative TLC (SiO_2; petroleum ether (b.p. 40-60 °C)/EtOAc 7:1 + 0.1% TFA) to yield 768 mg (4.00 mmol, 13%) of pure **82** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.64 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 15.9 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.60 (dd, J = 15.9, 7.7 Hz, 1H), 5.21 (s, 2H), 3.47 (s, 3H).

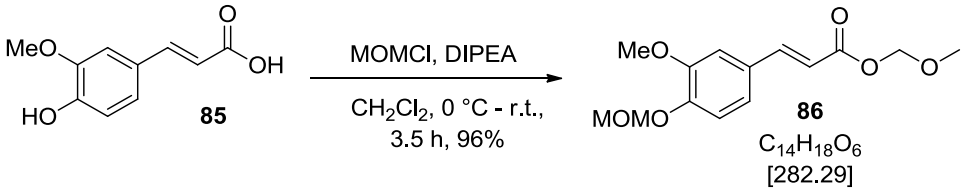
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.6, 159.7, 152.5, 130.2 (2C), 127.7, 126.8, 116.5 (2C), 94.0, 56.2.

EI-MS m/z (%) 192 $[M]^{+\cdot}$ (21), 131 (5)

HR EI-MS m/z 192.0788 $[M]^{+\cdot}$ (calcd. for $C_{11}H_{12}O_3$ 192.0786)

UV λ_{max} 230, 313 nm.

5.1.8.5 (*E*)-Methoxymethyl-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylate (86)[102]



Ferulic acid **85** (5.87 g, 30.2 mmol, 1.0 eq.) and DIPEA (13.2 ml, 75.5 mmol, 2.5 eq.) were mixed in 37 ml CH_2Cl_2 and cooled to 0 °C, forming a yellowish slurry. Methoxymethyl chloride (5.96 ml, 78.5 mmol, 2.6 eq.) was dropwise added, resulting in the formation of a yellow solution. The ice bath was removed after 20 min and the mixture was further stirred at r.t.. After 3.5 h overall time, the reaction was stopped by the addition of saturated aqueous NH_4Cl solution (50 ml). The CH_2Cl_2 layer was separated and the aqueous phase was extracted with EtOAc (2 × 70 ml). The organic layers (CH_2Cl_2 and EtOAc) were combined and dried with $MgSO_4$ and the solvent was removed *in vacuo*, yielding 8.17 g (29.0 mmol, 96%) of **86** as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (d, J = 15.9 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.33 (d, J = 15.9 Hz, 1H), 5.35 (s, 2H), 5.26 (s, 2H), 3.91 (s, 3H), 3.50 (s, 3H), 3.50 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.4, 149.7, 148.6, 145.4, 128.5, 122.3, 115.7 (CH), 115.7 (CH), 110.3 (CH), 95.1 (CH_2), 90.4 (CH_2), 57.6 (CH_3), 56.3 (CH_3), 55.8 (CH_3).

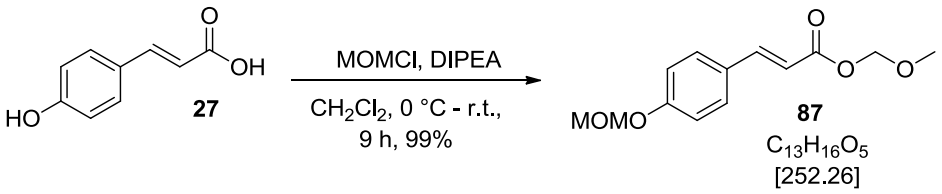
EI-MS m/z (%) 282 $[M]^{+\cdot}$ (19), 176 (24), 146 (12)

HR EI-MS m/z 282.1108 $[M]^{+\cdot}$ (calcd. for $C_{14}H_{18}O_6$: 282.1103).

m.p.: 46 °C.

UV λ_{max} 233, 294, 320 nm.

5.1.8.6 (*E*)-methoxymethyl 3-(4-(methoxymethoxy)phenyl)acrylate (87)[102]



p-Coumaric acid **27** (4.08 g, 24.9 mmol, 1.0 eq.) was dissolved in 30 ml CH_2Cl_2 and cooled to 0 °C. DIPEA (14.8 ml, 84.5 mmol, 3.5 eq.) was added, followed by a slow addition of methoxymethyl chloride (6.98 ml, 92.0 mmol, 3.7 eq.). The mixture was stirred at r.t. until a complete conversion was reached after 9 h. The reaction mixture was then quenched with sat. aqueous NH_4Cl solution (40 ml), the CH_2Cl_2 layer was separated and the aqueous residue was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were washed with brine (80 ml), dried with $MgSO_4$ and concentrated under reduced pressure. The reaction afforded 6.20 g (24.6 mmol, 99%) of **87** as yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (d, J = 16.0 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.32 (d, J = 16.0 Hz, 1H), 5.33 (s, 2H), 5.18 (s, 2H), 3.49 (s, 3H), 3.45 (s, 3H).

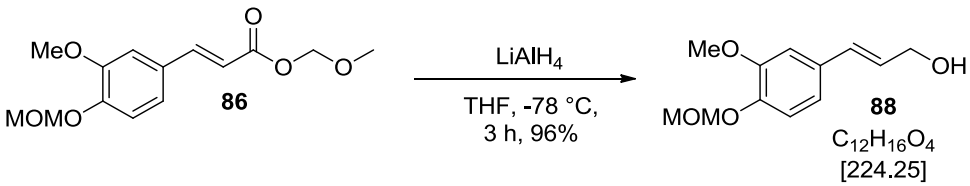
^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.0, 145.1 (CH), 129.7 (2 × CH), 127.9, 116.4 (2 × CH), 115.4 (CH), 94.0 (CH_2), 90.3 (CH_2), 57.5 (CH_3), 56.0 (CH_3).

ESI-MS m/z (%) 253 $[MH]^+$ (6), 191 $[MH - CH_3OCH_2OH]^+$ (100), 145 (23)

HR ESI-MS m/z 253.1068 $[MH]^+$ (calcd. for $C_{13}H_{17}O_5$, 253.1071).

UV λ_{max} 225, 306 nm.

5.1.8.7 (*E*)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol (88)[105]



The ester **86** (7.58 g, 26.9 mmol, 1.0 eq.) was dissolved in dry THF (150 ml) under nitrogen atmosphere and cooled to -78 °C. Lithium aluminium hydride (1.64 g, 43.2 mmol, 1.6 eq.) was added in portions and the mixture was stirred until the conversion was complete (after 3 h). The reaction was slowly quenched with MeOH till gas evolution stopped, followed by addition of H_2O (200 ml). The aqueous solution was neutralized by 1 M HCl and extracted with EtOAc (2 × 200 ml). After drying with $MgSO_4$, the solvent was evaporated to afford pure **88** (5.77 g, 25.8 mmol) as yellow oil in 96% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.08 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 15.8, 5.8 Hz, 1H), 5.21 (s, 2H), 4.29 (dd, *J* = 5.8, 1.4 Hz, 2H), 3.88 (s, 3H), 3.50 (s, 3H).

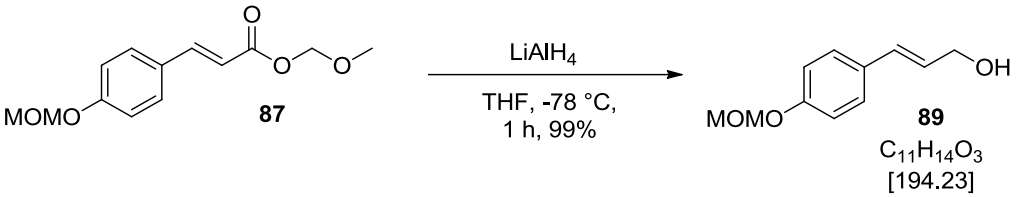
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.7, 146.2, 131.3, 130.9, 127.1, 119.5, 116.2, 109.3, 95.4, 63.7, 56.2, 55.8.

ESI-MS *m/z* (%) 175 $[MH - H_2O - MeOH]^+$ (100), 207 $[MH - H_2O]^+$ (67), 247 $[MNa]^+$ (27).

HR ESI-MS *m/z* 247.0940 $[MNa]^+$ (calcd. for $C_{12}H_{16}NaO_4$ 247.0941).

UV λ_{max} 259 nm.

5.1.8.8 (*E*)-3-(4-(Methoxymethoxy)phenyl)prop-2-en-1-ol (89)[105]



The ester **87** (6.53 g, 24.9 mmol, 1.0 eq.) was dissolved in dry THF (120 ml) under N_2 atmosphere and cooled to -78 °C, followed by the addition of lithium aluminium hydride (1.96 g, 51.6 mmol, 2.1 eq.). The reaction was stopped after 60 min by quenching of unreacted $LiAlH_4$ with MeOH (until the evolution of gas stopped). The mixture was then mixed with H_2O (150 ml), acidified with 3 M HCl (aq.) and extracted with EtOAc (2 × 200 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed by rotary evaporator, affording pure alcohol **89** (4.79 g, 24.7 mmol, 99%) as yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.56 (dd, *J* = 15.9, 7.3 Hz, 1H), 6.24 (dt, *J* = 15.8, 5.9 Hz, 1H), 5.17 (s, 1H), 4.29 (dd, *J* = 5.9, 1.4 Hz, 2H), 3.47 (s, 3H).

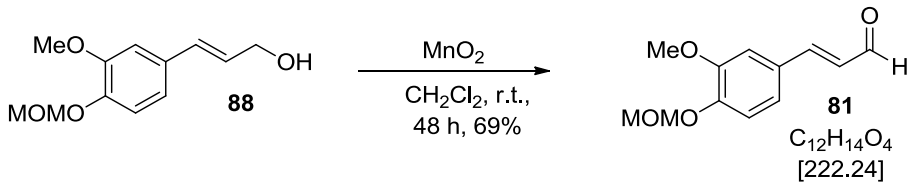
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.6, 130.5, 130.3, 127.5 (2C), 126.8, 116.2 (2C), 94.2, 63.4, 55.9.

ESI-MS *m/z* (%) 145 $[MH - H_2O - MeOH]^+$ (100), 177 $[MH - H_2O]^+$ (17), 217 $[MNa]^+$ (3).

HR ESI-MS *m/z* 177.0911 $[MH - H_2O]^+$ (calcd. for $C_{11}H_{13}O_2$ 177.0910).

UV λ_{max} 261 nm.

5.1.8.9 (*E*)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)acrylaldehyde (81)[105]



The allylic alcohol **88** (5.72 g, 23.5 mmol, 1.0 eq.) was dissolved in 300 ml CH_2Cl_2 and stirred at r.t. in a presence of manganese dioxide (37.5 g, 431 mmol, 18.4 eq.) until complete conversion of the starting material. The black slurry was filtered through a pad of celite while eluted by CH_2Cl_2. The solvent was then evaporated and the crude product was submitted to flash chromatography (SiO_2; *n*-hexane/EtOAc 3:1, 50 ml/min) affording pure aldehyde **81** (3.58 g, 16.1 mmol, 69%) as pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.59 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 15.8 Hz, 1H), 7.18 – 6.97 (m, 3H), 6.55 (dd, *J* = 15.8, 7.7 Hz, 1H), 5.21 (s, 2H), 3.85 (s, 3H), 3.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 193.5, 152.6, 149.9, 149.4, 128.3, 127.1, 123.0, 115.7, 110.5, 95.1, 56.4, 55.9.

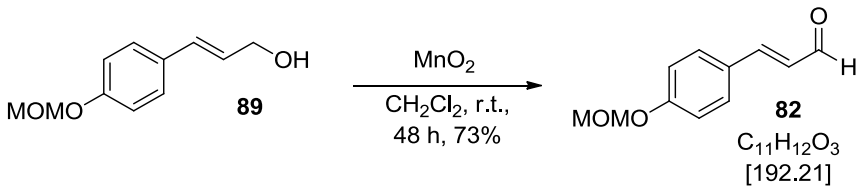
EI-MS *m/z* (%) 222 $[M]^{+\cdot}$(23), 192 (6), 161 (7).

HR EI-MS *m/z* 222.0889 $[M]^{+\cdot}$ (calcd. for $C_{12}H_{14}O_4$, 222.0892).

UV λ_{max} 236, 330 nm.

m.p.: 67-69 °C.

5.1.8.10 (*E*)-3-(4-(Methoxymethoxy)phenyl)acrylaldehyde (82)[105]



The allylic alcohol **89** (4.74 g, 24.4 mmol, 1.0 eq.) was dissolved in 300 ml CH_2Cl_2 and stirred in presence of manganese dioxide (17.5 g, 198 mmol, 8.2 eq.) for 48 h. The resulted slurry was filtered through a short SiO_2/celite column while eluted with CH_2Cl_2, concentrated *in vacuo* and purified by flash chromatography (SiO_2; *n*-hexane/EtOAc 4:1) yielding pure aldehyde **82** (3.45 g, 17.9 mmol, 73%) as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.64 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 15.9 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 15.9, 7.7 Hz, 1H), 5.21 (s, 2H), 3.47 (s, 3H).

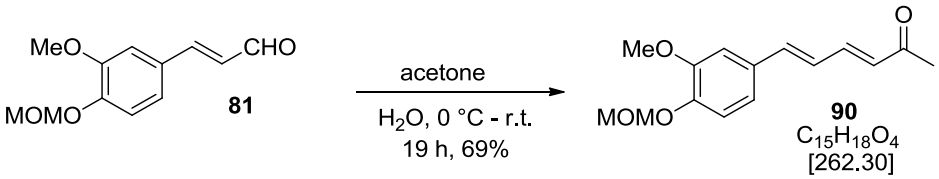
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.6, 159.7, 152.5, 130.2 (2C), 127.7, 126.8, 116.5 (2C), 94.0, 56.2.

EI-MS *m/z* (%) 192 $[M]^{+\cdot}$(21), 131 (5).

HR EI-MS *m/z* 192.0788 $[M]^{+\cdot}$ (calcd. for $C_{11}H_{12}O_3$ 192.0786).

UV λ_{max} 230, 313 nm.

5.1.8.11 (3*E*,5*E*)-6-(3-Methoxy-4-(methoxymethoxy)phenyl)hexa-3,5-dien-2-one (90)[101]



The aldehyde **81** (2.10 g, 9.47 mmol, 1.0 eq.) was dissolved in 7.5 ml acetone and 1.2 ml H_2O and cooled to 0 °C. NaOH solution (aq., 10% w/w, 1.2 ml) was added dropwise and the mixture was allowed to warm up to r.t. and stirred overnight. The conversion of the reaction was monitored by TLC. After 19 hours, the mixture was neutralized by 1 M HCl, H_2O was added (50 ml) and the aqueous solution was extracted with EtOAc (3 × 70 ml). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified with CC (SiO_2; PE/EtOAc 3:1) yielding 1.71 g (6.54 mmol, 69%) of pure **90** as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (dd, *J* = 15.9, 10.3 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.02 – 6.98 (m, 2H), 6.88 (d, *J* = 15.5 Hz, 1H), 6.76 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.24 (s, 2H), 3.92 (s, 3H), 3.50 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 198.5, 150.0, 147.8, 143.8, 141.2, 130.7, 129.9, 125.4, 121.2, 116.2, 109.9, 95.4, 56.4, 56.1, 27.4.

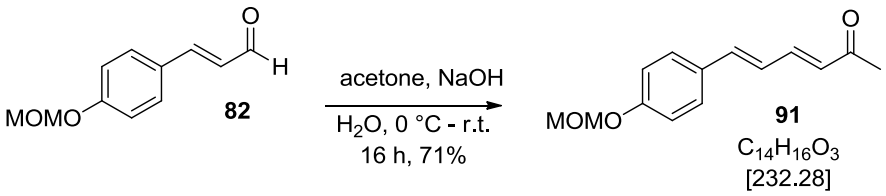
ESI-MS *m/z* (%) 263 $[MH]^+$ (100)

HR ESI-MS *m/z* 263.1276 $[MH]^+$ (calcd. for $C_{15}H_{19}O_4$, 263.1278)

mp: 77 °C

UV λ_{max} 254, 350 nm.

5.1.8.12 (3*E*,5*E*)-6-(4-(Methoxymethoxy)phenyl)hexa-3,5-dien-2-one (91)[101]



To the cooled (0 °C) stirred solution of aldehyde **82** (388 mg, 2.02 mmol, 1.0 eq.) in acetone (1.6 ml) and H_2O (0.3 ml), 10% aqueous NaOH solution (0.3 ml) was added dropwise. The mixture was stirred overnight at r.t. until a complete conversion and subsequently neutralized by addition of 1 M HCl aq. (the resulting pH was 6-7). The solution was mixed with H_2O (10 ml) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. After the purification by flash chromatography (RP-18; MeOH/H_2O 50 – 100% MeOH gradient over 30 min, then 10 min 100% MeOH, flow 25-30 ml/min), 333 mg of **91** (1.44 mmol, 71%) was obtained as yellow solid (after evaporation of MeOH and lyophilization).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.42 (d, J = 8.7 Hz, 1H), 7.28 (dd, J = 15.5, 10.5 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 15.6 Hz, 1H), 6.77 (dd, J = 15.5, 10.6 Hz, 1H), 6.23 (d, J = 15.5 Hz, 1H), 5.20 (s, 2H), 3.48 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 198.5, 158.1, 143.9, 140.9, 129.8, 129.7, 128.7 (2C), 125.0, 116.5 (2C), 94.2, 56.1, 27.3.

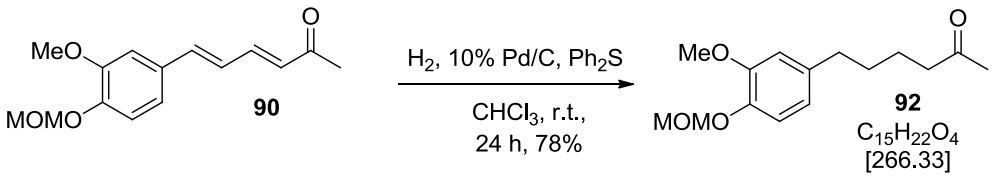
ESI-MS m/z (%) 233 $[MH]^+$ (100)

HR ESI-MS m/z 233.1170 $[MH]^+$ (calcd. for $C_{14}H_{17}O_3$, 233.1172)

mp: 60 – 62 °C

UV λ_{max} 241, 340 nm.

5.1.8.13 6-(3-Methoxy-4-(methoxymethoxy)phenyl)hexan-2-one (92)[106]



The unsaturated ketone **90** (1.66 g, 6.34 mmol, 1.0 eq.) was dissolved in 40 ml of $CHCl_3$ and Pd/C (166 mg, 10% Pd on charcoal) and diphenyl sulfide (53 µl, 59 mg, 0.317 mmol, 0.05 eq.) were added. The mixture was stirred for 24 h under H_2 atmosphere (H_2-balloon, ~1 bar). After the completation of the reaction, Pd/C was filtered off through a pad of celite (eluted with EtOAc) and the solvent was removed *in vacuo*. The crude product was

purified by CC (SiO_2; PE/EtOAc 2:1) yielding 1.33 g (4.98 mmol, 78%) of **92** as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.04 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 6.68 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.12 (s, 3H), 1.65 – 1.54 (m, 4H).

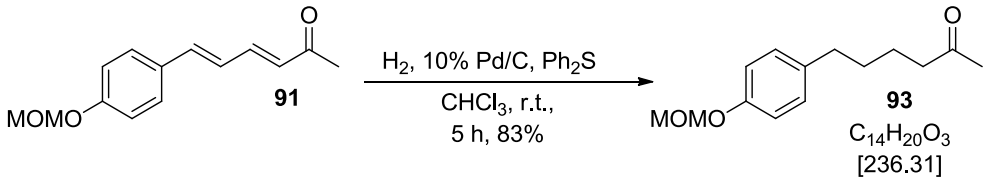
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 209.0, 149.5, 144.4, 136.7, 120.3, 116.5, 112.0, 95.6, 56.1, 55.77, 43.5, 35.4, 31.0, 29.9, 23.4.

ESI-MS *m/z* (%) 235 $[MH - CH_3OH]^+$, 284 $[MNH_4]^+$

HR ESI-MS *m/z* 266.1505 $[M^{+\cdot}]$ (calcd. for $C_{15}H_{22}O_4$, 266.1513)

UV λ_{max} 223, 277 nm.

5.1.8.14 6-(4-(Methoxymethoxy)phenyl)hexan-2-one (93)[106]



The unsaturated ketone **91** (316 mg, 1.36 mmol) was mixed with 32 mg Pd/C (10% Pd on charcoal) and 11 µl diphenyl sulfide (12.7 mg, 11.4 µl, 6.80 µmol, 0.05 eq.) in 8.5 ml $CHCl_3$. The slurry was stirred under H_2 atmosphere (H_2-balloon, ~1 bar) until the completion of reaction (5 h). The mixture was subsequently passed through a pad of celite and concentrated under reduced pressure. The resulting oil was purified by CC (SiO_2; PE/EtOAc 5:1) to yield 268 mg (1.14 mmol, 83%) of **93** as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.07 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.13 (s, 2H), 3.45 (s, 3H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.10 (s, 3H), 1.68 – 1.49 (m, 4H).

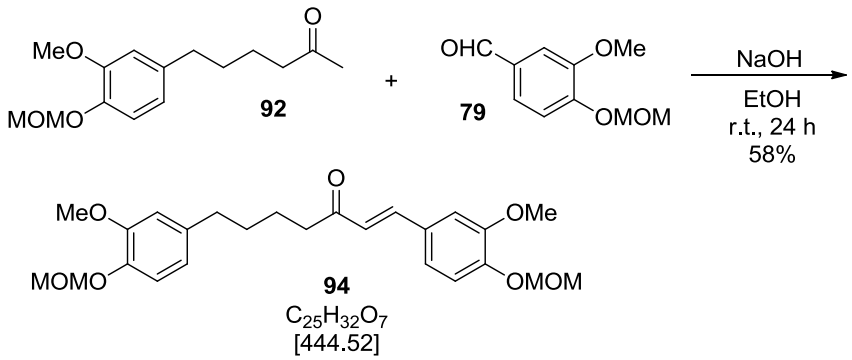
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 208.8, 155.2, 135.4, 129.1 (2C), 116.0 (2C), 94.4, 55.7, 43.4, 34.7, 30.9, 29.7, 23.2.

EI-MS *m/z* (%) 236 $[M]^{+\cdot}$ (19), 151 (8), 121 (31)

HR EI-MS 236.1414 $[M]^{+\cdot}$ (calcd for $C_{14}H_{20}O_3$, 236.1412)

UV λ_{max} 220, 273 nm.

5.1.8.15 1,7-Bis(3-methoxy-4-(methoxymethoxy)phenyl)heptan-3-one (94)[101]



Ketone **92** (200 mg, 0.751 mmol, 1.0 eq.) and MOM-protected vanillin **79** (265 mg, 1.35 mmol, 1.8 eq.) were dissolved in 15 ml EtOH and stirred at r.t. Powdered NaOH (75.0 mg, 1.88 mmol, 2.5 eq.) was slowly added and the mixture was stirred at r.t. for 24 h. The reaction was stopped by acidification with 1 M HCl aq. (the pH was 3 – 4 afterwards), the solvent was removed *in vacuo*, 10 ml H_2O was added and the aqueous solution was extracted with CH_2Cl_2 (2 × 15 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by CC (SiO_2; PE/EtOAc 3:1) yielding 193 mg (0.434 mmol, 58%) of the diarylheptanoid **93** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.46 (d, J = 16.1 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.09 – 7.04 (m, 2H), 7.02 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 6.67 (dd, J = 8.1, 2.0 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 5.23 (s, 2H), 5.15 (s, 2H), 3.88 (s, 3H), 3.83 (s, J = 4.5 Hz, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 2.65 (t, J = 7.0 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 1.78 – 1.57 (m, 4H).

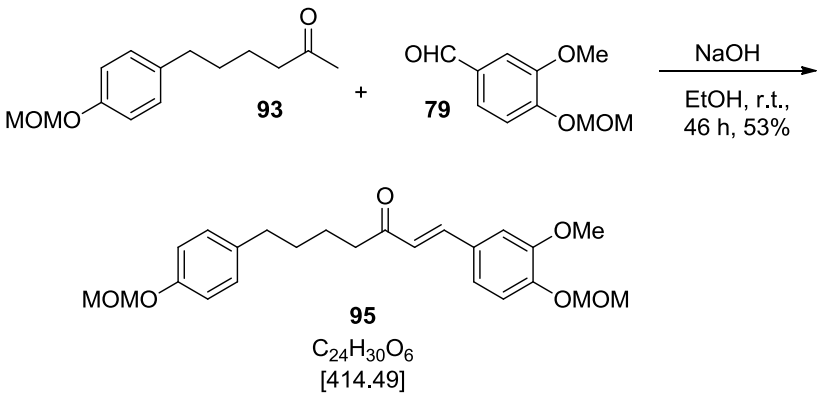
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 200.0, 149.6, 149.4, 148.5, 144.3, 142.1, 136.6, 128.6, 124.6, 122.3, 120.2, 116.4, 115.6, 111.9, 110.2, 95.4, 94.9, 56.1, 55.9, 55.69, 55.6, 40.3, 35.2, 31.0, 23.8.

ESI-MS m/z (%) 445 $[MH]^+$ (100)

HR ESI-MS m/z 445.2224 $[MH]^+$ (calcd. for $C_{25}H_{33}O_7$, 445.2221)

UV λ_{max} 220, 273 nm.

5.1.8.16 1-(3-Methoxy-4-(methoxymethoxy)phenyl)-7-(4-(methoxymethoxy) phenyl)heptan-3-one (95)[101]



Ketone **93** (130 mg, 0.551 mmol, 1.0 eq.) and MOM-protected vanillin **79** (194 mg, 0.991 mmol, 1.8 eq.) were dissolved in 11 ml EtOH, followed by addition of sodium hydroxide (77.0 mg, 1.93 mmol, 3.5 eq.). After stirring at r.t. for 46 h, the reaction was stopped by acidification with 1 M HCl aq. to give pH 5. The reaction mixture was mixed with 10 ml H_2O and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product was performed by flash chromatography (RP-18 silica; MeOH/H_2O 50 – 100% over 30 min, 100% MeOH 10 min; flow 25 ml/min), yielding 121 mg (0.291 mmol, 53%) of **95** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47 (d, J = 16.1 Hz, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.12 – 7.04 (m, 4H), 6.94 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 16.1 Hz, 1H), 5.26 (s, 2H), 5.13 (s, 2H), 3.91 (s, 3H), 3.50 (s, 3H), 3.46 (s, 3H), 2.66 (t, J = 7.0 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 1.83 – 1.54 (m, 4H).

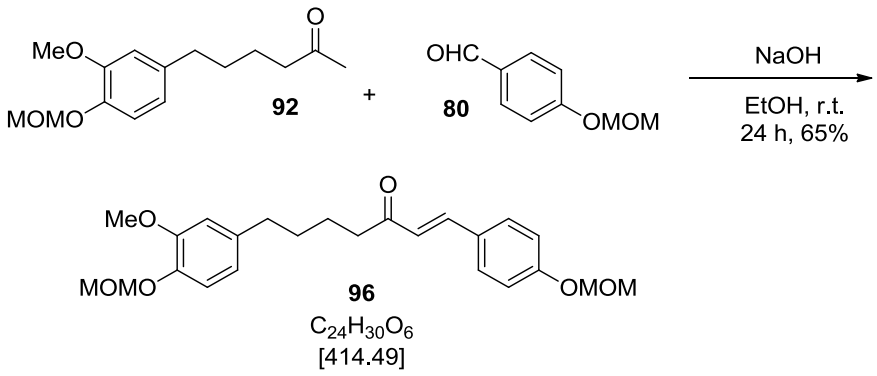
^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 155.3, 149.7, 148.6, 142.2, 135.6, 129.2 (2C), 128.7, 124.7, 122.5, 116.1 (2C), 115.7, 110.3, 95.1, 94.5, 56.3, 55.8, 55.8, 40.4, 34.8, 31.2, 23.9.

ESI-MS m/z (%) 415 $[MH]^+$ (100)

HR ESIMS m/z 415.2114 $[MH]^+$ (calcd for $C_{24}H_{31}O_6$, 415.2115)

UV λ_{max} 220, 328 nm.

5.1.8.17 (*E*)-7-(3-Methoxy-4-(methoxymethoxy)phenyl)-1-(4-(methoxymethoxy)phenyl)hept-1-en-3-one (96)[101]



To the stirred solution of the aldehyde **80** (264 mg, 1.59 mmol, 1.8 eq.) and the ketone **92** (219 mg, 0.822 mmol, 1.0 eq.) in 16 ml EtOH, 82.0 mg of NaOH (2.06 mmol, 2.5 eq.) was added. The yellow to orange solution was stirred for 24 h at room temperature. The reaction was stopped by addition of 1 M HCl aq. to give pH 5 and the ethanol was removed *in vacuo*. The residue was diluted by 10 ml of H_2O and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by CC (SiO_2; petroleum ether (b.p. 40-60 °C)/EtOAc 2:1) to yield 221 mg (0.534 mmol, 65%) of **96** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.55 – 7.44 (m, 3H), 7.08 – 7.01 (m, 3H), 6.73 (d, J = 1.8 Hz, 1H), 6.70 (dd, J = 8.0, 2.0 Hz, 1H), 6.63 (d, J = 16.1 Hz, 1H), 5.21 (s, 2H), 5.19 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 2.67 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 7.3 Hz, 2H), 1.78 – 1.64 (m, 4H).

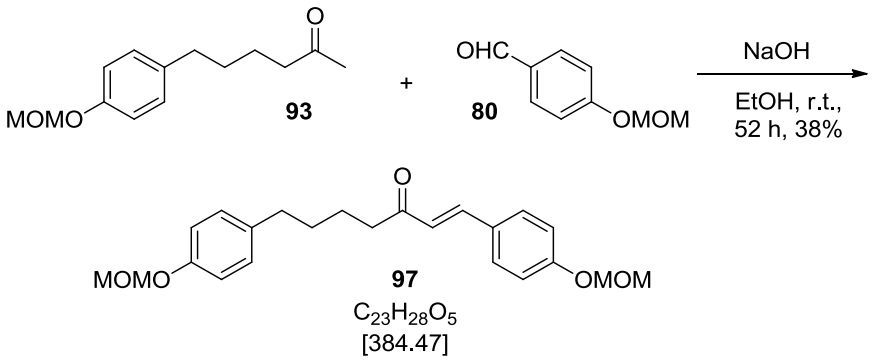
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 200.3, 159.1, 149.6, 144.5, 142.0, 136.8, 129.8 (2C), 128.2, 124.5, 120.4, 116.54, 116.49 (2C), 112.1, 95.7, 94.2, 56.2, 56.1, 55.8, 40.6, 35.5, 31.2, 24.1.

ESIMS m/z (%) 415 $[MH]^+$ (100)

HR ESIMS m/z 415.2122 $[MH]^+$ (calcd. for $C_{24}H_{31}O_6$, 415.2115)

UV λ_{max} 226, 316 nm.

5.1.8.18 (E)-1,7-Bis(4-(methoxymethoxy)phenyl)hept-1-en-3-one (97)[101]



Ketone **93** (130 mg, 0.551 mmol, 1.0 eq.) and aldehyde **80** (165 mg, 0.991 mmol, 1.8 eq.) were dissolved in 11 ml EtOH, followed by the addition of NaOH (77.0 mg, 1.93 mmol, 3.5 eq.). The slurry was stirred for 52 h at room temperature. The reaction was stopped by addition of 1 M HCl aq. (resulting pH 5-6), the mixture was diluted with H_2O (10 ml) and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (RP-18; MeOH/H_2O 50 – 100% over 30 min, 100% MeOH 10 min; flow 25 ml/min) to yield 80 mg (0.208 mmol, 38%) of pure **97** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.49 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 16.1 Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 3.47 (s, 3H), 3.47 (s, 3H), 2.66 (t, *J* = 7.jjj1 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.68 (m, 4H).

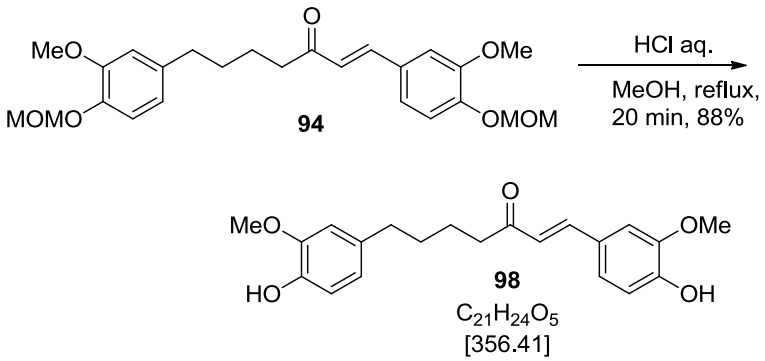
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 200.2, 159.0, 155.2, 141.9, 135.6, 129.8 (2C), 129.2 (2C), 128.1, 124.4, 116.4 (2C), 116.1 (2C), 94.5, 94.0, 56.0, 55.8, 40.5, 34.8, 31.1, 23.9.

ESI-MS *m*/*z* (%) 385 $[MH]^+$ (100)

HR ESI-MS *m*/*z* 385.2009 $[MH]^+$ (calcd. for $C_{23}H_{29}O_5$, 385.2010)

UV λ_{max} 223, 314 nm.

5.1.8.19 (*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hept-1-en-3-one (98)[107]



Protected diarylheptanoid **94** (63 mg, 0.141 mmol, 1.0 eq.) was dissolved in 7.5 ml MeOH and an aqueous 3 M HCl solution was added dropwise (1.46 ml, 4.38 mmol, 31 eq.) at room temperature. The mixture was heated to reflux and stirred for 20 min reaching complete conversion. The solution was quenched with 30 ml ice cold H_2O and extracted with CH_2Cl_2 (3 × 45 ml). The combined organic layers were washed with brine (100 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by preparative TLC (SiO_2; PE/EtOAc 2:1) to yield 44.0 mg (0.124 mmol, 88%) of **98** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.46 (d, J = 16.1 Hz, 1H), 7.07 (dd, J = 8.2, 1.8 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.70 – 6.63 (m, 2H), 6.58 (d, J = 16.1 Hz, 1H), 6.30 (br s, 1H), 5.68 (br s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.65 (t, J = 7.1 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 1.81 – 1.54 (m, 4H).

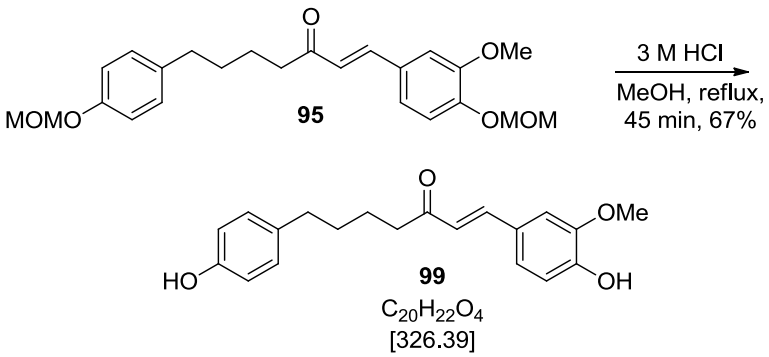
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 200.5, 148.2, 146.8, 146.3, 143.5, 142.8, 134.2, 126.9, 123.9, 123.4, 120.8, 114.8, 114.1, 110.9, 109.4, 55.9, 55.8, 40.4, 35.4, 31.3, 24.1.

ESI-MS m/z (%) 357 $[MH]^+$ (100)

HR ESI-MS m/z 357.1697 $[MH]^+$ (calcd. for $C_{25}H_{33}O_7$, 357.1697)

UV(MeOH) λ_{max} (log ε) 235 (4.96), 338 (5.23) nm.

5.1.8.20 (*E*)-1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)hept-1-en-3-one (99)[107]



Diarylheptanoid **95** (121 mg, 0.291 mmol) was dissolved in 17 ml MeOH, followed by a dropwise addition of 3 M aqueous HCl (2.91 ml, 8.73 mmol). The solution was heated to reflux for 45 min and subsequently quenched with 100 ml ice-cold H_2O. The aqueous solution was extracted with EtOAc (2 × 100 ml), the combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude yellow oil was purified by CC (SiO_2; PE/EtOAc 2:1 + 1% MeOH) to yield 64.0 mg (0.196 mmol, 67%) of **99** as yellow solid.

^{1}H NMR (300 MHz, MeOD) δ ppm 7.56 (d, J = 16.1 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.12 (dd, J = 8.2, 1.9 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.2 Hz, 1H), 6.72 – 6.61 (m, 3H), 3.90 (s, 3H), 2.70 (t, J = 6.9 Hz, 2H), 2.55 (t, J = 6.9 Hz, 2H), 1.75 – 1.53 (m, 4H).

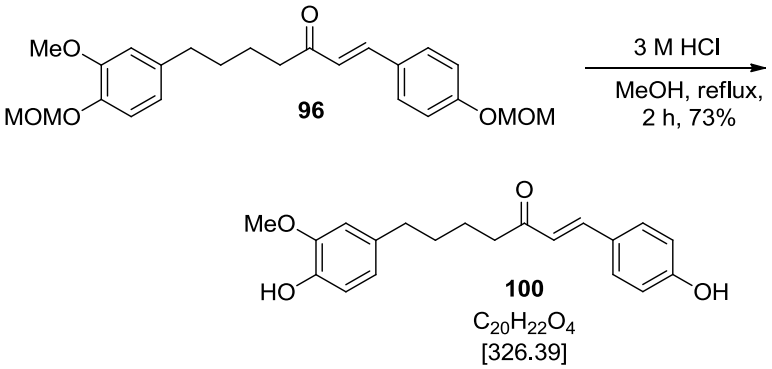
^{13}C NMR (101 MHz, MeOD) δ ppm 203.7, 156.3, 150.9, 149.4, 145.4, 134.4, 130.3 (2C), 127.9, 124.6, 124.2, 116.6, 116.1 (2C), 112.0, 56.5, 41.2, 35.8, 32.5, 25.4.

ESI-MS m/z (%) 327 $[MH]^+$ (100)

HR ESI-MS m/z 327.1592 $[MH]^+$ (calcd for $C_{20}H_{23}O_{24}$, 327.1591)

UV(MeOH) λ_{max} (log ε) 228 (5.12), 338 (5.38) nm.

5.1.8.21 (*E*)-7-(4-Hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)hept-1-en-3-one (100)[107]



Enone **96** (250 mg, 0.604 mmol, 1.0 eq.) was dissolved in 33 ml MeOH, followed by dropwise addition of 3 M HCl (6.04 ml, 18.1 mmol, 30 eq.). The solution was stirred under reflux for 2 h and subsequently quenched with 200 ml ice H_2O. The aqueous solution was extracted with EtOAc (2 × 150 ml), the resulting organic layers were combined, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; PE/EtOAc 2:1), yielding 143 mg (0.438 mmol, 73%) of **100** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.50 (d, J = 16.1 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 1H), 6.70 – 6.65 (m, 2H), 6.61 (d, J = 16.1 Hz, 1H), 3.86 (s, 3H), 2.67 (t, J = 7.1 Hz, 2H), 2.58 (t, J = 7.3 Hz, 2H), 1.82 – 1.54 (m, 4H).

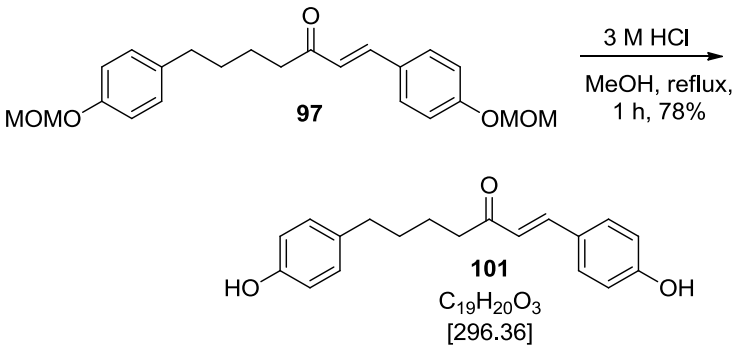
^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 158.1, 146.3, 143.5, 142.6, 134.2, 130.2 (2C), 127.1, 123.8, 120.9, 116.0 (2C), 114.1, 110.9, 55.8, 40.6, 35.4, 31.3, 24.1.

ESI-MS m/z (%) 327 $[MH]^+$ (100)

HR ESI-MS m/z 327.1595 $[MH]^+$ (calcd. for $C_{20}H_{22}O_4$, 327.1591)

UV(MeOH) λ_{max} (log ε) 233 (5.21), 323 (5.48) nm.

5.1.8.22 (*E*)-1,7-Bis(4-hydroxyphenyl)hept-1-en-3-one (101)[107]



The protected diarylheptanoid **97** (79.5 mg, 0.207 mmol) was dissolved in 11 ml MeOH. 3 M HCl aq. was added dropwise (2.07 ml, 6.21 mmol) and the solution was heated to reflux. The reaction was stopped after 1 h by addition of ice-cold H_2O (80 ml) and the aqueous solution was extracted with EtOAc (2 × 30 ml). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The purification was carried out by CC (SiO_2; PE/EtOAc + 1% MeOH) to yield 48.0 mg (0.162 mmol, 78%) of **101** as yellow solid.

^{1}H NMR (300 MHz, MeOD) δ 7.56 ppm (d, J = 16.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 7.7 Hz, 2H), 6.64 (d, J = 15.3 Hz, 1H), 2.69 (t, J = 6.9 Hz, 2H), 2.55 (t, J = 6.9 Hz, 2H), 1.63 (dd, J = 6.8, 3.3 Hz, 4H).

^{13}C NMR (101 MHz, MeOD) δ 203.7, 161.5, 156.3, 145.1, 134.4, 131.5 (2C), 130.3 (2C), 127.3, 124.0, 116.9 (2C), 116.1 (2C), 41.1, 35.8, 32.5, 25.3.

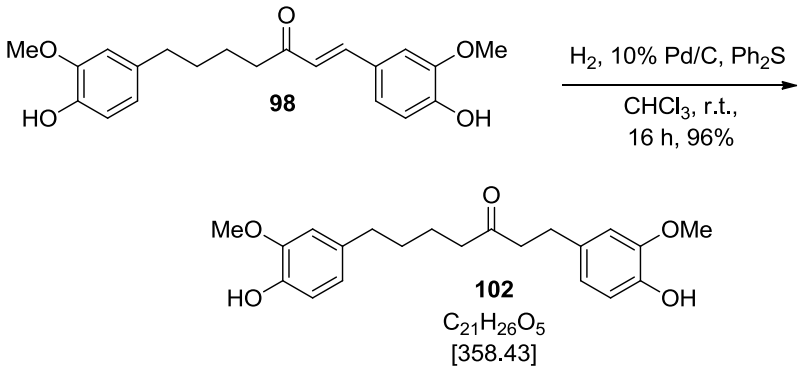
EI-MS m/z (%) 296 $[M]^{+\cdot}$ (29), 162 (30), 147 (100)

HR EI-MS m/z 296.1415 $[M]^{+\cdot}$ (calcd for $C_{19}H_{20}O_3$, 296.1412)

m.p.: 116 °C

UV(MeOH) λ_{max} (log ε) 229 (5.10), 332 (5.39) nm.

5.1.8.23 1,7-Bis(4-hydroxy-3-methoxy phenyl)heptan-3-one (102)[106]



Diarylheptanoid **98** (10 mg, 0.028 mmol), dissolved in $CHCl_3$ (0.3 ml), was mixed with Pd/C (1.0 mg, 10% Pd on charcoal) and Ph_2S (0.23 µl, 1.4 µmol, 0.05 eq.) and stirred at r.t. under H_2 atmosphere (balloon, ~1 bar) for 16 h. The black slurry was passed through a pad of celite (eluted with EtOAc) and the solvent was removed under reduced pressure affording **102** (9.5 mg, 0.027 mmol, 96%) as colorless oil.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.73 (d, *J* = 1.9 Hz, 1H), 6.70 (d, *J* = 1.9 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 2H), 6.58 (dd, *J* = 9.3, 1.9 Hz, 1H), 6.56 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.80 – 2.71 (m, 2H), 2.71 – 2.65 (m, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.40 (t, *J* = 6.7 Hz, 2H), 1.57 – 1.44 (m, 4H)

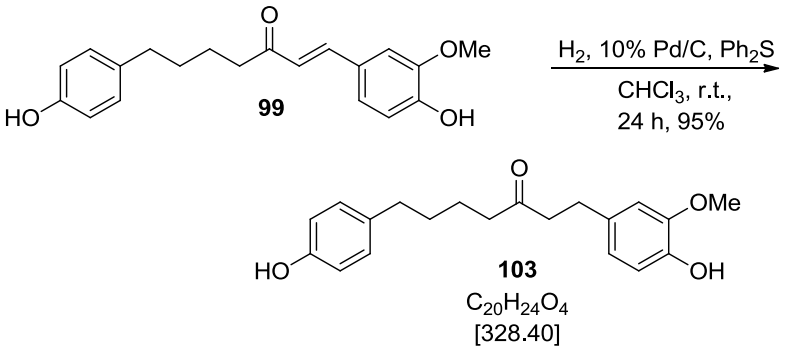
^{13}C NMR (100 MHz, CD_3OD) δ ppm 213.5, 148.8, 148.8, 145.7, 145.4, 135.1, 134.0, 121.7 (2C), 116.1, 116.0, 113.1, 113.0, 56.3 (2C), 45.4, 43.9, 36.2, 32.3, 30.6, 24.3

ESI-MS *m/z* (%) 376 $[MNH_4]^+$ (100), 341 $[MH - H_2O]^+$ (51)

HR ESI-MS *m/z* 341.1751 $[MH - H_2O]^+$ (calcd. for $C_{21}H_{24}O_4$ 341.1747)

UV(MeOH) λ_{max} (log ε) 230 (5.01), 281 (4.79) nm.

5.1.8.24 1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)heptan-3-one (103)[106]



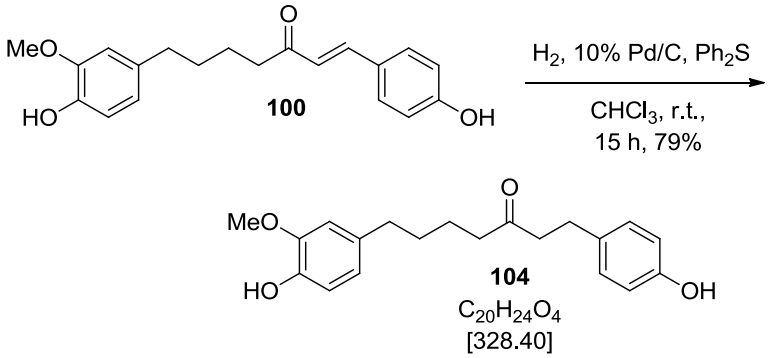
The unsaturated diarylheptanoid **99** (25 mg, 0.077 mmol) was dissolved in 0.4 ml $CHCl_3$. Diphenyl sulfide (0.64 µl, 3.8 µmol, 0.05 eq.) and Pd/C (2.5 mg, 10% Pd on charcoal) were added and the mixture was stirred for 24 h under H_2 atmosphere (balloon, ~1 bar). The catalyst residue was removed by filtration through a pad of celite and the solvent was removed *in vacuo* to yield 24.0 mg (0.073 mmol, 95%) of **103** as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.00 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.70 – 6.61 (m, 2H), 5.49 (s, 1H), 4.89 (s, 1H), 3.85 (s, 3H), 2.87 – 2.76 (m, 2H), 2.68 (m, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.56 (m, 4H).

UV(MeOH) λ_{max} (log ε) 226 (5.12), 279 (4.61) nm

The NMR data agree with the literature.[110]

5.1.8.25 1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-one (104)[106]



The unsaturated diarylheptanoid **100** (93.0 mg, 0.285 mmol), dissolved in 4 ml $CHCl_3$, was mixed with 14 mg Pd/C (10% Pd on charcoal) and 3.7 µl Ph_2S (0.022 mmol, 0.08 eq.). The black slurry was stirred for 15 h at r.t. under H_2 atmosphere (balloon, ~1 bar) until complete conversion of the starting material. The mixture was then passed through a pad of celite (eluted with 30 ml EtOAc) and after the evaporation of the solvent, pure **104** was obtained as colorless oil (74.0 mg, 0.225 mmol, 79%).

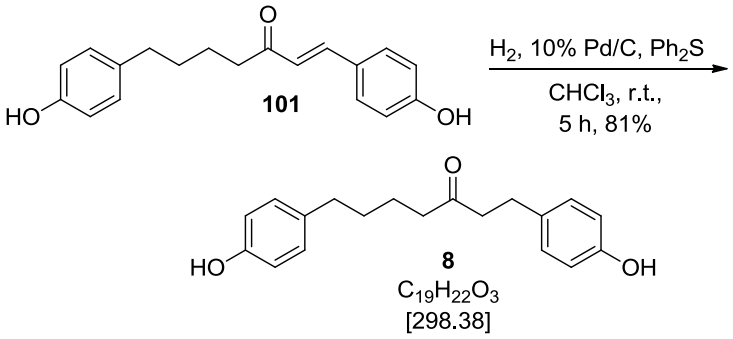
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.03 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.67 – 6.60 (m, 2H), 5.46 (s, 1H), 4.74 (s, 1H), 3.87 (s, 3H), 2.91 – 2.74 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 2.38 (t, *J* = 6.9 Hz, 2H), 1.72 – 1.45 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 210.9, 154.2, 146.3, 143.5, 134.1, 132.7, 129.3 (2C), 120.8, 115.3 (2C), 114.1, 110.9, 55.8, 44.5, 42.9, 35.3, 31.2, 28.9, 23.3

UV(MeOH) λ_{max} (log ε) 229 (5.07), 280 (4.70) nm

The NMR data are in agreement with the literature.[110]

5.1.8.26 1,7-Bis(4-hydroxyphenyl)heptan-3-one (acerogenin G, 8)[106]



Ketone **101** (20 mg, 0.068 mmol) was dissolved in 0.4 ml $CHCl_3$ and mixed with 0.6 mg diphenyl sulfide (3.4 µmol, 0.05 eq.) and 2 mg Pd/C (10% Pd on charcoal). The black

slurry was stirred for 5 h at r.t. under H_2 atmosphere (balloon, ~1 bar). After completion of the reaction, the mixture was filtered through a pad of celite and the solvent was removed *in vacuo*, yielding **8** (16.5 mg, 0.055 mmol, 81%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.01 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.76 (s, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.62 – 1.46 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 210.4, 153.5 (2C), 134.4, 133.3, 129.4 (4C), 115.3 (2C), 115.1 (2C), 44.5, 42.9, 34.8, 31.1, 28.9, 23.3.

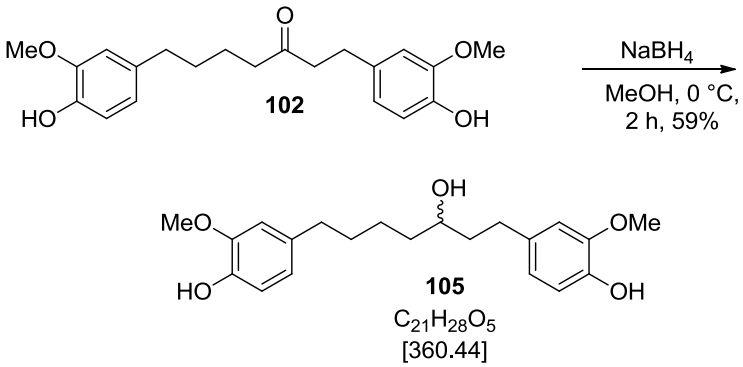
EI-MS *m/z* (%) 298 $[M]^{+\cdot}$ (10), 133 (21), 107 (100)

HR EI-MS *m/z* 298.1565 $[M]^{+\cdot}$ (calcd for $C_{19}H_{22}O_3$, 298.1569)

UV(MeOH) λ_{max} (log ε) 227 (5.00), 279 (4.54) nm.

The NMR data is in agreement with previously reported spectra.[29]

5.1.8.27 4,4'-(3-Hydroxyheptane-1,7-diyl)bis(2-methoxyphenol) (105)[109]



Diarylheptanoid **102** (20 mg, 0.056 mmol) was dissolved under N_2 atmosphere in 0.4 ml MeOH and cooled to 0 °C. Sodium borohydride (3.0 mg, 0.084 mmol, 1.5 eq.) was added and the mixture was stirred at 0 °C for 2 h until complete conversion of the starting material. The solution was then quenched by 10 ml H_2O and extracted with EtOAc (3 × 10 ml). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative HPLC (RP-18; MeOH/H_2O gradient 50 – 100% MeOH over 20 min, 100% MeOH for 5 min, flow rate 10 ml/min) to yield **105** (12 mg, 0.033 mmol, 59%) as colorless oil.

^{1}H NMR (300 MHz, MeOD) δ ppm 6.73 (d, *J* = 1.8 Hz, 2H), 6.68 (d, *J* = 8.0, 2H), 6.59 (dd, *J* = 7.8, 1.8 Hz, 2H), 3.81 (s, 6H), 3.62 – 3.42 (m, 1H), 2.79 – 2.39 (m, 4H), 1.84 – 1.17 (m, 8H).

^{13}C NMR (101 MHz, MeOD) δ ppm 148.8 (2C), 145.5, 145.4, 135.6, 135.3, 121.8 (2C), 116.1, 116.0, 113.2, 113.2, 71.7, 56.4 (2C), 40.6, 38.2, 36.5, 33.0, 32.6, 26.3.

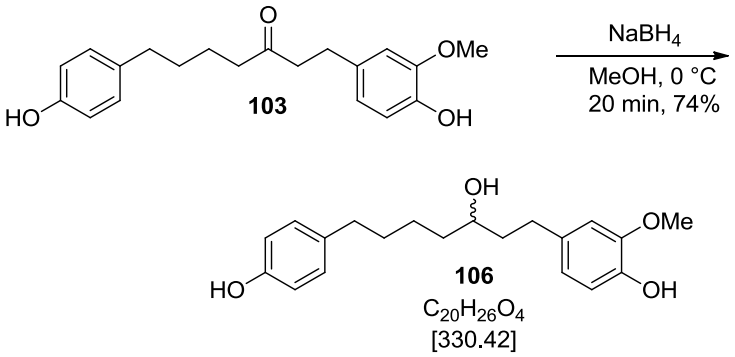
ESI-MS m/z (%) 359 $[M - H]^-$ (100)

HR ESIMS m/z 359.1860 $[M - H]^-$ (calcd for $C_{21}H_{27}O_5$, 359.1864)

UV(MeOH) λ_{max} (log ε) 227 (5.29), 281 (4.97) nm.

The compound was described before in the literature.[166]

5.1.8.28 4-(3-Hydroxy-7-(4-hydroxyphenyl)heptyl)-2-methoxyphenol (106)[109]



Diarylheptanoid **103** (12 mg, 0.037 mmol) was dissolved in 0.2 ml MeOH. The solution was cooled to 0 °C and sodium borohydride (2.0 mg, 0.052 mmol, 1.4 eq.) was added. The reaction was quenched with H_2O (10 ml) after 20 min. The aqueous solution was extracted with EtOAc (3 × 10 ml), the organic layers were combined and dried with $MgSO_4$. The solvent was removed *in vacuo* and the crude colorless oil was purified by preparative HPLC (RP-18; MeOH/H_2O gradient 50 – 100% MeOH over 30 min, 100% MeOH for 5 min, 100 – 50% over 2 min, flow rate 10 ml/min), yielding 9.0 mg (0.027 mmol, 74%) of **106** as colorless oil.

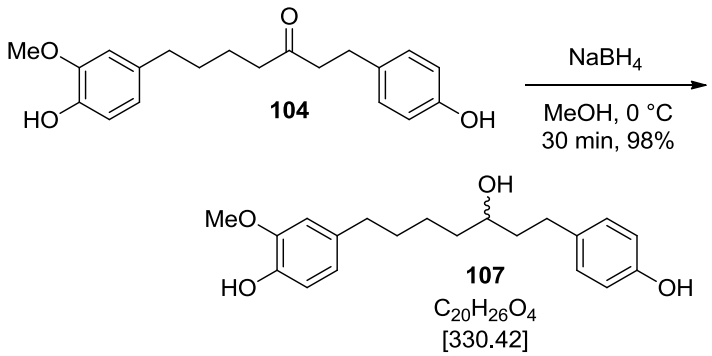
^{1}H NMR (300 MHz, MeOD) δ ppm 6.97 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 1.8 Hz, 1H), 6.72 – 6.57 (m, 4H), 3.82 (s, 3H), 3.62 – 3.44 (m, 1H), 2.78 – 2.41 (m, 4H), 1.89 – 1.22 (m, 8H).

^{13}C NMR (101 MHz, MeOD) δ ppm 156.3, 148.8, 145.4, 135.4, 134.8, 130.3 (2C), 121.8, 116.1, 116.0 (2C), 113.2, 71.7, 56.4, 40.6, 38.2, 36.0, 33.0, 32.6, 26.3.

UV(MeOH) λ_{max} (log ε) 225 (5.45), 280 (4.98) nm

The NMR data correspond to the literature.[110]

5.1.8.29 4-(5-Hydroxy-7-(4-hydroxyphenyl)heptyl)-2-methoxyphenol (107)[109]



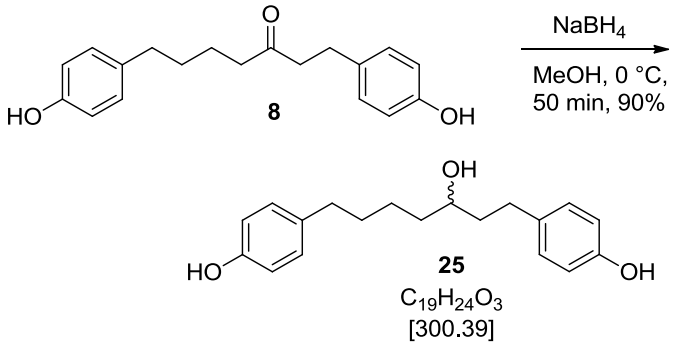
Compound **104** (11 mg, 0.033 mmol, 1.0 eq.) was dissolved in 0.4 ml MeOH and cooled to 0 °C. Sodium borohydride (1.9 mg, 0.050 mmol, 1.5 eq.) was added and the solution was stirred at 0 °C until complete conversion (30 min). The reaction was quenched with 10 ml H_2O and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by preparative HPLC (RP-18; MeOH/H_2O gradient 50 – 100% MeOH over 20 min, 100% MeOH for 5 min, 100 – 50% over 2 min, flow rate 10 ml/min). Alcohol **107** (10.7 mg, 0.032 mmol, 98%) was obtained as colorless oil.

^{1}H NMR (300 MHz, MeOD) δ ppm 6.98 (d, J = 8.4 Hz, 2H), 6.75 – 6.62 (m, 4H), 6.58 (dd, J = 8.0, 1.8 Hz, 1H), 3.81 (s, 3H), 3.50 (m, 1H), 2.76 – 2.57 (m, 1H), 2.57 – 2.38 (m, 1H), 2.51 (t, J = 7.4 Hz, 2H), 1.82 – 1.20 (m, 8H).

UV(MeOH) λ_{max} (log ε) 228 (5.05), 280 (4.73) nm.

The NMR data agree with the literature.[110]

5.1.8.30 4,4'-(3-Hydroxyheptane-1,7-diyl)diphenol ((±)-centrolobol, 25)[109]



Ketone **8** (8.0 mg, 0.027 mmol, 1.0 eq.) was dissolved in 0.2 ml MeOH in and cooled to 0 °C. Sodium borohydride (1.4 mg, 0.037 mmol, 1.4 eq.) was added and the solution was stirred for 50 min at 0 °C. Subsequently, the reaction was stopped by addition of H_2O (8 ml) and

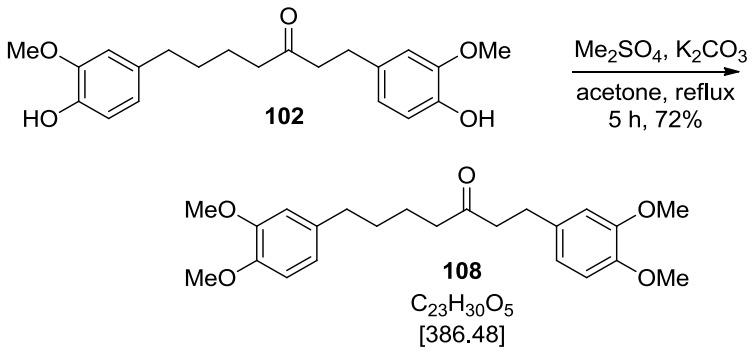
the aqueous solution was extracted with EtOAc (3 × 10 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude brown oil was purfied by preparative HPLC (RP-18; MeOH/H_2O gradient 50 – 100% MeOH over 30 min, 100% MeOH for 5 min, 100 – 50% over 2 min, flow rate 10 ml/min) to yield 7.3 mg of **25** as colorless oil (0.024 mmol, 90%).

^{1}H NMR (300 MHz, MeOD) δ ppm 6.99 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.56 – 3.45 (m, 1H), 2.74 – 2.39 (m, 4H), 1.77 – 1.21 (m, 8H).

UV(MeOH) λ_{max} (log ε) 228 (4.99), 280 (4.70) nm

NMR data agree with the literature.[111]

5.1.8.31 1,7-Bis(3,4-dimethoxyphenyl)heptan-3-one (108)[116]



Diarylheptanoid **102** (22 mg, 0.061 mmol, 1.0 eq.) was dissolved in 0.3 ml acetone. Dimethyl sulfate (23 µl, 0.25 mmol, 4.0 eq) and K_2CO_3 (37 mg, 0.27 mmol, 4.4 eq) were added and the mixture was stirred for 5 h under reflux. The reaction was stopped by addition of H_2O (10 ml), followed by extraction with EtOAc (3 × 15 ml). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to yield pure **108** (17 mg, 0.044 mmol, 72%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 6.81 – 6.74 (m, 2H), 6.73 – 6.65 (m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 1.65 – 1.52 (m, 4H).

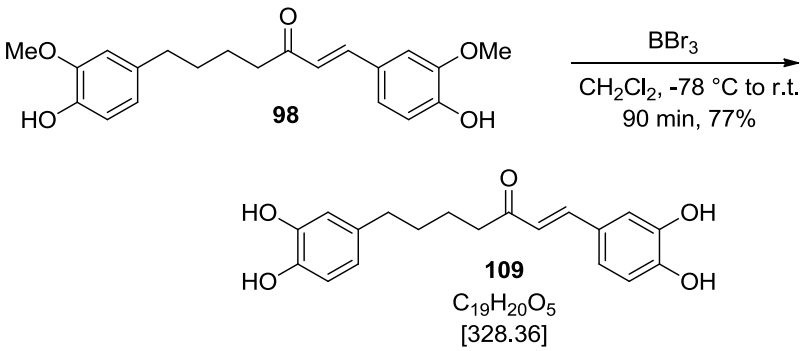
^{13}C NMR (101 MHz, $CDCl_3$) *δ* 210.2, 148.82, 148.75, 147.3, 147.1, 134.8, 133.7, 120.1, 120.0, 111.7 (2C), 111.24, 111.15, 55.9 (2C), 55.8 (2C), 44.5, 42.9, 35.3, 31.1, 29.4, 23.3.

ESI-MS *m/z* (%) 387 $[MH]^+$ (87)

HR ESI-MS *m/z* 387.2170 $[MH]^+$ (calcd. for $C_{23}H_{31}O_5$ 387.2166)

UV(MeOH) λ_{max} (log ε) 230 (5.05), 281 (4.82) nm.

5.1.8.32 (*E*)-1,7-Bis(3,4-dihydroxyphenyl)hept-1-en-3-one (109)[117]



Diarylheptanoid **98** (38.0 mg, 0.107 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (1.5 ml) under nitrogen and cooled to -78 °C. Boron tribromide (632 µl of 1 M CH_2Cl_2 solution, 0.632 mmol, 6.0 eq.) was added and the mixture was stirred at -78 °C. The cooling bath was removed after 75 min and the reaction was continued for 15 min at r.t. The reaction mixture was then poured into saturated sodium bicarbonate solution (30 ml) and extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with H_2O (2 × 40 ml) and dried with $MgSO_4$. The crude product was purified by CC (SiO_2; PE/EtOAc 1:2 + 0.1% TFA) to yield 27 mg (0.082 mmol, 77%) of **109** as brown oil.

^{1}H NMR (400 MHz, MeOD) δ ppm 7.48 (d, *J* = 16.1 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.60 – 6.54 (d, *J* = 16.1 Hz, 1H), 6.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.69 – 1.53 (m, 4H).

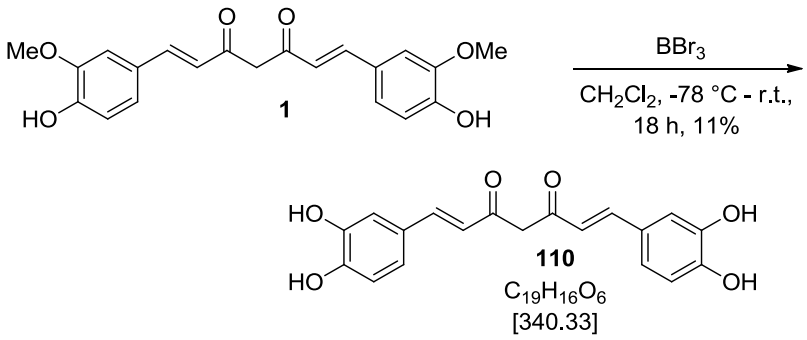
^{13}C NMR (101 MHz, MeOD) δ ppm 203.7, 149.9, 146.8, 146.1, 145.5, 144.2, 135.2, 127.8, 123.9, 123.5, 120.7, 116.6, 116.5, 116.2, 115.3, 41.0, 36.0, 32.4, 25.4

ESI-MS *m/z* (%) 329 $[MH]^+$ (100)

HR ESI-MS *m/z* 329.1386 $[MH]^+$ (calcd. for $C_{19}H_{21}O_5$, 329.1384)

UV(MeOH) λ_{max} (log ε) 342 (5.08) nm.

5.1.8.33 (1*E*,6*E*)-1,7-Bis(3,4-dihydroxyphenyl)hepta-1,6-diene-3,5-dione (110)[117]



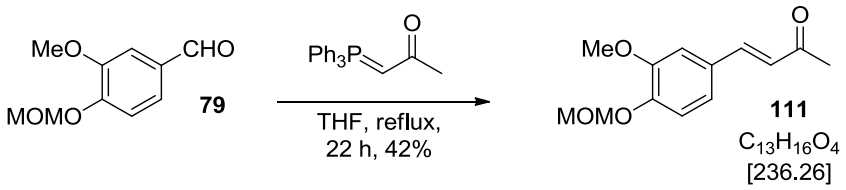
Curcumin (**1**) (143 mg, 0.388 mmol), dissolved under N_2 atmosphere in 5.8 ml CH_2Cl_2, was cooled to -78 °C and boron tribromide (2.33 ml of a 1 M sol. in CH_2Cl_2, 2.33 mmol, 6.0 eq.) was slowly added. The mixture was stirred for 2 h at -78 °C and further 16 h at r.t., followed by an aqueous work-up (40 ml sat. Na_2CO_3 aq.). After separation of the CH_2Cl_2 layer, the aqueous solution was acidified with 1 M HCl aq. (pH 5) and extracted with EtOAc (2 × 50 ml). The CH_2Cl_2 and EtOAc layers were combined, dried with $MgSO_4$ and concentrated *in vacuo*. The crude mixture was passed through a short SiO_2 column (eluted with CH_2Cl_2/MeOH 4:1) and subsequently purified by semi-preparative HPLC (method 1, 5.1.2) affording 13.9 mg (0.041 mmol, 11%) of **110** as orange solid.

^{1}H NMR (300 MHz, MeOD) δ ppm 7.51 (d, J = 15.8 Hz, 2H), 7.07 (d, J = 1.9 Hz, 2H), 6.99 (dd, J = 8.2, 1.9 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 6.53 (d, J = 15.8 Hz, 2H), 5.93 (s, 1H)

ESI-MS m/z 341 $[MH]^+$ (100).

NMR data agree with the literature.[117]

5.1.8.34 (*E*)-4-(3-Methoxy-4-(methoxymethoxy)phenyl)but-3-en-2-one (111)[103]



MOM-protected vanillin **79** (100 mg, 0.510 mmol), dissolved in 4 ml THF, was mixed with 1-(triphenylphosphoraneylidene)-2-propanone (186 mg, 0.585 mmol, 1.15 eq.) and stirred under reflux for 22 h. The reaction was then stopped and the solvent was removed under reduced pressure, followed by CC (SiO_2; PE/EtOAc 3:1) to afford 50.0 mg (0.212 mmol, 42%) of **111** as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (d, J = 16.2 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.60 (d, J = 16.2 Hz, 1H), 5.25 (s, 2H), 3.90 (s, 3H), 3.50 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 198.3, 149.8, 148.7, 143.3, 128.6, 125.7, 122.6, 115.7, 110.2, 95.1, 56.3, 55.9, 27.3.

m.p.: 71 °C

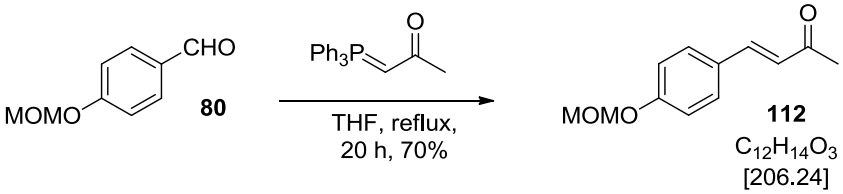
APCI-MS *m/z* (%) 237 $[MH]^+$ (100).

HR APCI-MS *m/z* 237.1126 $[MH]^+$ (calcd. for $C_{13}H_{17}O_4$ 237.1121).

UV λ_{max} 236, 328 nm.

The compound has been described before in the literature.[23]

5.1.8.35 (*E*)-4-(4-(Methoxymethoxy)phenyl)but-3-en-2-one (112)[103]



4-(Methoxymethoxy)benzaldehyde **80** (100 mg, 0.602 mmol, 1.0 eq.) was dissolved in 4 ml THF, followed by addition of 1-(triphenylphosphoraneylidene)-2-propanone (249 mg, 0.808 mmol, 1.3 eq.). The mixture was stirred at 75 °C for 20 h, then the solvent was removed under reduced pressure and the residue purified by CC (SiO_2; PE/EtOAc 3:1) affording 87.0 mg (0.422 mmol, 70%) of **112** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 – 7.40 (m, 2H), 7.02 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 5.17 (s, 2H), 3.44 (s, 3H), 2.32 (s, 3H).

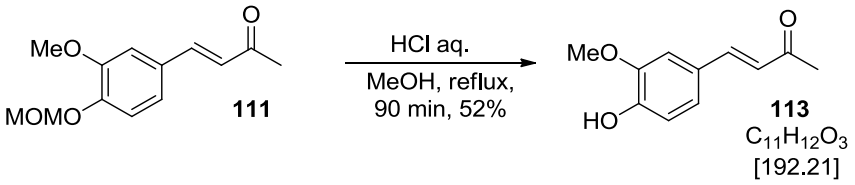
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 198.2, 159.0, 142.9, 129.7 (2C), 127.9, 125.28, 116.4 (2C), 94.0, 56.0, 27.2.

APCI-MS *m/z* (%) 207 $[MH]^+$ (100).

HR APCI-MS *m/z* 207.1020 $[MH]^+$ (calcd. for $C_{12}H_{15}O_3$ 207.1016).

UV λ_{max} 228, 313 nm.

5.1.8.36 (*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (113)[107]



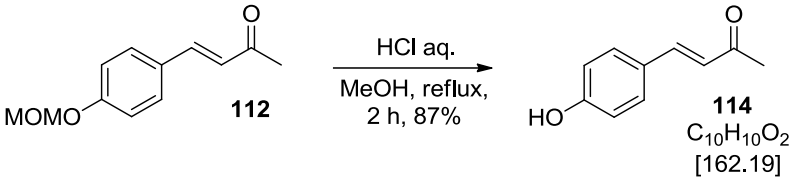
Ketone **111** (50.0 mg, 0.212 mmol) was dissolved in MeOH and 3 M HCl aq. (1.06 ml, 3.18 mmol, 15 eq.) was dropwise added. The solution was stirred under reflux for 90 min, subsequently quenched by ice-cold H_2O (17 ml) and extracted with EtOAc (3 × 20 ml). The organic layers were combined, dried with $MgSO_4$ and after evaporating the solvent, the residue was purified by CC (SiO_2; petroleum ether/EtOAc 2:1) yielding **113** (21.0 mg, 0.109 mmol, 52%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 16.1 Hz, 1H), 7.07 (m, 2H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* =16.1 Hz, 1H), 3.93(s, 3H), 2.36(s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 198.4, 148.3, 146.9, 143.7, 126.8, 124.9, 123.5, 114.8, 109.3, 56.0, 27.3.

NMR data agree with the literature.[167]

5.1.8.37 (*E*)-4-(4-Hydroxyphenyl)but-3-en-2-one (114)[107]



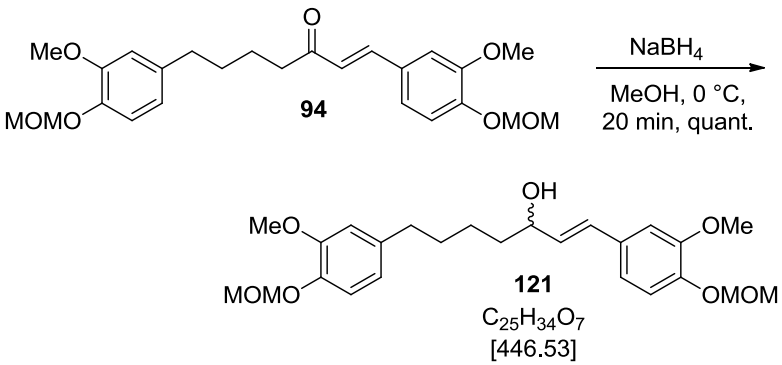
Ketone **112** (87.0 mg, 0.422 mmol) was dissolved in 22.5 ml MeOH, followed by the addition of 3 M HCl aq. (2.11 ml, 6.33 mmol). The mixture was stirred under reflux for 2 h, then H_2O (20 ml) was added and the aqueous solution was extracted with EtOAc (3 × 50 ml). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by CC (SiO_2; PE/EtOAc 2:1) yielding 59.6 mg (0.368, 87%) of **114** (yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 2.39 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 200.5, 159.3, 145.2, 130.5 (2C), 126.1, 124.0, 116.2 (2C), 27.2.

The NMR spectra match the data published in the literature.[168]

5.1.8.38 (*E*)-1,7-Bis(3-methoxy-4-(methoxymethoxy)phenyl)hept-1-en-3-ol (121)



Diarylheptanoid **94** (160 mg, 0.360 mmol) was dissolved in 3 ml MeOH and cooled to 0 °C. Sodium borohydride (18.0 mg, 0.468 mmol, 1.3 eq.) was added in one portion and the mixture was stirred at 0 °C until complete conversion of the starting material. The reaction was stopped after 20 min by addition of H_2O (20 ml). The aqueous solution was extracted with EtOAc (3 × 25 ml), the combined organic layers were dried ($MgSO_4$) and after the evaporation of the solvent, pure product **121** (160 mg, 359 mmol, 99%) was obtained as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.06 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 1.9 Hz, 1H), 6.86 (dd, J = 8.3, 1.9 Hz, 1H), 6.70 – 6.62 (m, 2H), 6.46 (d, J = 15.8 Hz, 1H), 6.07 (dd, J = 15.8, 6.9 Hz, 1H), 5.19 (s, 2H), 5.15 (s, 2H), 4.22 (q, J = 6.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.48 (s, 6H), 2.58 – 2.50 (m, 2H), 1.69 – 1.54 (m, 4H), 1.54 – 1.35 (m, 2H).

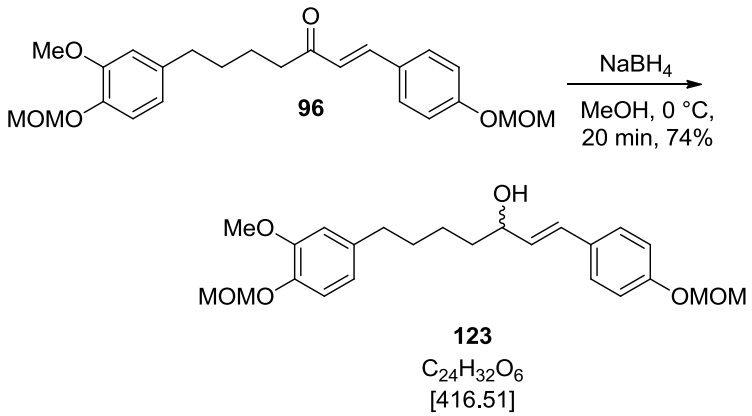
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.6, 149.4, 146.0, 144.2, 137.0, 131.3 (CH), 131.1, 129.7 (CH), 120.2 (CH), 119.4 (CH), 116.5 (CH), 116.2 (CH), 112.0 (CH), 109.2 (CH), 95.5 (CH_2), 95.3 (CH_2), 72.8 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.7 (CH_3), 55.6 (CH_3), 37.1 (CH_2), 35.4 (CH_2), 31.4 (CH_2), 25.0 (CH_2).

ESI-MS m/z (%) 469 $[MNa]^+$ (100).

HR ESI-MS m/z 469.2199 $[MNa]^+$ (calcd. for $C_{25}H_{34}NaO_7$ 469.2197).

UV λ_{max} 274 nm.

5.1.8.39 (*E*)-7-(3-methoxy-4-(methoxymethoxy)phenyl)-1-(4-(methoxymethoxy) phenyl)hept-1-en-3-ol (123)



To a stirred, cooled (0 °C) solution of diarylheptanoid **96** (123 mg, 0.297 mmol) in 2.5 ml MeOH, sodium borohydride (15.0 mg, 0.386 mmol, 1.3 eq.) was added in one portion. The reaction was stopped after 20 min by addition of H_2O (20 ml) and the resulting aqueous solution was extracted with EtOAc (3 × 25 ml). The organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to yield pure **123** (91.0 mg, 0.219 mmol, 74%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 1.9 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9, 7.0 Hz, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 4.33 – 4.18 (m, 1H), 3.85 (s, 3H), 3.51 (s, 3H), 3.47 (s, 3H), 2.60 – 2.54 (m, 2H), 1.71 – 1.57 (m, 4H), 1.53 – 1.37 (m, 2H).

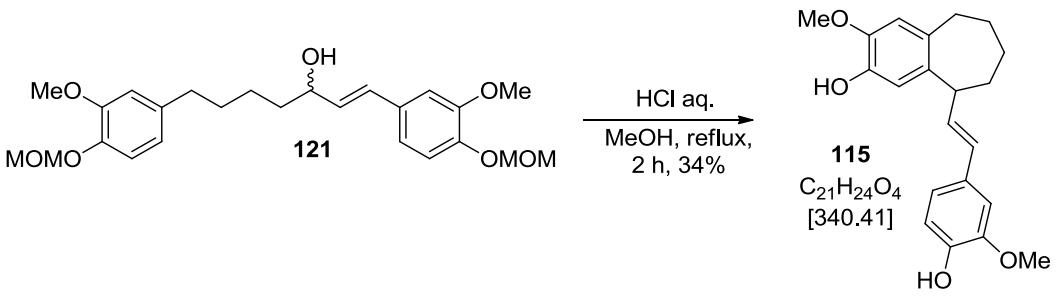
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 156.8, 149.6, 144.4, 137.1, 130.8, 130.6, 129.7, 127.5, 120.3, 116.6, 116.3, 112.1, 95.6, 94.3, 73.0, 56.0, 55.9, 55.8, 37.2, 35.5, 31.5, 25.1.

ESI-MS m/z (%) 439 $[MNa]^+$ (30), 399 $[MH - H_2O]^+$ (35).

HR ESI-MS m/z 439.2093 $[MNa]^+$ (calcd. for $C_{24}H_{32}NaO_6$ 439.2091).

UV λ_{max} 260 nm.

5.1.8.40 (*E*)-9-(4-Hydroxy-3-methoxystyryl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-ol (115)



MOM-protected allylic alcohol **121** (82.0 mg, 0.184 mmol) was dissolved in 12 ml MeOH. 3 M HCl aq. (1.84 ml, 5.52 mmol, 30 eq.) was slowly added and the mixture was heated to 75 °C. After 2 h, the reaction was stopped by the addition of ice-cold H_2O (30 ml), followed by an extraction with EtOAc (3 × 40 ml). The combined organic layers were dried with $MgSO_4$, the solvent was removed on a rotary evaporator and the crude mixture was submitted to a purification by preparative HPLC (RP-18; MeOH/H_2O 50-100%, 37 min, 10 ml/min) affording **115** (21.0 mg, 0.062 mmol, 34%) as orange solid

m.p.: 80 – 82 °C.

^{1}H NMR (600 MHz, MeOD) δ ppm 6.96 (d, J = 1.7 Hz, 1H), 6.81 (dd, J = 8.1, 1.8 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.69 (s, 1H), 6.65 (s, 1H), 6.35 (dd, J = 15.9, 6.7 Hz, 1H), 6.13 (d, J = 15.9 Hz, 1H), 3.86 (s, J = 5.8 Hz, 3H), 3.82 (s, J = 5.2 Hz, 3H), 3.64 – 3.58 (m, 1H), 2.86 – 2.68 (m, 2H), 1.98 – 1.75 (m, 4H), 1.69 – 1.54 (m, 2H).

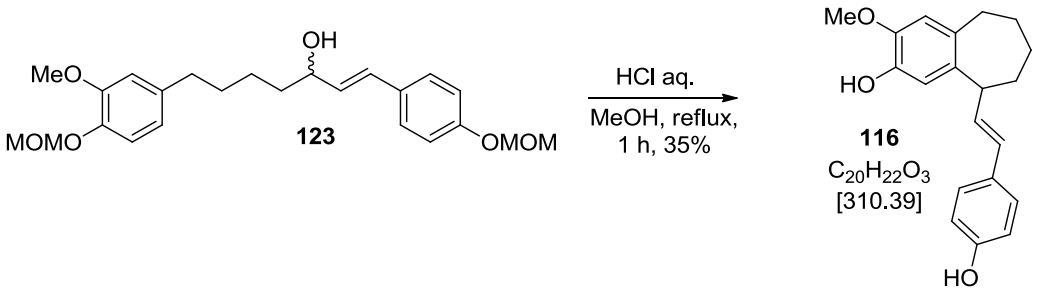
^{13}C NMR (151 MHz, MeOD) δ ppm 149.1, 147.0, 146.5, 144.9, 138.4, 135.3, 131.8, 131.5, 130.7, 120.3, 117.3, 116.2, 115.2, 110.3, 56.6, 56.4, 36.8, 35.5, 31.6, 29.7, 26.3.

ESI-MS m/z (%) 341 $[MH]^+$ (100), 340 $[M]^{+\cdot}$ (71), 363 $[MNa]^+$ (16).

HR ESI-MS m/z 341.1745 $[MH]^+$ (calcd. for $C_{21}H_{25}O_4$ 341.1747).

UV λ_{max} 280 nm.

5.1.8.41 (*E*)-9-(4-Hydroxystyryl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo [7]annulen-2-ol (116)



Diarylheptanoid **123** (91.0 mg, 0.219 mmol) was dissolved in 15 ml MeOH, mixed with 3 M HCl aq. (2.19 ml, 6.57 mmol, 30 eq.) and stirred under reflux for 1 h. When the reaction was finished, H_2O (30 ml) was added and the resulting aqueous solution was extracted with EtOAc (3 × 40 ml). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by CC (SiO_2; PE/EtOAc 2:1) yielding 24 mg (0.077 mmol, 35%) of **116** as colorless oil.

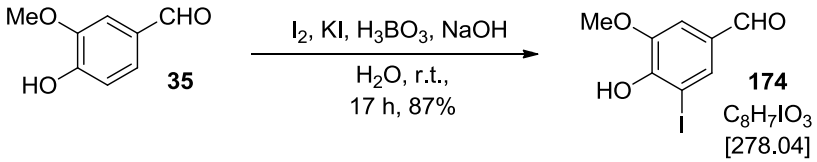
^{1}H NMR (600 MHz, MeOD) δ ppm 7.21 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.69 (s, 1H), 6.65 (s, 1H), 6.33 (dd, J = 15.9, 6.7 Hz, 1H), 6.13 (d, J = 15.9 Hz, 1H), 3.82 (s, 3H), 3.60 (t, J = 6.0 Hz, 1H), 2.84 – 2.69 (m, 2H), 1.93 – 1.78 (m, 2H), 1.86 (m, 2H), 1.62 (s, 2H).

^{13}C NMR (151 MHz, MeOD) δ ppm 157.7, 146.5, 144.9, 137.8, 135.3, 131.5, 130.9, 130.4, 128.2 (2C), 117.2, 116.3 (2C), 115.2, 56.6, 49.0, 36.8, 35.5, 30.7, 29.7.

ESI-MS m/z (%) 311 $[MH]^+$ (100), 333 $[MNa]^+$ (45).

HR ESI-MS m/z 311.1639 $[MH]^+$ (calcd. for $C_{20}H_{23}O_3$ 311.1642).

5.1.8.42 4-Hydroxy-3-iodo-5-methoxybenzaldehyde (174)[137]



Boric acid (2.00 g, 32.9 mmol, 5.0 eq.) was dissolved in 100 ml H_2O and alkalized with 1 M NaOH (aq.) till pH > 8.5. Potassium iodide (3.27 g, 19.7 mmol, 3.0 eq.), iodine (5.00 g, 19.7 mmol, 3.0 eq.) and vanillin (**33**) (1.00 g, 6.57 mmol, 1.0 eq.) were added and stirred for 17 h at r.t. The mixture was then acidified with 2 M H_2SO_4 (pH ~ 2-3) and extracted with EtOAc (2 × 100 ml). The combined organic layers were washed with 5% aqueous $Na_2S_2O_3$ solution (3 × 100 ml) until the organic solution turned to pale yellow and additionally washed with brine (100 ml). The organic fraction was dried with $MgSO_4$ and concentrated *in vacuo*, affording pure 5-iodovanillin **174** (1.59 g, 5.72 mmol, 87%) as yellowish solid.

m.p.: 180-183 °C

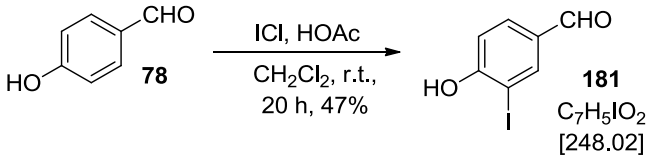
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.77 (s, 1H), 7.82 (d, J = 1.7 Hz, 1H), 7.38 (d, J = 1.7 Hz, 1H), 6.68 (s, 1H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 189.5, 151.4, 146.5, 136.2, 131.1, 108.6, 80.5, 56.5.

EI-MS m/z (%) 278 $[MH]^+$ (100).

NMR spectroscopic data are in accordance with the literature.[169]

5.1.8.43 4-Hydroxy-3-iodobenzaldehyde (181)[148]



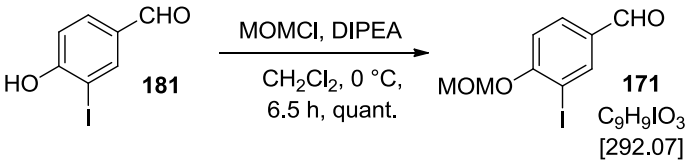
4-Hydroxybenzaldehyde (**78**) (154 mg, 1.26 mmol, 1.0 eq.) was stirred in CH_2Cl_2 (2.5 ml) while ICl (72.7 µl, 1.39 mmol, 1.1 eq.), mixed with HOAc (0.13 ml), was slowly added. The

reaction was quenched after 20 h with 20 ml H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 ml). The yellow organic phases were combined and washed with an aqueous solution of $Na_2S_2O_3$ (5%w/v, 40 ml), whilst turning to a colorless solution. This mixture was then dried ($MgSO_4$) and evaporated. The crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH 80:1) to yield **181** (147 mg, 0.593 mmol, 47%) as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.80 (s, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.79 (dd, J = 8.4, 1.9 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H).

The ^{1}H NMR spectrum is in accordance with previously reported data.[170]

5.1.8.44 3-Iodo-4-(methoxymethoxy)benzaldehyde (171)

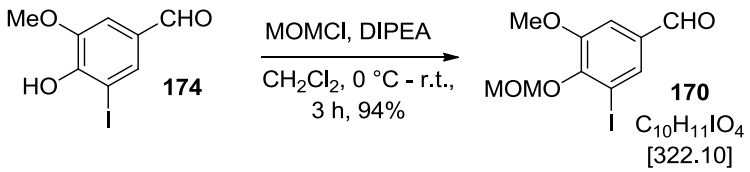


3-Iodo-4-hydroxybenzaldehyde **181** (320 mg, 1.29 mmol, 1.0 eq.) was dissolved in 4 ml CH_2Cl_2 and the solution was cooled to 0 °C. Subsequently, DIPEA (266 mg, 361 µl, 2.06 mmol, 1.6 eq.) was slowly added, followed by MOMCl (135 mg, 127 µl, 1.68 mmol, 1.3 eq.). The reaction was allowed to warm up to the ambient temperature and proceed until complete conversion (6.5 h). A saturated aqueous solution of NH_4Cl (10 ml) was used to quench the reaction and the aqueous solution was extracted with CH_2Cl_2 (2 × 15 ml). After drying with $MgSO_4$ and removal of the solvent, the pure product **171** was obtained as colorless oil (375 mg, 1.29 mmol, quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.83 (s, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.5, 2.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 5.34 (s, J = 3.5 Hz, 2H), 3.52 (s, J = 3.1 Hz, 3H).

The obtained ^{1}H NMR spectrum agrees with the literature.[171]

5.1.8.45 3-Iodo-5-methoxy-4-(methoxymethoxy)benzaldehyde (170)



5-Iodovanillin **174** (3.63 g, 13.1 mmol, 1.0 eq.) was stirred in 20 ml CH_2Cl_2 at 0 °C, while DIPEA (3.67 mmol, 21.0 mmol, 1.6 eq.) was dropwise added, followed by a slow addition of MOMCl (1.12 g, 14.8 mmol, 1.3 eq.). The mixture was stirred for 2 h at 0 °C, then the ice bath was removed and the reaction was continued at r.t. for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 ml), the layers were separated and the aqueous

phase was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*, before being submitted to a purification by CC (SiO_2; PE/EtOAc 3:1). The product **170** was obtained as a white solid in 94% yield (3.97 g, 12.3 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.82 (s, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 5.29 (s, 2H), 3.90 (s, 3H), 3.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 189.6, 152.4, 151.2, 135.1, 133.8, 111.1, 98.8, 92.1, 58.5, 56.1.

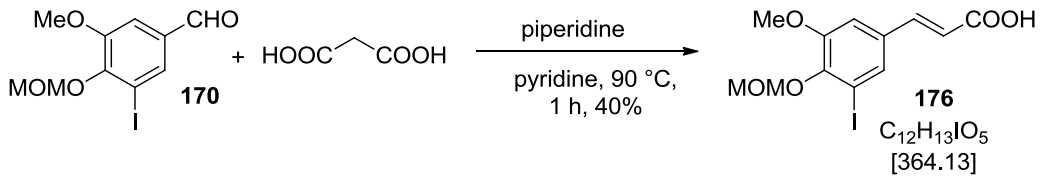
EI-MS m/z (%) 322 $[MH]^+$ (100).

m.p.: 87 – 88 °C.

UV λ_{max} 225, 280 nm.

NMR data are in agreement with the literature.[172]

5.1.8.46 (*E*)-3-(3-Iodo-5-methoxy-4-(methoxymethoxy)phenyl)acrylic acid (176)



The MOM-protected 5-iodovanillin **170** (8.19 g, 25.4 mmol), dissolved in 38 ml pyridine, was mixed with malonic acid (3.67 g, 38.1 mmol, 1.5 eq.) and piperidine (433 g, 0.503 ml, 5.09 mmol, 0.2 eq.) and stirred under reflux (90 °C) for 1 h. The reaction was then quenched with saturated aqueous solution of NH_4Cl (100 ml) and extracted with EtOAc (3 × 100 ml). The organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (RP-18; MeOH/H_2O gradient, 50 - 100% MeOH for 20 min, 100% MeOH for 5 min) and CC (SiO_2; PE/EtOAc 3:1), respectively. MOM-protected 5-iodo-ferulic acid **176** (3.68 g, 10.1 mmol, 40%) was obtained as white solid.

^{1}H NMR (300 MHz, MeOD) δ ppm 7.60 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 16.0 Hz, 1H), 7.27 (d, J = 1.9 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 5.17 (s, 2H), 3.88 (s, 3H), 3.63 (s, 3H).

^{13}C NMR (75 MHz, MeOD) δ ppm 170.2, 153.6, 149.0, 144.4, 134.0, 132.4, 119.8, 113.0, 99.9, 93.3, 58.8, 56.6.

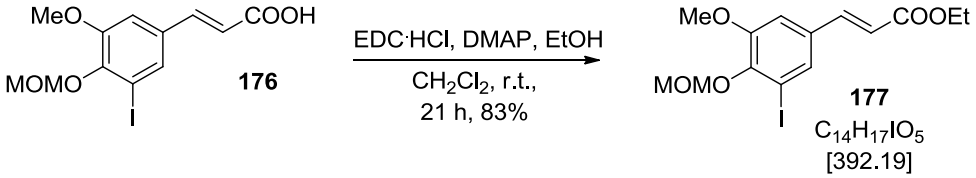
EI-MS m/z (%) 364 $[MH]^+$ (67), 332 $[MH - MeOH]^+$ (100).

HR EI-MS m/z 362.9743 $[MH]^-$ (calc. for $C_{12}H_{12}IO_5$ 362.9735).

mp: 144 - 145 °C.

UV λ_{max} 232, 287 nm.

5.1.8.47 (*E*)-Ethyl 3-(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl) acrylate (171)[147]



5-Iodo-ferulic acid **176** (225 mg, 0.618 mmol) was stirred in 1.2 ml CH_2Cl_2, while DMAP (8.0 mg, 0.062 mmol, 0.10 eq.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimid-hydrochloride (EDC·HCl, 125 mg, 0.649 mmol, 1.05 eq.) were added. The resulting orange solution was then mixed with EtOH (360 µl, 6.18 mmol, 10.0 eq.) and the reaction proceeded to complete conversion within 21 h. After removing the solvent *in vacuo*, the residue was mixed with H_2O (20 ml) and extracted with EtOAc (3 × 30 ml). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (80 ml), saturated aqueous solution of Na_2CO_3 (80 ml) and brine (80 ml), concentrated under reduced pressure and purified by CC (SiO_2; *n*-hexane/EtOAc 4:1) to afford **177** as white solid (212 mg, 0.515 mmol) in 83% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.55 (m, 1H), 7.52 (d, J = 15.8 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 5.20 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.6, 152.0, 147.5, 142.5, 132.3, 131.2, 118.4, 111.5, 98.7, 92.8, 60.6), 58.5, 55.9, 14.3.

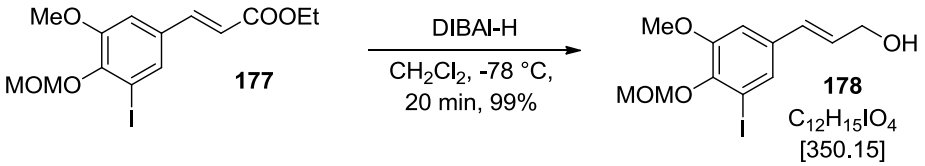
EI-MS m/z (%) 393 $[MH]^+$ (100).

HR EI-MS m/z 393.0195 $[MH]^+$ (calcd. for $C_{14}H_{18}IO_5$ 393.0193).

m.p.: 73-74 °C.

UV λ_{max} 235, 296 nm.

5.1.8.48 (*E*)-3-(3-Iodo-5-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-ol (178)[147]



Ester **177** (147 mg, 0.375 mmol) was dissolved in 0.8 ml dry CH_2Cl_2 and cooled to -78 °C, followed by a dropwise addition of DIBAl-H solution (1 M DIBAl-H in CH_2Cl_2, 787 µl, 0.787 mmol, 2.1 eq.). A TLC control showed a complete conversion after 10 min. The reaction was quenched after 20 min with 10% NaOH (aq.) at -78 °C and subsequently allowed to warm to r.t. The mixture was divided between H_2O (10 ml) and CH_2Cl_2 (10 ml), the layers were separated and the aq. phase was repeatedly extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were washed with brine (30 ml), dried with $MgSO_4$ and concentrated under reduced pressure, yielding pure allylic alcohol **178** (130 mg, 0.371 mmol, 99%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.33 (d, J = 1.9 Hz, 1H), 6.83 (d, J = 1.9 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.8, 5.4 Hz, 1H), 5.12 (s, 2H), 4.25 (m, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 2.37 (s, 1H).

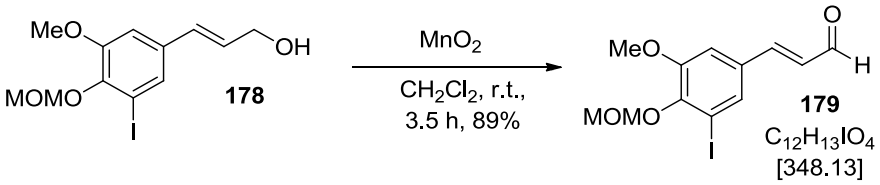
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.9, 145.1, 134.9, 129.2, 128.9, 128.6, 110.3, 98.6, 92.6, 63.1, 58.3, 55.8.

EI-MS m/z (%) 351 $[MH]^+$ (16), 332 $[MH - H_2O]^+$ (100).

HR EI-MS m/z 351.0086 $[MH]^+$ (calc. for $C_{12}H_{16}IO_4$ 351.0088).

UV λ_{max} 228, 262, 298 nm

5.1.8.49 (*E*)-3-(3-Iodo-5-methoxy-4-(methoxymethoxy)phenyl)acrylaldehyde (179)



Allylic alcohol **178** (1.33 g, 3.79 mmol) was dissolved in 30 ml CH_2Cl_2 and stirred in presence of manganese dioxide (5.88 g, 68.2 mmol, 18 eq.) for 3.5 h at r.t. The solid residue was then removed by filtration through short celite column (eluted with CH_2Cl_2) and the filtrate was evaporated to afford pure aldehyde **179** (1.18 g, 3.38 mmol, 89%) as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.67 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 15.9 Hz, 1H), 7.06 (d, J = 1.9 Hz, 1H), 6.61 (dd, J = 15.9, 7.6 Hz, 1H), 5.24 (s, 2H), 3.88 (s, 3H), 3.66 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 193.2, 152.2, 150.6, 148.4, 132.1, 131.8, 128.6, 111.6, 98.8, 92.9, 58.6, 56.1.

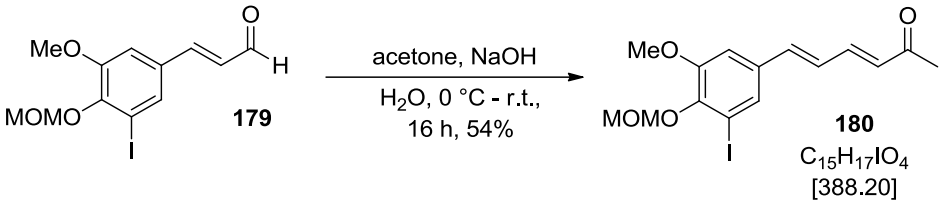
EI-MS *m/z* (%) 348 $[M]^{+\cdot}$ (8), 221 $[M - I]^{+\cdot}$ (11).

HR EI-MS *m/z* 347.9856 $[M]^{+\cdot}$ (calcd. for $C_{12}H_{13}IO_4$ 347.9859).

m.p. 73-76 °C

UV λ_{max} 236, 307 nm.

5.1.8.50 (3*E*,5*E*)-6-(3-Iodo-5-methoxy-4-(methoxymethoxy)phenyl)hexa-3,5-dien-2-one (180)



Aldehyde **179** (1.18 g, 3.38 mmol) was dissolved in acetone/H_2O mixture (7:1, 3.2 ml) and cooled to 0 °C, followed by addition of 10% w/v aqueous NaOH solution (0.4 ml). The reaction proceeded overnight at r.t. Then it was neutralized by 1 M HCl (aq.), mixed with H_2O (20 ml) and extracted with EtOAc (3 × 30 ml). The organic phases were dried ($MgSO_4$) and the solvent was evaporated. The crude mixture was submitted to CC (SiO_2; PE/EtOAc 3:1) and flash chromatography (RP-18; MeOH/H_2O 50-100% MeOH within 25 min, 100% MeOH for 5 min, 20 ml/min), respectively, and ketone **180** (710 mg, 1.83 mmol, 54%) was obtained as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.40 (d, *J* = 1.8 Hz, 1H), 7.23 – 7.11 (m, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.72 – 6.66 (m, 2H), 6.18 (d, *J* = 15.5 Hz, 1H), 5.12 (s, 2H), 3.79 (s, 3H), 3.60 (s, 3H), 2.24 (s, 3H).

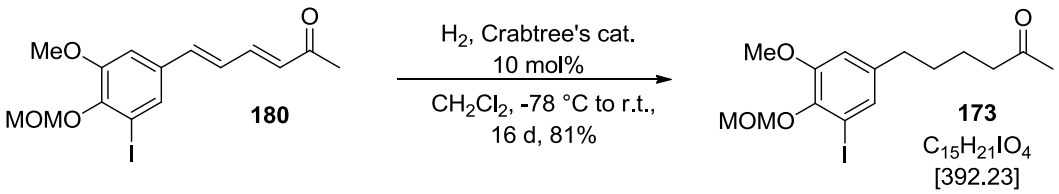
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 198.0, 151.8, 146.4, 142.7, 138.8, 133.8, 130.4, 129.9, 126.7, 110.7, 98.5, 92.7, 58.2, 55.7, 27.2.

EI-MS *m/z* (%) 388 $[M]^{+\cdot}$ (11), 261 $[M - I]^{+\cdot}$ (13).

HR EI-MS *m/z* 388.0172 $[M]^{+\cdot}$ (calcd. for $C_{15}H_{17}IO_4$ 388.0172).

UV λ_{max} 257, 336 nm.

5.1.8.51 6-(3-Iodo-5-methoxy-4-(methoxymethoxy)phenyl)hexan-2-one (173)



The unsaturated ketone **180** (635 mg, 1.64 mmol) was dissolved in 33 ml dry CH_2Cl_2 under N_2, followed by addition of (tricyclohexylphosphine)(1,5-cyclooxadiene)(pyridine)iridium(I) hexa-fluorophosphate (Crabtree's catalyst, 132 mg, 0.164 mmol, 0.1 eq.). The mixture was cooled to -78 °C and the N_2 atmosphere was replaced by H_2, applied via a balloon. The reaction slowly proceeded at r.t., reaching a complete conversion after 16 days (determined by TLC). The solvent was evaporated and the crude mixture was purified by CC (SiO_2; PE/EtOAc 3:1) to give **173** (520 mg, 1.33 mmol, 81%) as yellow oil.

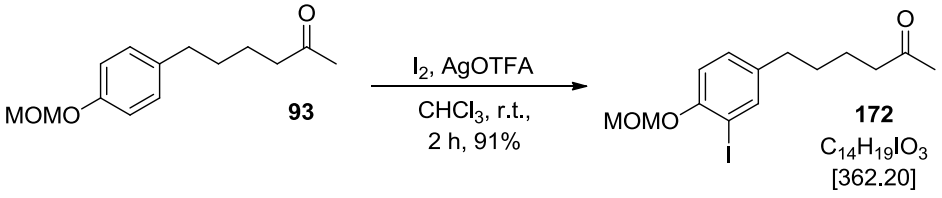
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.17 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.66 (s, 3H), 2.51 (t, J = 7.0 Hz, 2H), 2.44 (t, J = 6.7 Hz, 2H), 2.13 (s, 3H), 1.69 – 1.48 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 208.9, 152.0, 143.8, 140.4, 130.4, 113.1, 98.7, 92.4, 58.3, 55.9, 43.4, 35.0, 30.7, 29.9, 23.3.

ESI-MS m/z (%) 415 $[MNa]^+$ (31), 410 $[MNH_4]^+$ (54), 361 $[MH - MeOH]^+$ (100).

HR ESI-MS m/z 410.0828 $[MNH_4]^+$ (calcd. for $C_{15}H_{25}INO_4$, 410.0823).

5.1.8.52 6-(3-Iodo-4-(methoxymethoxy)phenyl)hexan-2-one (172)[29]



Ketone **93** (721 mg, 3.05 mmol) was dissolved in 28 ml $CHCl_3$, followed by addition of silver trifluoroacetate (1.35 g, 6.10 mmol, 2.0 eq.). Iodine (1.55 g, 6.10 mmol, 2.0 eq.) was meanwhile dissolved in $CHCl_3$ (28 ml) and then slowly added to the stirred slurry of ketone **93** via a dropping funnel. The reaction was stopped after 2 h, solid residues were filtered off (celite pad, elution with 100 ml $CHCl_3$) and the yellow filtrate was washed with saturated aqueous solution of Na_2SO_3 (100 ml). The organic layer was subsequently dried

with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified with CC (SiO_2; PE/EtOAc 3:1), affording **172** (1.01 g, 2.78 mmol, 91%) as yellow oil.

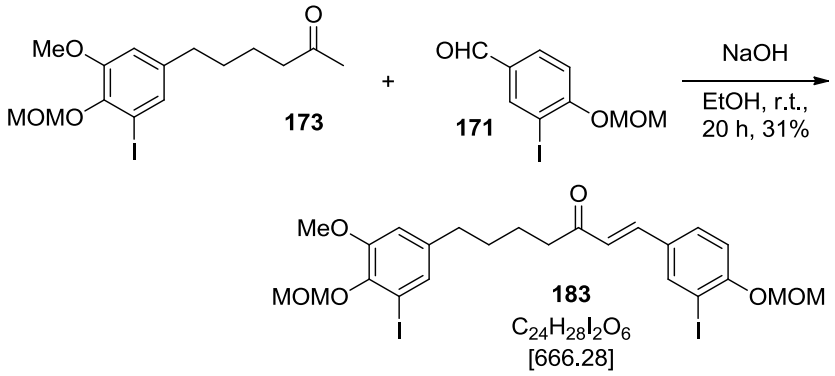
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.58 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.19 (s, 2H), 3.50 (s, 3H), 2.51 (t, J = 7.0 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H), 2.12 (s, 3H), 1.65 – 1.49 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 208.9, 154.1, 139.0, 137.8, 129.3, 114.8, 95.1, 87.2, 56.4, 43.4, 34.3, 30.9, 29.9, 23.2.

ESI-MS m/z (%) 331 $[MH - MeOH]^+$ (100), 380 $[MNH_4]^+$ (35), 385 $[MNa]^+$ (27).

HR ESI-MS m/z 380.0710 $[MNH_4]^+$ (calcd. for $C_{14}H_{23}INO_3$, 380.0717).

5.1.8.53 (*E*)-1-(3-Iodo-4-(methoxymethoxy)phenyl)-7-(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)hept-1-en-3-one (183)



Ketone **173** (296 mg, 0.754 mmol) was dissolved in 15 ml EtOH and was stirred in presence of NaOH (76.0 mg, 1.89 mmol, 2.5 eq.) while aldehyde **171** (397 mg, 1.36 mmol, 1.8 eq.) was added in small portions. The mixture was stirred for 20 h at r.t., then, the solvent was removed and the residue mixed with 20 ml of saturated aqueous solution of NH_4Cl. The aqueous solution was extracted with EtOAc (3 × 15 ml), the combined organic layers were dried with $MgSO_4$ and EtOAc was removed on a rotary evaporator. The crude mixture was purified with flash chromatography (RP-18; MeOH/H_2O 50-100% MeOH within 25 min, 100% MeOH for 5 min, 20 ml/min) providing **183** as yellowish oil (157 mg, 0.236 mmol) in 31% yield.

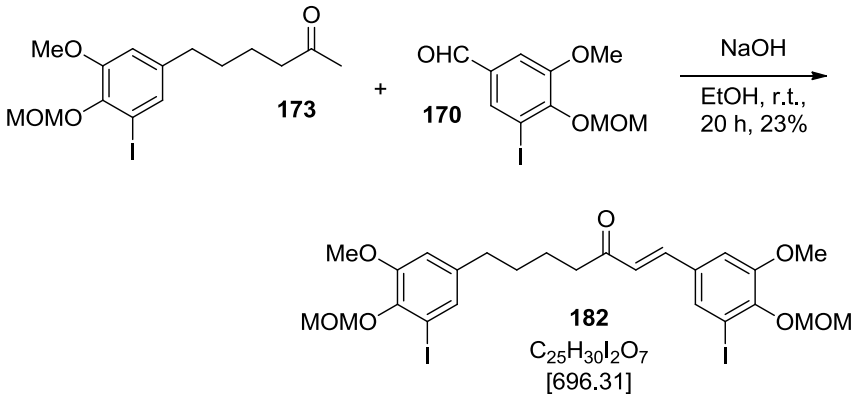
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.97 (d, J = 2.0 Hz, 1H), 7.47 – 7.42 (dd, J = 8.9, 2.1 Hz, 1H), 7.39 (d, J = 16.3 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 5.25 (s, 2H), 5.10 (s, 2H), 3.79 (s, 3H), 3.65 (s, 3H), 3.48 (s, 3H), 2.64 (t, J = 6.9 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 1.77 – 1.53 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 199.7, 157.5, 151.8, 143.7, 140.3, 140.2, 139.0, 130.3, 130.0, 129.7, 125.1, 114.3, 113.0, 98.5, 94.6, 92.4, 87.4, 58.2, 56.4, 55.8, 40.6, 34.9, 30.8, 23.7.

ESI-MS *m/z* (%) 667 $[MH]^+$ (100), 689 $[MNa]^+$ (17)

HR ESI-MS *m/z* 667.0043 $[MH]^+$ (calcd. for $C_{24}H_{29}I_2O_6$, 667.0048)

5.1.8.54 (*E*)-1,7-Bis(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)hept-1-en-3-one (182)



To a stirred solution of ketone **173** (191 mg, 0.487 mmol) and sodium hydroxide (48.7 mg, 1.22 mmol, 2.5 eq.) in EtOH (10 ml), aldehyde **170** (282 mg, 0.877 mmol, 1.8 eq.) was added in portions. After stirring at r.t. for 20 h, the reaction was stopped, EtOH was evaporated and 20 ml of saturated aqueous solution of NH_4Cl were added. The aqueous solution was extracted with EtOAc (3 × 30 ml), the combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified with by flash chromatography (RP-18; MeOH/H_2O 50-100% MeOH in 25 min, 100% MeOH for 5 min), which provided **182** (78.0 mg, 0.122 mmol, 23%) as yellowish oil.

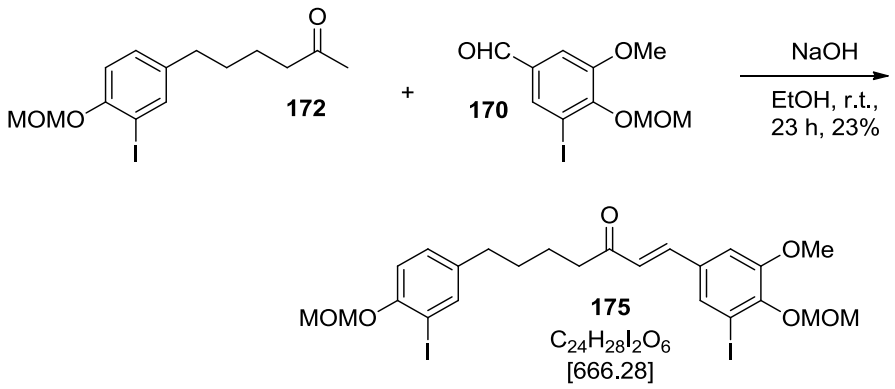
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.57 (d, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 16.1 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.68 (d, *J* = 1.8 Hz, 1H), 6.61 (d, *J* = 16.1 Hz, 1H), 5.20 (s, 2H), 5.10 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 3.65 (s, 3H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 1.77 – 1.53 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 199.7, 152.0, 151.9, 147.6, 143.7, 140.4, 140.3, 132.3, 131.3, 130.3, 126.2, 113.0, 111.7, 98.7, 98.6, 92.8, 92.4, 58.4, 58.3, 55.9, 55.8, 40.5, 35.0, 30.8, 23.7.

ESI-MS *m/z* (%) 718 $[MNa]^+$ (100), 697 $[MH]^+$ (24), 664 $[MH - MeOH]^+$ (39).

HR ESI-MS *m/z* 718.9968 $[MNa]^+$ (calcd. for $C_{25}H_{30}I_2NaO_7$, 718.9973).

5.1.8.55 (*E*)-7-(3-Iodo-4-(methoxymethoxy)phenyl)-1-(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)hept-1-en-3-one (175)



Ketone **172** (797 mg, 2.20 mmol) and NaOH (220 mg, 5.50 mmol, 2.5 eq.), dissolved in 44 ml EtOH, were mixed with aldehyde **170** (1.28 g, 3.96 mmol) and stirred for 23 h at r.t. EtOH was then removed on a rotary evaporator, saturated aqueous solution of NH_4Cl (40 ml) was added to the residue and the aqueous solution was extracted with EtOAc (3 × 40 ml). After drying with $MgSO_4$ and removal of EtOAc under reduced pressure, the crude product was purified by flash chromatography (RP-18; MeOH/H_2O 50-100% MeOH within 25 min, 100% MeOH for 5 min) and column chromatography (SiO_2; PE/EtOAc 3:1) to get **175** (333 mg, 0.50 mmol, 23%) as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.59 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 16.1 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 16.1 Hz, 1H), 5.21 (s, J = 3.0 Hz, 2H), 5.19 (s, J = 2.5 Hz, 3H), 3.86 (s, 3H), 3.66 (s, J = 4.3 Hz, 3H), 3.49 (s, J = 2.4 Hz, 4H), 2.65 (t, J = 7.0 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.77 – 1.54 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 199.7, 154.1, 152.1, 147.7, 140.4, 139.0, 137.7, 132.4, 131.4, 129.3, 126.2, 114.9, 111.8, 98.7, 95.1, 92.8, 87.2, 58.4, 56.3, 56.0, 40.6, 34.3, 30.9, 23.7.

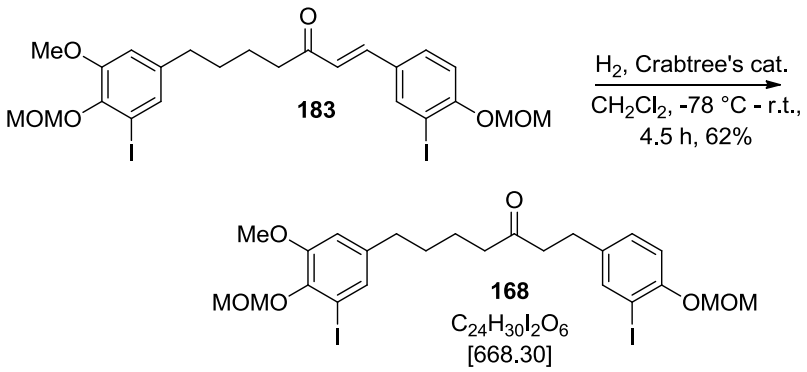
ESI-MS m/z (%) 667 $[MH]^+$ (100).

HR ESI-MS m/z 667.0052 $[MH]^+$ (calcd. for $C_{24}H_{29}I_2O_6$, 667.0048).

m.p.: 99 °C

UV λ_{max} 227, 290, 306 nm

5.1.8.56 1-(3-Iodo-4-(methoxymethoxy)phenyl)-7-(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)heptan-3-one (168)



The unsaturated diarylheptanoid **183** (157 mg, 0.236 mmol) was dissolved in dry CH_2Cl_2 under N_2 atmosphere. (Tricyclohexylphosphine)(1,5-cyclooxadiene)(pyridine)iridium(I) hexafluoro-phosphate (Crabtree's catalyst, 14.2 mg, 17.7 µmol, 0.075 eq.) was added, the mixture was cooled to -78 °C and the N_2 was replaced by H_2 atmosphere. The cooling bath was removed after 30 min and the reaction was allowed to stirr for 4.5 h. After finishing the reaction, the solvent was removed and the residue purified by CC (SiO_2; PE/EtOAc 2:1) affording 97.8 mg (0.146 mmol, 62%) of **168** as colorless oil.

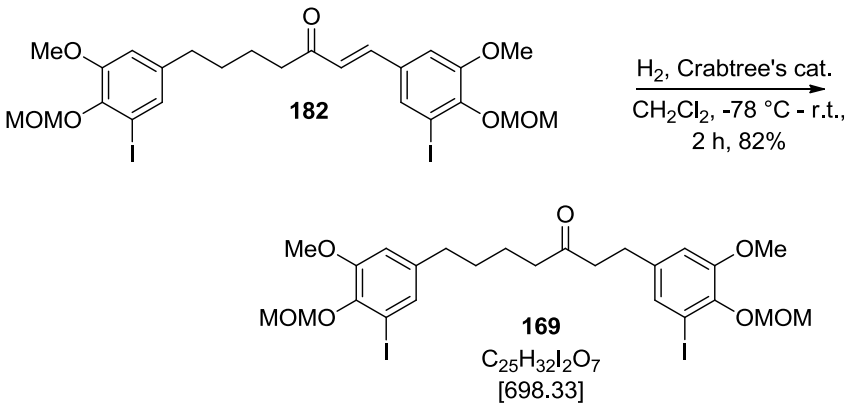
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.58 (d, *J* = 2.1 Hz, 1H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.06 (dd, *J* = 2.2, 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.48 (s, 3H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.70 – 2.59 (m, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.38 (m, 2H), 1.63 – 1.48 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 209.5, 154.3, 151.9, 143.7, 140.3, 139.0, 136.5, 130.3, 129.3, 114.8, 113.0, 98.6, 95.0, 92.4, 87.2, 58.3, 56.3, 55.9, 44.1, 42.6, 34.9, 30.7, 28.2, 23.2.

ESI-MS *m/z* (%) 691 $[MNa]^+$ (100), 686 $[MNH_4]^+$ (36).

HR ESI-MS *m/z* 691.0031 $[MNa]^+$ (calcd. for $C_{24}H_{30}I_2NaO_6$, 691.0024).

5.1.8.57 1,7-Bis(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)heptan-3-one (169)



Enone **182** (78.0 mg, 0.112 mmol), dissolved in dry CH_2Cl_2, was mixed with (tricyclohexylphosphine)(1,5-cyclooxadiene)(pyridine)iridium(I) hexafluorophosphate (Crabtree's catalyst, 9.0 mg, 11 µmol, 0.1 eq.) and the orange solution was cooled to -78 °C. The Schlenk flask was filled with H_2 atmosphere, the reaction was stirred for 30 min at -78 °C and further 1.5 h at r.t. The solvent was evaporated and the crude product was purified with CC (SiO_2; PE/EtOAc 3:1), providing **169** (64 mg, 0.092 mmol, 82%) as colorless oil.

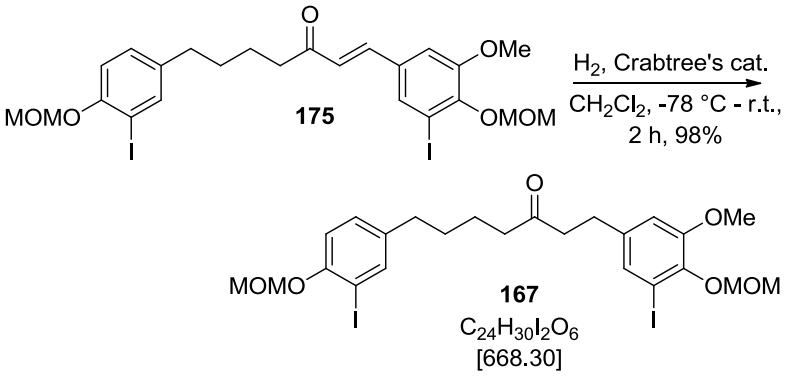
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.17 (d, J = 1.6 Hz, 2H), 6.70 (d, J = 1.9 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H), 5.11 (s, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.72 – 2.64 (m, 2H), 2.54 – 2.46 (m, 2H), 2.45 – 2.35 (m, 2H), 1.63 – 1.48 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.4, 151.99, 151.96, 144.1, 143.9, 140.3, 139.3, 130.4, 130.3, 113.3, 113.1, 98.6 (2C), 92.5, 92.4, 58.3 (2C), 55.9 (2C), 44.0, 42.7, 35.0, 30.8, 28.9, 23.2.

ESI-MS m/z (%) 716 $[MNH_4]^+$ (40), 721 $[MNa]^+$ (100).

HR ESI-MS m/z 721.0131 $[MNa]^+$ (calcd. for $C_{25}H_{32}I_2NaO_7$, 721.0130).

5.1.8.58 7-(3-iodo-4-(methoxymethoxy)phenyl)-1-(3-iodo-5-methoxy-4-(methoxymethoxy)phenyl)heptan-3-one (167)



Diarylheptanoid **175** (329 mg, 0.494 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 under N_2 atmosphere and mixed with (tricyclohexylphosphine)(1,5-cyclooxadiene)(pyridine)iridium(I) hexafluorophosphate (Crabtree's catalyst, 39 mg, 0.049 mmol, 0.1 eq.). The orange solution was cooled to -78 °C, the reaction vessel was filled with H_2 (balloon, ~1 bar) and the reaction was stirred for 2 h at r.t. until complete conversion of the starting material. The solvent was subsequently removed under reduced pressure and the crude product was purified by CC (SiO_2; PE/EtOAc 2:1) affording **167** (325 mg, 0.487 mmol, 98%) as yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.58 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 1.8 Hz, 1H), 5.20 (s, 2H), 5.12 (s, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.51 (s, 3H), 2.79 (m, 2H), 2.67 (m, 2H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 6.8 Hz, 2H), 1.70 – 1.46 (m, 4H).

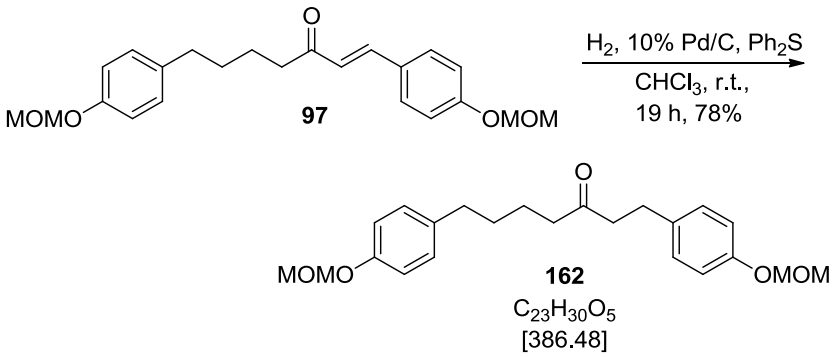
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 209.5, 154.2, 152.0, 144.1, 139.3, 139.0, 137.7, 130.3, 129.3, 114.8, 113.3, 98.6, 95.1, 92.5, 87.2, 58.4, 56.4, 55.9, 44.1, 42.8, 34.3, 30.9, 28.9, 23.2.

ESI-MS *m/z* (%) 686 $[MNH_4]^+$ (100).

HR ESI-MS *m/z* 691.0030 $[MNH_4]^+$ (calcd. for $C_{24}H_{30}I_2NaO_6$, 691.0024).

UV λ_{max} 281, 339 nm.

5.1.8.59 1,7-Bis(4-(methoxymethoxy)phenyl)heptan-3-one (162)



The unsaturated diarylheptanoid **97** (108 mg, 0.281 mmol), dissolved in 2 ml $CHCl_3$, was mixed with 10% Pd/C (11 mg) and diphenyl sulfide (2.4 µl, 0.014 mmol, 0.05 eq.). The black slurry was stirred under H_2 atmosphere (balloon, ~1 bar) for 19 h, followed by filtration through a pad of celite (eluted with $CHCl_3$). The crude mixture was purified with the aid of CC (SiO_2; *n*-hexane/EtOAc 5:1), yielding 84.5 mg (0.219 mmol, 78%) of **162** as colorless oil.

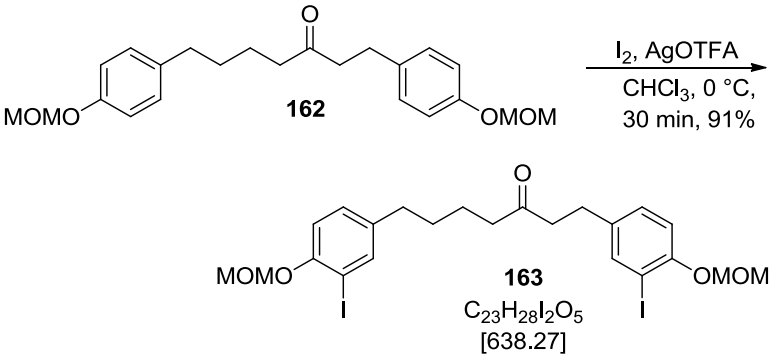
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 – 7.05 (m, 4H), 6.98 – 6.93 (m, 4H), 5.15 (s, 2H), 5.14 (s, 2H), 3.48 (s, 3H), 3.47 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.69 – 1.45 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 210.0, 155.5, 155.3, 135.5, 134.4, 129.2 (4C), 116.3 (2C), 116.1 (2C), 94.51, 94.47, 55.8 (2C), 44.3, 42.7, 34.8, 31.0, 28.9, 23.2.

ESI-MS *m/z* (%) 323 $[MH - 2MeOH]^+$ (100), 404 $[MNH_4]^+$ (63), 409 $[MNa]^+$ (37).

HR ESI-MS *m/z* 404.2421 $[MNH_4]$ (calcd. for $C_{23}H_{34}NO_5$, 404.2431).

5.1.8.60 1,7-Bis(3-iodo-4-(methoxymethoxy)phenyl)heptan-3-one (163)



Silver trifluoroacetate (96.0 mg, 0.434 mmol, 4.0 eq.) was added to a stirred solution of **162** (42.0 mg, 0.109 mmol, 1.0 eq.) in 1 ml $CHCl_3$. The resulting slurry was cooled to 0 °C and iodine solution (110 mg, 0.434 mmol, 4.0 eq., in 2 ml $CHCl_3$) was added dropwise. The mixture was stirred for 30 min at 0 °C, subsequently, it was passed through a pad of celite (eluted with $CHCl_3$, 50 ml) and the resulting $CHCl_3$ solution was washed with saturated aqueous solution of Na_2SO_3 (20 ml). The organic solvent was then dried ($MgSO_4$) and removed under reduced pressure. The purification with CC (SiO_2; *n*-hexane/EtOAc 4:1) gained **163** (63.0 mg, 0.099 mmol, 91%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.59 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 2H), 5.19 (s, 2H), 3.50 (s, 3H), 3.49 (s, 3H), 2.82 – 2.75 (m, 2H), 2.70 – 2.62 (m, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 2.38 (t, *J* = 6.8 Hz, 2H), 1.63 – 1.46 (m, 4H).

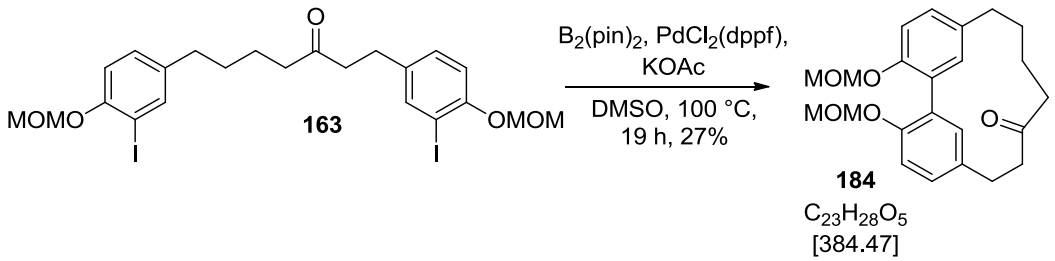
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 209.5, 154.3, 154.1, 139.0 (2 × CH), 137.7, 136.6, 129.4 (CH), 129.3 (CH), 114.8 (CH), 114.8 (CH), 95.02 (OCH_2O), 94.97 (OCH_2O), 87.2, 87.1, 56.3 (2 × OCH_3), 44.1 (CH_2), 42.7 (CH_2), 34.3 (CH_2), 30.9 (CH_2), 28.2 (CH_2), 23.1 (CH_2).

EI-MS *m/z* (%) 638 $[M]^{+\cdot}$ (8), 561 (100), 308 (33).

HR EI-MS *m/z* 638.0026 $[M]^{+\cdot}$ (calcd. for $C_{23}H_{28}I_2O_5$, 638.0026).

UV λ_{max} 224, 282 nm

5.1.8.61 3,17-Dimethoxymethoxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (184)



The diiodinated diarylheptanoid **163** (583 mg, 0.914 mmol, 1.0 eq.), bis(pinacolato)diboron (279 mg, 1.10 mmol, 1.2 eq.), [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II) (74 mg, 0.091 mmol, 0.1 eq.) and potassium acetate (897 mg, 9.14 mmol, 10 eq.) were loaded into a Schlenk flask under N_2 atmosphere. Degassed, dried DMSO (95 ml) was added and the cyclization was started by stirring at 100 °C. After 19 h, the reaction was allowed to cool to ambient temperature, saturated aqueous solution of NH_4Cl (200 ml) was added and subsequently extracted with EtOAc (4 × 200 ml). Combined organic layers were dried with $MgSO_4$ and liberated of solvent under reduced pressure. The crude mixture was passed through a short column (SiO_2; eluted with PE/EtOAc 2:1), concentrated *in vacuo* and finally purified with CC (SiO_2; PE/EtOAc 3:1), affording **184** (94.9 mg, 0.247 mmol, 27%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 – 7.03 (m, 4H), 6.77 (d, J = 1.5 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 5.17 (s, 2H), 5.14 (s, 2H), 3.46 (s, 3H), 3.43 (s, 3H), 3.32 – 2.49 (m, 8H), 2.00 – 1.50 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 213.5, 152.9, 152.4, 134.7, 134.3, 133.9, 132.9, 130.2, 129.3, 129.3, 128.2, 115.4, 115.2, 95.0 (2C), 55.74, 55.69, 46.8, 42.5, 31.8, 29.6, 25.3, 20.9.

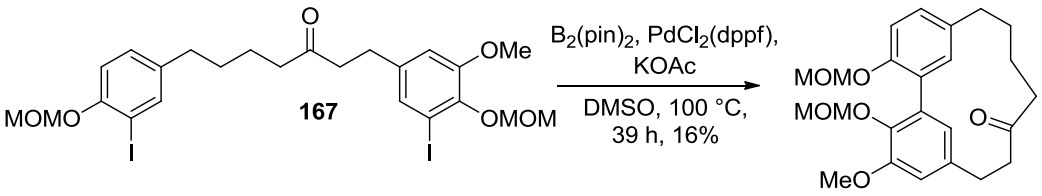
ESI-MS m/z (%) 402 $[MNH_4]^+$ (100), 353 $[MH - MeOH]^+$ (80)

HR ESI-MS m/z 402.2273 $[MNH_4]^+$ (calcd. for $C_{23}H_{32}NO_5$, 402.2275).

UV λ_{max} 285 nm.

m.p. 102 °C.

5.1.8.62 16-Methoxy-3,17-dimethoxymethoxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (185)



185
$C_{24}H_{30}O_6$
[414.49]

Diiodinated linear diarylheptanoid **167** (236 mg, 0.353 mmol, 1.0 eq.), bis(pinacolato)diboron (109 mg, 0.430 mmol, 1.2 eq.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (29 mg, 0.035 mmol, 0.1 eq.) and potassium acetate (346 mg, 3.53 mmol, 10 eq.) were mixed with degassed dry DMSO (35 ml) in a Schlenk flask and stirred at 100 °C for 39 h. The black solution was then allowed to cool to r.t., saturated aqueous NH_4Cl solution (90 ml) was added and subsequently extracted with EtOAc (4 × 100 ml). The organic phase was dried with $MgSO_4$, the solvent was evaporated and the crude mixture was purified by CC (SiO_2; PE/EtOAc 2:1), yielding 22.9 mg (55.2 µmol, 16%) of the product **185** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.04 (s, 2H), 6.81 (s, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 5.14 (s, 2H), 4.99 (br s, 2H), 3.88 (s, 3H), 3.44 (s, 3H), 3.20 (s, 3H), 3.00 – 2.47 (m, 8H), 1.91 – 1.68 (m, 4H).

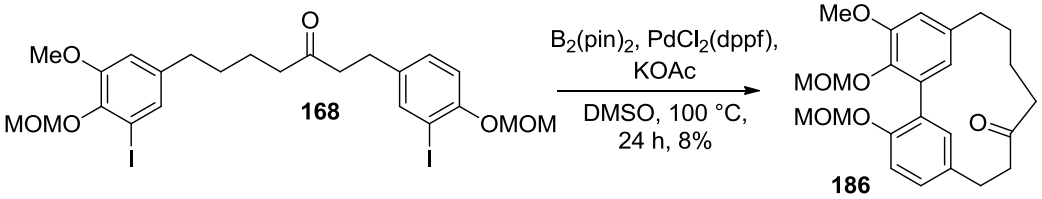
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 213.3, 152.1, 152.1, 141.5, 135.8, 134.5, 134.3, 132.8, 129.5, 129.4, 126.1, 115.1, 111.3, 97.9, 94.8, 56.6, 55.8, 46.5, 42.0, 31.9, 29.9, 25.5, 21.0.

ESI-MS m/z (%) 432 $[MNH_4]^+$ (100), 437 $[MNa]^+$ (37).

HR ESI-MS m/z 432.2383 $[MNH_4]^+$ (calcd. for $C_{24}H_{34}NO_6$, 432.2381).

UV λ_{max} 284 nm.

5.1.8.63 4-Methoxy-3,17-dimethoxymethoxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (186)



186
$C_{24}H_{30}O_6$
[414.49]

Compound **168** (97.0 mg, 0.145 mmol, 1.0 eq.), together with bis(pinacolato)diboron (44.2 mg, 0.174 mmol, 1.2 eq.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12 mg, 0.015 mmol, 0.1 eq.) and potassium acetate (142 mg, 1.45 mmol, 10 eq.), was loaded into a Schlenk flask under protective atmosphere (N_2). Degassed and dry DMSO was added (14.5 ml) and the mixture was stirred at 100 °C. After 21 h, the reaction was allowed to cool to ambient temperature, to be subsequently quenched with 40 ml of saturated aqueous solution of NH_4Cl. The resulting aqueous solution was extracted with EtOAc (4 × 40 ml), the organic phase was then dried ($MgSO_4$) and the solvent evaporated. The crude product was purified by CC (SiO_2; PE/EtOAc 3:1) and preparative HPLC (RP-18, MeOH/H_2O, method 1, 5.1.2), providing after lyophilisation **186** (4.7 mg, 11 µmol, 8%) as amorphous powder.

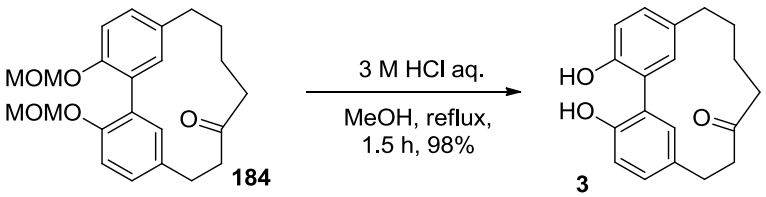
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.05 (d, J = 1.4 Hz, 2H), 6.70 – 6.64 (m, 2H), 6.35 (d, J = 2.1 Hz, 1H), 5.17 (s, 2H), 4.95 (s, 2H), 3.86 (s, 3H), 3.47 (s, 3H), 3.14 (s, 3H), 3.05 – 2.47 (m, 8H), 1.68 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 213.7, 152.7, 152.3, 141.2, 135.1, 134.1, 133.9, 133.5, 130.4, 128.3, 126.4, 115.0, 112.1, 98.0, 94.8, 56.6, 56.0, 55.9, 47.3, 42.7, 32.6, 29.9, 25.2, 21.0.

ESI-MS m/z (%) 339 (100), 383 $[MH - MeOH]^+$ (76), 432 $[MNH_4]^+$ (51), 437 $[MNa]^+$ (51).

HR ESI-MS m/z 432.2383 $[MNH_4]^+$ (calcd. for 432.2381, $C_{24}H_{34}NO_6$).

5.1.8.64 3,17-Dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-one (acerogenin E, 3)



The MOM-protected acerogenin E **184** (61.4 mg, 0.160 mmol, 1.0 eq.) was dissolved in 8 ml MeOH, mixed with 1.60 ml of 3 M HCl aq. solution (4.79 mmol, 30 eq.) and stirred under reflux for 1.5 h. After this time, the mixture was allowed to cool to r.t., MeOH was evaporated and the residue was mixed with ice-cold H_2O (30 ml). The aqueous solution was extracted with EtOAc (3 × 30 ml), the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*, yielding pure acerogenin E (**3**) (46.5 mg, 0.157 mmol, 98%) as yellowish solid.

^{1}H NMR (400 MHz, acetone-d_6) δ ppm 7.04 (m, 2H), 6.96 (d, J = 1.9 Hz, 1H), 6.86 (m, 2H), 6.76 (d, J = 1.8 Hz, 1H), 2.96 (m, 2H), 2.87 (m, 2H), 2.74 (t, J = 6.2 Hz, 4H), 1.94 (m, 2H), 1.84 – 1.68 (m, 2H).

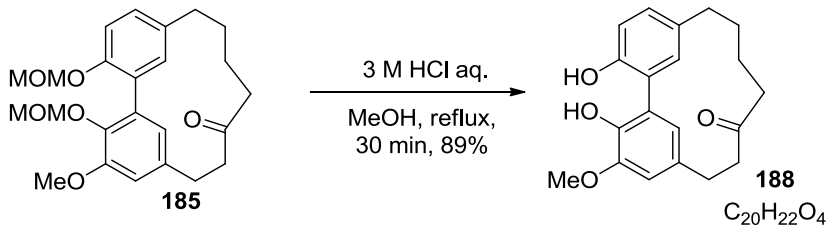
^{13}C NMR (101 MHz, acetone-d_6) δ ppm 212.7, 152.2, 152.1, 134.5, 134.4, 133.3, 132.5, 130.3, 129.4, 127.16, 126.8, 117.0, 116.8, 45.0, 42.5, 32.0, 28.4, 26.5, 22.9.

ESI-MS m/z (%) 297 $[MH]^+$ (100).

HR ESI-MS m/z (%) 297.1488 $[MH]^+$ (calcd. for $C_{19}H_{21}O_3$, 297.1485).

For the exact assignment of the NMR data, see 3.3.3.1.

5.1.8.65 16-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (188)



Compound **185** (23 mg, 55 µmol, 1.0 eq.), dissolved in 2.8 ml MeOH, was stirred under reflux for 30 min in presence of 3 M HCl aq. (55.3 µl, 1.66 mmol, 30 eq.). Subsequently, the solvent was evaporated and ice cold H_2O (20 ml) was added, followed by the extraction with EtOAc (3 × 25 ml). The combined organic phases were dried with $MgSO_4$ and after removal of the EtOAc under reduced pressure, **188** was obtained as yellowish oil (16.1 mg, 49.3 µmol, 89%).

^{1}H NMR (600 MHz, acetone-d_6) δ ppm 7.02 (dd, J = 8.2, 2.3 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 1.9 Hz, 1H), 3.89 (s, 3H), 2.99 – 2.96 (m, 2H), 2.87 (m, 2H), 2.74 (m, 4H), 1.94 (m, 2H), 1.75 (dt, J = 14.4, 7.1 Hz, 2H).

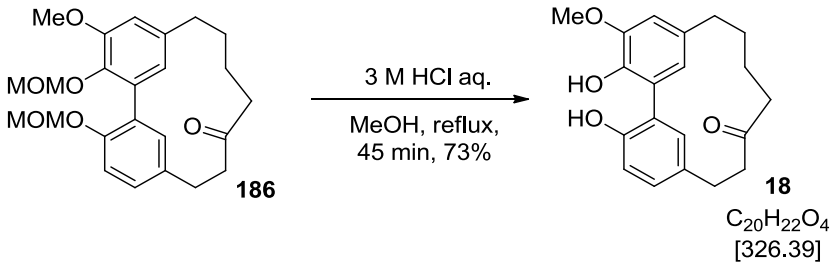
^{13}C NMR (151 MHz, acetone-d_6) δ 211.6, 152.2, 147.7, 140.2, 133.1, 132.4, 131.2, 129.6, 125.9, 125.7, 125.4, 116.7, 110.7, 55.8, 44.2, 41.5, 31.1, 28.0, 25.7, 22.0.

ESI-MS m/z (%) 327 $[MH]^+$ (100).

HR ESI-MS m/z 327.1593 $[MH]^+$ (calcd. for $C_{20}H_{23}O_4$, 327.1591).

For the exact assignment of the NMR data, see 3.3.3.1.

5.1.8.66 4-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (myricananin C, 18)



Substrate **186** (4.0 mg, 9.7 µmol, 1.0 eq.) and 3 M HCl aq. (96.5 µl, 0.290 mmol, 30 eq.) were stirred under reflux for 45 min in 0.5 ml MeOH. The reaction was then finished by the addition of ice cold H_2O (10 ml), followed by the extraction with EtOAc (3 × 10 ml). The combined organic layers provided after drying ($MgSO_4$) and evaporation of the solvent crude myricananin C, which was immediately purified with preparative HPLC (RP-18; MeOH/H_2O, method 2, 5.1.2). The purification afforded myricananin C (**18**) in 73% yield (2.3 mg, 7.1 µmol).

^{1}H NMR (600 MHz, acetone-d_6) δ ppm 7.03 (dd, J = 8.2, 2.2 Hz, 1H), 6.80 (m, 2H), 6.77 (d, J = 2.1 Hz, 1H), 6.54 (br s, 1H), 3.85 (s, 3H), 2.94 (m, 2H), 2.74 (m, 4H), 1.95 – 1.88 (m, 2H), 1.82 – 1.75 (m, 2H).

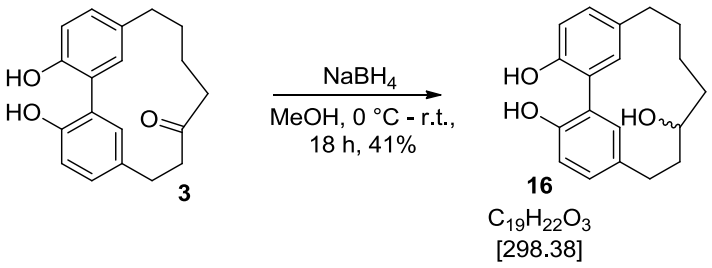
^{13}C NMR (151 MHz, acetone-d_6) δ ppm 211.9, 152.2, 148.0, 140.5, 133.1, 132.1, 131.5, 128.6, 126.2, 125.6, 125.3, 116.5, 111.5, 55.8, 44.6, 41.7, 31.7, 27.8, 25.6, 22.0.

ESI-MS m/z (%) 327 $[MH]^+$ (100).

HR ESI-MS m/z 327.1590 $[MH]^+$ (calcd. for $C_{20}H_{23}O_4$, 327.1591).

For the exact assignment of the NMR data, see 3.3.3.1.

5.1.8.67 3,17-Dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-ol (16)



Acerogenin E (**3**) (4.9 mg, 17 µmol, 1.0 eq.), dissolved in 0.4 ml MeOH, was stirred in presence of $NaBH_4$ (96 mg, 2.5 mmol, 150 eq.) at 0 °C and subsequently at r.t. for 18 h. The reaction was stopped by the addition of 10 ml H_2O, followed by the extraction with EtOAc

(3 × 15 ml). Combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by a preparative HPLC (RP-18; MeOH/H_2O, method 2) providing acerogenin K (**16**) as white amorphous powder in 41% yield (2.0 mg, 6.7 µmol).

^{1}H NMR (600 MHz, acetone-d_6) δ ppm 7.25 (br s, 1H), 7.21 (br s, 1H), 7.06 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.05 (t, *J* = 9.7 Hz, 1H), 2.93 (m, 2H), 2.83 (m, 1H), 2.49 (m, 1H), 2.27 (m, 1H), 2.01 (m, 1H), 1.85 (m, 2H), 1.66 (m, 2H), 1.58 (m, 1H), 1.48 (m, 1H).

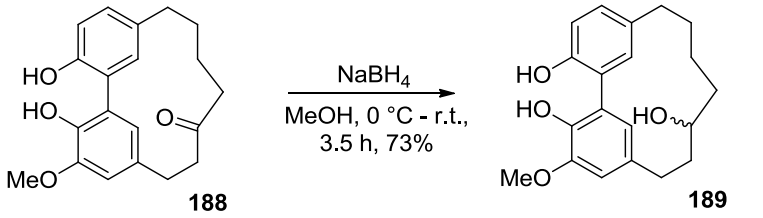
^{13}C NMR (151 MHz, acetone-d_6) δ ppm 152.18, 152.17, 135.1, 134.7, 132.3, 131.9, 130.4, 130.3, 127.1, 126.9, 116.97, 116.95, 68.5, 40.7, 35.7, 30.7, 27.6, 27.5, 23.8.

ESI-MS *m/z* (%) 299 $[MH]^+$ (6), 281 $[MH - H_2O]^+$ (100).

HR ESI-MS *m/z* (%) 281.1539 $[MH - H_2O]^+$ (calcd. for $C_{19}H_{21}O_2$, 281.1536).

For the exact assignment of the NMR data, see 3.3.3.1.

5.1.8.68 16-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-ol (189)



Diarylheptanoid **188** (2.1 mg, 6.4 µmol, 1.0 eq.) was dissolved in 0.2 ml MeOH, followed by the addition of $NaBH_4$ (24 mg, 0.64 mmol, 100 eq.) at 0 °C. The ice bath was removed after 15 min and the reaction was allowed to continue at ambient temperature. H_2O (10 ml) was used to stop the reaction after 3.5 h. The aqueous solution was extracted with EtOAc (3 × 15 ml), combined organic layers were concentrated at reduced pressure and the crude mixture was directly submitted to purification with preparative HPLC (RP-18; MeOH/H_2O, method 2, 5.1.2). This afforded **189** as colorless oil (1.5 mg, 4.7 µmol, 73%).

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.18 (br s, 1H), 7.12 (s, 1H, OH), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.85 (br s, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.31 (s, 1H, OH), 4.17 (t, *J* = 9.6 Hz, 1H), 3.94 (s, 3H), 2.95 (m, 3H), 2.52 (m, 1H), 2.31 (m, 1H), 2.01 (m, 1H), 1.91 (m, 1H), 1.89 (m, 1H), 1.68 (m, 2H), 1.55 (m, 1H), 1.51 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 151.6, 146.7, 139.1, 133.3, 131.4, 130.9, 130.0, 126.4, 124.9, 124.5, 117.0, 110.2, 69.1, 56.4, 39.7, 34.9, 30.0, 27.4, 26.8, 22.7.

ESI-MS *m/z* (%) 311 $[MH - H_2O]^+$ (100), 329 $[MH]^+$ (25).

HR ESI-MS *m/z* 311.1647 $[MH - H_2O]^+$ (calcd. for $C_{20}H_{23}O_3$, 311.1642).

For the exact assignment of the NMR data, see 3.3.3.1.

5.2 General cell culture materials and methods

5.2.1 Cell culture chemicals and reagents

Following chemicals and reagents were used during the biological testing in the cell culture:

Dulbecco's Modified Eagle Medium (DMEM, Gibco®, Life technologies corporation, New York, USA)

Dulbecco's Phosphate Buffered Saline (PBS, Sigma Aldrich, Steinheim, Germany)

Fetal Calf Serum (FCS, Superior, Biochrom, Berlin, Germany)

(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, ~98%, used as 4 mg/ml solution in PBS, Sigma Aldrich, Steinheim, Germany)

Trypan blue (~37% dye content, Sigma Aldrich, Steinheim, Germany)

Sodium dodecyl sulfate (92.5 – 100.5%, used as 10% (w/v) solution, Sigma Aldrich, Steinheim, Germany)

Trypsin ((1:250)/EDTA (0.5%/0.2%), used as 10% solution (v/v) in PBS, Merck, Darmstadt, Germany)

Quercetin (≥98%, Sigma Aldrich, Steinheim, Germany)

Curcumin (97%, Roth, Karlsruhe, Germany)

Demethoxycurcumin (≥98%, Sigma Aldrich, Steinheim, Germany)

Bisdemethoxycurcumin (98%, ABCR, Karlsruhe, Germany)

DMSO (Uvasol®, Merck, Darmstadt, Germany)

5.2.2 Cell culture instruments and consumables

Autoflow IR Direct Heat CO_2 incubator, Nuaire™, Integra Biosciences, Fernwald, Germany

Megafuge 1.0R, Thermo Scientific, Waltham, USA

Laminar flow bench HERAsafe KS, Thermo SK 1200, BDK, Sonnenbühl, Germany

Multiwell plate reader, Tecan, Crailsheim, Germany

Cell culture flasks (40 and 200 ml), TPP, Trasadingen, Switzerland

Centrifuge tubes (15 and 50 ml), TPP, Trasadingen, Switzerland

Safe lock tubes (1.5 and 2 ml), Eppendorf, Hamburg

96-well microtiter plates, TPP, Trasadingen, Switzerland

Pipette tips (200 µl and 1000 µl), Sarstedt, Nümbrecht, Germany

Pipette tips (10 µl), Axygen, Union City, New Jersey, USA

Serological pipettes, TPP, Trasadingen, Switzerland

Neubauer hemocytometer, Brand, Wertheim, Germany

5.2.3 Cultivation of cells

The HT22 cells were cultivated in an incubator at 37 °C in 5% CO_2 atmosphere using Dulbecco's Modified Eagle Medium (DMEM) with 10% heat inactivated FCS (inactivation: 56 °C, 30 min). Cell splitting was performed three times a week when confluence was reached. For this matter, the old medium was aspired and the cells were rinsed with 10 ml PBS, followed by trypsinization (1 ml trypsin/EDTA solution, 1 min at 37 °C in the incubator). The cells detached upon this treatment and were suspended in additional 9 ml medium, transferred into a falcon tube and centrifuged for 3 min at 700 × "g". The supernatant was aspired after the centrifugation and the cell pellet was re-suspended in 5 ml medium. The cell suspension was then reseeded in 1:20 suspension/medium dilution ratio in a new cell culture flask.

For the testing, the actual cell number had to be determined in order to a seed defined amount of cells. The cell suspension was therefore diluted in a 1:10 ratio with medium and trypan blue solution (70 µl medium/20 µl trypan blue solution/10 µl cell suspension) and transferred into a Neubauer hemocytometer. Living cells can be distinguished from the damaged since only the latter can be stained by the trypan blue dye. The cell number was calculated according to following equation:

$$\frac{Cell\ number}{ml} = \frac{(N \times f \times 10^4)}{8}$$

N number of counted cells in the eight squares of the hemacytometer

f dilution factor (10)

The calculated cell number was used to prepare cell suspensions in DMEM with defined cell concentrations and 100 µl of this suspension were then seeded in every well of a 96-well microtiteter plate (5000 cell/well for the Glu assay; 50,000 cell/well for the *t*-BuOOH assay).

5.2.4 MTT cell viability assay – set-up 1

The HT22 cells were treated 24 h after the seeding in the microtiter plate with the tested substances. All compounds were stored in form of a 100 mM DMSO stock solution at 4 °C and were diluted with the cell culture medium to the desired concentrations before being transferred onto the cells. The cells were then incubated with the compounds at 37 °C and 5% CO_2 for 24 h. The supernatant was subsequently replaced with MTT solution in DMEM (1:10 dilution, MTT used as a 4 mg/ml solution in PBS), the cells were incubated with MTT under the above described conditions for additional 3 h and finally treated with the SDS lysis buffer after removal of the untransformed MTT. The read-out was performed with a multiwell plate reader at 560 nm 24 h after the SDS lysis.

5.2.5 Glutamate assay

The neuroprotectivity of the compounds against Glu-induced toxicity was assessed via the MTT assay described above (5.2.4). The HT22 cells were in this case treated at the same time with the tested substances and glutamate (100 µl/well, final concentration of Glu 5 mM).

5.2.6 MTT cell viability assay – set-up 2

Gelatin solution (0.5% in H_2O) was used for pre-coating of the microtiter plates prior to the seeding of the HT22 cells. Therefore, a concentrated gelatin solution (5% v/v) was warmed to 37 °C and diluted with sterile H_2O (Millipore) in 1:10 ratio. In each well, 40 µl of the gelatin solution was added and the plate was incubated for 1 h. The supernatant H_2O was removed and the cells were then seeded in the density of 50,000 cell/well (100 µl cell suspension per well).

The cell viability assay was carried out 24 h after the seeding. The old medium was removed and 100 µl of the compounds in DMEM at defined concentrations (1-100 µM) were added to each well. The MTT/DMEM addition (1:10 dilution, MTT used as a 4 mg/ml solution in PBS) took place after 23 h of incubation at 37 °C and 5% CO_2 and the removal of the supernatant. The dye was used in 1:10 dilution of the stock solution (4 mg/ml MTT in PBS) with DMEM. The cells were subsequently incubated (37 °C, 5% CO_2) for 1 h with MTT, the untransformed residue was then removed and the SDS lysis was performed (100 µl SDS solution per well). Absorbance of the produced formazan dye was measured at 560 nm by a Tecan reader (10 s shaking, 10 s settle time).

5.2.7 *t*-BuOOH assay

The protective activity of the compounds against *t*-BuOOH toxicity was determined by the cell viability assay in the set-up 2 (5.2.6). Briefly, the cells were seeded in the gelatin-pre-

coated microtiter plates and treated with the compounds after 24 h. The *t*-BuOOH (1 µl of 30 mM *t*-BuOOH, final concentration in the wells 300 µM) was added to the cells 3 h after the treatment of the cells with the substances. The supernatant was removed after additional 20 h (23 h after the treatment with the compounds) and replaced with the MTT solution in DMEM medium (1:10 dilution, MTT used as a 4 mg/ml solution in PBS). The removal of MTT/DMEM supernatant and the SDS lysis was performed after 1 h of incubation (37 °C, 5% CO_2), since the cell number was higher compared to the Glu-assay (set-up 1, 5.2.4). The optical density was measured after 24 h by Tecan reader at 560 nm (see 5.2.6)

5.2.8 Statistical analysis

All experiments were performed in quadruplicate and repeated independently three times or more. The results are expressed as mean ± SD, the untreated cells represent 100% values. The statistical analysis was carried out with the aid of GraphPad Prism 6 software, using one-way analysis of variances (ANOVA) to determine significant differences. Post hoc analysis was done using the Dunnett's test. Statistic significant levels: $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***).

5.3 Michael acceptor activity assay

The Michael acceptor activity assay was performed in 96-well plates (ELISA Microplates, MICROLON 200, Greiner Bio-one, Germany), covered by PCR foil (Viewseal transparent, 80 × 140 mm, Greiner Bio-one, Germany) to avoid the evaporation of the reaction medium during the measurement. 100 mM TRIS-HCl buffer pH 7.4 with 2 mM EDTA/ethylene glycol (20:80), filtered and degassed before use, was used as a solvent system. Cysteamine hydrochloride (**192**) was purchased from Alfa Aeasar (Karslruhe, Germany). The measurement was conducted at 25 °C in a Thermo Scientific Multiskan Spectrum UV/Vis microplate and cuvette spectrophotometer (Thermo Fisher Scientifc Inc., Finland).

The assay was carried out as follows: Stock solutions of compound **1** and **98** (100 mM in DMSO) were dilued in the buffer/ethylene glycol mixture to 80 µM. Thiol **192** was dissolved in the same reaction medium to form a 24 mM solution. The instrument was set up for photoscans between 280-700 nm in defined time intervals and allowed to equilibrate. Equal amonuts (100 µl) of compound and thiol solutions were mixed in the 96-well plate directly prior the measurement, providing 40 µM solutions of the elctrophiles with 300 fold excess of the thiol (12 mM). At the same time, 100 µl of the 80 µM substance solution was mixed with 100 µl of the buffer/ethylene glycol mixture as a positive control and 100 µl of the 24 mM cysteamine solution was mixed with 100 µl of the solvent system providing a negative control. The wells were covered with the PCR foil and

the plate was submitted to the spectrophotometric measurement. The collected data were evaluated using MS Excel 2010 and expressed UV spectra of the compounds at different times (Fig. 39).

6 Literature

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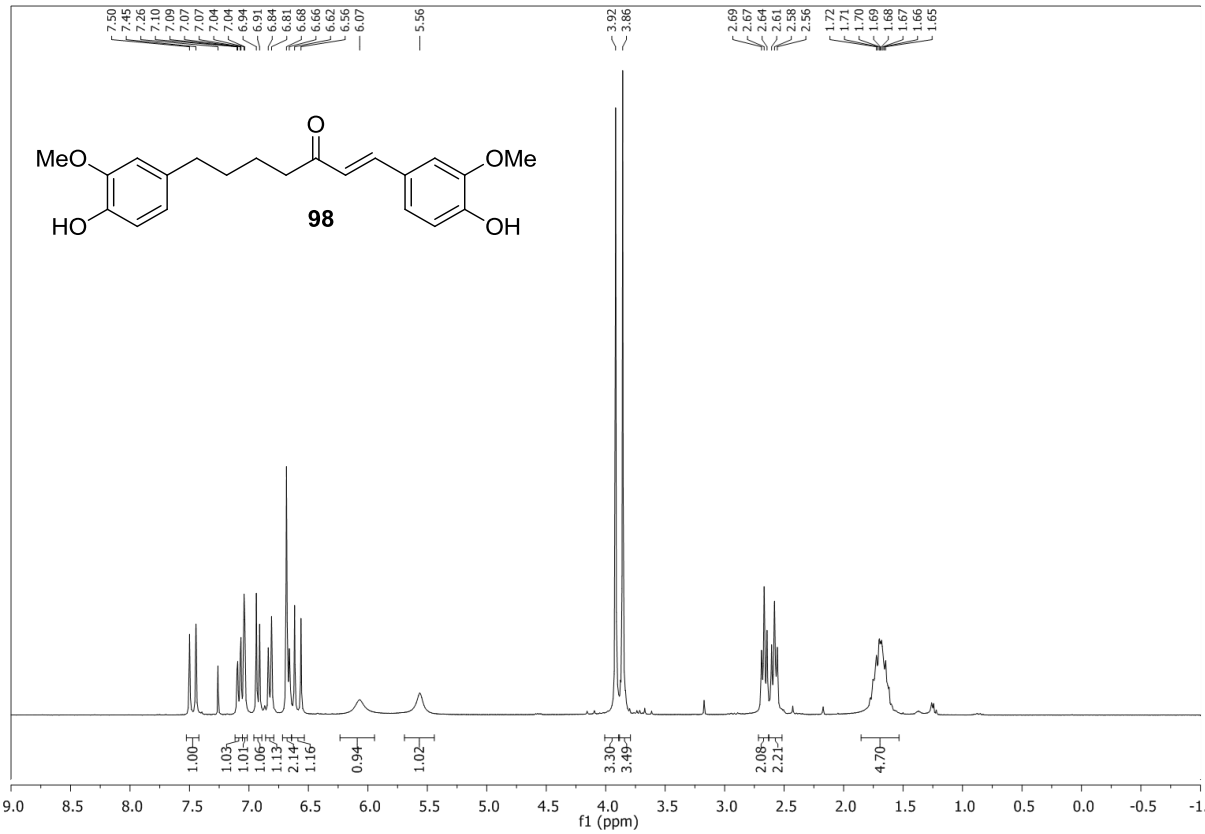
7 Appendix

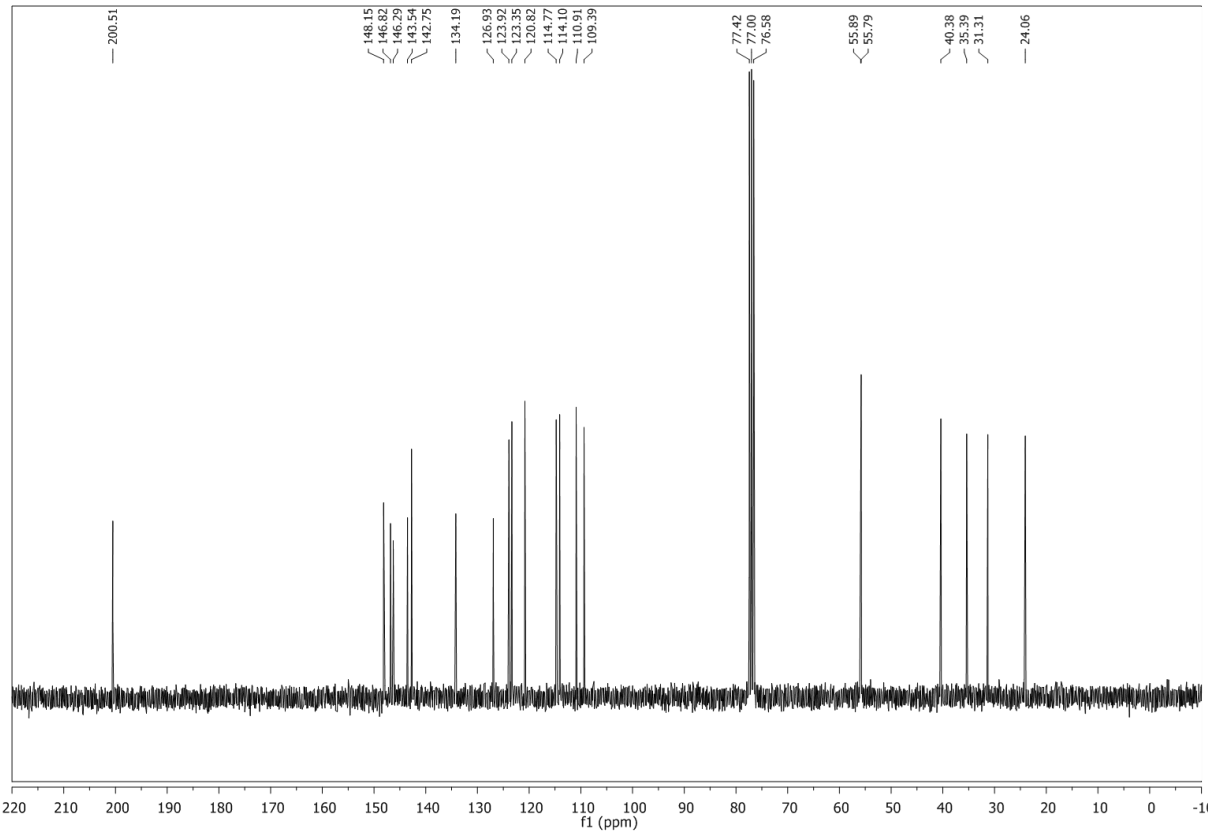
7.1 NMR spectra

(*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hept-1-en-3-one (98)

^{1}H-NMR



^{13}C-NMR



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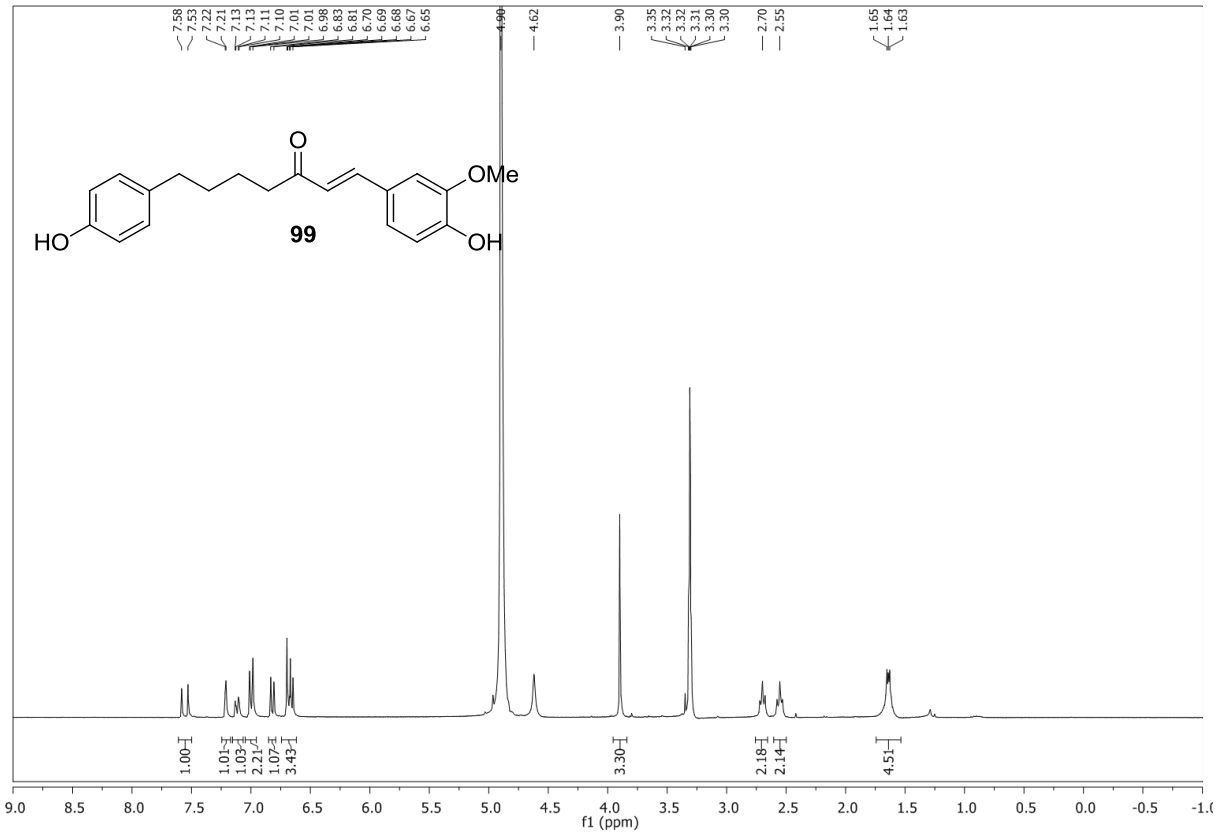
^{1}H-NMR



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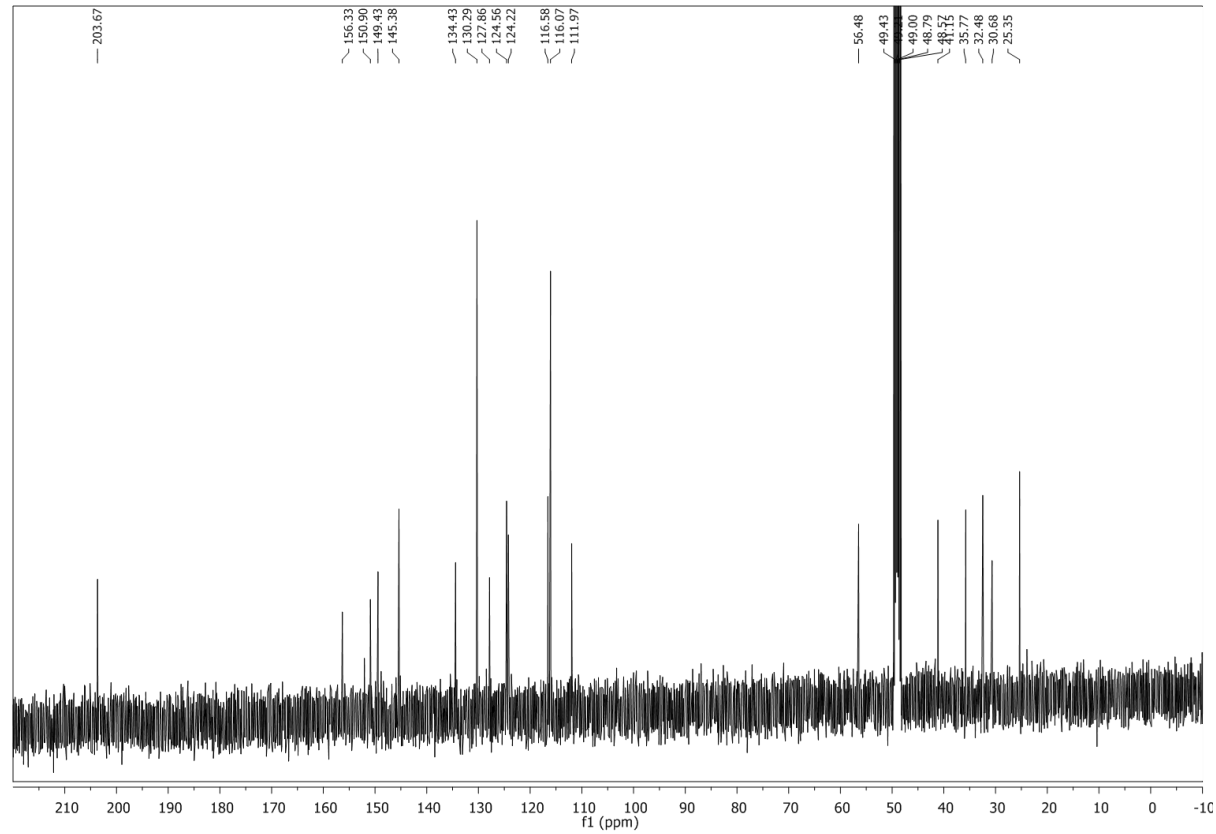
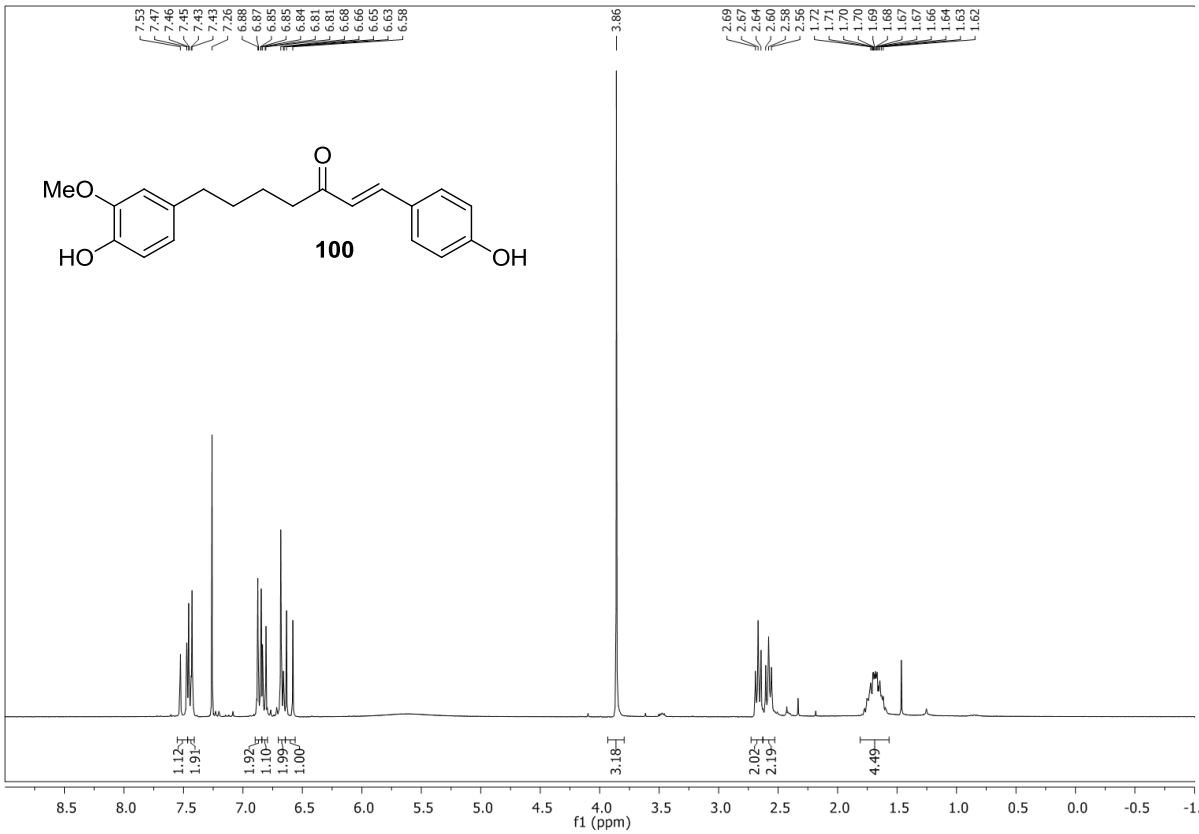
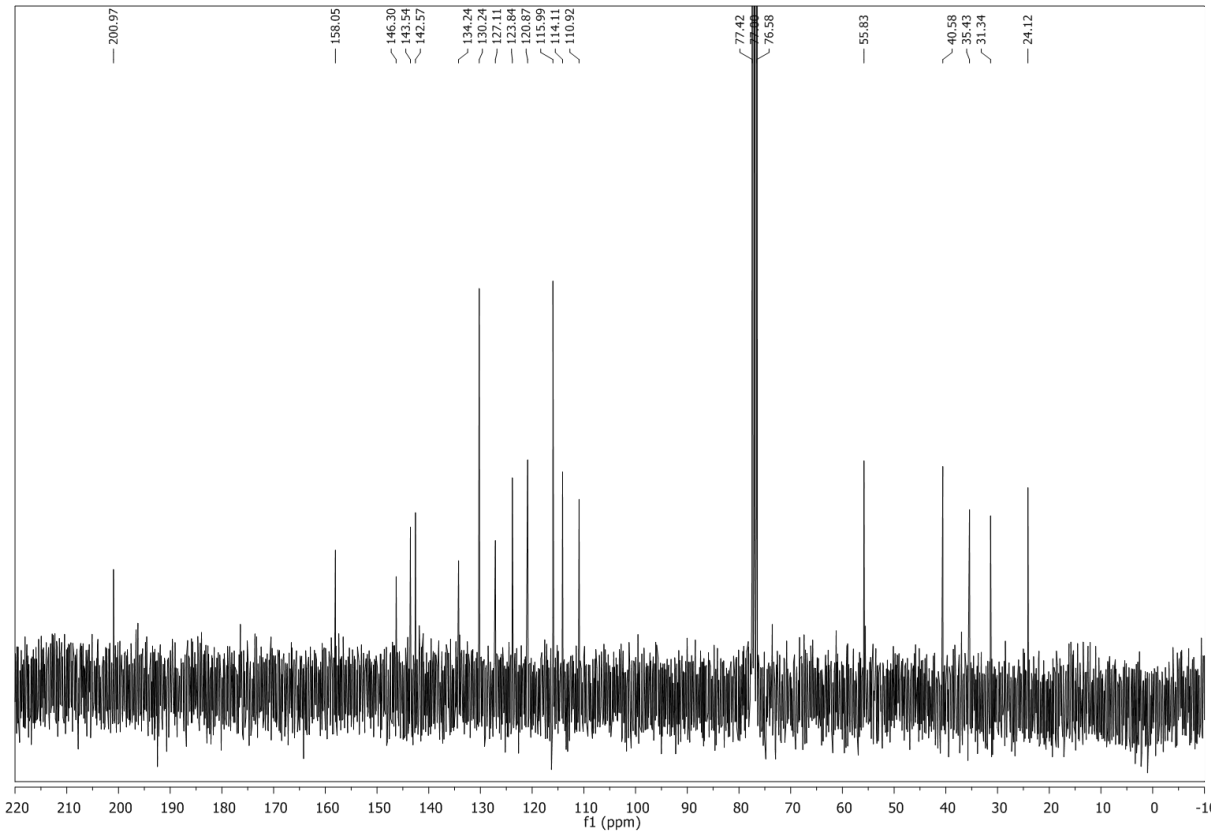


(*E*)-7-(4-Hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)hept-1-en-3-one (100)

^{1}H-NMR

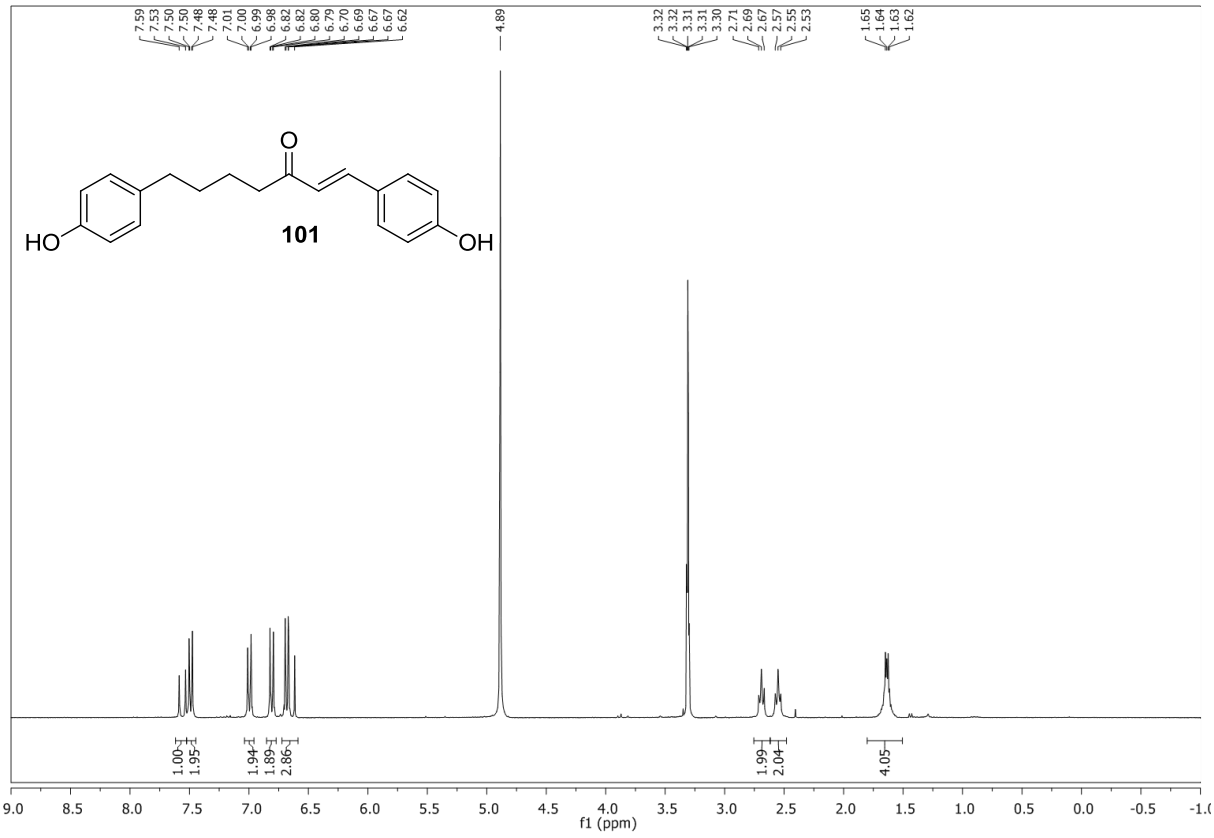


^{13}C-NMR

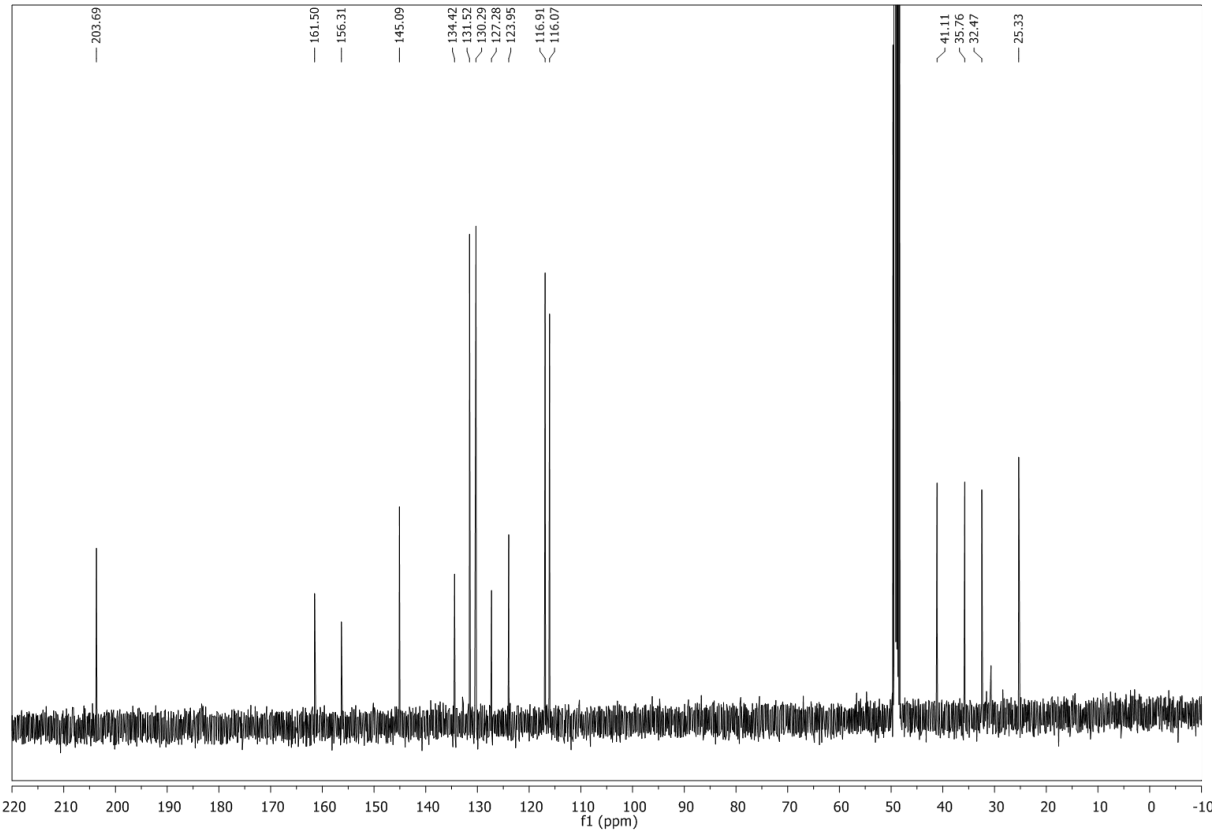


(*E*)-1,7-Bis(4-hydroxyphenyl)hept-1-en-3-one (101)

^{1}H-NMR

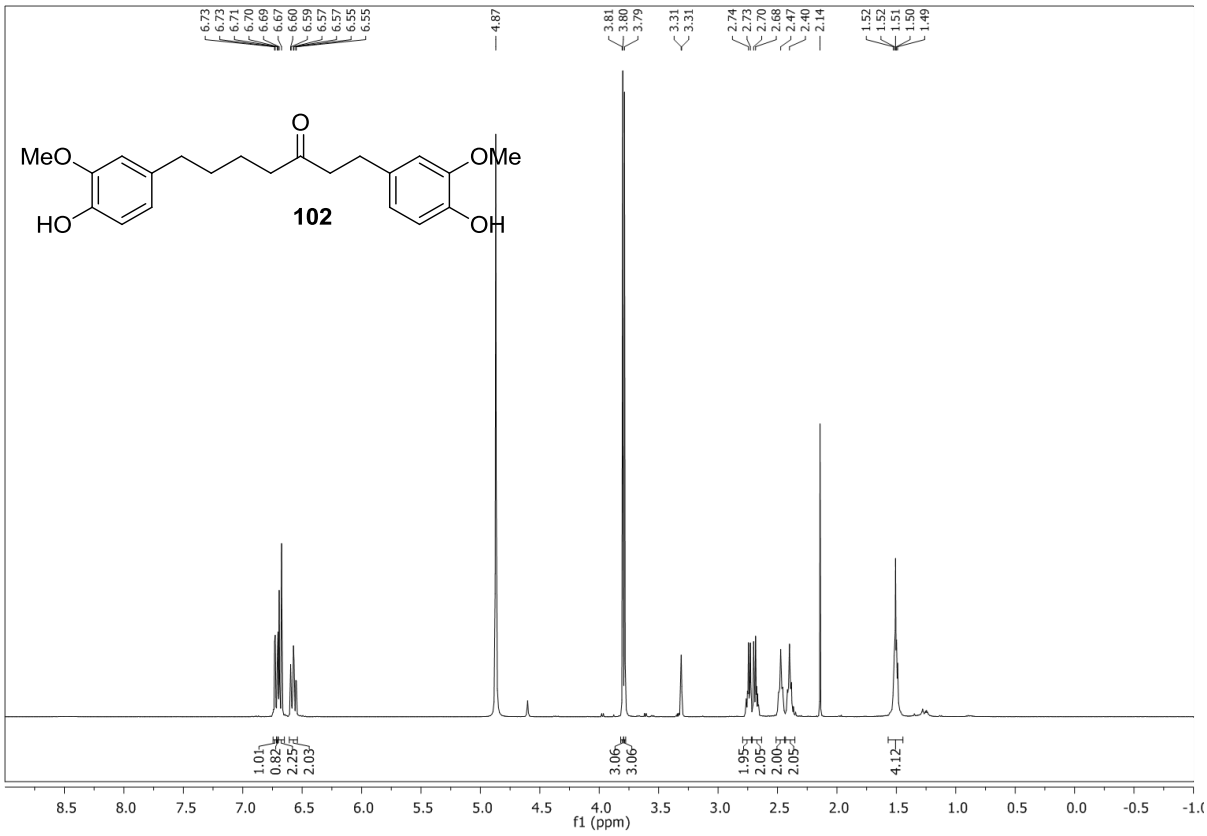


^{13}C-NMR

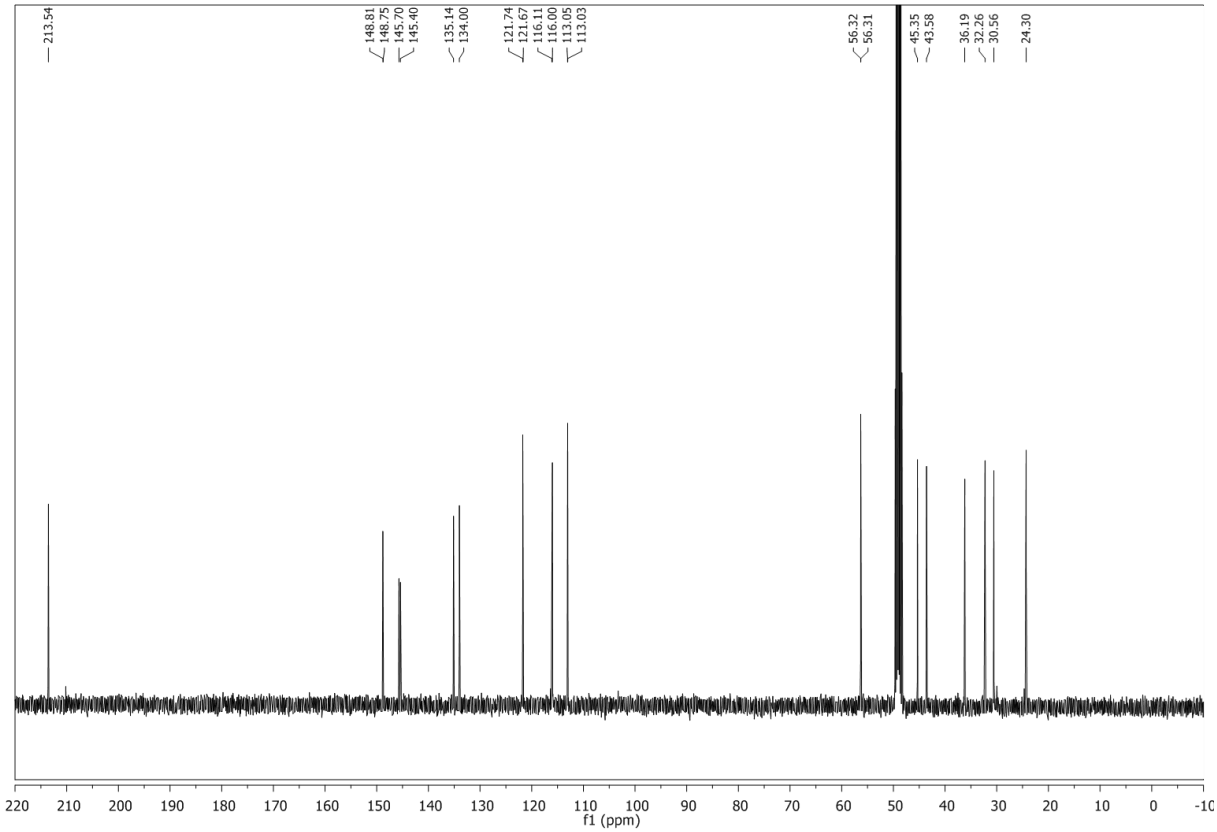


1,7-Bis(4-hydroxy-3-methoxy phenyl)heptan-3-one (102)

^{1}H-NMR

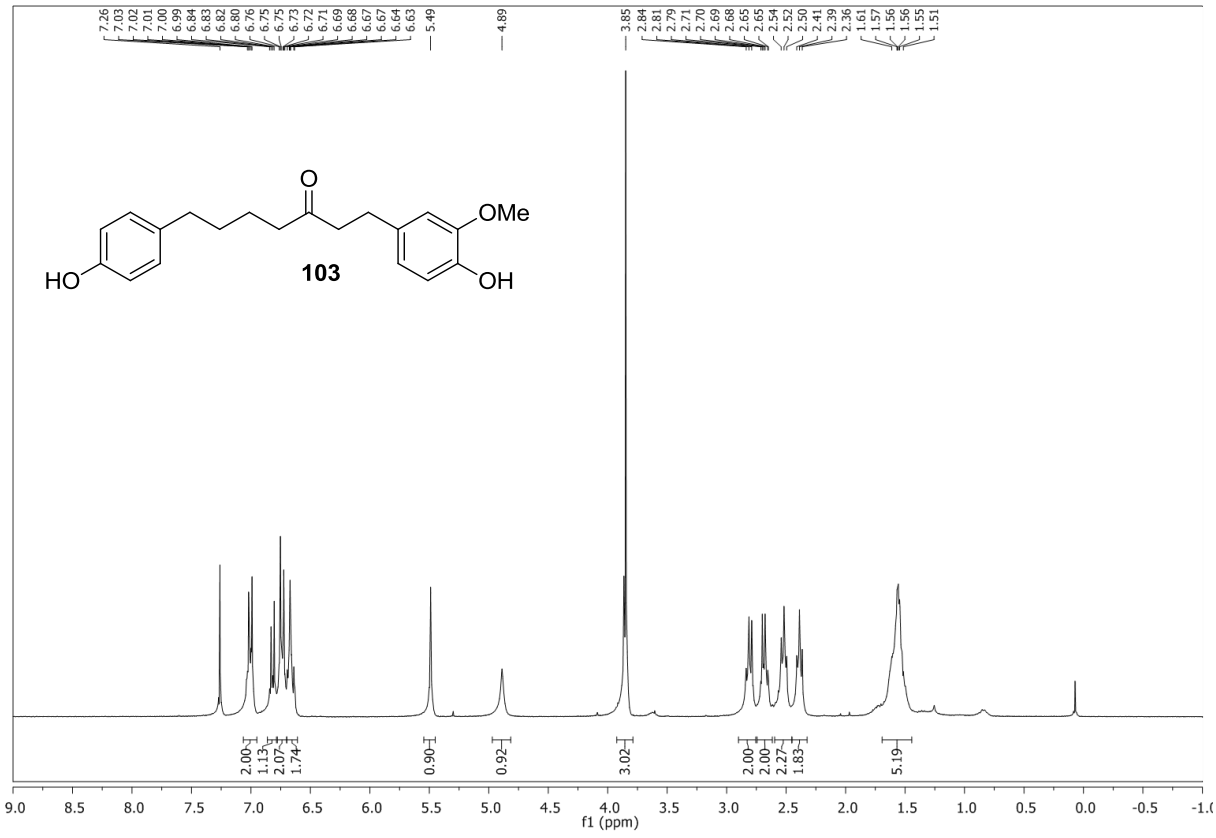


^{13}C-NMR



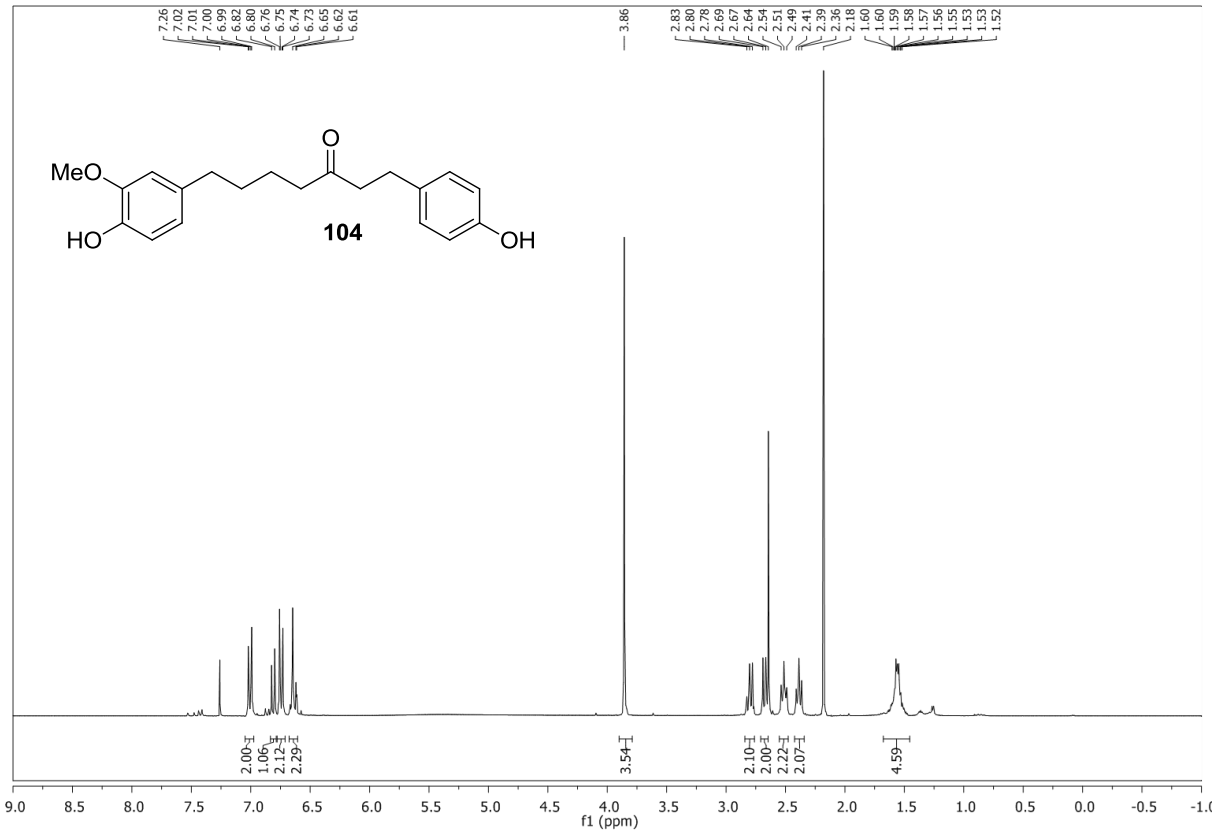
1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)heptan-3-one (103)

^{1}H-NMR

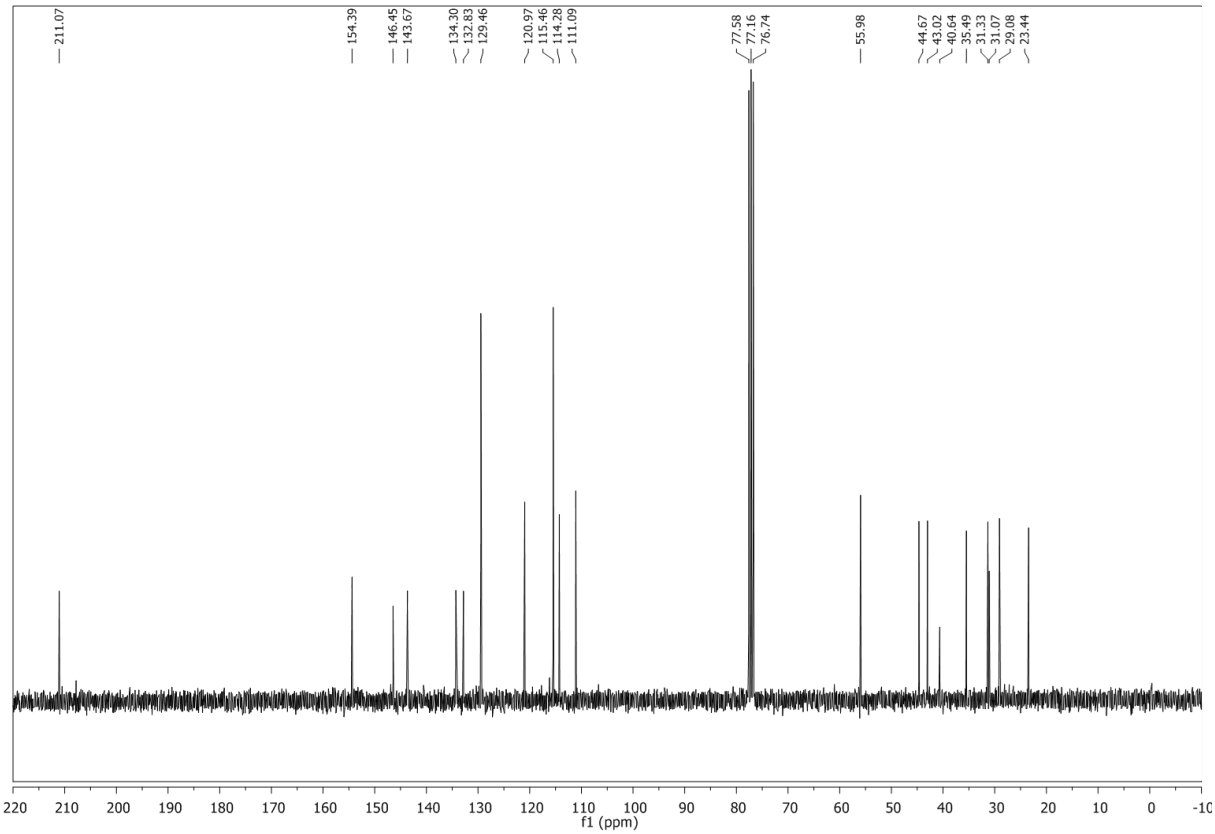


1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)heptan-3-one (104)

^{1}H-NMR

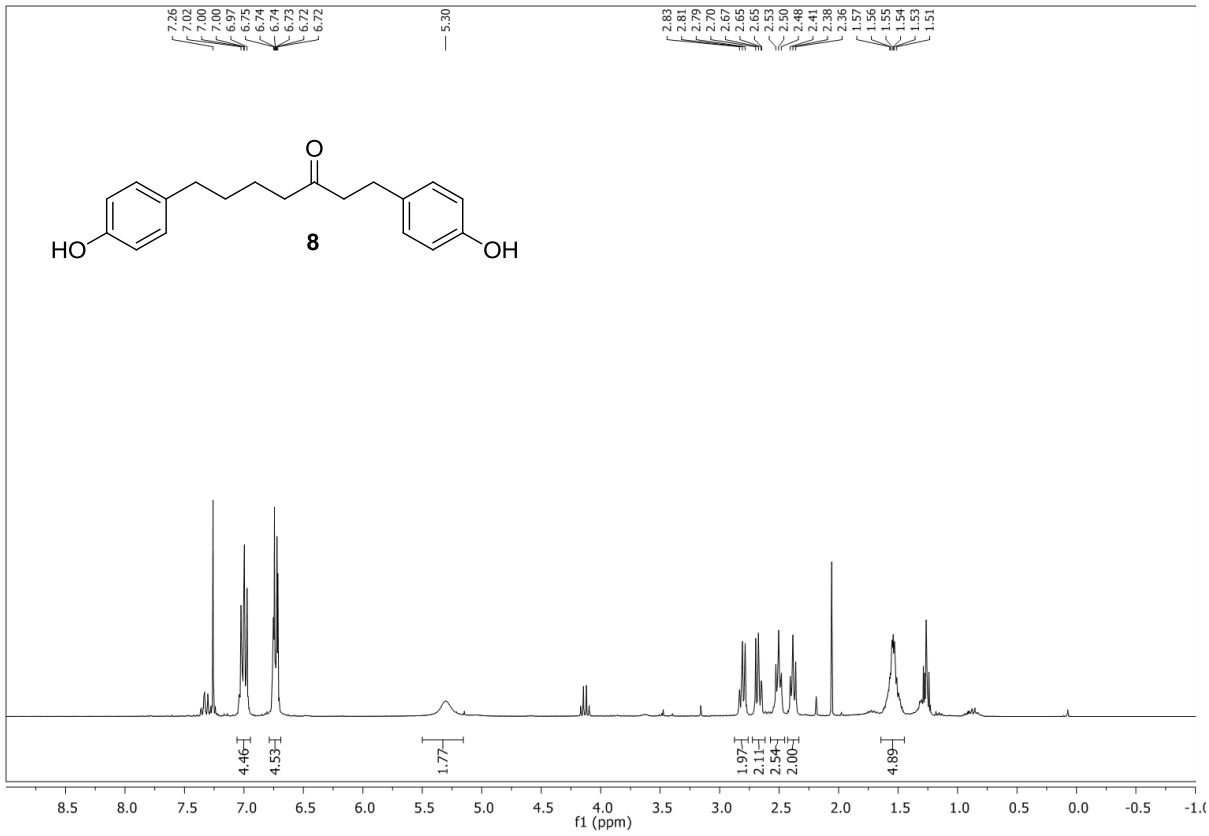


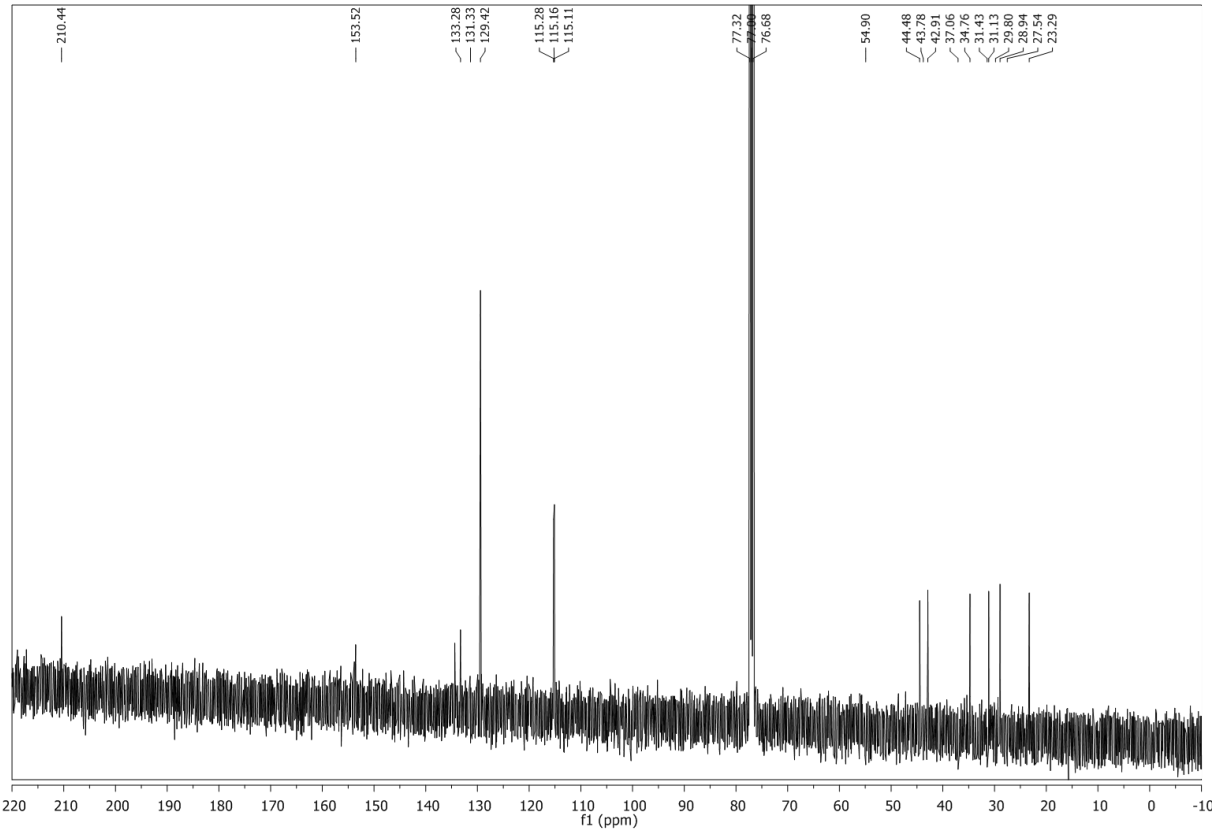
^{13}C-NMR



1,7-Bis(4-hydroxyphenyl)heptan-3-one (acerogenin G, 8)

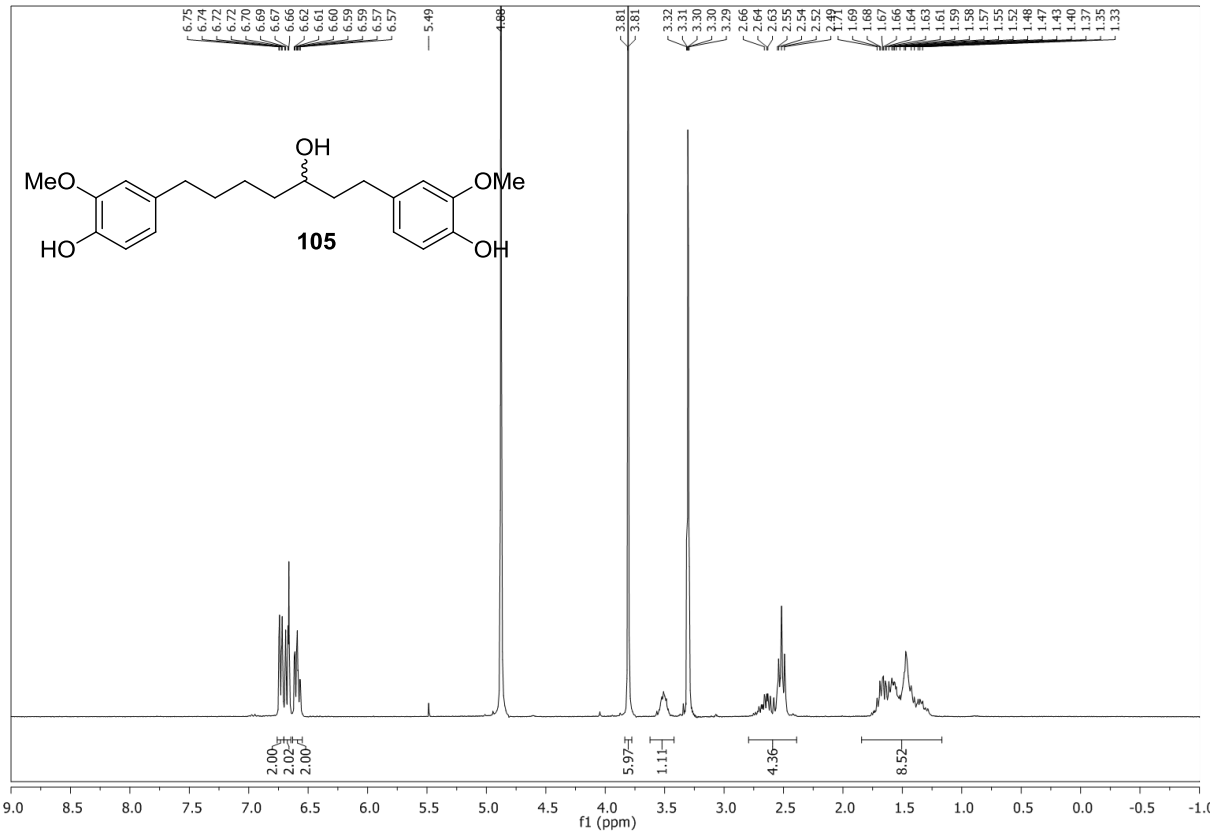
^{1}H-NMR



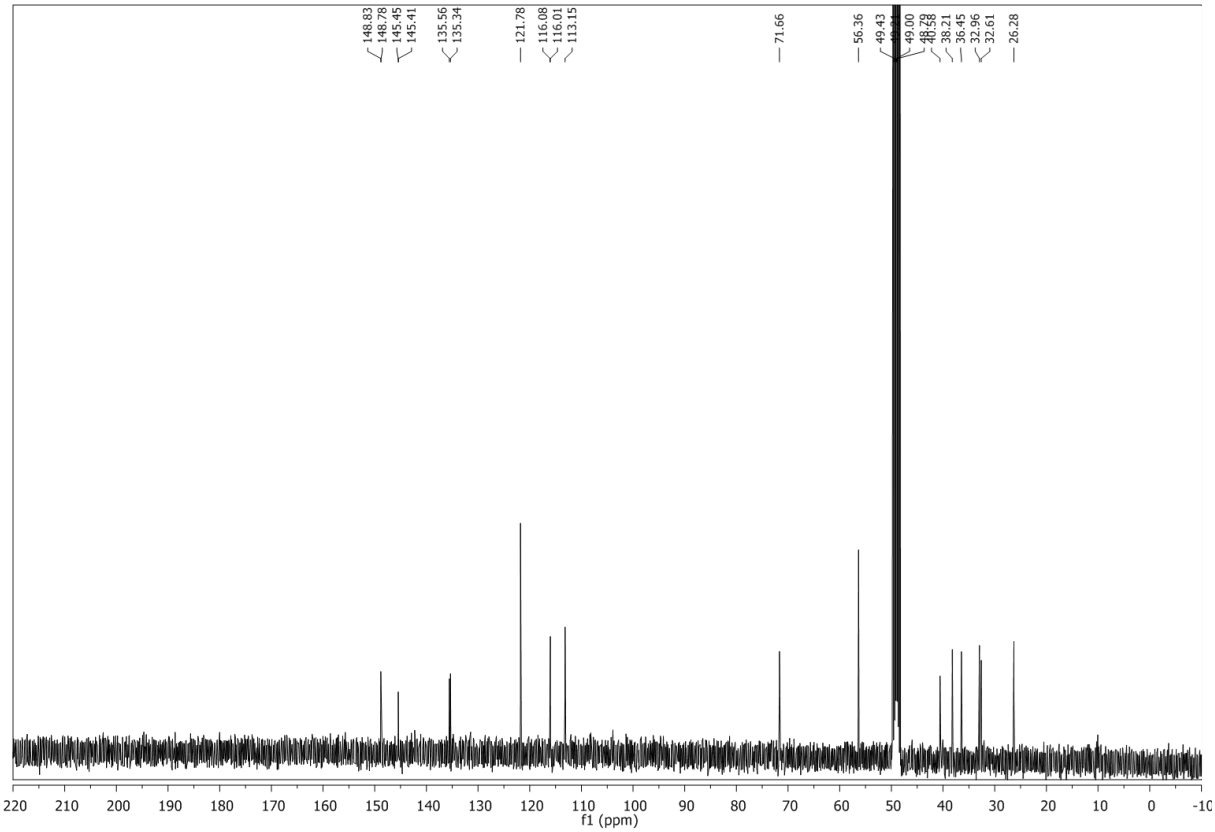


4,4'-(3-Hydroxyheptane-1,7-diyl)bis(2-methoxyphenol) (105)

^{1}H-NMR

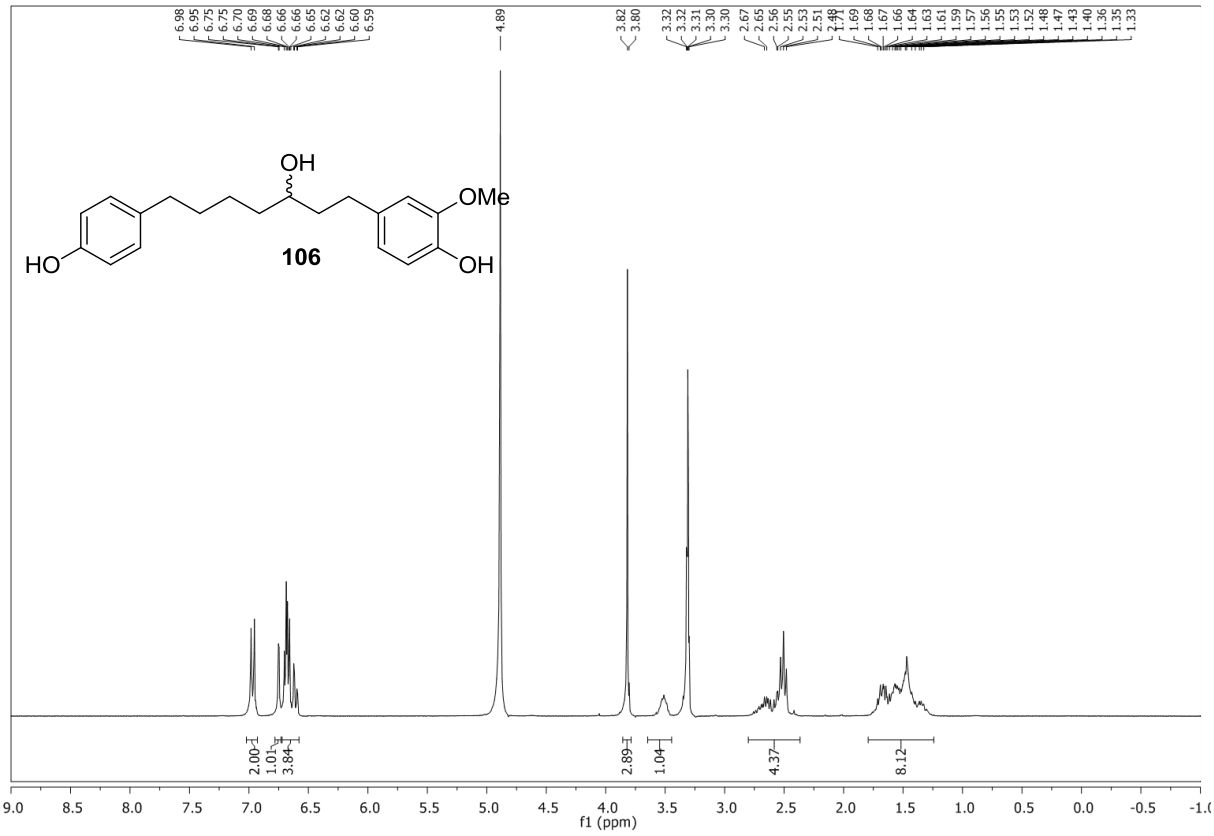


^{13}C-NMR

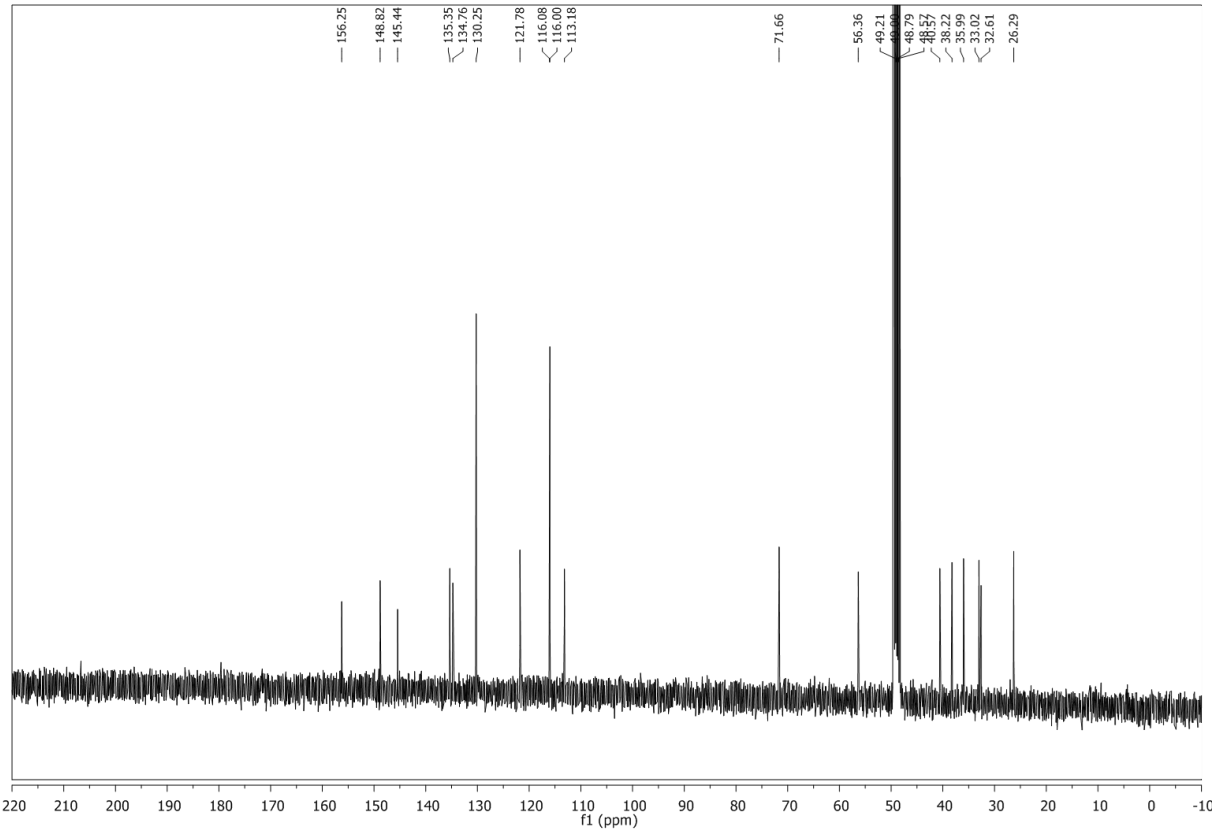


4-(3-hydroxy-7-(4-hydroxyphenyl)heptyl)-2-methoxyphenol (106)

^{1}H-NMR

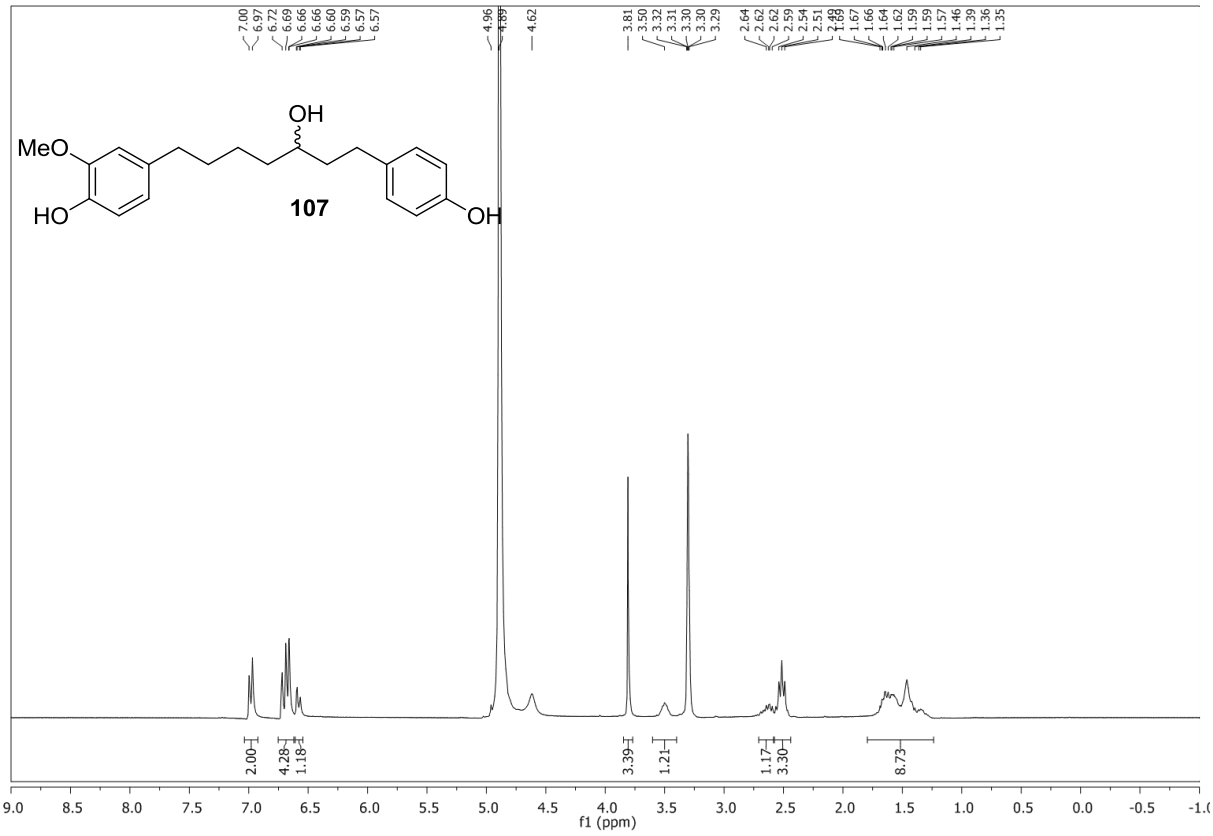


^{13}C-NMR



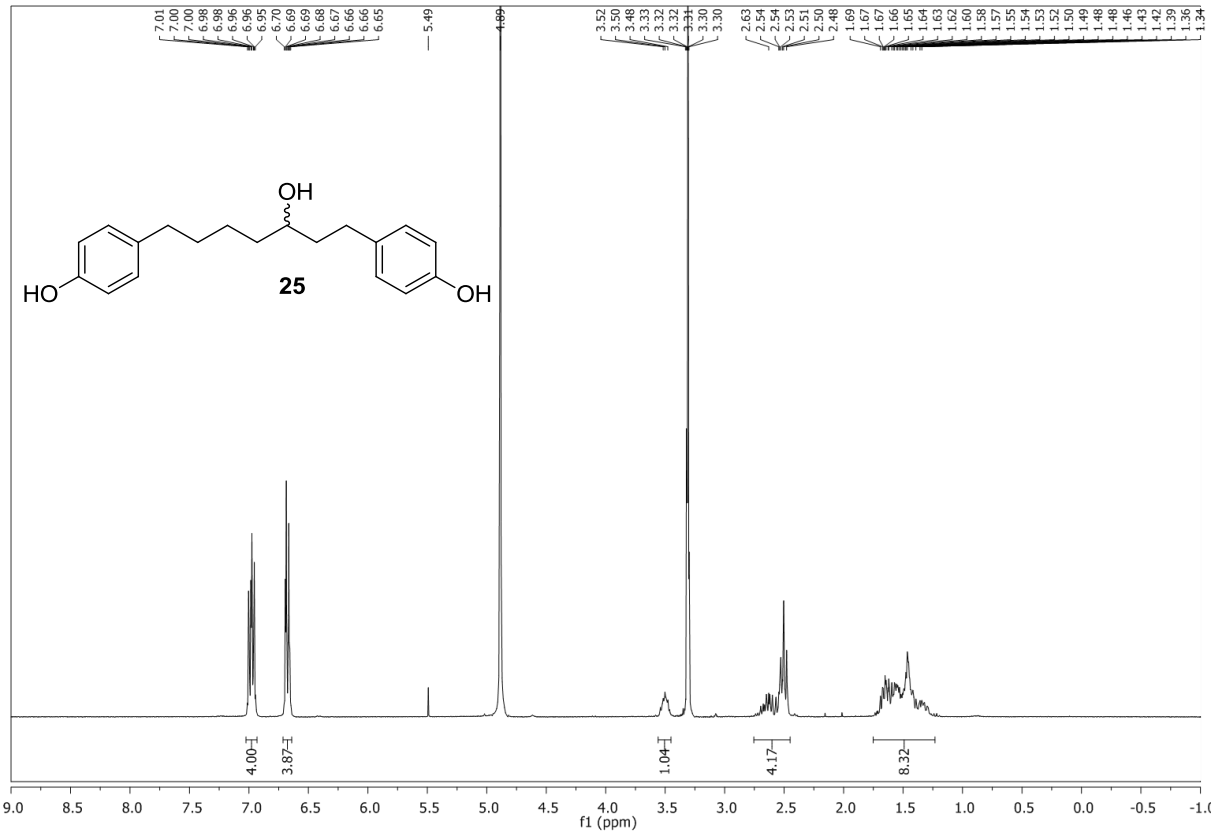
4-(5-Hydroxy-7-(4-hydroxyphenyl)heptyl)-2-methoxyphenol (107)

^{1}H-NMR

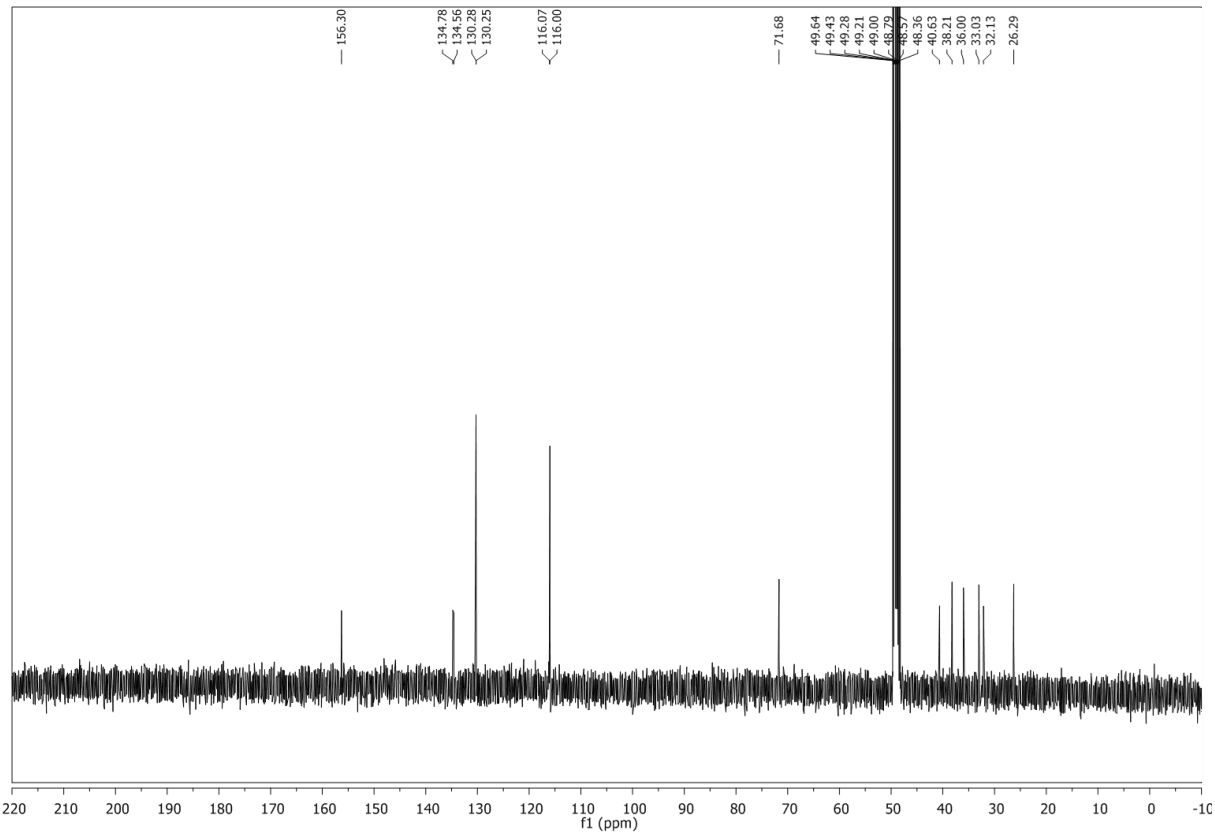


4,4'-(3-Hydroxyheptane-1,7-diyl)diphenol ((±)-centrolobol, 25)

^{1}H-NMR

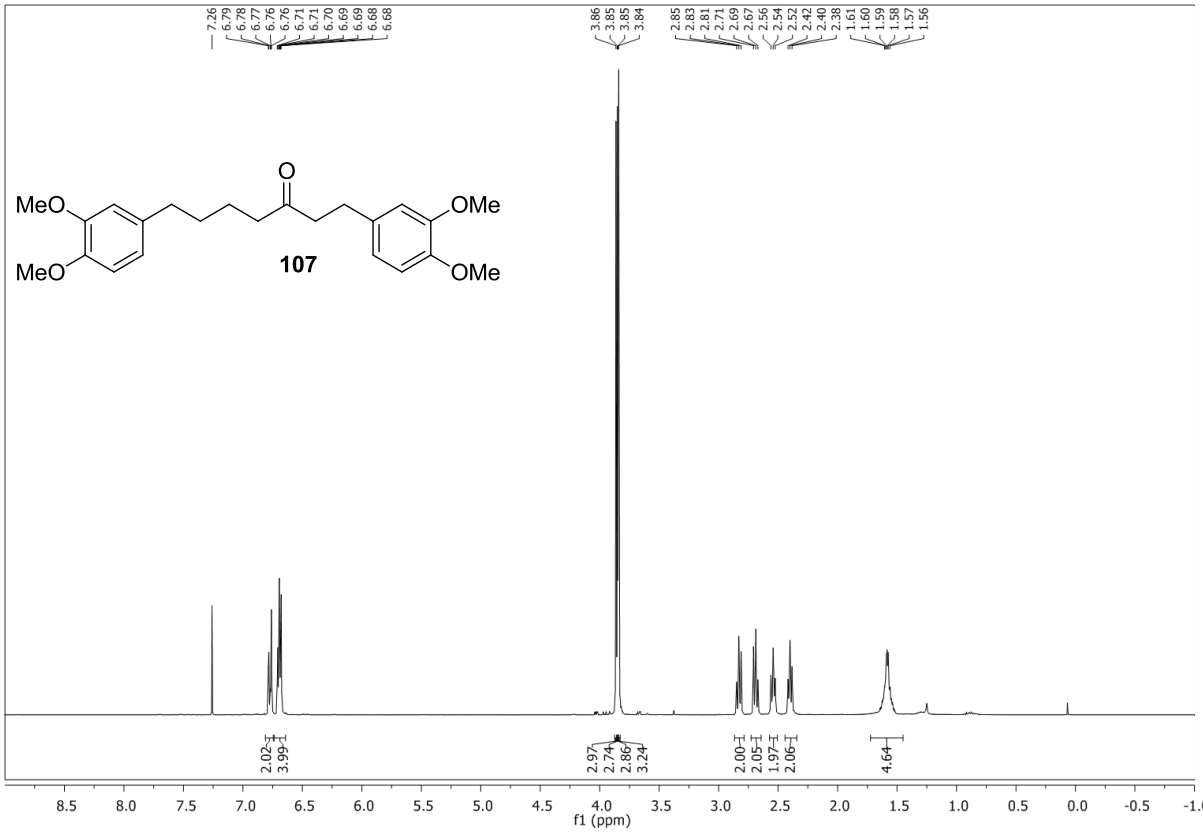


^{13}C-NMR

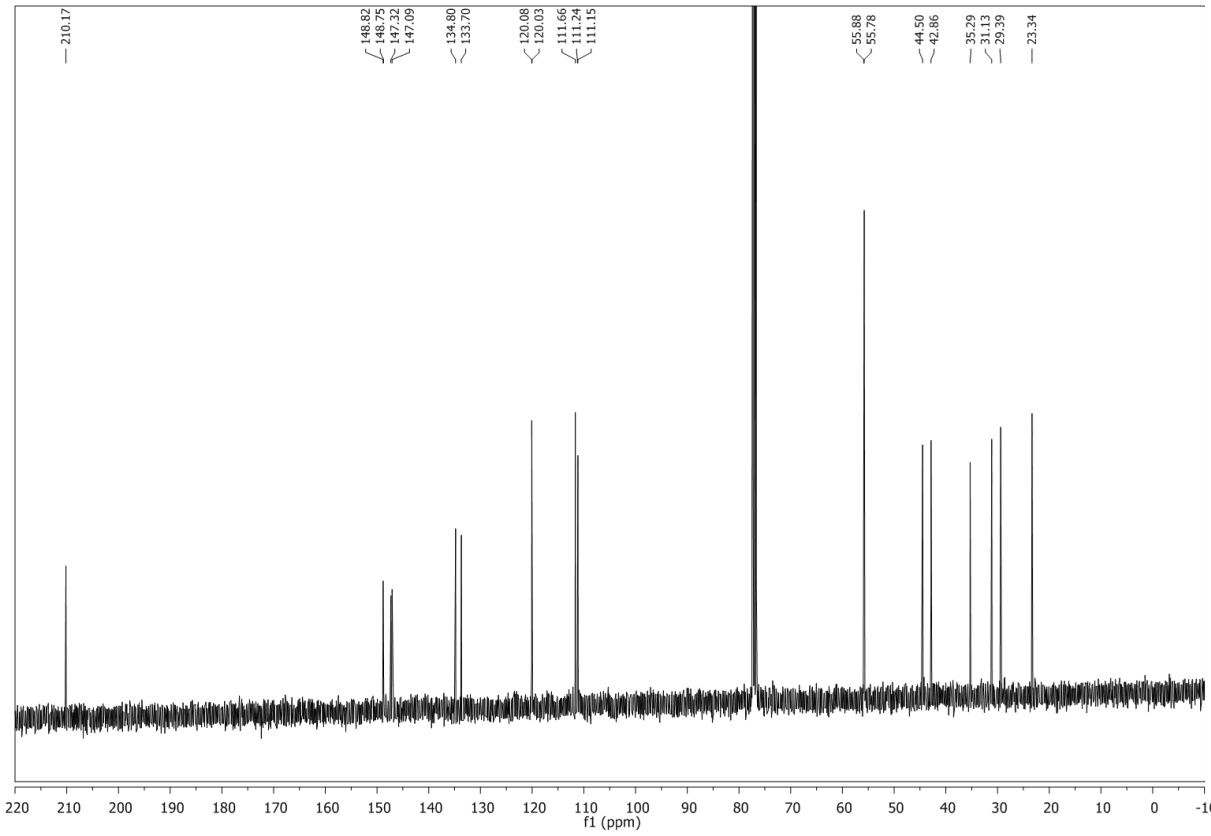


1,7-Bis(3,4-dimethoxyphenyl)heptan-3-one (108)

^{1}H-NMR

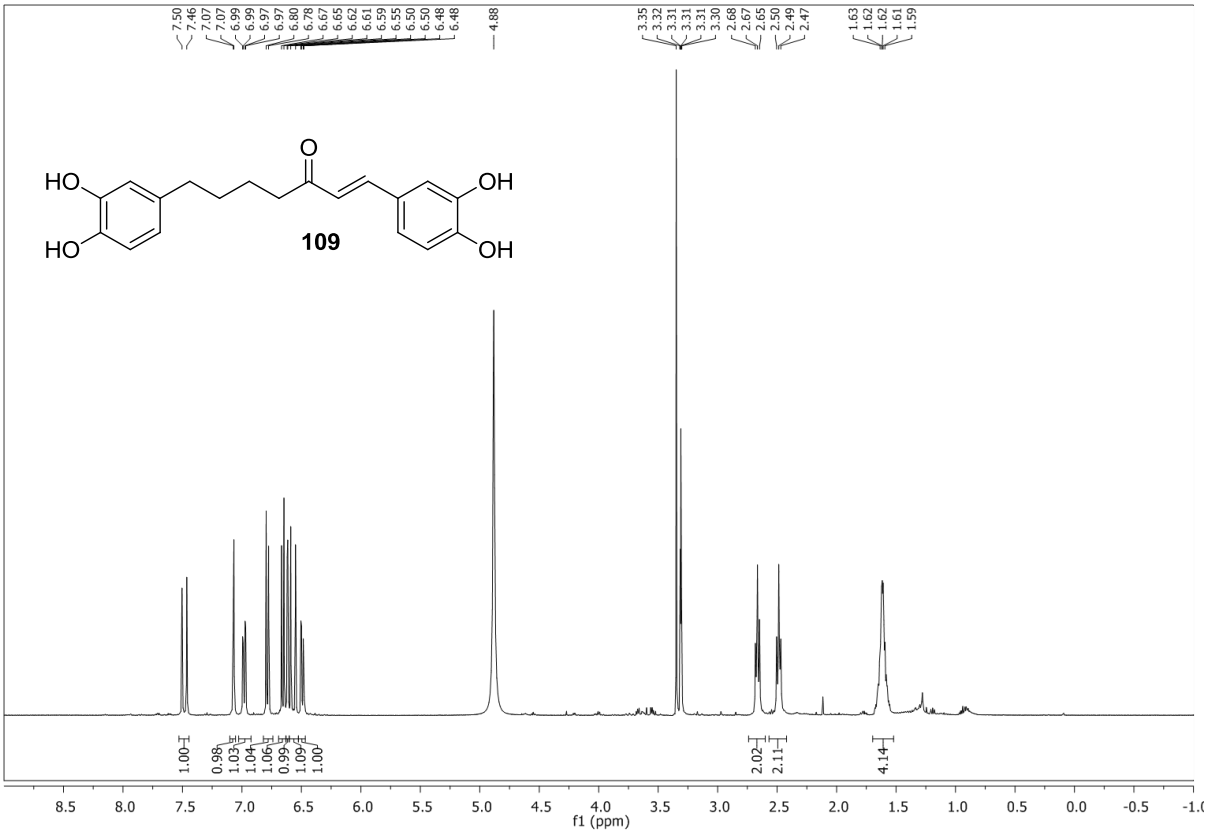


^{13}C-NMR

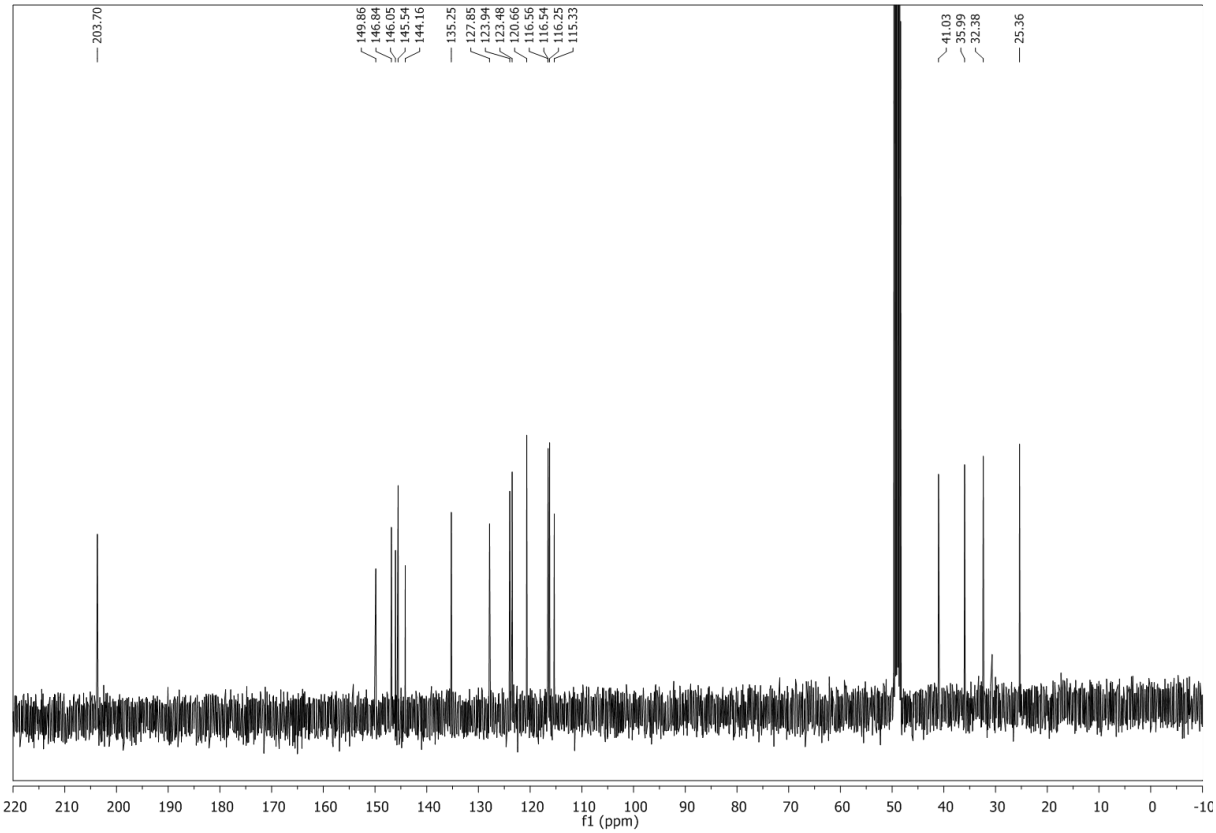


(*E*)-1,7-Bis(3,4-dihydroxyphenyl)hept-1-en-3-one (109)

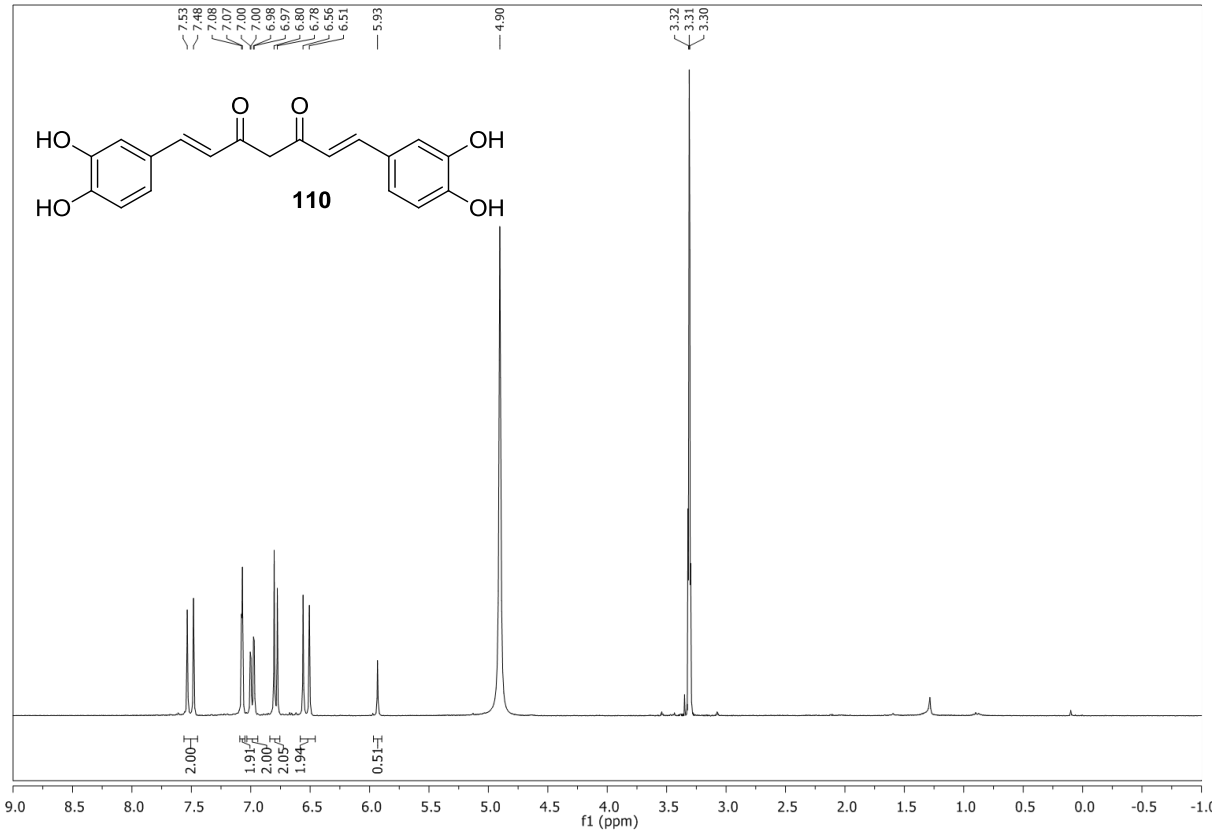
^{1}H-NMR



^{13}C-NMR

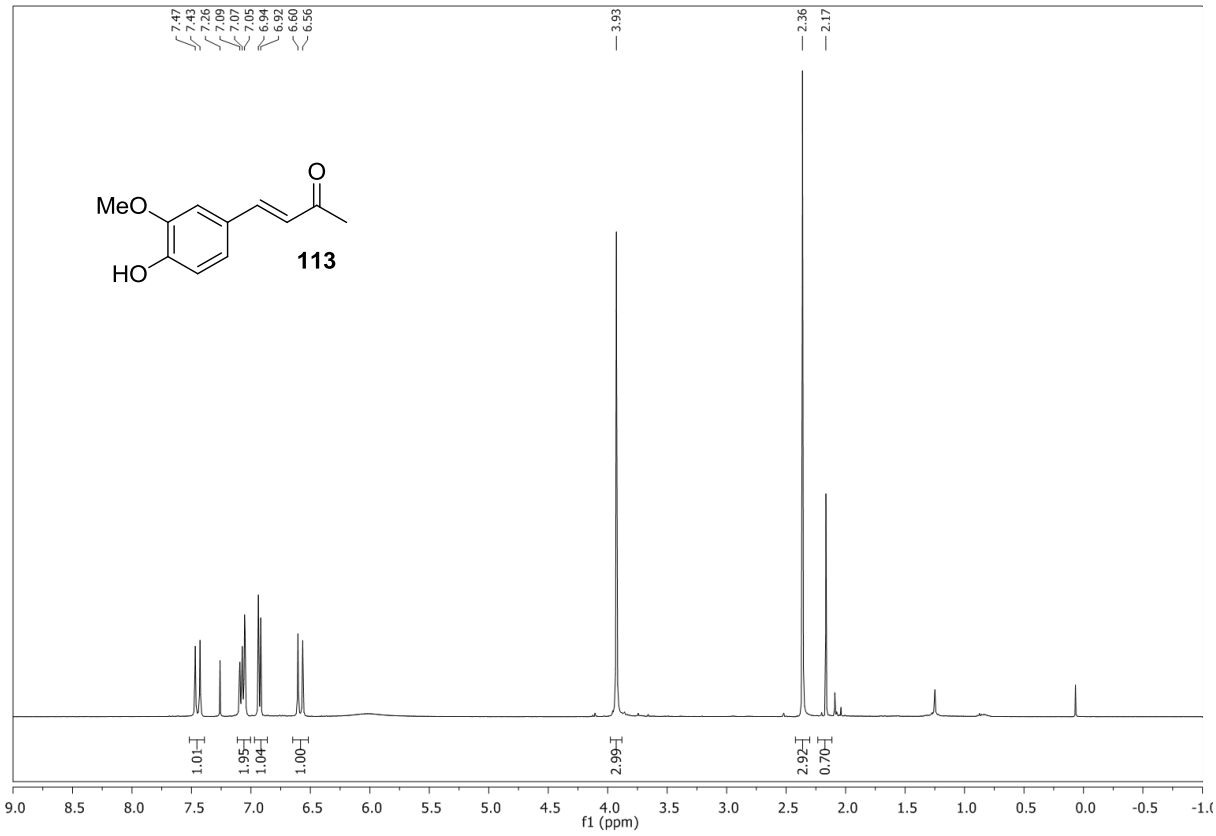


(1*E*,6*E*)-1,7-Bis(3,4-dihydroxyphenyl)hepta-1,6-diene-3,5-dione (110)

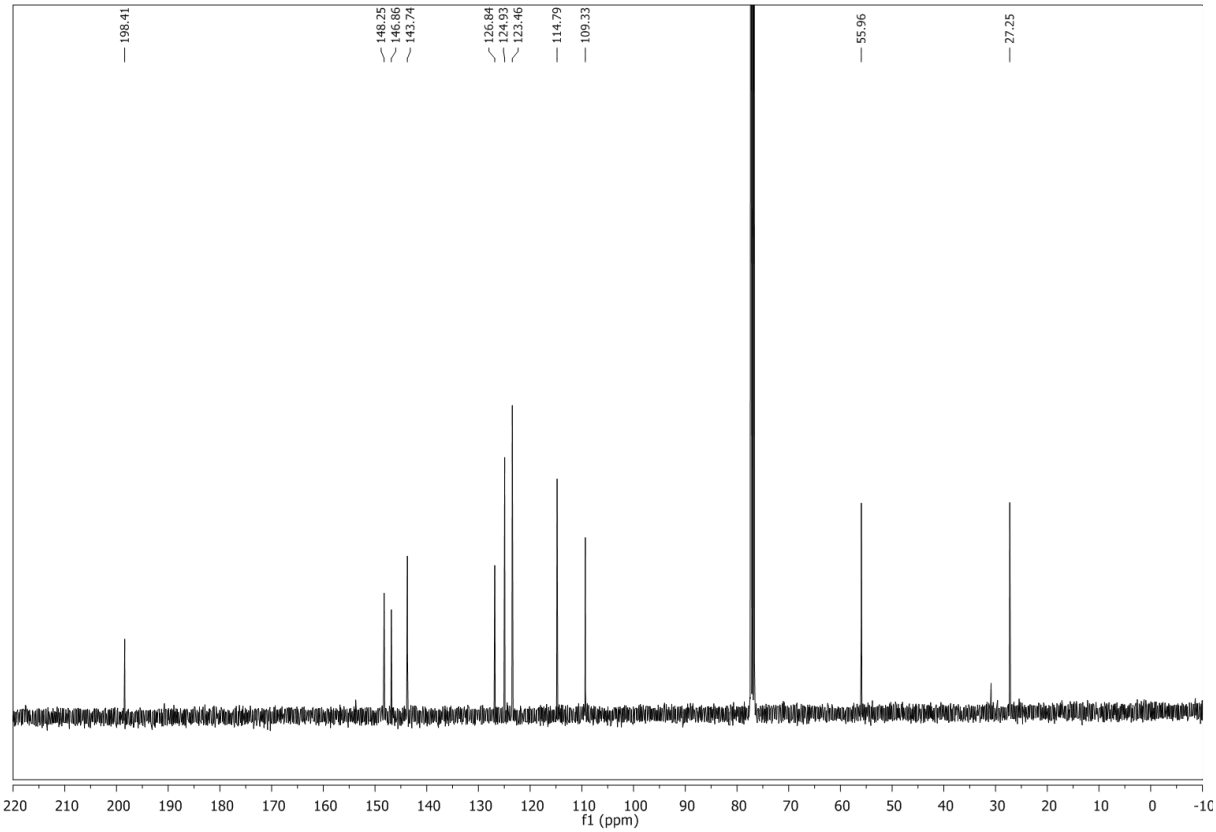


(*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (113)

^{1}H-NMR

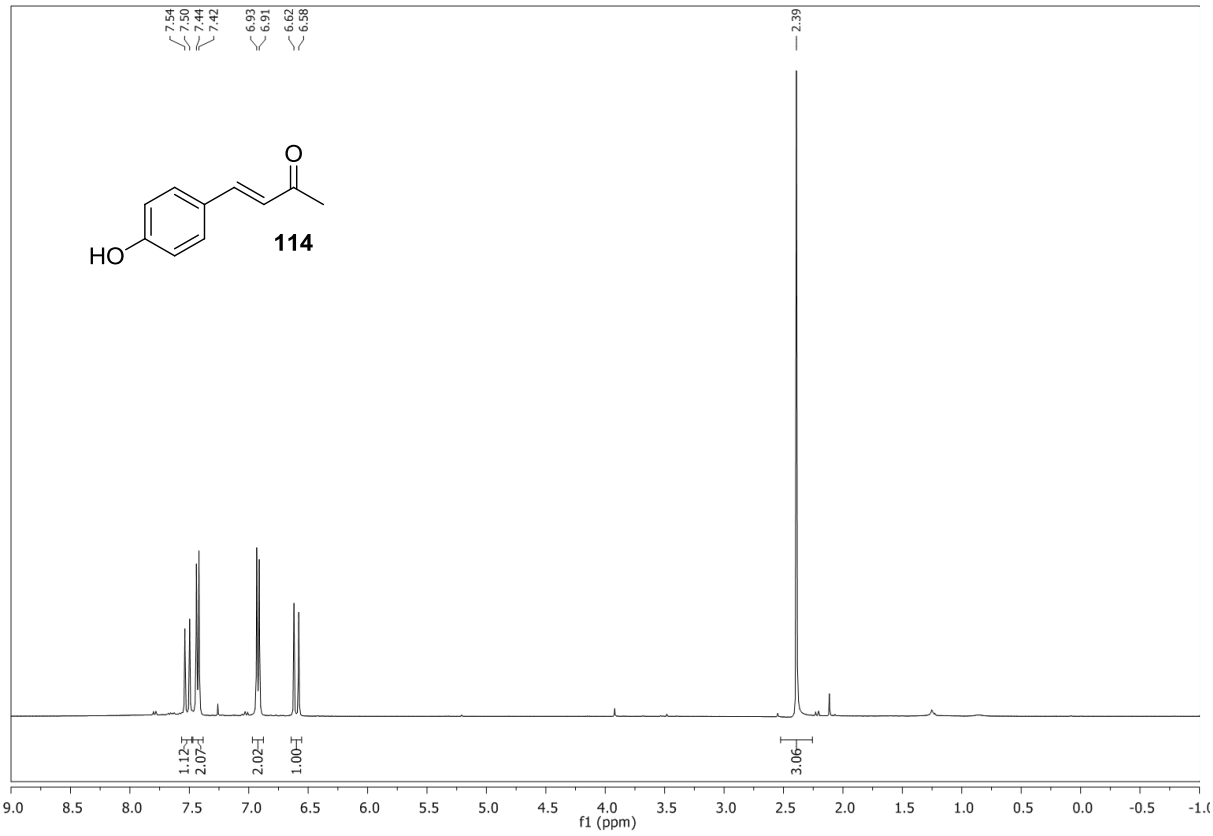


^{13}C-NMR

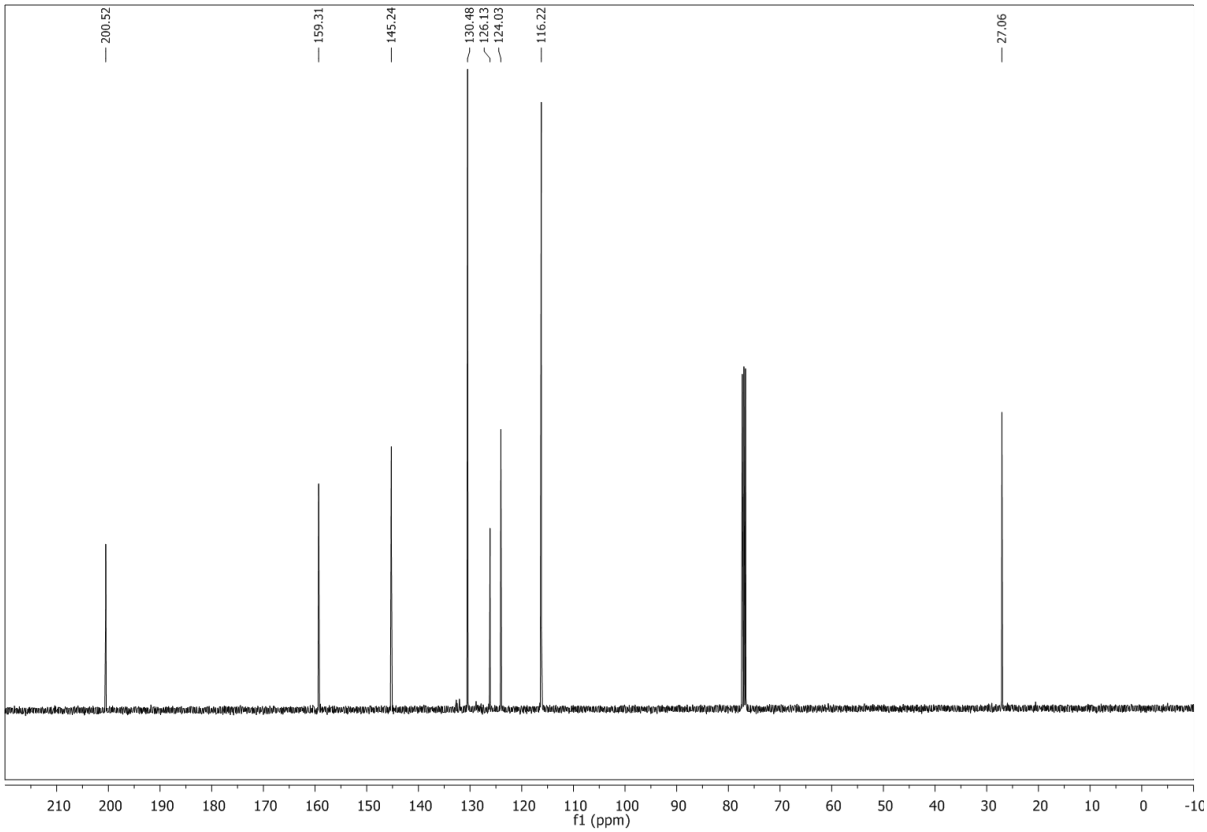


(*E*)-4-(4-Hydroxyphenyl)but-3-en-2-one (114)

^{1}H-NMR

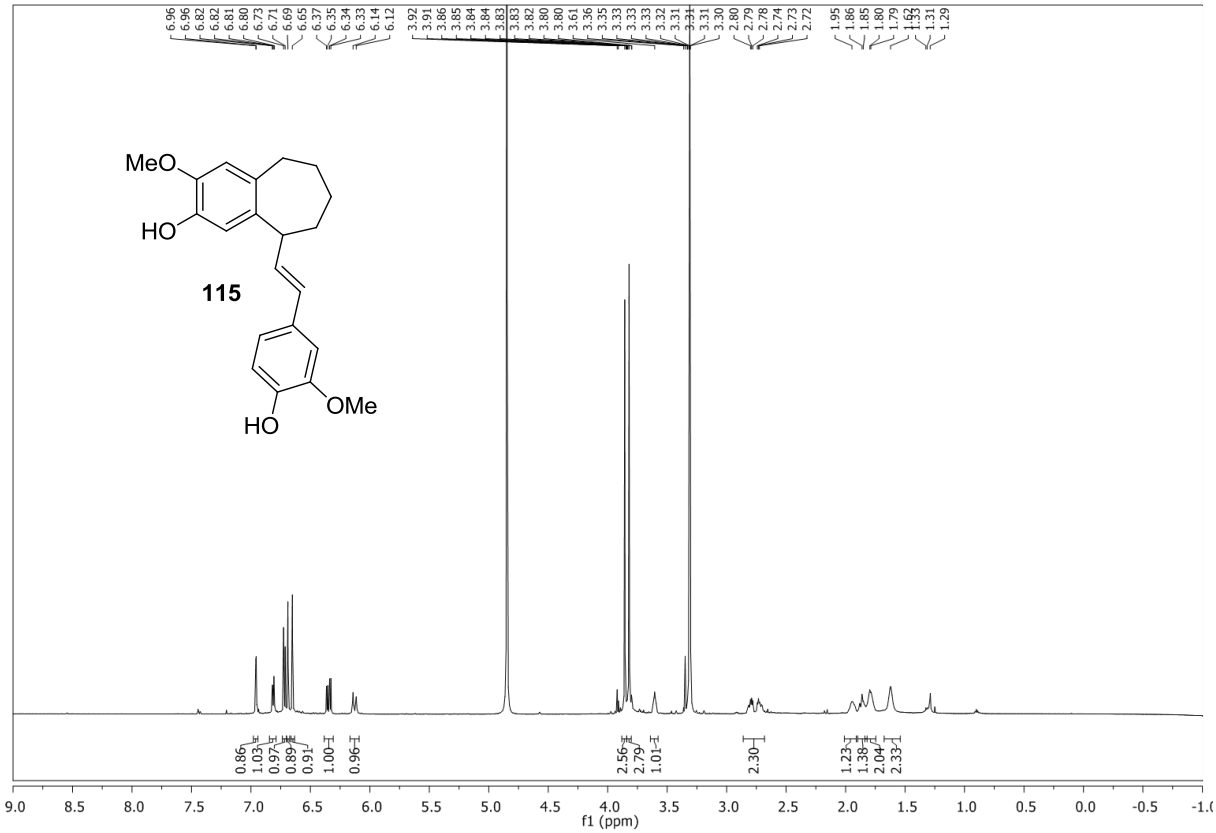


^{13}C-NMR

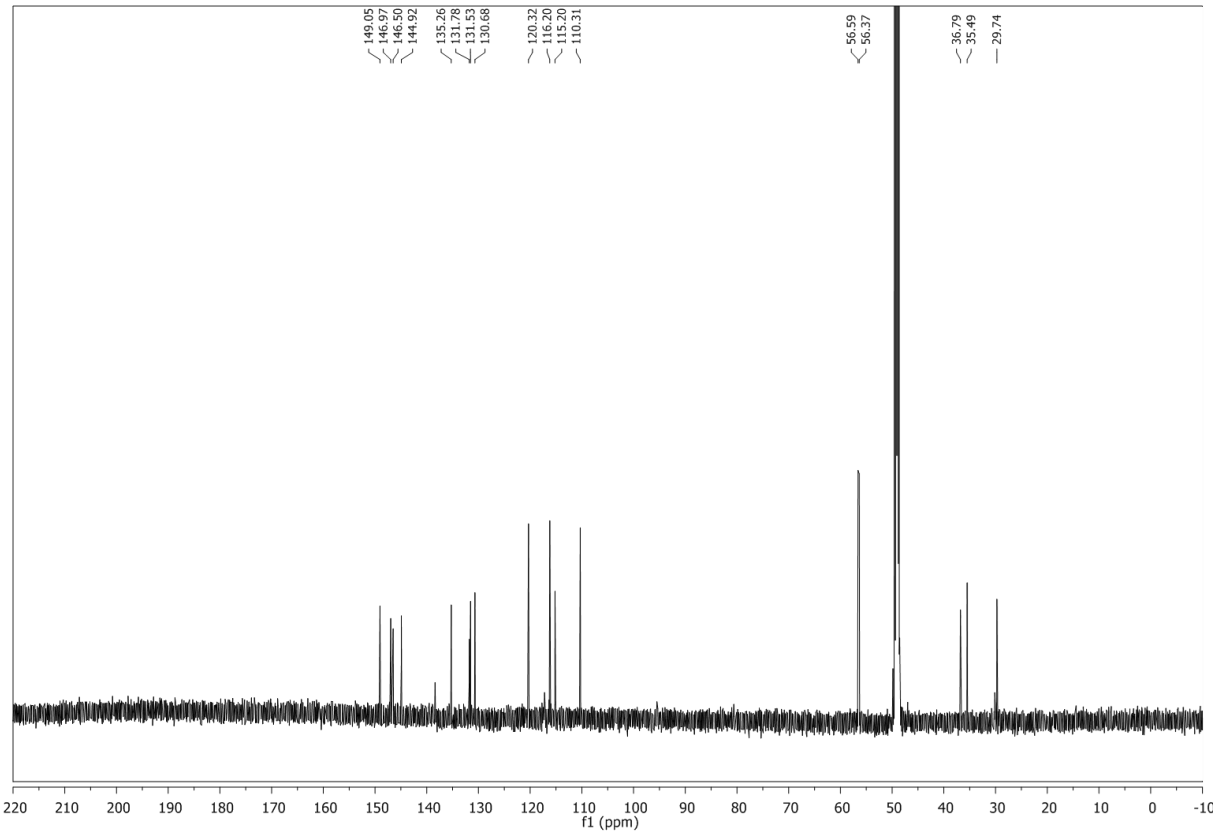


(*E*)-9-(4-Hydroxy-3-methoxystyryl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-ol (115)

^{1}H-NMR

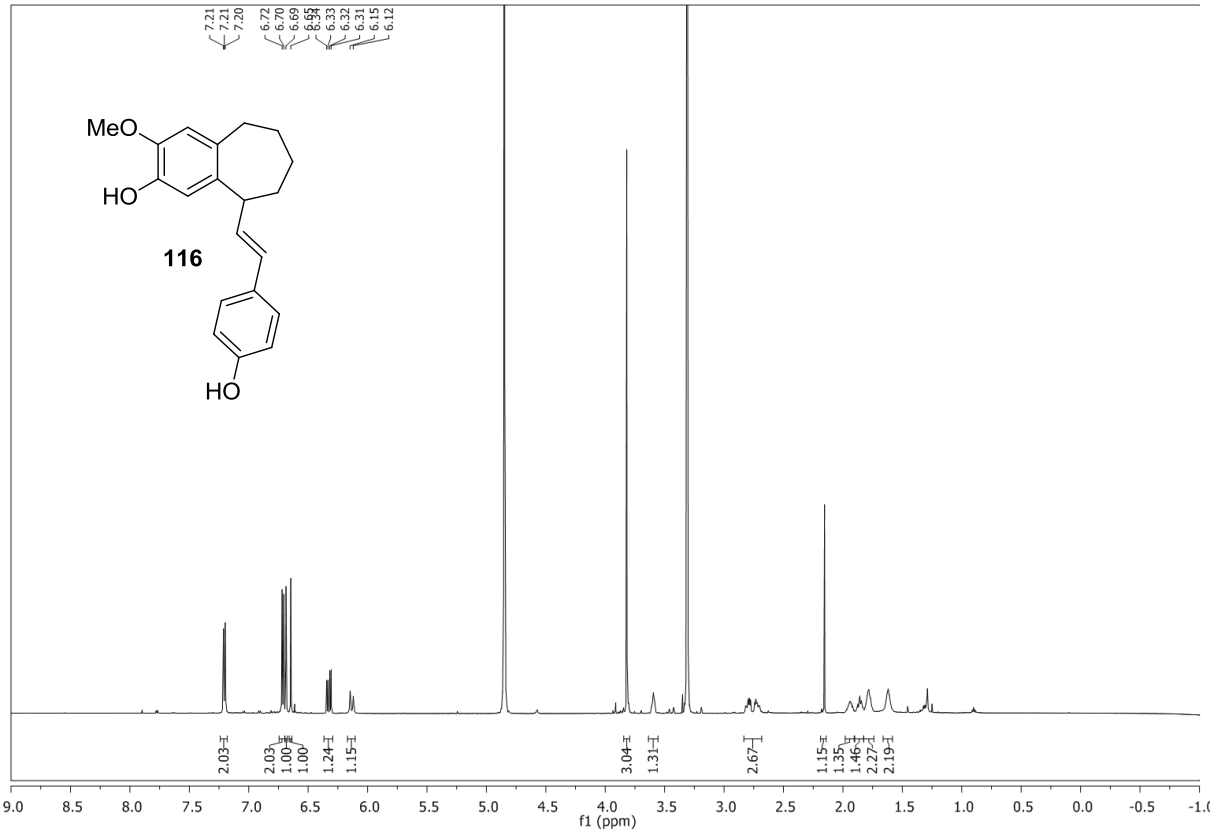


^{13}C-NMR

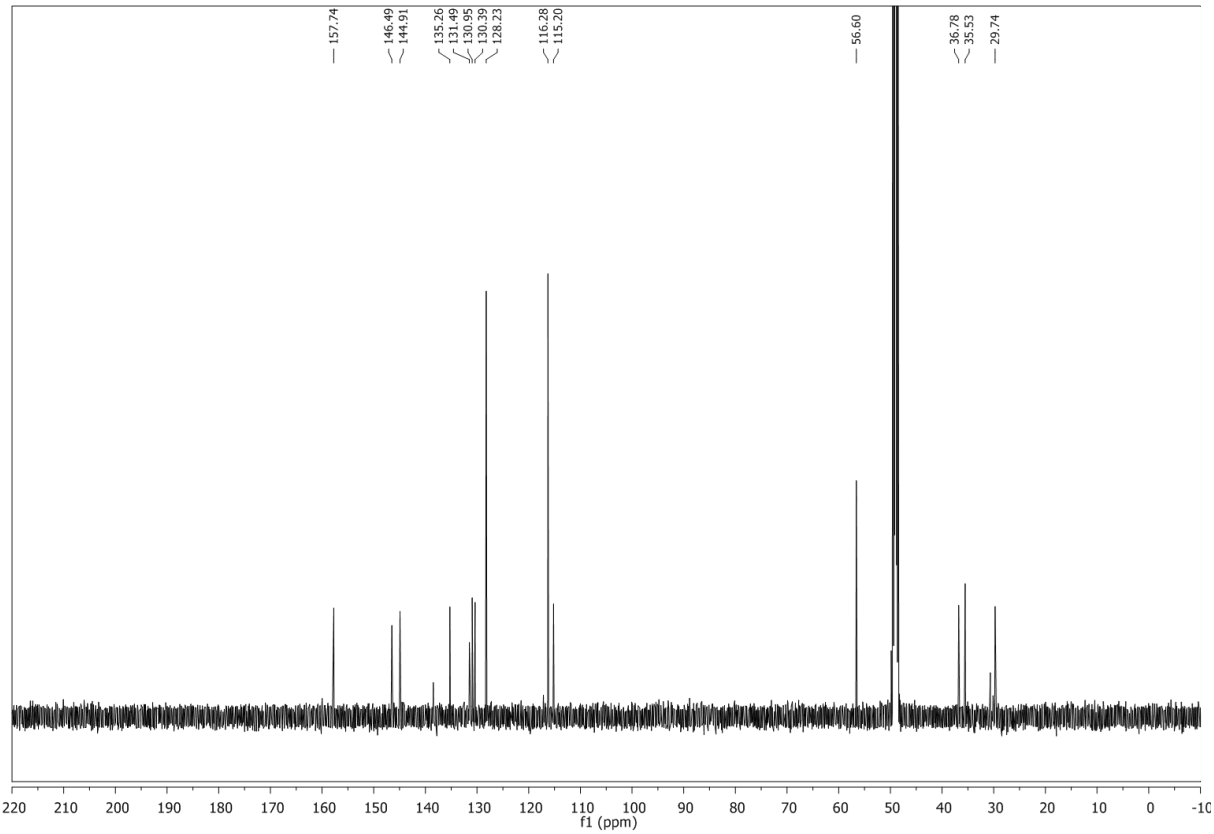


(*E*)-9-(4-Hydroxystyryl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo [7]annulen-2-ol (116)

^{1}H-NMR

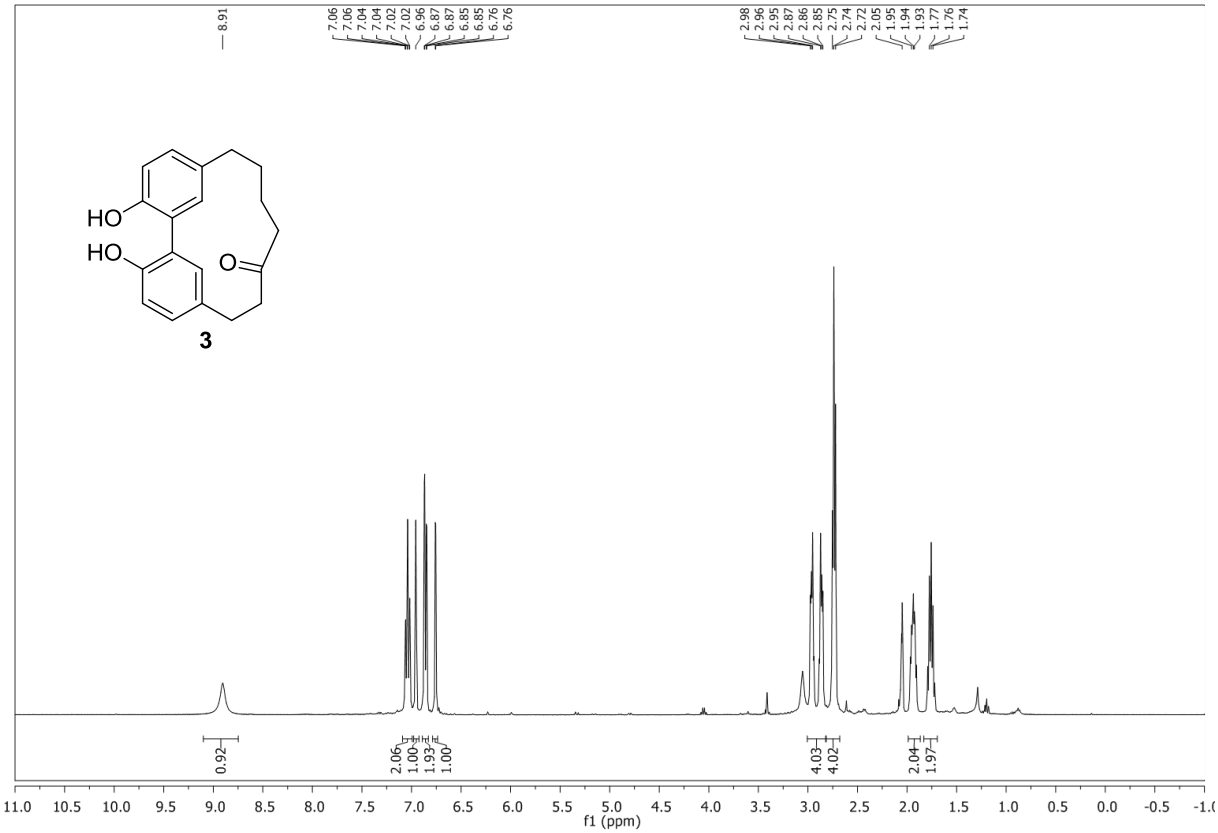


^{13}C-NMR

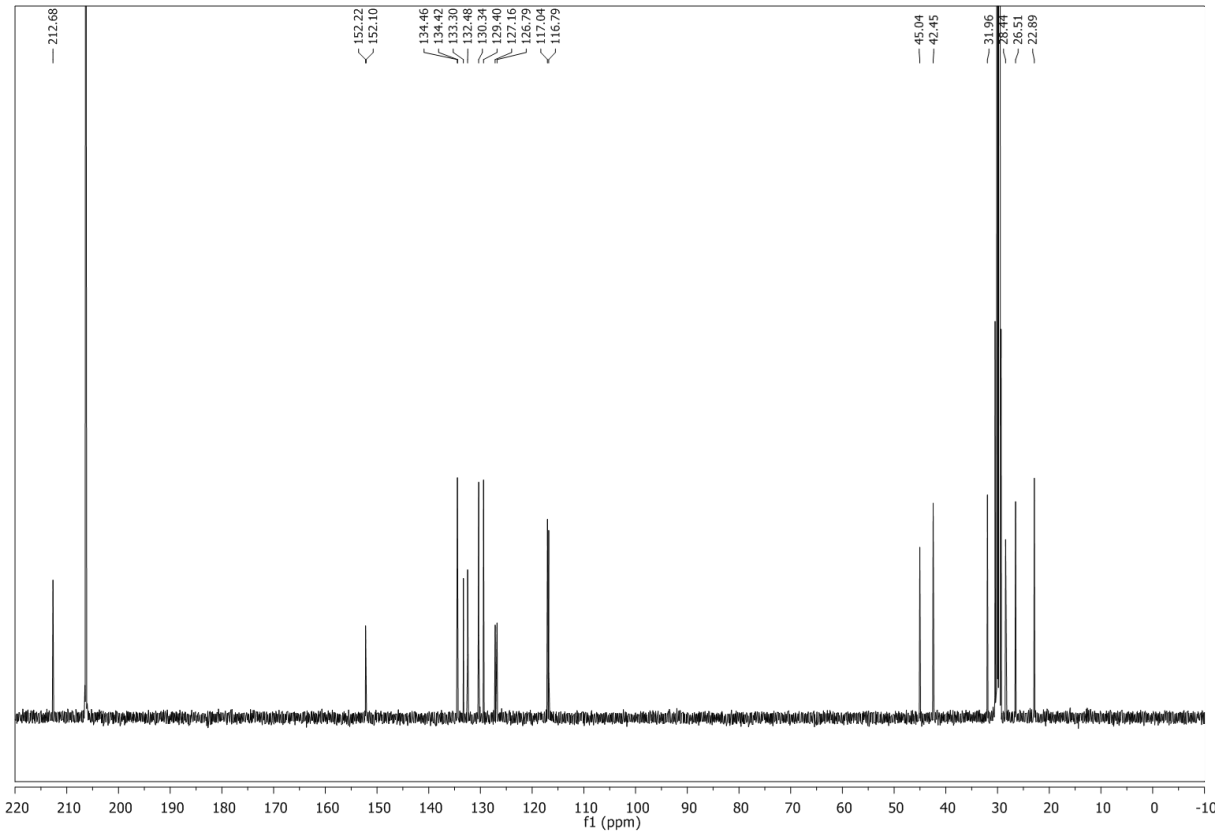


3,17-Dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-one (acerogenin E, 3)

^{1}H-NMR

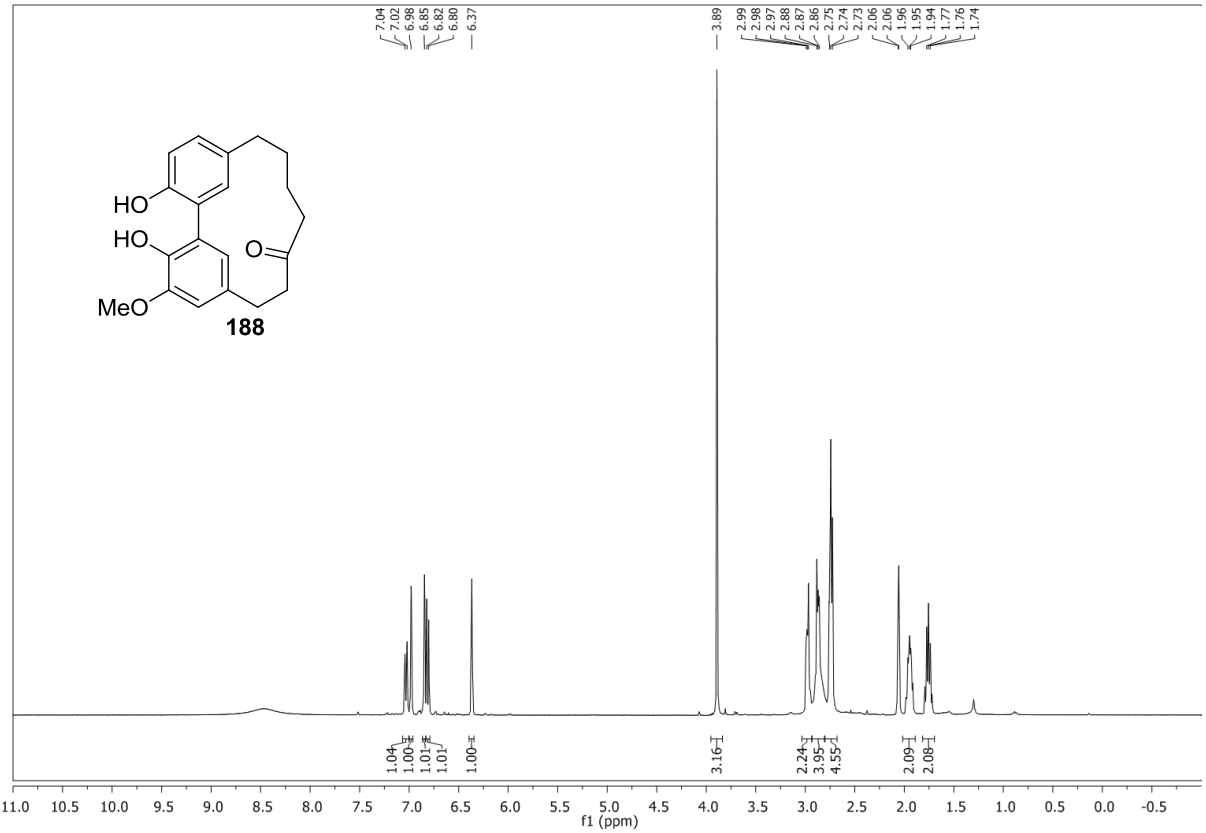


^{13}C-NMR

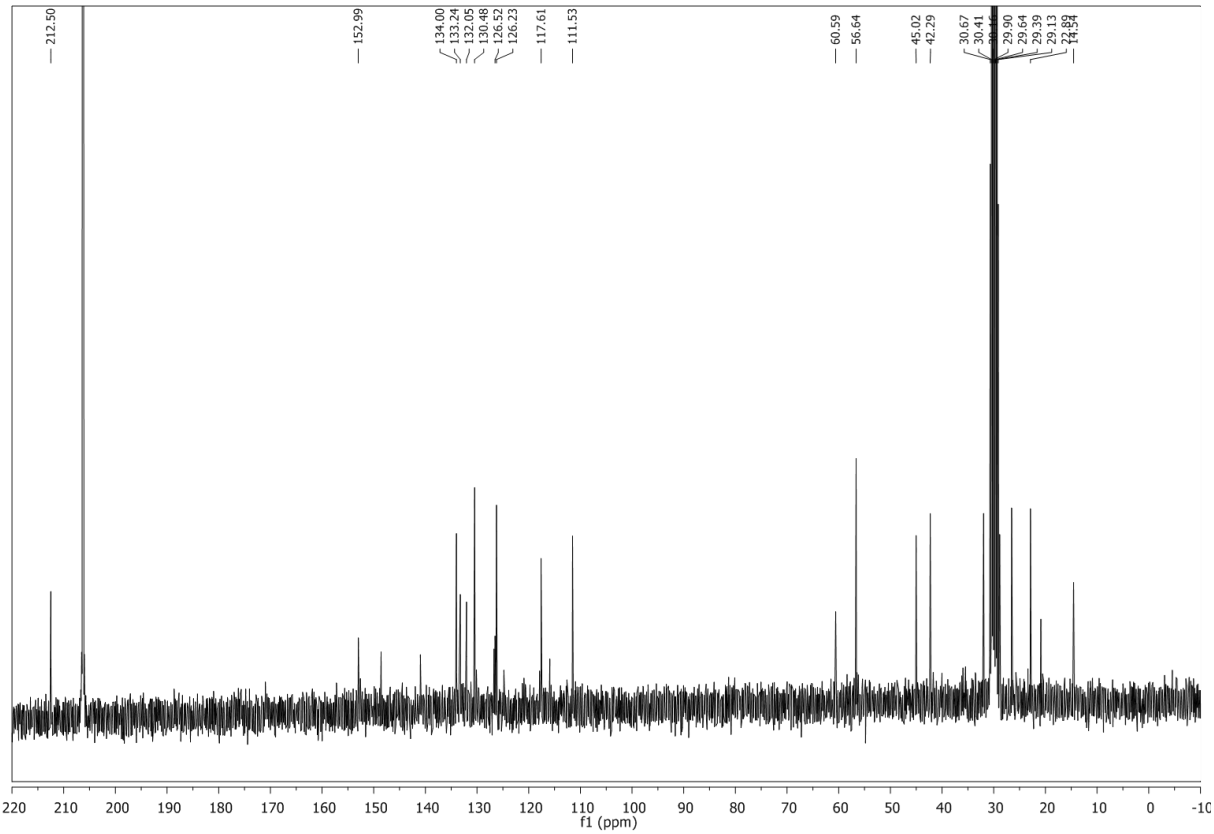


16-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (188)

^{1}H-NMR

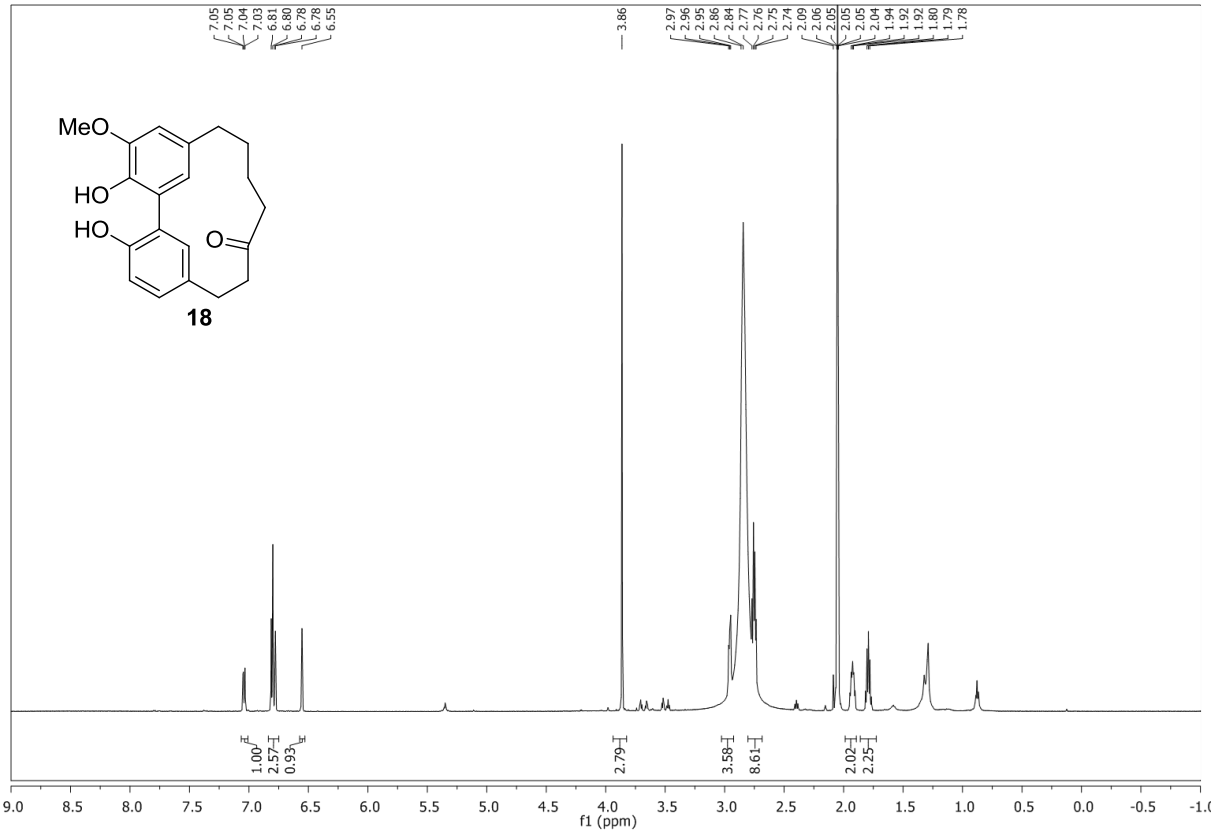


^{13}C-NMR

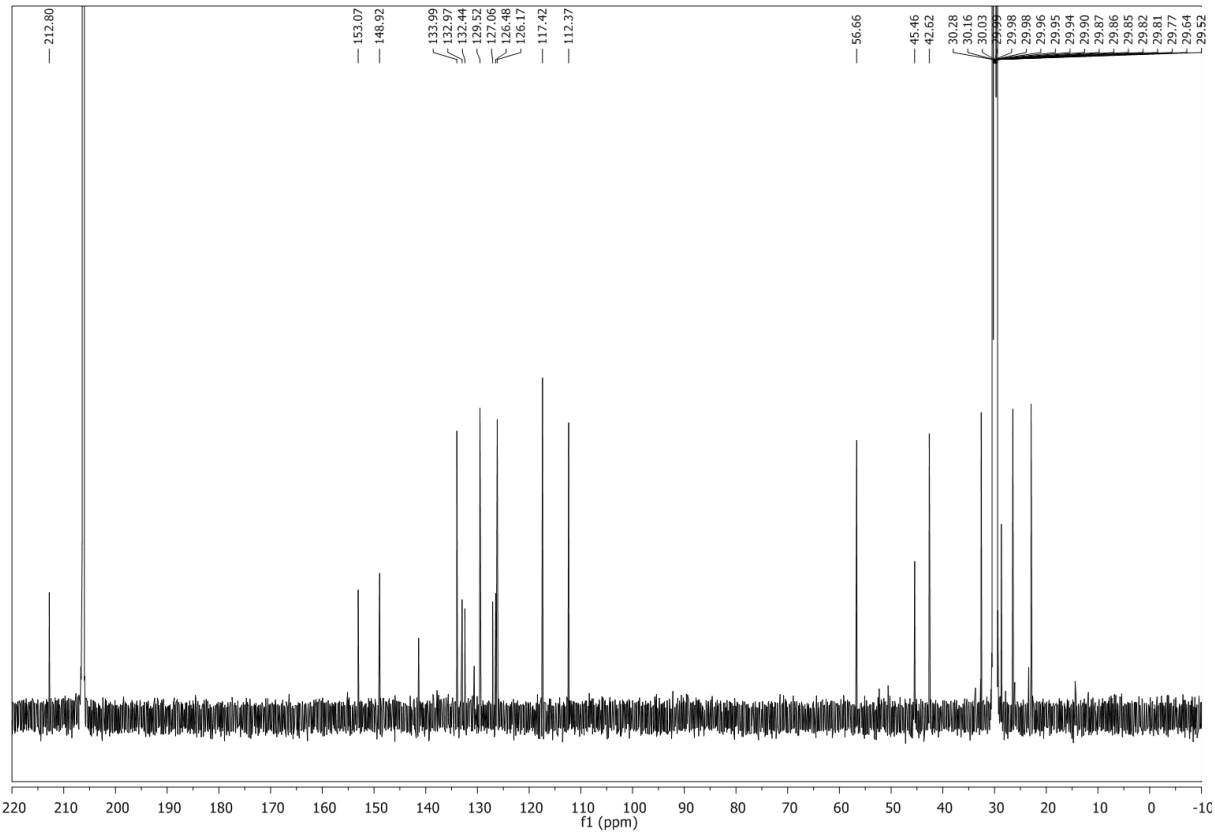


4-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-one (myricananin C, 18)

^{1}H-NMR

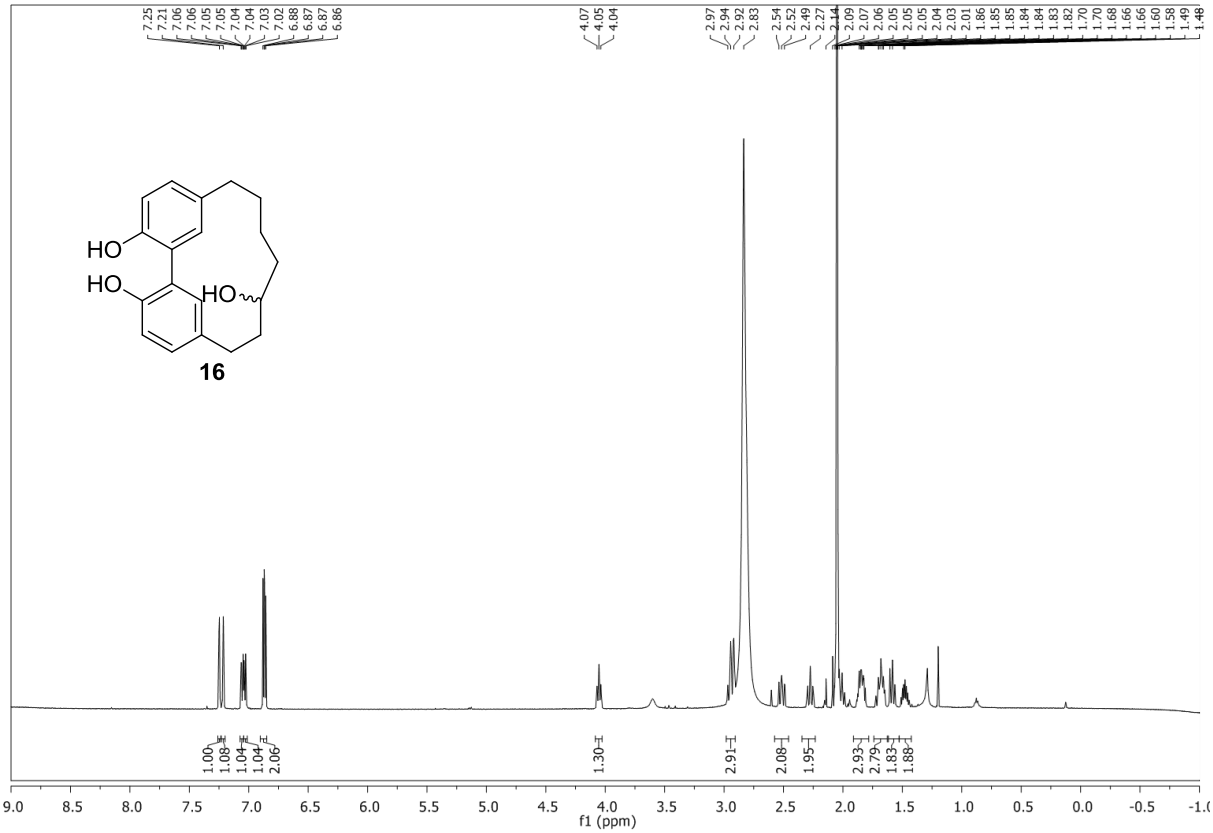


^{13}C-NMR

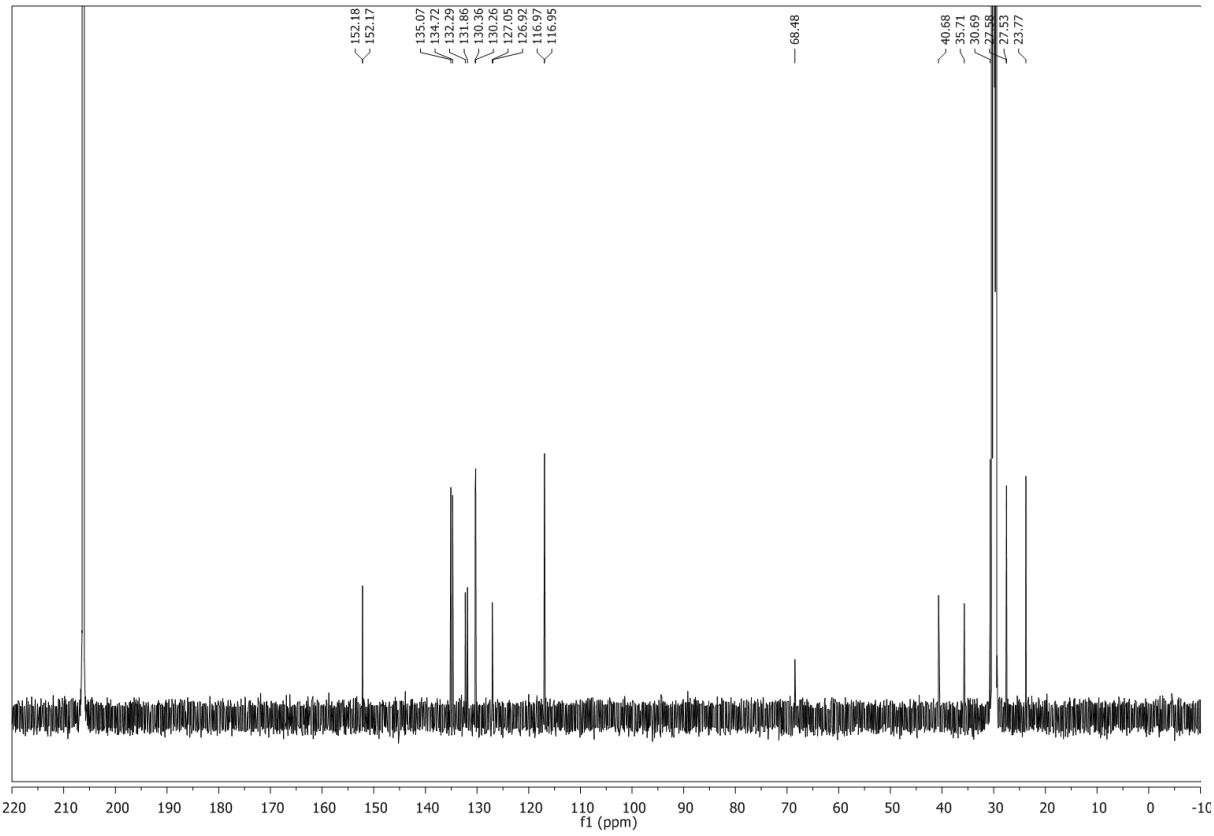


3,17-Dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19),3,5,14(18),15-hexaen-9-ol (axerogenin K, 16)

^{1}H-NMR

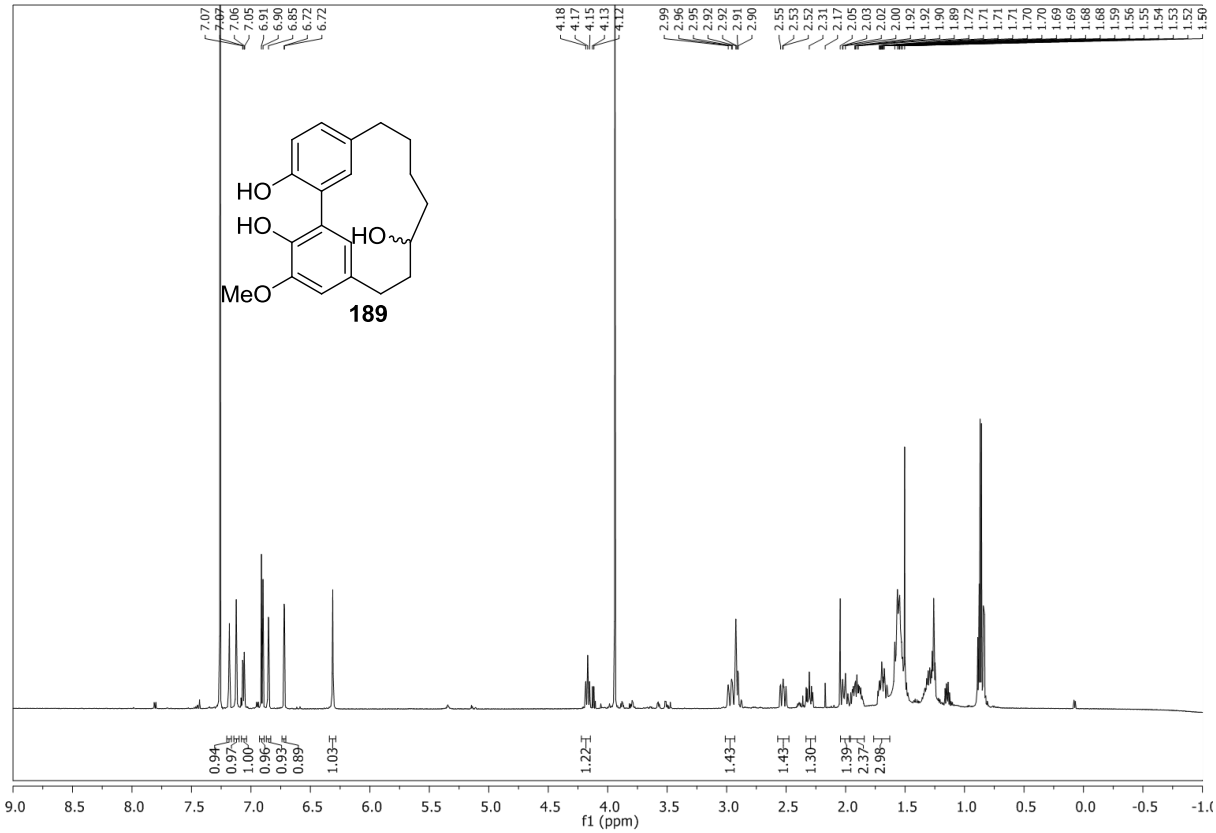


^{13}C-NMR

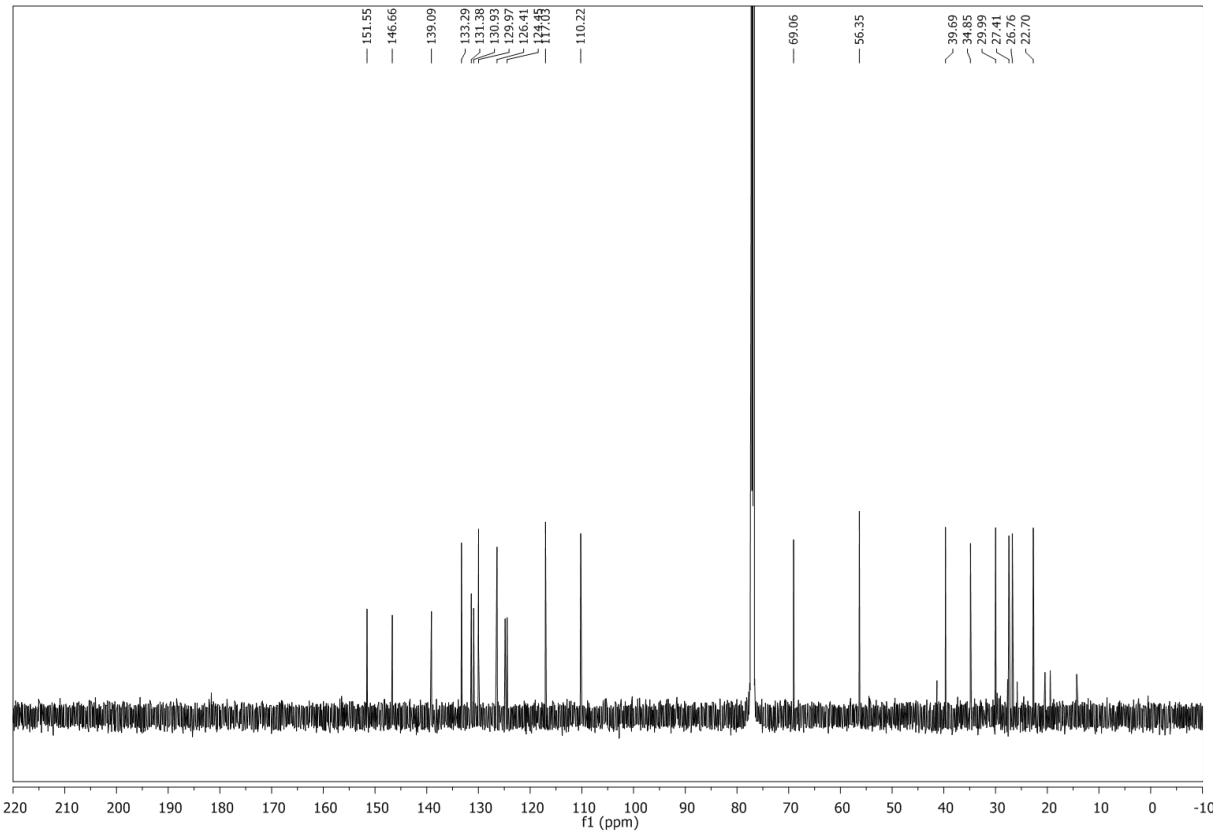


16-Methoxy-3,17-dihydroxy-tricyclo[12.3.1.^{12,6}]nonadeca-1(17),2(19), 3,5,14(18),15-hexaen-9-ol (189)

^{1}H-NMR

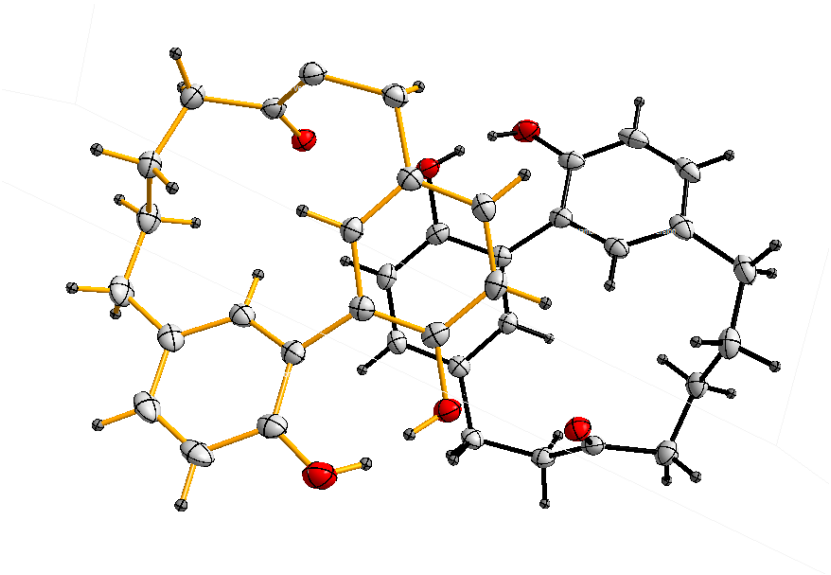


^{13}C-NMR



7.2 X-ray data

7.2.1 Acerogenin E (3) crystallized from EtOH



Dihedral angle between the two aromatic rings is 31.78°

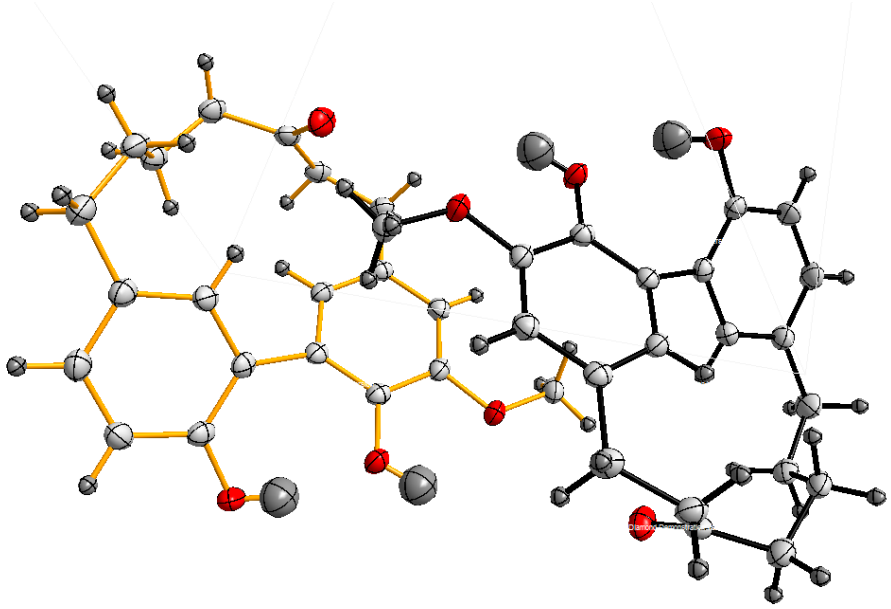
Empirical formula	$C_{19}H_{20}O_3$
Formula weight	296.35
Temperature/K	123.01(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	15.13045(17)
b/Å	11.38773(14)
c/Å	17.5489(2)
α/°	90
β/°	103.2355(12)
γ/°	90
Volume/Å^3	2943.39(6)
Z	8
ρ_{calc}g/cm^3	1.338
μ/mm^{-1}	0.716

F(000)	1264.0
Crystal size/mm^3	0.08 × 0.07 × 0.03
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.818 to 141.372
Index ranges	-18 ≤ h ≤ 18, -13 ≤ k ≤ 13, -20 ≤ l ≤ 21
Reflections collected	13596
Independent reflections	2810 [R_{int} = 0.0258, R_{sigma} = 0.0152]
Data/restraints/parameters	2810/0/201
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0343, wR_2 = 0.0909
Final R indexes [all data]	R_1 = 0.0358, wR_2 = 0.0924
Largest diff. peak/hole / e Å^{-3}	0.23/-0.19

Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

7.2.2 Compound 188 crystallized from EtOH



Dihedral angle between the two aromatic rings is 36.58°. The crystal contains two molecules of EtOH per molecule of **188.**

Empirical formula	$C_{22}H_{28}O_5$
Formula weight	372.44
Temperature/K	122.95(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.07755(15)
b/Å	10.39210(18)
c/Å	11.6256(2)
α/°	85.4133(14)
β/°	70.1186(16)
γ/°	67.9417(16)
Volume/Å^3	954.41(3)
Z	2
ρ_{calc}g/cm^3	1.296

μ/mm^{-1}	0.737
F(000)	400.0
Crystal size/mm^3	0.339 × 0.23 × 0.099
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.1 to 133.522
Index ranges	-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	16148
Independent reflections	3360 [R_{int} = 0.0194, R_{sigma} = 0.0133]
Data/restraints/parameters	3360/36/274
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0334, wR_2 = 0.0873
Final R indexes [all data]	R_1 = 0.0365, wR_2 = 0.0901
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.17

Using Olex2 [1], the structure was solved with the SIR2004 [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using CGLS minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Burla, M.C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G.L., De Caro, L., Giacovazzo, C., Polidori, G., Siliqi, D., Spagna, R. (2007). J. Appl. Cryst. 40, 609-613.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

7.3 HPLC-based stability test of curcumin (1) and compound 98

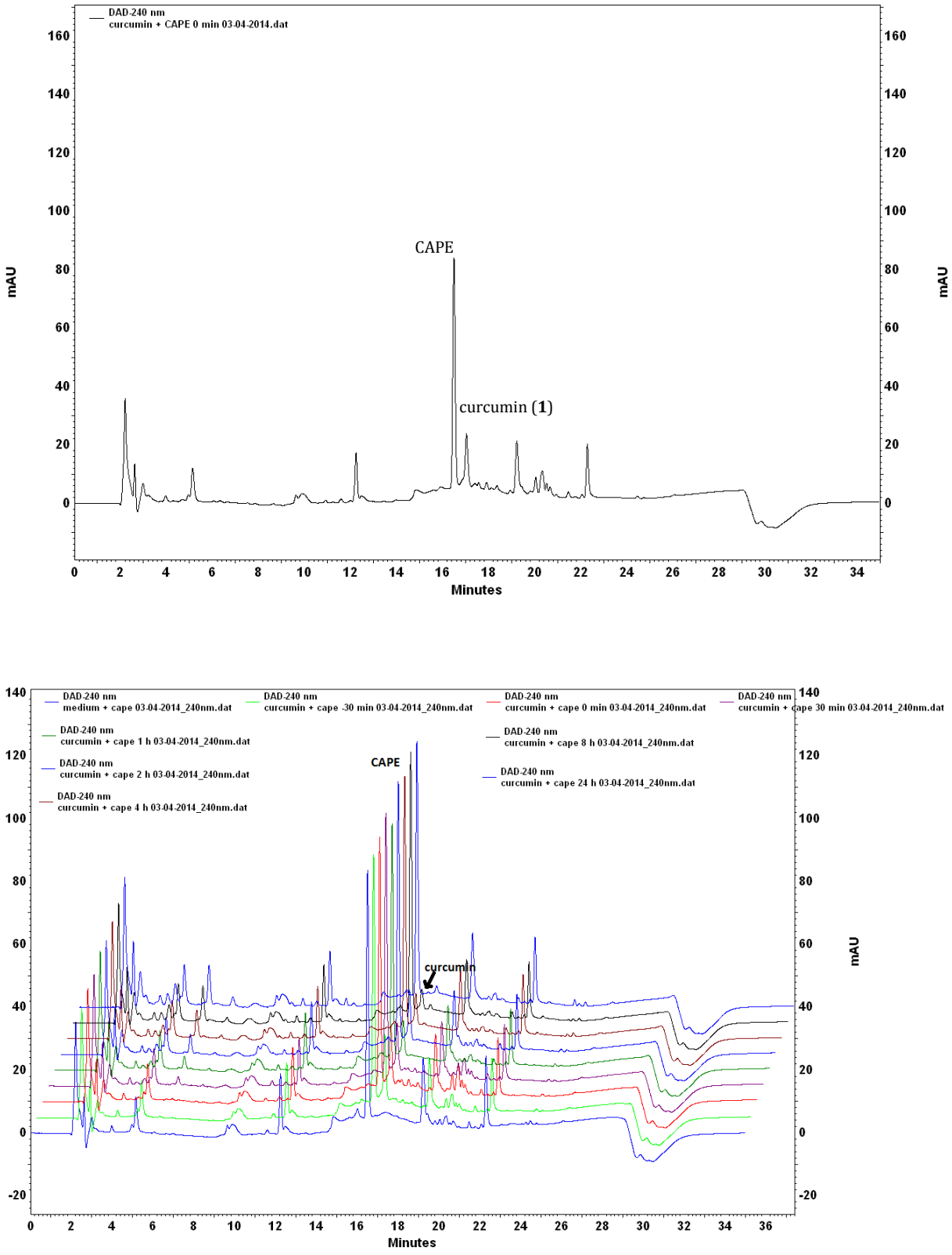


Fig. 44: Curcumin (**1**) + CAPE in cell culture medium

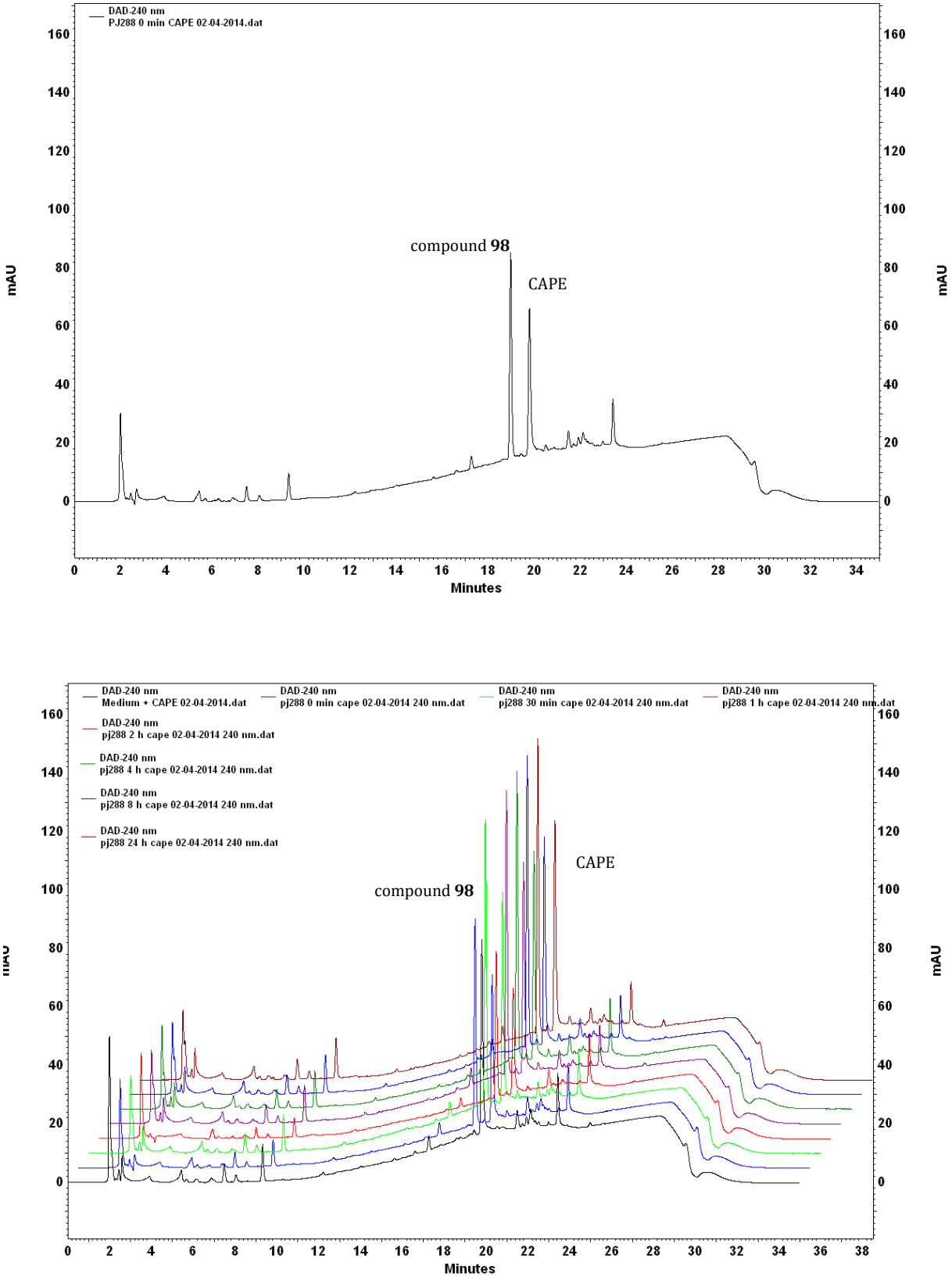
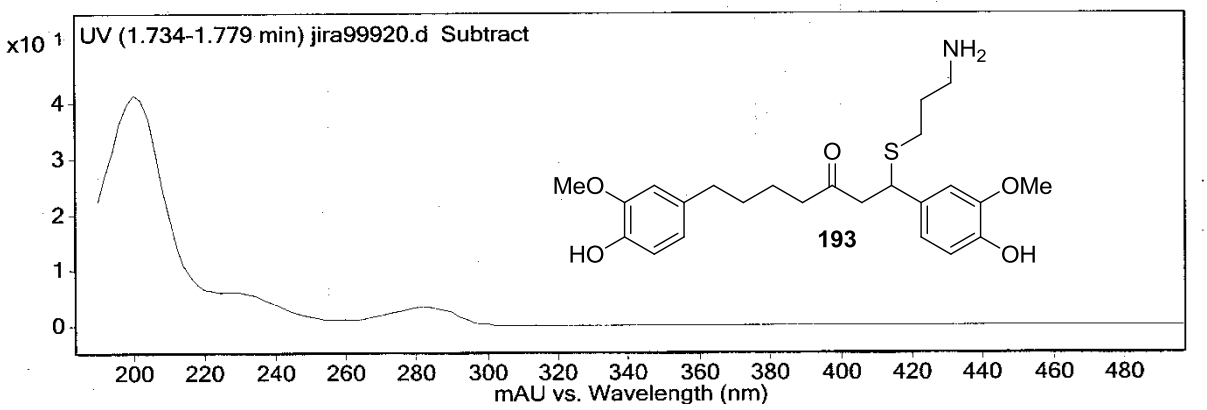


Fig. 45: Compound **98** + CAPE in cell culture medium

7.4 Michael acceptor activity assay – MS data

UV spectrum of curcuminoid-cysteamine adduct **193**



Mass spectrum of adduct **193**