Synthesis of Functionalized Homophthalates, Salicylates, Diaryl Ethers and Dihydroisocoumarins based on Cyclocondensation Reactions of 1,3-Dicarbonyl Compounds and 1,3-Bis(silyloxy)-1,3-butadienes

DISSERTATION

zur

Erlangung des akademischen Grades

doctor rerum naturalium (Dr. rer. nat.)

der Mathematisch-Naturwissenschaftlichen Fakultät

der Universität Rostock

vorgelegt von

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Rostock, July 2008

urn:nbn:de:gbv:28-diss2008-0105-5

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Tag der Promotion : 29-10-2008

Affectionately Dedicated to

My mother , Father And

Sweet Brothers

CONTENTS

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ACKNOWLEDGEMENTS

By the grace of Allah, the Almighty, the creator of universe, who granted Hidayah to the mankind and peace and blessings be upon his prophet, Hazrat Muhammad (Peace be upon Him), who exhorted his followers to seek knowledge from cradle to grave, I've been able to complete this academic enterprise.

It is my first and foremost obligation to express my sincere gratitude to Professor Dr. Peter Langer my supervisor. His proper supervision, experience, time devotion and keen interest enable me to accumulate this humble work. Special thanks to Dr. Andreas Schmidt and Dr. Frormann for their help and care during my stay in TU Clausthal.

I would like to acknowldge to Dr. Zafar and Dr. Ehsan Ullah for helpful discussions and friendship. Without their help, my work would result in partial success.

I ought to submit my thanks to my dear friends, who remembered me in their prayers and heart. I wish to acknowledge support and encouragement provided by M. Imran-Ul-Haq, R. Shahid, Ahsan, Tabraiz, Adil, M. A. Yawer, Ibrar, Zahid, Mubarak, K. Rehan and Mukhtar Ullah.

I am thankful to all my past and present colleagues, Sven, Alina, Thomas, Asad, Ehsan, Abid, Ahmad, Adeel, Gerson, Jope , Inam, Imran, Majid, Nasir, Rasheed, Rüdiger and Shkoor for their support encouragement and help to pursue this work and all others whom I have missed here do deserve equal credit.

Thanks also go to Dr. Martin Hein, Prof. Helmut Reinke and all members of technical sections (NMR, IR, MS, EA and X-Ray etc) of Rostock University.

Finally I express my heartiest gratitude and respect to my mother, father sweet brothers and all family who encouraged through-out my studies and supported me what and whenever they could. May God provide me the way to fulfill their promises. Special thanks to my fiance Rashida for her prayers and moral support.

Muhammad Sher 04/07/2008

Abbreviations

Ar	Aromatic
APT	Attached Proton Test
ATCC	American Type Culture Collection
*n*BuLi	*n*-Butylithium
DEPT	Distortionless Enhancement by Polarisation Transfer
EI	Electronic Impact
ESI	Electrospray Ionization
EtOAc	Ethylacetate
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
MS	Mass Spectrometry
Ph	Phenyl
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Correlated Spectroscopy
NOESY	Nuclear Overhauser and Exchange Spectroscopy
Me_3SiOTf	Trimethylsilyl-trifluoromethanesulfonate
Me_3SiCl	Trimethylsilylchloride
mp.	Melting Point
RCM	Ring Closing Metathesis
TBAI	Tetrabutyl Amonium Iodie
TFA	Trifluoroacetic Acid
Tf_2O	Trifluoromethanesulfonic Anhydride
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
UV	Ultraviolet Spectroscopy

General introduction

Instead of simply analyzing naturally existing molecules, chemists began to synthesize organic compounds including molecules that did not exist in nature. The combination of this new synthetic approach with more traditional analytical approaches revolutionized chemistry, leading to a deep understanding of the fundamental principles of chemical structure and reactivity and to the emergence of the modern pharmaceutical and chemical industries. Natural products continue to play an important role in discovery and development of new pharmaceuticals, as clinically useful drugs, as starting materials to produce synthetic drugs, or as lead structures from which a synthetic drug can be designed.[1] At the same time, synthetic compounds not related to natural products play an increasingly important role for drug discovery. Continuous improvements in synthetic methodology have provided a convenient access to a vast array of synthetic substances.

Bioactive products include, for example, antibiotic, anti-infective, anticancer, cardio-vascular agents. The development of new antimicrobial agents represents an important field in medicinal chemistry, due to the increasing problem of the formation of resistant strains of bacterial pathogens. Natural products often represent important lead structures for the development of new antibiotics.[2] In fact, a number of natural products exhibit antibiotic activity. Since the discovery of penicillin, a large number of antibiotics have been isolated from scores of microorganisms.[3] The discovery of new important anti-infective compounds includes both plant and animal sources. For example, astemisinin, a sesquiterpene with endoperoxide moiety, was isolated from *Astemisia annua*, a Chinese medicinal plant, which has been used in China for centuries for treatment of malaria. Subsequent efforts included the development of astemisinin derivatives with more desirable pharmaceutical properties. The development of new drugs includes synthetic and semi-synthetic studies, microbial transformations, the biological screening and the study of the mechanism of action.[4] The effort to design better anti-malaria agents has also led to the discovery of other antimicrobial agents including a class of synthetic antibacterial products that is in clinical use today - the fluoroquinolones.

In the chemotherapy of cancer, natural products have provided the most important success. A number of anticancer drugs represent unmodified natural products isolated from plants or microorganisms:[5] this includes bleomycin, doxorubicin, mitomycin, paclitaxel (Taxol^{TM});

examples of semi-synthetic derivatives of natural products, which are important anticancer drugs are, for example, ironotecan (a camptothecin derivative), etoposide or tenoposide (a podophyllotoxin derivative). Currently, both a semi-synthetic derivative with improved water solubility, docetaxel (Taxotene^{TM}) and paclitaxel (Taxol^{TM}) are approved and used clinically in the treatment of ovarian breast cancers.

Many important drugs have been developed by a combination of natural product and synthetic chemistry. In this context, combinatorial chemistry provides an ever-increasing pool for evaluation of therapeutic potential; advances in molecular biology will provide insights into the biological processes and, hence, possible targets for the treatment of disease. Bioactive natural products can serve as probes to study these molecular and pharmacological processes.[6]

My studies are focused on the development of new and reliable synthetic strategies and their application to the preparation of natural products and pharmacologically active carba- and heterocycles.

In the present thesis, the synthesis of natural product analogues is studied. These structures include salicylates, diary ethers, resorcins, dihydroisocoumarins, 4,5-diary-1,2,3-benzenetricarboxylates and 1,2,3-triazoles.

Summary

A significant part of the present dissertation has been recently published. Each chapter contains the content of one publication and the text and schemes of these publications were directly used for writing the thesis. The thesis can be summarized as follows:

1. *Efficient synthesis of salicylates by catalytic [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane*. This chapter includes the synthesis of novel alkyl-substituted 1,3-bis(silyl enol ethers) **4a-v** based on the known procedures. The 1,3-bis(silyl enol ethers) are used as starting materials for the synthesis of salicylates by catalytic [3+3] cyclization with 1,1,3,3-tetramethoxypropane.

2 *Synthesis of diaryl ethers based on one-pot [3+3] cyclizations of 1,3-bis(silyl enol ethers)*. This chapter includes the synthesis of diary ethers **15a-u** which were prepared by

formal [3+3] cyclocondensation of 2-aryloxy-3-(silyloxy)alk-2-en-1-one **14a-i** with 1,3-bis(silyl enol ethers) **4**. By using this methodology I successfully synthesized highly functionalized diaryl ethers which are not readily available by other methods.

3. *Regioselective synthesis of functionalized resorcins by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride*. In this chapter, I have described the regioselective synthesis of fuctionalized resorcins by formal [3+3] cyclocondensation of 1,3-bis(silyl enol ethers) **4** with 3,3-dimethoxypentanoyl chloride. The effect of Lewis acids (Me_3SiOTf and $TiCl_4$) on the regioselectivity of resorsins studied in this chapter.

4 *Synthesis of 3-aryl-3,4-dihydroisocoumarins by regioselective domino '[3+3] cyclization / lactonization' reactions of 1,3-bis-(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones.* This chapter includes the synthesis of 3-aryl-3,4-dihydroisocoumarins (3-aryl-isochroman-1-ones) by regioselective domino ′[3+3] cyclization/lactonization′ reactions of 1,3-bis-(silyloxy)-1,3-butadienes **4** with 1-hydroxy-5-silyloxy-4-en-3-ones. 3-aryl-3,4-dihydroisocoumarins are of considerable pharmacological relevance and occur in many natural products.

5. *Synthesis of 4,5-diaryl-1,2,3-benzenetricarboxylates by reaction of 4-hydroxycyclopent-2-en-1-one-2-carboxylates with dimethyl acetylenedicarboxylat*e. This chapter includes the synthesis synthesis of 4-hydroxycyclo-2-penten-1-one-2-carboxylates **33a-j** by cyclization of 1,2-diketones with 1,3-dicarbonyl dianions and their conversion to novel 4,5-diaryl-1,2,3-benzenetricarboxylates **34a-i** by acid-mediated reaction with dimethyl acetylenedicarboxylate.

6. *Regioselective synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles by copper(I)-catalyzed [3+2] cyclization of 2-azido-2,2-dimethoxyethane with alkynes.* In this chapter, I have described the regioselective synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **40a-k** by copper(I)-catalyzed [3+2] cyclization of 2-azido-2,2-dimethoxyethane with alkynes. 2-Azido-1,1-dimethoxyethane (ADE) represents a small, but versatile C_2-building block containing a masked aldehyde and a masked amino group. It can be readily prepared by reaction of 1-chloro- or 1-bromo-2,2-dimethoxyethane with sodium azide.

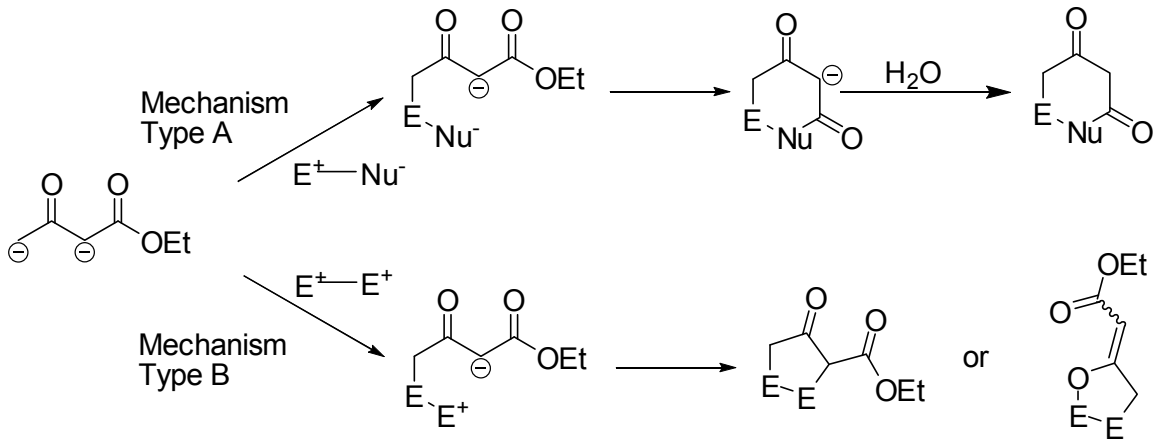
8. This chapter includes the experimental, spectroscopic data and full characterization of all new products has been described.

1. Efficient synthesis of salicylates by catalytic [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane

1.1 Synthesis of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes

1.1.1 Introduction

Dianions represent important building blocks for the regioselective formation of carbon-carbon bonds. Ambident dianions are organic substrates containing two delocalized negative charges. Dianions can be generated by reaction of 1,3-dicarbonyl compounds in the presence of strong base, such as LDA or *n*-BuLi[7]. The functionalization of the terminal carbon atom of 1,3-dicarbonyl compounds by reaction of the corresponding dianions with electrophiles represents an important synthetic method which has been used in the synthesis of natural products. The terminal carbon atom of the dianion can be regioselectively coupled with one equivalent of an electrophile E^+ to give a monoanion which can be subsequently trapped by addition of a second electrophile. Two general mechanistic pathways for *cyclization* reactions of dianions can be discussed as follows[7] (Scheme 1-1):



Scheme 1-1: Possible mechanistic pathways for cyclization reactions of 1,3-dicarbonyl dianions. Nu = nucleophile center, E = electrophile center

Mechanism type A: the dianion can react with monofunctional electrophiles with transposition of a negative charge from the dianion to the electrophile. This carbanion attacks

an E^+ centre of the former dianion moiety (e.g. the ester group) to give a cyclic monoanion which is subsequently quenched with water.

Mechanism type B: the dianion can react as a dinucleophile with a dielectrophile. A monoanion is formed, followed by attack of the latter onto a second E^+ center.

Cyclization reactions of dianions with dielectrophiles are synthetically useful. However, problems can arise since both starting materials are highly reactive compounds which have low reactivity matching. In addition, 1,2-dielectrophiles are often rather labile, and reactions with nucleophiles can result in polymerization, decomposition, formation of open-chained products, elimination or SET-process. These intrinsic limitations can be overcome by two ways: a) a proper tuning of the reactivity of dianion and dieletrophile and b) the use of eletroneutral dianion equivalents (masked dianions) in Lewis acid catalyzed reactions.[7]

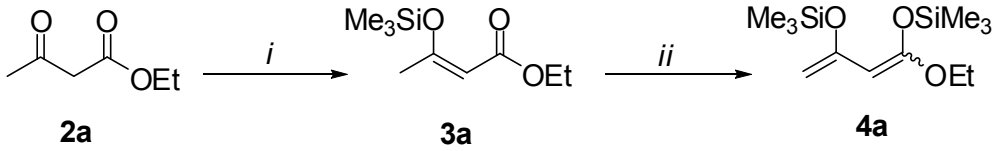
Many studies proved that 1,3-bis-enol silyl ethers can be considered as equivalents of the corresponding 1,3-dicarbonyl dianions.[8] The chemistry of bis-silyl enol ethers has been developed during the last two decades.[8d] It is, for example, known that enol silyl ethers can condense with various carbonyl compounds in the presence of Lewis acids.[9] These Lewis-acid-mediated reactions[10] (e. g. alkylation and aldol condensation) provide useful alternatives to classical enolate chemistry. In cyclization reactions, 1,3-bis-silyl enol ethers can react as 1,3-dinucleophiles or, similar to the well-known Danishefsky diene[11], as functionalized butadienes. 1,3-Bis-silyl enol ethers undergo reactions with electrophiles at the terminal carbon atom followed by reaction of the central carbon or the oxygen atom. Enol silyl ethers can be cleaved with nucleophiles such as MeLi, $LiNH_2$ or $R_4N^+F^-$ to give enolates. They can be reacted with halides (Br_2, Cl_2, I_2) or pseudohalides (PhSCl, PhSeCl, Cl-N=O).[12] Whereas enolates can be alkylated only by primary or secondary halides, enol silyl ethers can be alkylated by tertiary halides.[13]

The preparation of silyl enol ethers mainly follows the procedures reported by Chan and Molander. These syntheses rely on the preparation of mono-silyl enol ethers which are subsequently transformed into bis-silyl enol ether by deprotonation with LDA and subsequent silylation.[14]

In this chapter, we present the synthesis of novel 4 substituted 1,3-bis(trimethylsilyoxy)-1,3-butadiens following the procedure of Chan.

1.1.2 Results and discussion

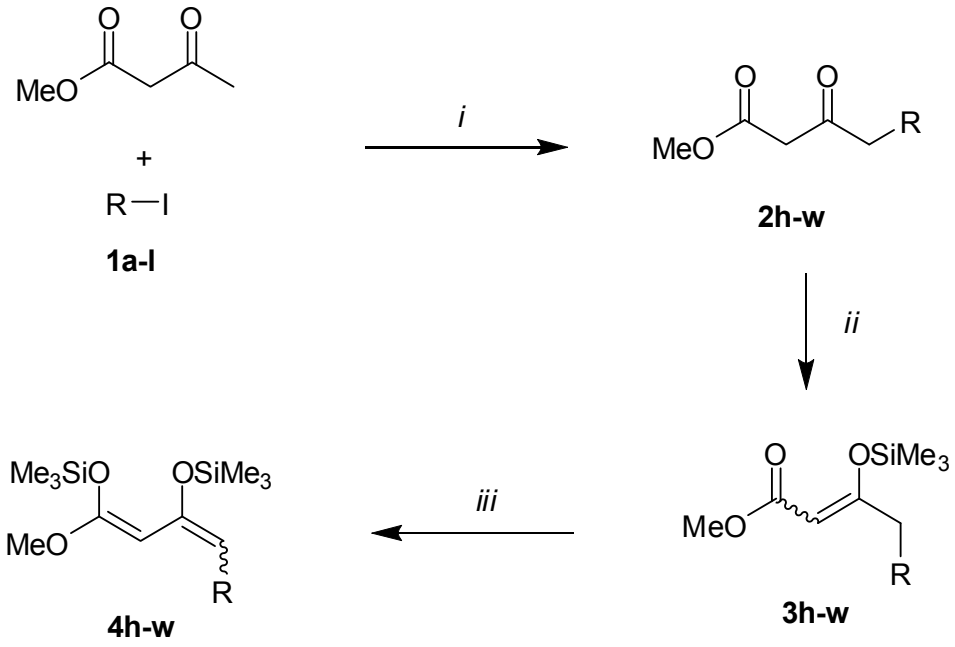
Following the procedures of Chan and Molander, 1,3-bis(trimethylsilyloxy)-1,3-butadiene **4a** can be prepared from the respective 1,3-dicarbonyl compound **2a** in two steps. Treatment of the *β*-ketoester with NEt_3, Me_3SiCl afforded silyl enol ether **3a** Deprotonation of the latter with LDA and subsequent addition of Me_3SiCl afforded the diene **4a**. Simchen *et al*. reported that 1,3-diketone derived bis-silyl enol ethers can be prepared in one step by treatment of an ether solution of the diketone with NEt_3 and Me_3SiOTf (2.0 equivalent)[8] (Scheme 1-2).



2a **3a** **4a**

Scheme 1-2: Synthesis of 1,3-bis-silyl enol ether 4a; *i*) 1) NEt_3 (1.5 equiv.); 2) Me_3SiCl (1.5 equiv.), C_6H_6, 20 °C, 12 - 48 h; *ii*) 1) LDA (1.5 equiv.), THF, 0 °C, 2 h; 2) Me_3SiCl (1.5 equiv.), –78 → 20 °C, 6 - 12 h.

The synthesis of alkyl-substituted-1,3-bis-silyl enol ether derivatives requires the synthesis of the respective β-ketoesters **2h-w**. It is known that the regioselectivities of the reactions of monoanions and dianions generally differ greatly. 1,3-Dicarbonyl monoanions are generally alkylated at the central carbon or at the oxygen atom, whereas the formation of dianions allows the functionalization of the terminal carbon atom. Based on this, the 4-alkyl-3-oxobutanoates **2h-w** were prepared by reactions of the dianion of ethyl acetoacetate with the respective alkylhalides **1a-l** (RI, RBr). These compounds were transformed, according to a known procedure,[8] into the desired 1,3-bis-silyl enol ethers **4h-w** via the respective mono-silyl enol ethers **3h-w** (Scheme 1-3, Table 1-1).



Scheme 1-3: Synthesis of alkyl-substituted 1,3-bis-silyl enol ether derivatives; *i*: 1) 2.5 LDA, THF, 0 °C, 1 h; 2) **1a-l**, –78 → 20 °C; *ii*: Me_3SiCl (1.5 equiv.), NEt_3 (1.5 equiv.), C_6H_6, 20 °C, 48 h; *iii*: 1) LDA (1.5 equiv.), THF, –78 °C, 1 h; 2) Me_3SiCl (1.5 equiv.), 20 °C, –78 → 20 °C.

All 4-alkyl-1,3-bis-silyl enol ethers prepared could be stored at suitable conditions (-20 ^{o}C, dry, inert gas atmosphere) for several months without decomposition. The 1,3-bis-silyl enol ethers **4** used in this thesis are listed in the following table.

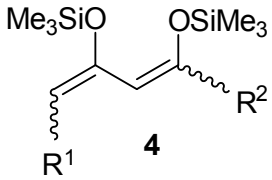


Table 1-1: 1,3-bis(silyl enol ethers) **4** used in this thesis

4	R^1	R^2
a	H	OEt
b	H	OMe
c	H	$O(CH_2)_2OMe$
d	H	Bn

e	H	O*i*Pr
f	Me	OEt
g	Et	OEt
h	*n*Bu	OMe
i	*i*Bu	OMe
j	*n*Hex	OEt
k	*n*Hex	OMe
l	*n*Hep	OMe
m	*n*Oct	Et
n	*n*Oc	OMe
o	*n*Dec	Et
p	CH_2Ph	OMe
q	OMe	OMe
r	O*t*Bu	OEt
s	$(CH_2)_2Ph$	OMe
t	$(CH_2)_3Ph$	OMe
u	$(CH_2)_3Cl$	OMe
v	$(CH_2)_6Cl$	OMe
w	Allyl	OMe
x	H	Me

1.1.3 Conclusions

The application of a the known procedure allows the synthesis of novel 4-alkyl-1,3-bis(silyl enol ethers). These masked dianions are used in the cyclization reactions for synthesis of heterocycles and aromatic rings - important building blocks of natural products analogue.

1.2 Synthesis of salicylates

1.2.1 Introduction

Salicylic acid derivatives are widespread in nature and are of considerable relevance in medicinal chemistry.[15] Synthetic approaches to salicylates mainly rely on the functionalization of phenols by electrophilic substitutions. The preparative scope of this approach is often limited by the formation of regioisomeric mixtures and by the availability of the starting materials. Salicylates are available also by base-mediated cyclization reactions of dimethyl acetone-1,3-dicarboxylate (DMAD) with 1,3-diketones,[16] yn-ones and yn-als.[17] The scope of these transformations is limited by the fact that a symmetrical, highly activated 1,3,5-tricarbonyl compound has to be employed. Barton *et al*. reported the synthesis of ethyl 5-ethylsalicylate by cyclization of the dianion of ethyl acetoacetate with 3-(*N*,*N*-dimethylamino)-2-ethylacrolein.[18] Functionalized phenols are available also by [4+2] cycloaddition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene),[19, 20] 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Chan's diene)[21] , 1,4-di(methoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Brassard's diene) or related dienes.[22]

The titanium tetrachloride ($TiCl_4$) mediated formal [3+3] cyclization of 1,3-bis(silyl enol ethers)[23] with 3-siloxy-2-en-1-ones provides a convenient approach to a variety of functionalized salicylates.[24, 21a,b] In addition, $TiCl_4$ mediated cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane and related bis(acetals) were reported[21a,b,25,26]. All these transformations rely on the employment of stoichiometric amounts of Lewis acid. Herein, I report what are, to the best of my knowledge, the first *catalytic* [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane. These reactions provide a convenient approach to a variety of functionalized salicylates under mild conditions. Notably, the products are not directly and readily available by other methods.

1.2.2 Results and discussion

The trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf) catalyzed condensation of silyl enol ethers with acetals, introduced by Noyori *et al.*,[27] has found a number of applications in organic synthesis. Recently, Langer *et al*. reported the Me_3SiOTf catalyzed condensation of 1,3-bis(silyl enol ethers) with 1-chloro-2,2-dimethoxyethane[28] and 2-azido-1,1-

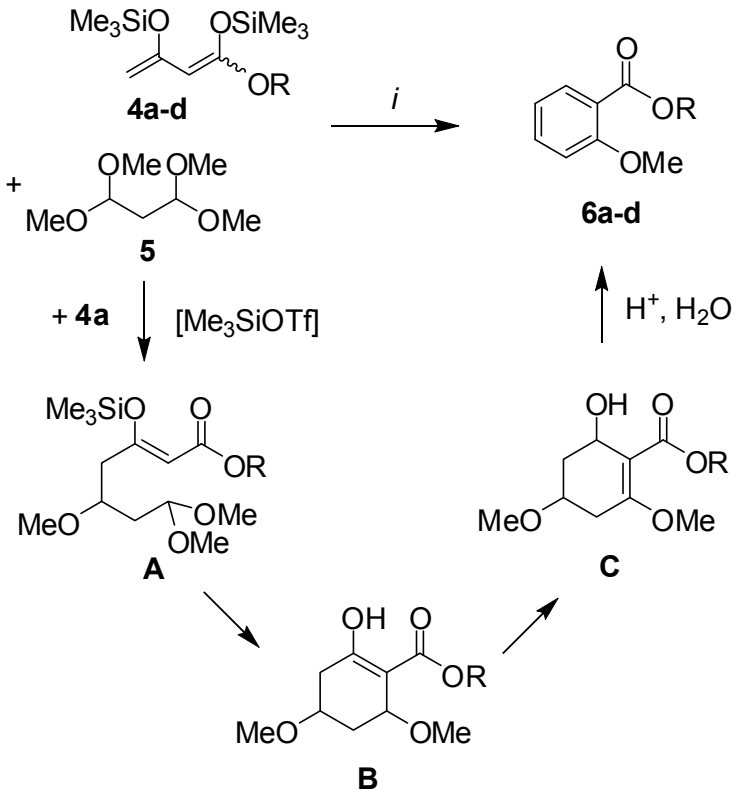
dimethoxyethane, respectively.[29] The reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**4a**) with 1,1,3,3-tetramethoxypropane (**5**), in the presence of a catalytic amount of Me_3SiOTf (0.1 equiv.), afforded ethyl 2-methoxybenzoate (**6a**) in up to 55% yield (Scheme 1-4, Tables 1-3 and 1-4). During the optimization (Table 1-2), the work-up procedure (10% HCl), the temperature (–78 → 20 °C, 6-12 h; then 20 °C, 2-6 h), and the concentration (ca. 15 mL of CH_2Cl_2 per 1 mmol of **4a**) proved to be important parameters. The use of tetraethoxypropane proved to be unsuccessful. The amount of Me_3SiOTf could be reduced to 0.1 equiv. without decrease of yield. The use of trifluoroacetic acid (rather than Me_3SiOTf) failed to give the desired product.

The Me_3SiOTf catalyzed cyclization of **5** with 1,3-bis(silyl enol ethers) **4a-d**, prepared from ethyl, methyl, methoxyethyl and benzyl acetoacetate, afforded the 2-methoxybenzoates **6a-d**. Their formation can be explained by the mechanism depicted in Scheme 1-4: the Me_3SiOTf catalyzed attack of the terminal carbon atom of **4** onto **5** gave intermediate **A**. The subsequent Me_3SiOTf catalyzed cyclization afforded intermediate **B** which underwent a shift of the double bond to give intermediate **C**. Extrusion of water and methanol from **C** afforded the final product. Notably, the formation of a 2-hydroxybenzoate was not observed. The mechanism is supported by the isolation of a small amount of 3,5-dimethoxycyclohexanone. The formation of this side-product can be explained by cleavage of the ester group of intermediate **C** and decarboxylation.

Table 1-2: Optimization of the synthesis of **6a**

entry	**4a/5**	Me_3SiOTf	CH_2Cl_2 [a]	work-up	% (**6a**) [b]
1	1:1	0.3 eq.	2	$NaHCO_3$	32
2	1:1	0.3 eq.	15	$NaHCO_3$	35
3	1:1	0.3 eq.	15	10% HCl	54
4	1:1	0.3 eq.	50	10% HCl	45
5	1:1.1	0.1 eq.	15	10% HCl	55

[a] mL (CH_2Cl_2) / mmol (**4a**); [b] yields of isolated products



Scheme 1-4: Cyclization of 1,3-bis(silyl enol ethers) **4a-d** with 1,1,3,3-tetramethoxypropane, *i*: 1) Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C; 2) HCl (10%)

Table 1-3: Synthesis of **6a-d**

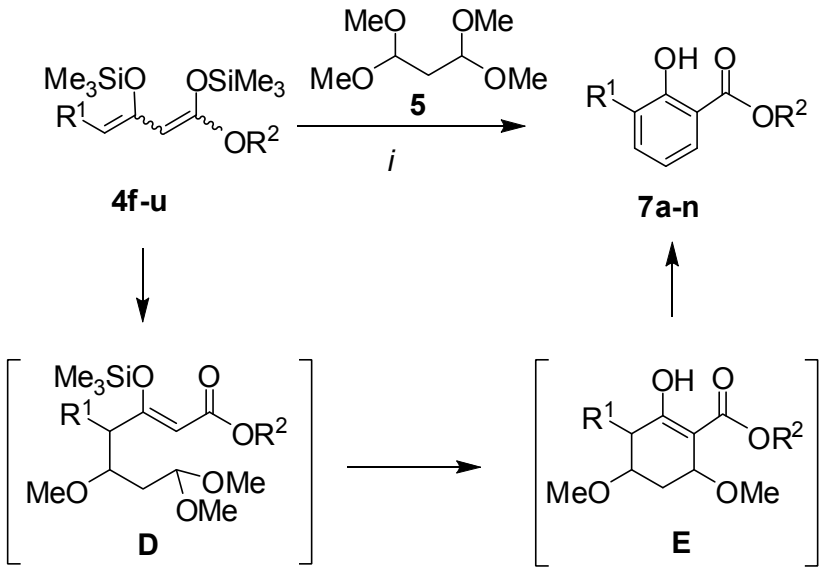
6	R	% (**6**) [a]
a	Et	55
b	Me	32
c	$(CH_2)_2OMe$	30
d	Bn	40

[a] Yields of isolated products

The Me_3SiOTf catalyzed cyclization of 1,3-bis(silyl enol ether) **4f**, prepared from ethyl 3-oxopentanoate, afforded ethyl 3-methylsalicylate (i. e. ethyl 3-methyl-2-hydroxybenzoate) (**7a**) (Scheme 1-5, Table 1-4). Notably, the formation of ethyl 5-methyl-2-methoxybenzoate was not observed. The formation of **7a** can be explained, in analogy to the formation of **6a-d**, by attack of **4f** onto **5** to give intermediate **D** and subsequent cyclization to give **E** (which

correspond to intermediates **A** and **B** shown in Scheme 1-4). Intermediate **E** undergoes a rapid extrusion of two molecules of methanol (rather than a shift of the double bond as discussed for the formation of **6a-d**). In fact, the presence of the substituent R^1 seems to enhance the rate of the elimination of methanol from intermediate **E**.

The Me_3SiOTf catalyzed cyclization of **5** with 1,3-bis(silyl enol ethers) **4f-v** afforded the salicylates **7a-n**. The cyclization of **5** with 1,4-di(methoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**4q**) gave salicylate **7m** containing a protected and a non-protected hydroxy group. Ethyl 2,3-dihydroxysalicylate (**7n**) was prepared from 1-ethoxy-4-(*tert*-butoxy)-1,3-bis(trimethylsiloxy)-1,3-butadiene (**4r**). The *tert*-butyl group was cleaved during the reaction. The Me_3SiOTf catalyzed cyclization of **5** with 1,3-bis(silyl enol ethers) derived from 1,3-diketones (e. g. acetylacetone and benzoylacetone) proved to be unsuccessful (formation of complex mixtures).



Scheme 1-5: Cyclization of 1,3-bis(silyl enol ethers) **4f-r** with 1,1,3,3-tetramethoxypropane, *i*: 1) Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C; 2) HCl (10%)

Table 1-4: Synthesis of **7a-n**

4	**7**	R^1	R^2	% (**7**) [a]
f	**a**	Me	Et	45
g	**b**	Et	Et	40
h	**c**	*n*Bu	Me	60
i	**d**	*i*Bu	Me	45
j	**e**	*n*Hex	Et	50
l	**f**	*n*Hept	Me	59
m	**g**	*n*Oct	Et	56
o	**h**	*n*Dec	Et	54
v	**i**	$(CH_2)_6Cl$	Me	67
n	**j**	$(CH_2)_2CH{=}CH_2$	Me	63
p	**k**	CH_2Ph	Me	57
t	**l**	$(CH_2)_3Ph$	Me	61
q	**m**	OMe	Me	32
r	**n**	OH	Et	27 [b]

[a] Yields of isolated products; [b] from **4r** (R^1 = O*t*Bu)

1.2.3 Conclusions

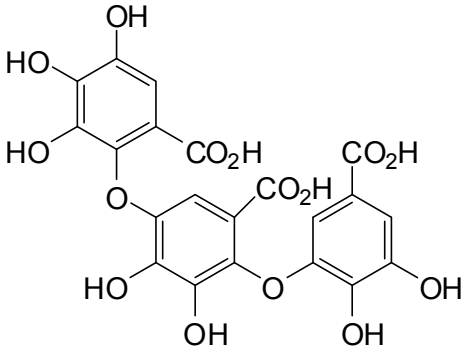
In conclusion, a variety of salicylates were prepared by Me_3SiOTf catalyzed formal [3+3] cyclization of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetamethoxypropane. The use of 1,3-bis(silyl enol ethers) **4a-d**, containing no substituent at carbon atom C-4, resulted in the formation of 2-methoxybenzoates **6a-d**. The best yield was obtained for salicylate **6a**. The yields depend on the quality of the silyl enol ether and on the handling of each individual experiment. 2-Hydroxy- rather than 2-methoxybenzoates were generally formed when 1,3-bis(silyl enol ethers) **4**, containing a substituent located at carbon atom C-4, were employed. The best yields were obtained for alkyl-, ω-chloroalkyl-, ω-phenylalkyl-, and thiophenoxy-

substituted 1,3-bis(silyl enol ethers) **4h-o**, **4v, 4n, 4p** and **4t**. The method reported provides a convenient approach to salicylates under mild conditions.

2. Synthesis of diaryl ethers based on one-pot [3+3] cyclizations of 1,3-bis(silyl enol ethers)

2.1 Introduction

Diaryl ethers containing an ester or carboxylic acid function constitute an import subgroup of the pharmacologically important substance class of diaryl ethers.[15] They occur in a number of natural product, such as geodinhydrate methylester and methyl chloroasterrate,[30a,b] 1-desgalloylsanguiin,[31] dehydrotrigallic acid **8**,[32] epiphorellic acid **9**,[33] jolkianin,[34] remurin A,[35] or micareic acid **10**.[36] Diaryl ethers are available by classic Ullmann reactions and related methods.[37] In recent years, the Buchwald-Hartwig reaction and related transformations proved to be versatile methods for the synthesis of diaryl ethers.[38] Recently, Beller *et al.* reported the transition metal catalyzed coupling of phenols with aryl chlorides.[39] Despite their great synthetic utility, the scope of all these methods is limited by the availability of the starting materials. In fact, the synthesis of more complex aryl halides or triflates by regioselective functionalization of arenes is often a difficult task. In addition, the transition metal catalyzed formation of diaryl ethers containing a sterically encumbered ether linkage often proceeds in low yield or not at all.



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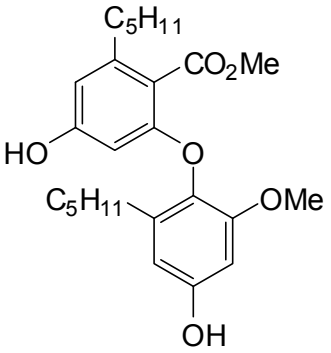

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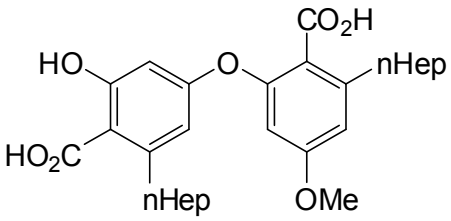
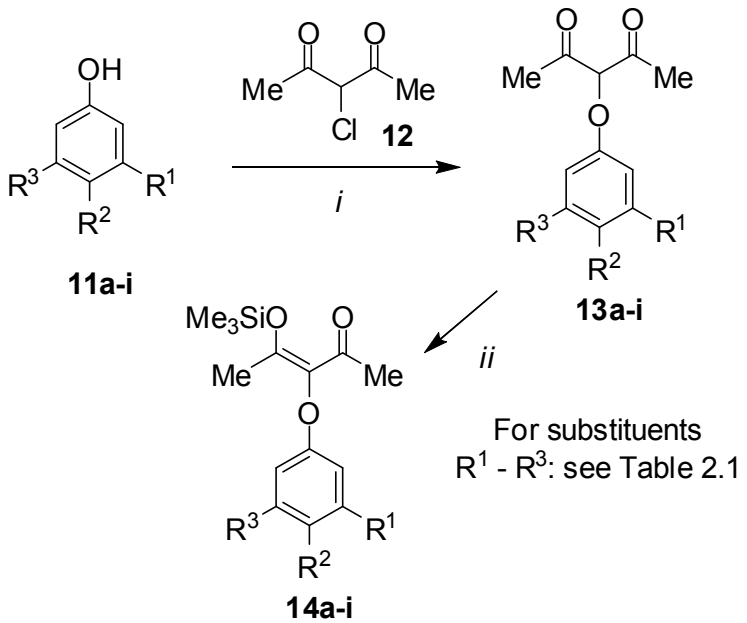


10

The formal [3+3] cyclization of 1,3-bis(silyl enol ethers)[23a] with 3-(siloxy)alk-2-en-1-ones provides a versatile method for the synthesis of functionalized arenes.[23b] Recently, Langer *et al*. reported the application of this method to the synthesis of functionalized diaryl ethers.[40] Herein, I report full details of these studies. With regard to our preliminary communication,[40] the preparative scope has been significantly extended. Our method relies on assembly of one of the two arene moieties (in contrast to transition metal catalysed C-O coupling reactions). Notably, functionalized and sterically encumberd diaryl ethers, which are not readily available by other methods, can be prepared.

2.2 Results and discussion

3-(Phenoxy)pentane-2,4-diones **13a-i** were prepared, following a known procedure,[41] by potassium carbonate mediated reaction of phenols **11a-i** with 3-(chloro)pentane-2,4-dione (**12**). The synthesis of derivatives **13a** and **13d** was previously reported.[41] The silylation[21c] of **13a-i** afforded the novel 2-aryloxy-3-(silyloxy)alk-2-en-1-ones **14a-i** (Scheme 2-1, Table 2-1). Only moderate to low yields were obtained for **13a-i**. The silylation proceeded in very good yields.



Scheme 2-1: Synthesis of **14a-i**, *i*: K_2CO_3, acetone, 2 h, reflux; *ii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h

Table 2-1: Synthesis of **13a-i** and **14a-i**

13,14	R^1	R^2	R^3	% (**13**)[a]	%(**14**)[a]
a	H	H	H	-[b]	91
b	Me	H	Me	20	94
c	H	Et	H	35	80
d	H	Cl	H	-[b]	96
e	H	OMe	H	24	95
f	OMe	OMe	H	40	97
g	H	Br	H	25	84
h	H	CN	H	25	82
i	H	CH_2CO_2Me	H	26	87

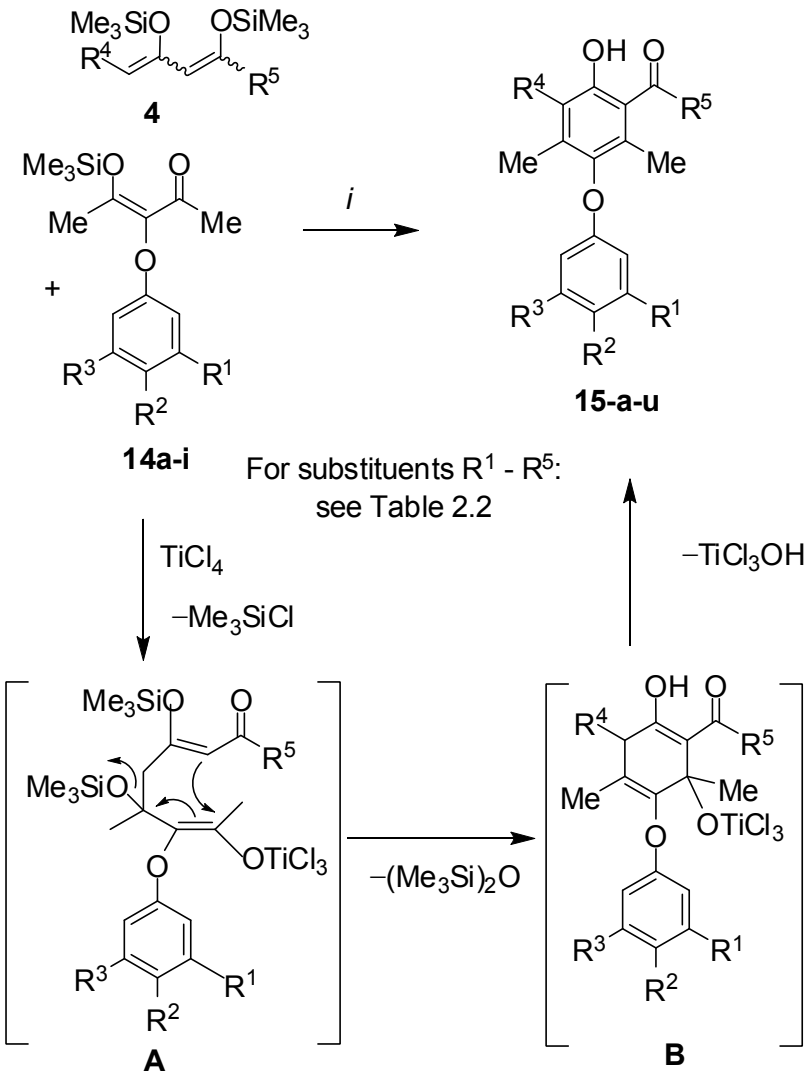
[a] Yields of isolated products; [b] commercially available

The $TiCl_4$ mediated cyclization of 2-aryloxy-3-(silyloxy)alk-2-en-1-one **14a-i** with 1,3-bis(silyl enol ethers) **4** afforded the diaryl ethers **15a-u** in moderate to good yields (Scheme 2-2, Table 2-2). The reactions were carried out following a typical procedure previously reported for related [3+3] cyclizations.[23b] The best results were obtained when stoichiometric amounts of the starting materials and of $TiCl_4$ were used. The latter was added to a dichloromethane solution of the starting materials at –78 °C with subsequent warming of the mixture to 20 °C. The high concentration of the solution (only 2 mL of solvent per 1 mmol of starting material) proved to be a very important parameter. The yields significantly decreased when the reactions were carried out in more dilute solutions. The quality of the starting materials, reagents and solvent also played an important role.

Notably, the presence of functional groups (chloride, bromide, cyano, ester or methoxy groups) proved to be – in principle - compatible with the reaction conditions. A variety of functionalized diaryl ethers (**15h-u**) were successfully prepared without any decrease in yield compared to reactions of non-functionalized substrates. In most of the cyclization reactions, β-ketoester derived 1,3-bis(silyl enol ethers) were employed. However, the use of 1,3-bis(silyl enol ether) **4x**, prepared from acetylacetone, also proved to be successful. In contrast,

employment of 1,3-bis(trimethylsilyloxy)-1-phenyl-1,3-butadiene (derived from benzoylacetone) resulted in the formation of complex mixtures. This can be explained by its lower reactivity compared to β-ketoester derived 1,3-bis(silyl enol ethers). The cyclization of 2-aryloxy-3-(silyloxy)alk-2-en-1-ones with 1,3-bis(silyl enol ethers) **15a**, **15b**, **15d**, **15f**, **15h**, **15i**, **15l**, **15s** and **5u**, containing an additional alkyl group attached to carbon atom C-4, afforded heavily substituted diaryl ethers in good yield. However, most derivatives (**15a**, **15b**, **15j**, **15l** and **15u**) were obtained in relatively low yield. On the other hand, no decrease of the yield was observed in case of **15h** and **15s**. In conclusion, relatively low yields were obtained for diaryl ethers **15a-b**, **15d**, **15f**, **15j**, **15l**, and **15u**. The reason for this remains unclear at present, since considerably better yields were obtained for closely related derivatives. Therefore, the quality of the starting materials employed for each individual experiment seems to play an important role.

The structures of diaryl ethers **15** were proved by spectroscopic methods. The structure of derivative **15c** and **15o** were independently confirmed by X-ray crystal structure analysis (Figure 2.1 and 2.2).[84]



Scheme 2-2: Synthesis of **15a-u:** Reagents and conditions: *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C,20h

Table 2-2: Synthesis of **15a-u**

4	**14**	**15**	R^1	R^2	R^3	R^4	R^5	%(**15**)[a]
f	**a**	**a**	H	H	H	Me	OEt	30
g	**a**	**b**	H	H	H	Et	OEt	32
a	**b**	**c**	Me	H	Me	H	OEt	58
f	**b**	**d**	Me	H	Me	Me	OEt	39
a	**c**	**e**	H	Et	H	H	OEt	60
f	**c**	**f**	H	Et	H	Me	OEt	36
b	**d**	**g**	H	Cl	H	H	OMe	54
f	**d**	**h**	H	Cl	H	Me	OEt	49
g	**d**	**i**	H	Cl	H	Et	OEt	43
a	**e**	**j**	H	OMe	H	H	OEt	30
a	**f**	**k**	OMe	OMe	H	H	OEt	58
f	**f**	**l**	OMe	OMe	H	Me	OEt	35
a	**g**	**m**	H	Br	H	H	OEt	58
d	**g**	**n**	H	Br	H	H	OCH_2Ph	59
a	**h**	**o**	H	CN	H	H	OEt	50
d	**h**	**p**	H	CN	H	H	OCH_2Ph	54
a	**i**	**q**	H	CH_2CO_2Me	H	H	OEt	50
d	**i**	**r**	H	CH_2CO_2Me	H	H	OCH_2Ph	65
j	**i**	**s**	H	CH_2CO_2Me	H	*n*Hex	OEt	54
x	**i**	**t**	H	CH_2CO_2Me	H	H	Me	55
f	**e**	**u**	H	OMe	H	Me	OEt	30

[a] Yields of isolated products

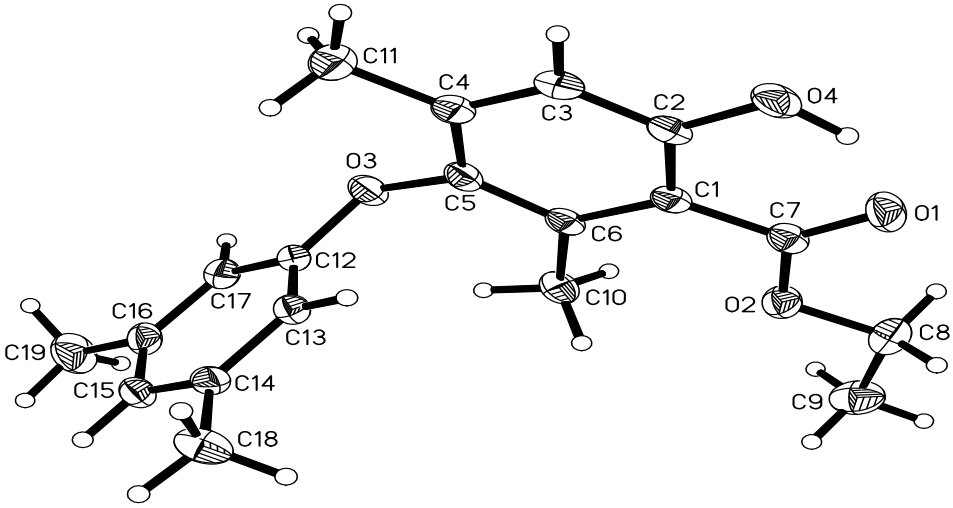


Figure 2.1: Ortep plot of **15c**

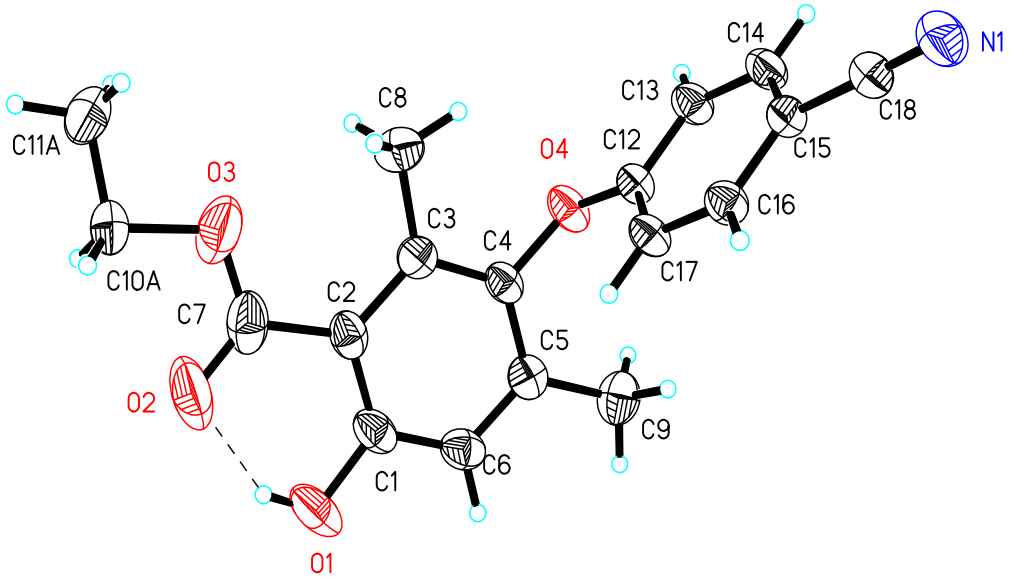


Figure 2.2: Ortep plot of **15o**

2.3 Conclusions

In conclusion, a variety of functionalized and sterically encumbered diaryl ethers were prepared by formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 2-aryloxy-3-(silyloxy)alk-2-en-1-ones. A general rule for the influence of a specific substitution pattern of the starting materials on the yield of the reactions could not be observed. In contrast, the quality of the starting materials employed for each individual experiment seems to play an important role.

3. Regioselective synthesis of functionalized resorcins by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride

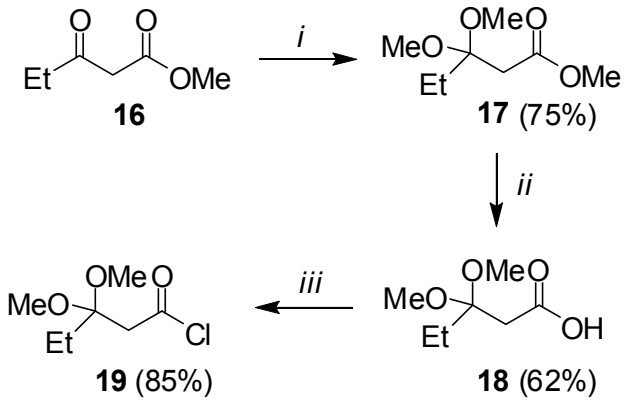
3.1 Introduction

A great variety of pharmacologically important natural products are biosynthetically derived from poly(β-oxo)carboxylic acids (polyketides).[42] Harris and coworkers reported the biomimetic synthesis of various 1,3,5,7-tetracarbonyl compounds and their higher homologues based on condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with esters and diesters, Weinreb amides, and salts of β-ketoesters.[43,16e] These products are unstable and rapidly undergo an intramolecular Aldol-condensation to give polyhydroxylated arenes present in many poylyketide-derived natural products. 1,3-Bis(trimethylsilyloxy)-1,3-butadienes can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions (masked dianions).[23] Chan and coworkers were the first to report the reaction of 1-methoxy-1,3-bis(trimethylsiloxy)-1,3-butadiene with acetyl chloride.[44] Salicylates were prepared by Lewis acid mediated [5+1] cyclization of 1-methoxy-1,3,5-tris(trimethylsiloxy)-1,3,5-hexatriene with acid chlorides and imidazolides.[45] Langer *et al*. reported the reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with various acid chlorides.[46,47] γ-Alkylidenebutenolides are available by cyclization of 1,3-bis(silyl enol ethers) with oxalyl chloride[48] and phthaloyl chloride.[49] Recently, Langer *et al*. reported the synthesis of new 1,3,5,7-tetracarbonyl compounds by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with methyl malonyl chloride.[50] Herein, I report an efficient synthetic approach to functionalized resorcins based on what are, to the best of my knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3,3-dimethoxypentanoyl chloride.[51]

3.2 Results and discussion

3,3-Dimethoxypentanoyl chloride was prepared in three steps as shown in Scheme 3-1. The Me_3SiOTf-catalyzed reaction of **19** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4**, prepared from the corresponding β-ketoesters,[23] afforded the 6-hydroxysalicylates **20a-m** (Scheme 3-2, Table 3-1). The best yields were obtained when 0.5 equiv. of Me_3SiOTf was employed. The yield decreased when the amount of Me_3SiOTf was reduced. The use of more Lewis acid (1.0 equiv.) did not result in an increase of the yield. The formation of the

products can be explained by regioselective attack of the terminal carbon atom of the **4** onto the acetal and subsequent attack of the central carbon onto the acid chloride. The structures of resorcins **20a-m** were proved by spectroscopic methods.

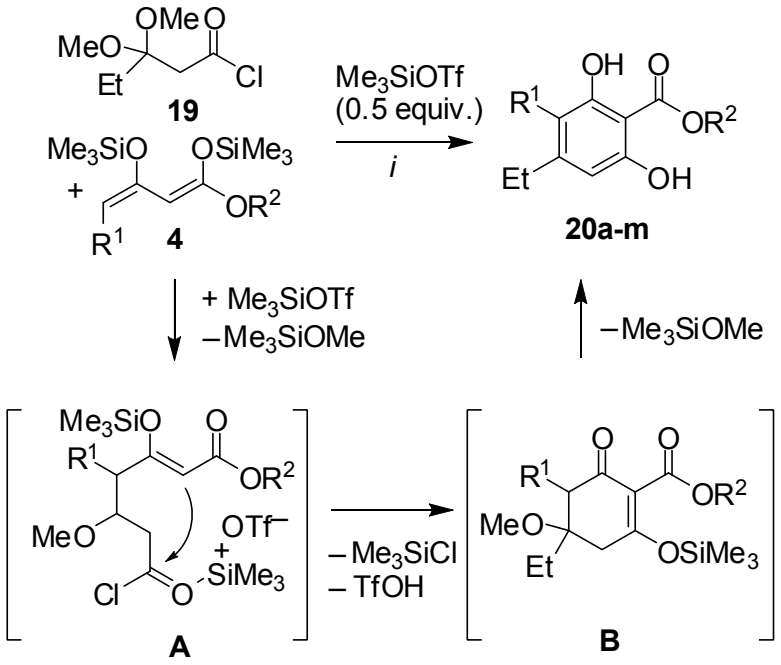


Scheme 3-1: Synthesis of **19**; *i*: $HC(OMe)_3$ (6.0 equiv.), amberlite IR 120^+; *ii*: NaOH, H_2O, 12 h, 20 ^0C; *iii*: $(COCl)_2$, C_6H_6, 2 h, reflux

Table 3-1: Synthesis of **20a-m**

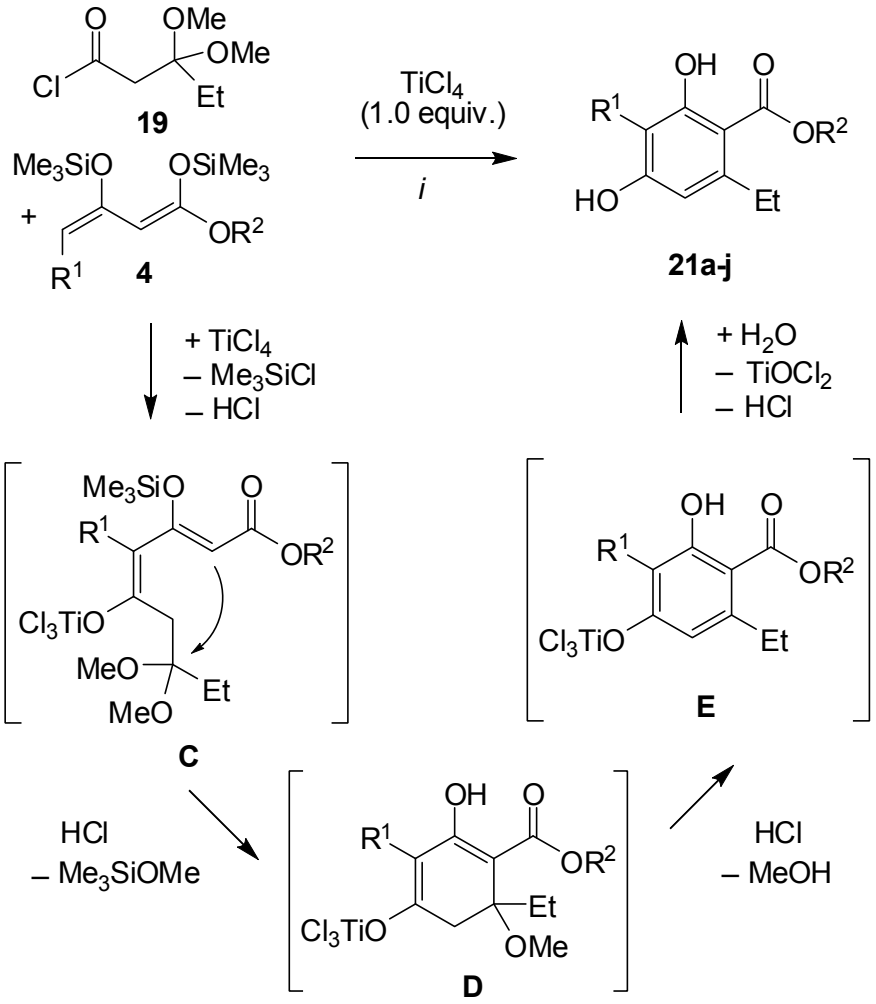
4	**20**	R^1	R^2	%(**20**)[a]
b	**a**	H	Me	43
a	**b**	H	Et	47
e	**c**	H	*i*Pr	56
d	**d**	H	CH_2Ph	52
c	**e**	H	$(CH_2)_2OMe$	38
f	**f**	Me	Me	35
i	**g**	$Cl(CH_2)_3$	Me	40
h	**i**	*n*Bu	Et	50
s	**j**	$(CH_2)_2Ph$	Me	36
q	**k**	MeO	Me	34
g	**l**	Et	Et	60
w	**m**	Allyl	Me	36

[a] Yields of isolated products



Scheme 3-2: Synthesis of **20a-m**; *i*: Me_3SiOTf (0.5 equiv.), CH_2Cl_2, –78 → 20 °C

The $TiCl_4$-mediated reaction of **19** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4** afforded the 4-hydroxysalicylates **21a-j** (Scheme 3-3, Table 3-2). The formation of products **21** can be explained by regioselective attack of the terminal carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene onto the acid chloride and subsequent attack of the central carbon atom onto the acetal. The structures of resorcins **21a-j** were proved by spectroscopic methods. The structure of **21a** independently confirmed by X-ray crystal structure analysis (Figure 3.1).[84]



Scheme 3-3: Synthesis of **21a-j**; *i*: 1) $TiCl_4$ (1.0 equiv.), CH_2Cl_2, –78 → 20 °C, 2) H_2O

Table 3-2: Synthesis of **21a-j**

4	**21**	R^1	R^2	%(**21**)[a]
b	**a**	H	Me	61
a	**b**	H	Et	40
d	**c**	H	CH_2Ph	34
c	**d**	H	$(CH_2)_2OMe$	40
f	**e**	Me	Me	65
i	**f**	*i*Bu	Me	66
m	**g**	*n*Oct	Et	53
l	**h**	*n*Hep	Me	57
k	**i**	*n*Hex	Me	52
t	**j**	$(CH_2)_3Ph$	Me	46

[a] Yields of isolated products

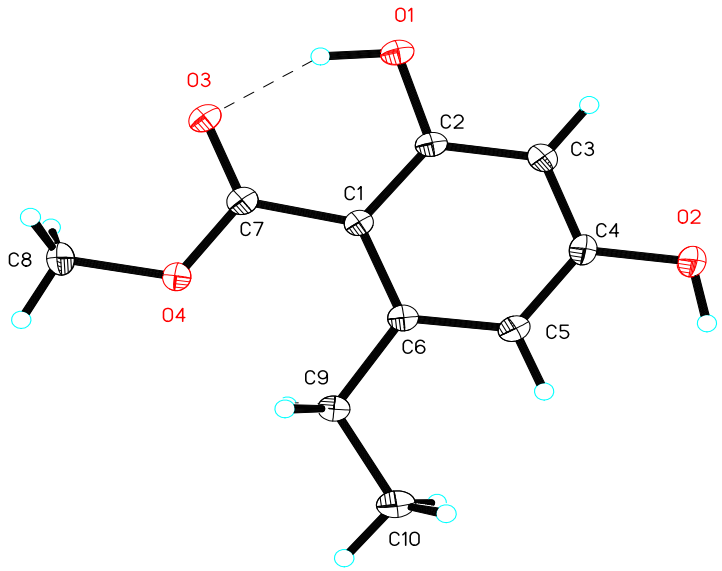


Figure: 3.1. Ortep plot of **21a**

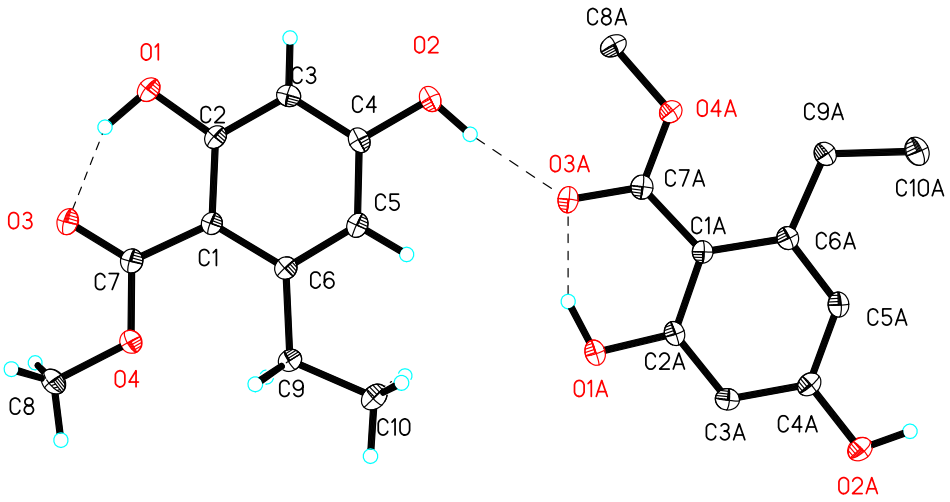


Figure 3.2: ORTEP-plot of the hydrogen bonding scheme for **21a** at the 50% level for the displacement ellipsoids

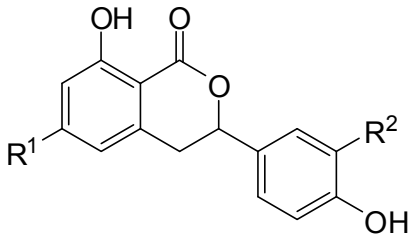
3.3 Conclusions

In conclusion, functionalized resorcins were prepared by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride. The regioselectivity depends on the type of Lewis acid employed.

4. Synthesis of 3-aryl-3,4-dihydroisocoumarins by regioselective domino [3+3] cyclization/lactonization′ reactions of 1,3-bis-(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones

4.1 Introduction

3-Aryl-3,4-dihydroisocoumarins (3-aryl-isochroman-1-ones) are of considerable pharmacological relevance and occur in many natural products. For example, the natural products thunberginol C, D, and E (**22**, **23**, **24**) and related natural products have been reported to promote the adipogenesis of murine 3T3-L1 cells[52a] and show antiproliferative activity against mouse splenocytes.[52b] Hydrangenol **22** exhibits cytotoxic activity against human gastric cancer cell lines and human nasopharyngeal carcinoma cell lines.[53] Related natural products[54] have been reported to show antifungal activity,[55] inhibition of rat basophilic leukemia RBL-2H3 cells,[56] antiproliferative activity against C57/BL6 mouse splenocytes,[57] antiallergic activity,[58] induction of steroidogenesis,[59] phagocytic activity,[60] immunomodulatory activity on spleen lymphocyte proliferation (activated by lipopolysaccharide, concanavalin A, and phytohemagglutinin in mice),[61] and antimicrobial activity.[62] In a number of natural products, one of the hydroxyl groups of the 3-aryl-3,4-dihydroisocoumarin core structure is glycosylated;[63] this includes, for example, (-)-hydrangenol 4'-O-glucoside,[60] and phyllodulcin 8-O-glucoside.[52a,62a]



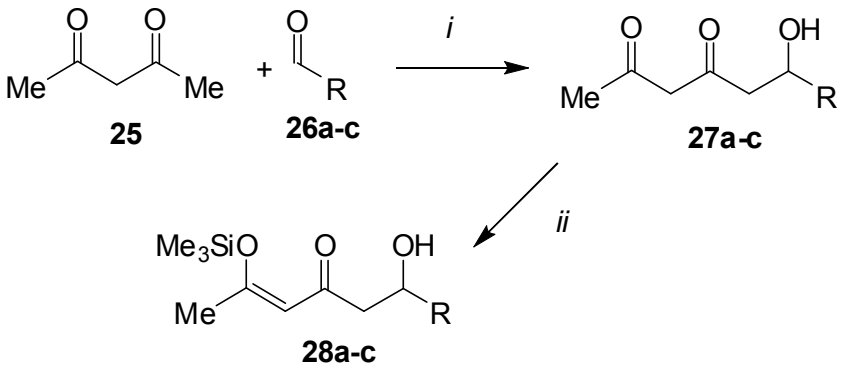
22:Hydrangenol (R^1 = H, R^2 = H)
23:Thunberginol C (R^1 = OH, R^2 = H)
24:Thunberginol D (R^1 = OH, R^2 = OH)

Chan and coworkers were the first to report[24] the $TiCl_4$-mediated [3+3] cyclization[23b] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[23a] with 3-silyloxy-2-en-1-ones which allows a convenient synthesis of salicylates. In recent years, Langer *et al*. studied the application of this reaction to the synthesis of various functionalized arenes.

Recently, Langer *et al*. reported the synthesis of dibenzo[*b*,*d*]pyran-6-ones based on a [3+3] cyclization / lactonization strategy.[64] Herein, I report what are, to the best of my knowledge, the first domino[65] ′[3+3] cyclization / lactonization′ reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones. These reactions proceed with very good regioselectivity and provide a convenient approach to 3-aryl-3,4-dihydroisocoumarins which are not readily available by other methods.

4.2 Results and discussion

The reaction of the dianion of acetylacetone (**25**) with aldehydes **26a-c** afforded, following a known procedure,[66] condensation products **27a-c** (Scheme 4-1, Table 4-1). The NEt_3-mediated reaction of **27a-c** with Me_3SiCl resulted in chemoselective formation of 1-aryl-1-hydroxy-5-silyloxy-4-en-3-ones **28a-c**. Notably, a silylation of the hydroxy group was not observed.



Scheme 4-1: Synthesis of 1-aryl-1-hydroxy-5-silyloxy-4-en-3-ones **28a-c:** *i*: 1), 2.5 LDA, THF, 1 h, 0 °C; 2), –78 → 20 °C, 14 h; 3) $NaHCO_3$, H_2O; *ii*: NEt_3, Me_3SiCl, CH_2Cl_2, 20 °C, 14 h

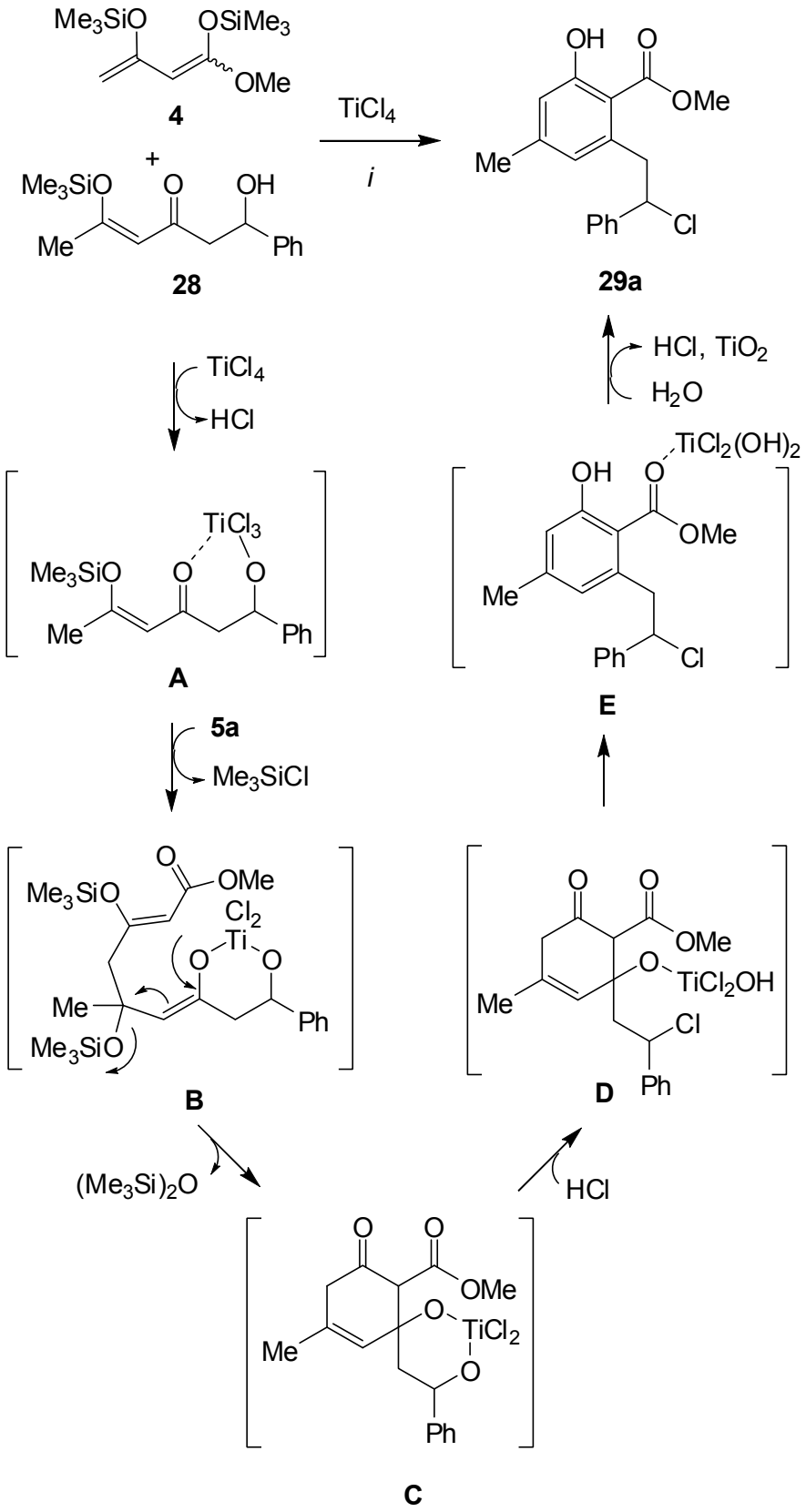
Table 4-1: Synthesis of 1-hydroxy-5-silyloxy-4-en-3-ones **28a-c**

27,28	R	%[a]	%[a]
a	Ph	70	86
b	4-MeC_6H_4	66	92
c	4-ClC_6H_4	60	88

[a] Yields of isolated products

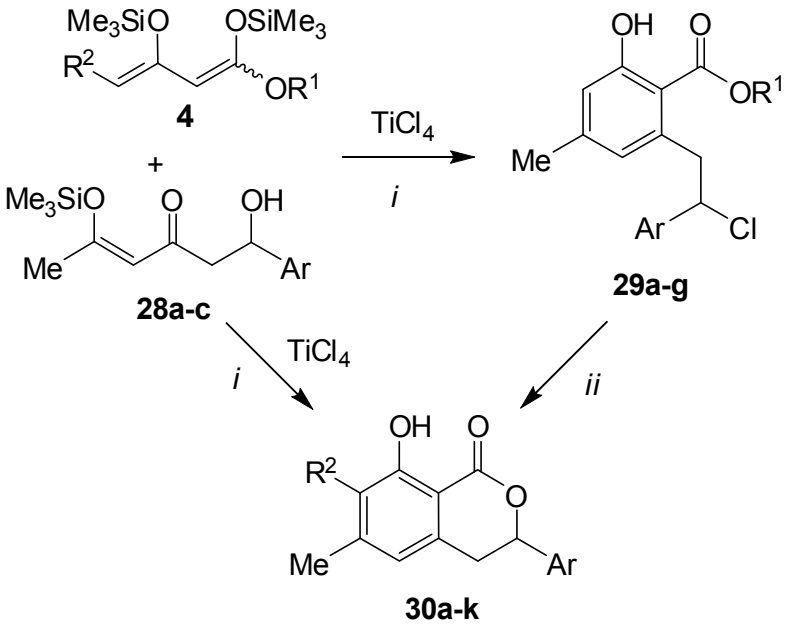
The $TiCl_4$-mediated [3+3] cyclization of **28a** with 1,3-bis(silyl enol ether) **4b**, readily available from methyl acetoacetate,[24] afforded the novel 6-(2-phenyl-2-chloroethyl)salicylate **29a** (Scheme 4-2). The best yield was obtained when the reaction was carried out in a highly concentrated solution. Notably, the cyclization proceeded with excellent regioselectivity. In fact, the formation of the regioisomeric 4-(2-phenyl-2-chloroethyl)salicylate was *not* observed. The formation of product **29a** might be explained by reaction of $TiCl_4$ with **28a** to give intermediate **A** and hydrogen chloride. The conjugate addition of the (most reactive) terminal carbon atom of **4b** to **A** afforded intermediate **B** which underwent a cyclization to give intermediate **C**. The reaction of HCl with the carbon atom attached to the phenyl group resulted in nucleophilic substitution and formation of intermediate **D**. The latter underwent aromatization to give intermediate **E**. Product **29a** is formed upon aqueous work-up. Interestingly, the presence of the *free* hydroxy group of **28a** seems to be important to achieve a high degree of regioselectivity. The presence of a methoxy rather than a hydroxyl group resulted in the formation of a mixture of regioisomers.

Stirring of a solution of **29a** in wet THF in the presence of silica gel afforded the 3-phenyl-3,4-dihydroisocoumarin **30a** in 69% yield (Scheme 4-3, Table 4-2). The formation of **30a** can be explained by acid-mediated hydrolysis of the chloride and subsequent lactonization.



Scheme 4-2: Possible mechanism of the formation of **29a:** *i*: 1) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 14 h; 2) $NaHCO_3$, H_2O

The [3+3] cyclization of **28a** with 1,3-bis(silyloxy)-1,3-butadienes **4**, containing an alkyl group attached to carbon atom C4, directly afforded the 3-phenyl-3,4-dihydroisocoumarins **30b-d**. The formation of **30b-d** can be explained by [3+3] cyclization to give 6-(2-phenyl-2-chloroethyl)salicylates which subsequently hydrolyzed and underwent a lactonization during the aqueous work-up or silica gel chromatography. This process can be regarded as a domino ′[3+3] cyclization / lactonization′ reaction. The cyclization of **28a** with 1,3-bis(silyloxy)-1,3-butadienes **4q,w** resulted in the formation of 6-(2-phenyl-2-chloroethyl)salicylates **29b,c** which were transformed, by treatment with silica gel, into the 3-phenyl-3,4-dihydroisocoumarins **30e,f**. The cyclization of **28a** with 1,3-bis(silyloxy)-1,3-butadienes **4a,e** afforded the ethyl and *iso*propyl salicylates **29d,e**. Notably, the SiO_2-mediated lactonization proved to be unsuccessful for these substrates. The cyclization of **28b** with **4b,f,h,w** directly afforded the 3-(4-tolyl)-3,4-dihydroisocoumarins **30g-j**. The reaction of **28b** with **4d** gave the benzyl salicylate **29f** which could not be transformed into **30g**. The cyclization of **4b** with **28c** directly afforded the 3-(4-chlorophenyl)-3,4-dihydroisocoumarin **30k**. The reaction of **28c** with **4d** gave the benzyl salicylate **29g**; its transformation into **30k** proved to be unsuccessful.



Scheme 4-3: Synthesis of **29a-g** and **30a-k:** *i*: 1) $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 14 h; 2) $NaHCO_3$, H_2O, *ii*: SiO_2, wet THF, 14 h

Table 4-2: Synthesis of 6-(2-aryl-2-chloroethyl)salicylates **29a-g** and 3-aryl-3,4-dihydroisocoumarins **30a-k**

4	**28**	**29**	**30**	R^1	R^2	Ar	% (**29**)[a]	% (**30**)[a]
b	**a**	**a**	**a**	Me	H	Ph	52	69
f	**a**		**b**	Me	Me	Ph	0	48
g	**a**		**c**	Me	Et	Ph	0	33
o	**a**		**d**	Me	*n*Dec	Ph	0	54
w	**a**	**b**	**e**	Me	Allyl	Ph	33	55
q	**a**	**c**	**f**	Me	OMe	Ph	44	66
a	**a**	**d**		Et	H	Ph	37	0
e	**a**	**e**		*i*Pr	H	Ph	40	0
b	**b**		**g**	Me	H	4-MeC_6H_4	0	41
f	**b**		**h**	Me	Me	4-MeC_6H_4	0	43
h	**b**		**i**	Me	*n*Bu	4-MeC_6H_4	0	62
w	**b**		**j**	Me	Allyl	4-MeC_6H_4	0	35
d	**b**	**f**		Bn	H	4-MeC_6H_4	32	0
b	**c**		**k**	Me	H	4-ClC_6H_4	0	55
d	**c**	**g**		Bn	H	4-ClC_6H_4	34	0

[a] Yields of isolated products

The structures of all products were confirmed by spectroscopic methods. The structure of **29a** was independently confirmed by X-ray crystal structure analysis (Figure 6.1).[84]

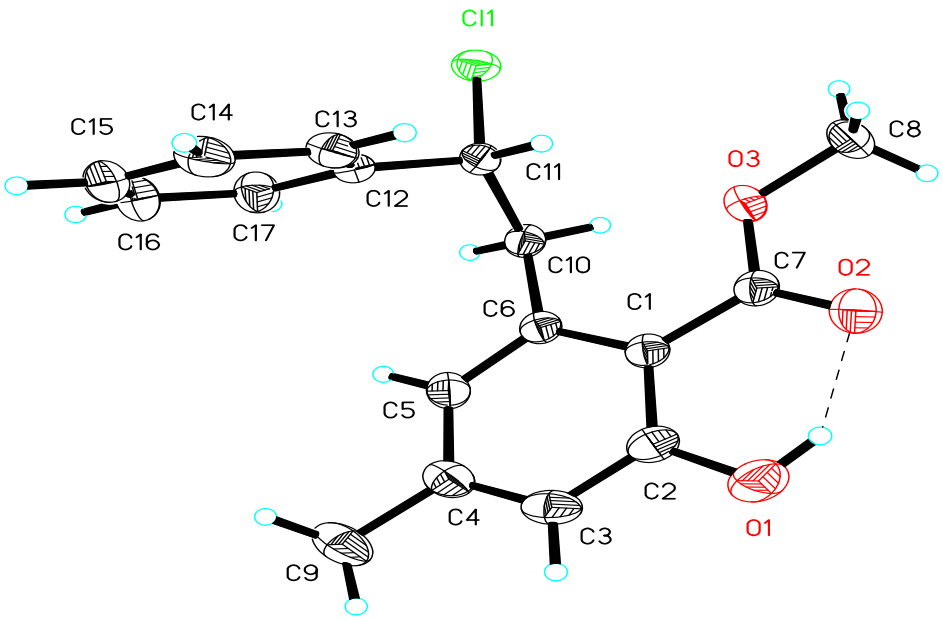


Figure 4.1: Ortep plot of **29a**

4.3 Conclusions

In conclusion, I reported a convenient synthesis of 3-aryl-3,4-dihydroisocoumarins by domino ′[3+3] cyclization / lactonization′ reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-hydroxy-5-silyloxy-4-en-3-ones. These reactions proceed by regioselective [3+3] cyclization to give 6-(2-aryl-2-chloroethyl)salicylates and subsequent silica gel-mediated lactonization. A smooth lactonization is observed for methyl, but not for ethyl, *iso*propyl and benzyl salicylates. We currently study the preparative scope of our methodology and applications to the synthesis of pharmacologically active natural products and their analogues.

5. Synthesis of 4,5-diaryl-1,2,3-benzenetricarboxylates by reaction of 4-hydroxycyclopent-2-en-1-one-2-carboxylates with dimethyl acetylenedicarboxylate

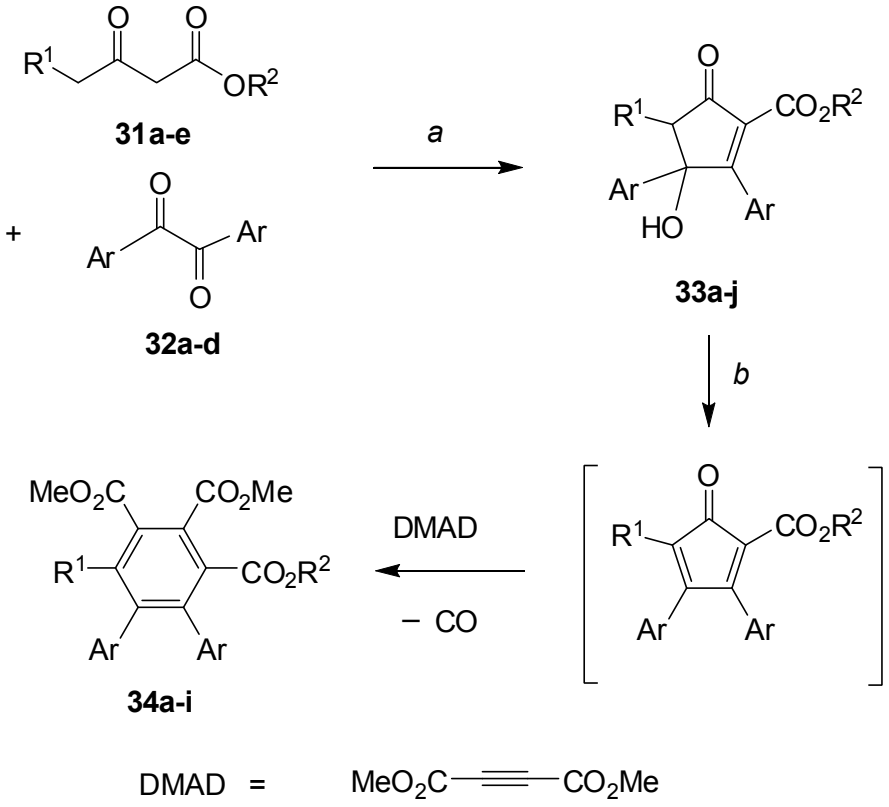
5.1 Introduction

Functionalized arenes represent important building blocks in organic and medicinal chemistry.[67] An important strategy for the synthesis of functionalized benzene derivatives relies on the [4+2] cycloaddition of 1,3-dienes with alkynes and subsequent oxidation.[68] It is known for a long time that the reaction of alkynes with heterocyclic dienes such as furans results in the formation of bridged oxacycles which can be transformed into functionalized benzene derivatives by acidic hydrolysis.[69] A related strategy has been reported for the cycloaddition of cyclopentadienones (fulvenones) with alkynes.[70] These reactions proceed by cycloaddition and subsequent extrusion of carbon monoxide. The acid-mediated reaction of alkynes with 4-hydroxycyclo-2-cyclopenten-1-ones, which represent precursors of highly reactive fulvenones, has been reported to give benzene derivatives.[71] Langer *et al.* have recently reported[72] the synthesis of 4-hydroxycyclo-2-penten-1-one-2-carboxylates[73] by cyclization of 1,2-diketones with 1,3-dicarbonyl dianions or 1,3-bis(silyl enol ethers) (masked dianions). Herein, I report the synthesis of a variety of new 4-hydroxycyclo-2-penten-1-one-2-carboxylates and their transformation into novel 4,5-diaryl-1,2,3-benzenetricarboxylates by acid-mediated cycloaddition.

5.2 Results and discussion

The reaction of the dianion of methyl acetoacetate **31a** with benzil (**32a**) regioselectively afforded 4-hydroxycyclo-2-penten-1-one-2-carboxylate **33a**. The reactions were carried as one-pot transformations: the condensation of the dianion with **32a** gave an open-chained product which underwent cyclization upon addition of silica gel to the reaction mixture and reflux. Notably, the cyclization exclusively afforded the hydroxylated product **33a** and not the corresponding fulvenone (by elimination of a second equivalent of water). This can be explained by the unstable nature of the fulvenone, due to its antiaromatic character.

The reaction of **33a** with dimethyl acetylenedicarboxylate (DMAD), in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA, 5 mol-%), afforded 4,5-diphenyl-1,2,3-benzenetricarboxylate **34a** (Scheme 5-1, Table 5-1). During the optimization of this reaction, the choice of the acid played an important role. The use of conc. sulphuric acid or of Lewis acids ($BF_3 \cdot OEt_2$, $TiCl_4$) resulted in decomposition. The formation of **34a** can be explained by PTSA-catalyzed elimination of water from **33a** to give a higly reactive fulvenone. The [4+2] cycloaddition of the latter with DMAD afforded a bridged cycloadduct which underwent extrusion of carbon monoxide and aromatization to give the final product.



Scheme 5-1: Synthesis of 4,5-diaryl-1,2,3-benzenetricarboxylates 34a-i, *a*: 1) LDA (2.3 equiv.), THF, 0 °C, 1 h; 2) 2, –78 → 20 °C, 12 h; 3) addition of SiO_2, THF, reflux, 19-26 h; *b*: DMAD (8.0 equiv.), PTSA (5 mol-%), toluene, 100 °C

The scope of the reaction was studied (Table 5-1). The reaction of the dianions of β-ketoesters **31a-e** with 1,2-diketones **32a-d** regioselectively afforded the 4-hydroxycyclo-2-penten-1-one-2-carboxylates **33a-j**. The reaction of cyclopentenones **33** with dimethyl

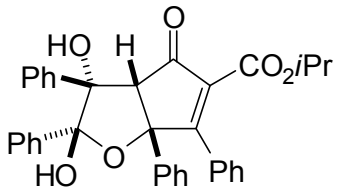
acetylenedicarboxylate (DMAD), in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA, 5 mol-%), afforded the 4,5-diaryl-1,2,3-benzenetricarboxylates **34a-i** (Scheme 5-1, Table 5-1). These experiments show that the presence of bromide or methoxy groups located at the aryl groups is compatible with the reaction conditions. All reactions proceeded in moderate to good yields. The PTSA mediated reaction of DMAD with methyl 3,4-dimethyl-4-hydroxycyclo-2-penten-1-one-2-carboxylate, prepared from butane-2,3-dione, resulted in formation of a complex mixture. Likewise, the reaction of **33a** with maleic anhydride proved to be unsuccessful (decomposition).

The structures of **33b, 33j, 34a** and **34c** were independently confirmed by X-ray crystal structure analysis (Figures 5.1, 5.2, 5.3 and 5.4).[84] In case of **33c**, the interesting side-product **35** was isolated in low yield. The formation of **35**, the structure of which was also confirmed by X-ray crystal structure analysis (Figure 5.5),[84] can be explained by cyclization of **33c** with benzil (**32a**) based on an aldol reaction and formation of a semi-ketal.

Table 5-1: Products and yields

31	**32**	**33**,**34**	R^1	R^2	Ar	% (**33**)[a]	% (**34**)[a]
a	**a**	**a**	H	Me	Ph	51	46
b	**a**	**b**	H	Et	Ph	60	46
c	**a**	**c**	H	*i*Pr	Ph	41 [b]	46
d	**a**	**d**	Et	Et	Ph	55 [c]	33 [d]
a	**b**	**e**	H	Me	4-MeC_6H_4	36	86
c	**b**	**f**	H	*i*Pr	4-MeC_6H_4	52	40
a	**c**	**g**	H	Me	4-$(MeO)C_6H_4$	32	40
c	**c**	**h**	H	*i*Pr	4-$(MeO)C_6H_4$	47	46
b	**d**	**i**	H	Et	4-BrC_6H_4	42	68
e	**a**	**j**	H	*t*Bu	Ph	48	0

[a] Isolated yields; [b] besides, a small amount of **35** was isolated (*vide infra*); [c] mixture of diastereomers: dr = 1:1; [d] a small amount of impurity could not be separated



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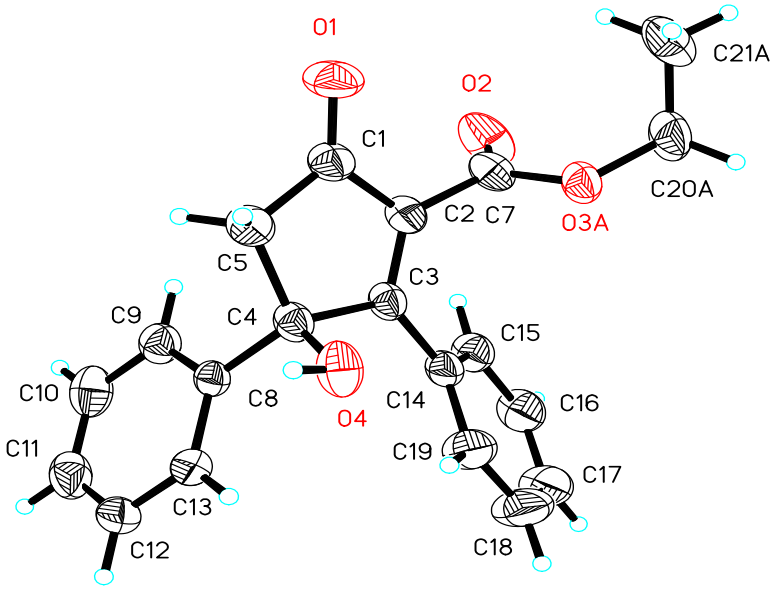


Figure 5.1: Ortep plot of **33b**

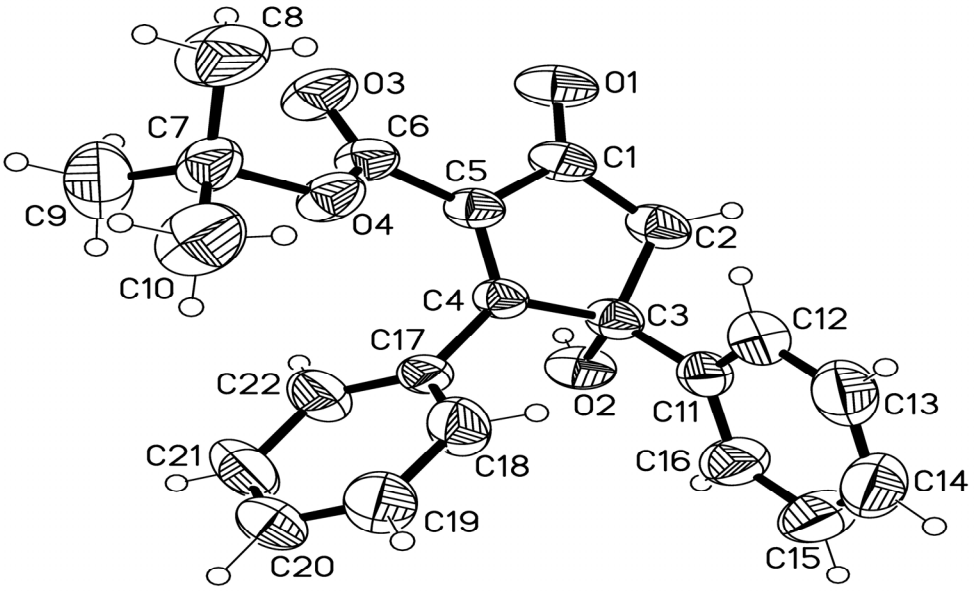


Figure 5.2: Ortep plot of **33j**

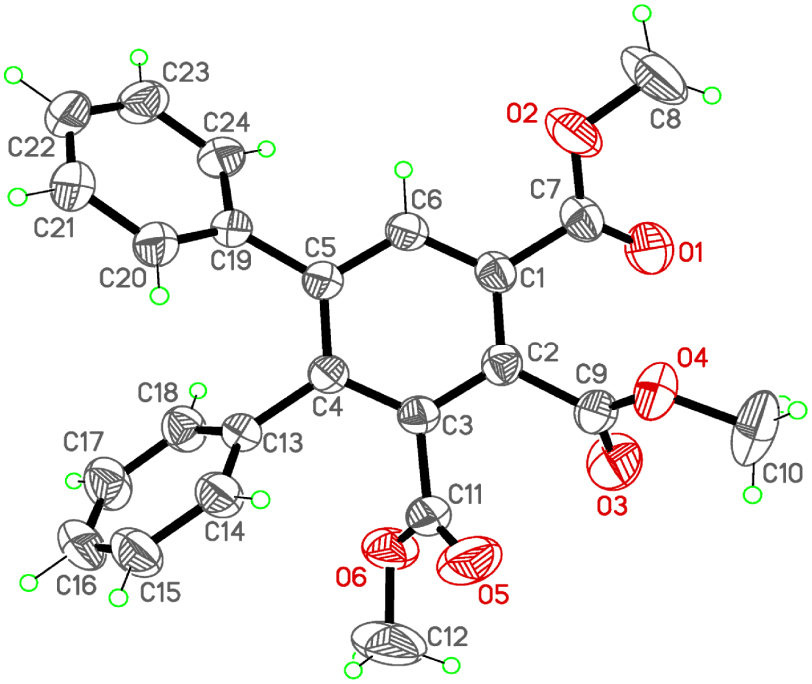


Figure 5.3: Ortep plot of **34a**

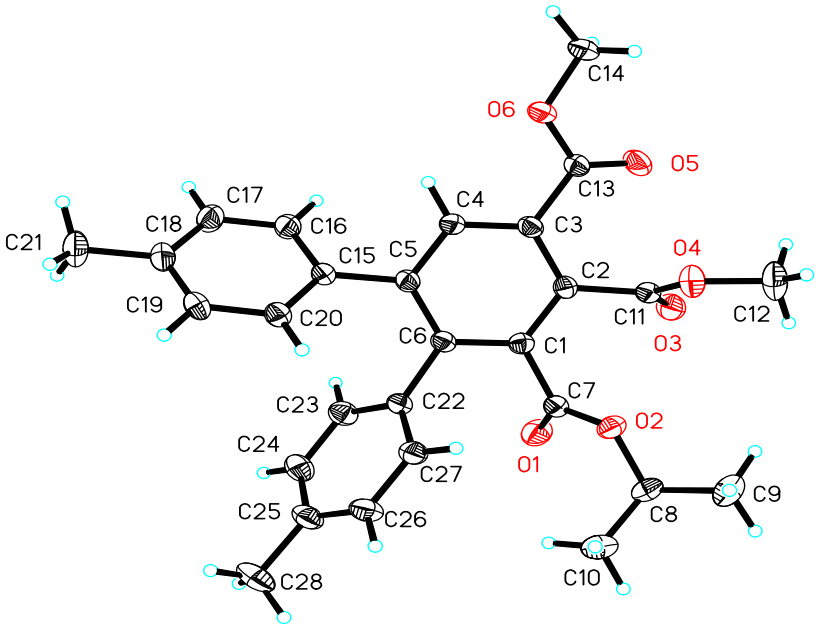


Figure 5.4: Ortep plot of **34c**

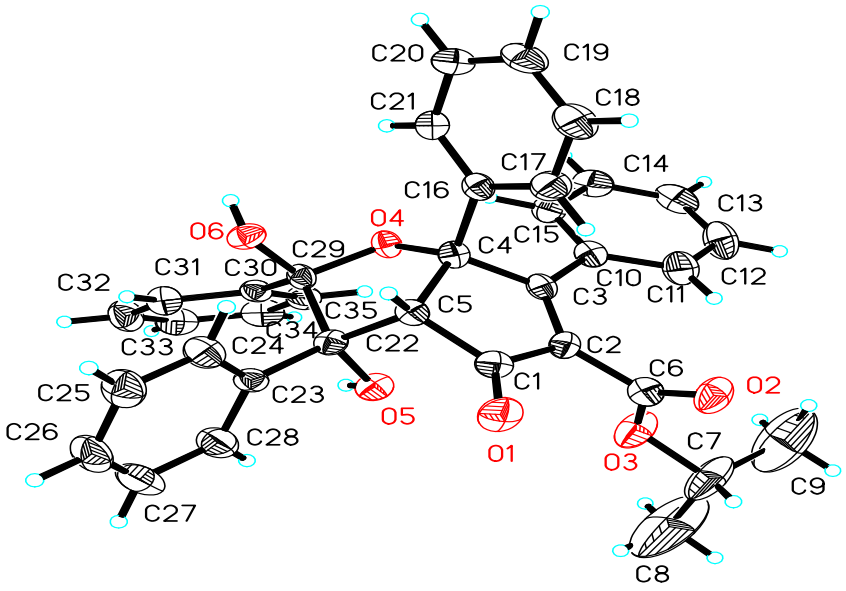
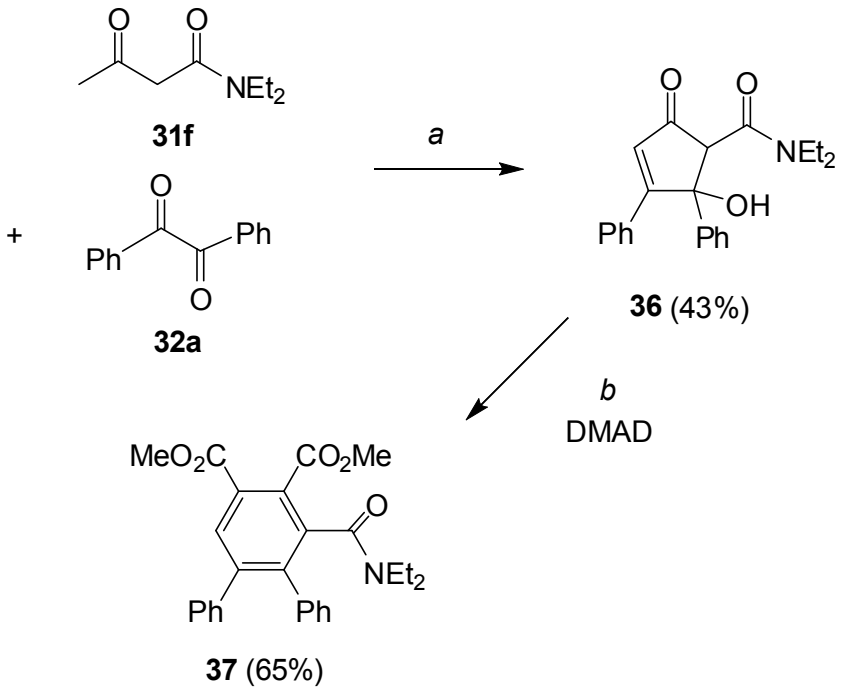


Figure 5.5: Ortep plot of **35**

The reaction of the dianion of *N, N*-diethyl-acetylacetic amide (**31f**) with **32a** afforded the 3-hydroxycyclo-4-penten-1-one-2-carboxylic amide **36** and not a 4-hydroxycyclo-2-penten-1-one-2-carboxylic amide (as observed for **33a-j**) (Scheme 5-2). The formation of the different positional isomers can be explained by the steric interaction between the phenyl and the (structurally rather rigid) amide group and by the relatively low electron-withdrawing effect of the amide (compared to the ester). The PTSA mediated cycloaddition of **36** with DMAD afforded phthalate **37**.



Scheme 5-2: Synthesis of phthalate 7, *a*: 1) 2.3 LDA, THF, 0 °C, 1 h, 2) 2a, –78 → 20 °C, 12 h, 3) addition of SiO_2, THF, reflux, 17 h; *b*: PTSA (5 mol-%), toluene, 100 °C, 10 h

5.3 Conclusions

In conclusion, an efficient synthesis of 4,5-diaryl-1,2,3-benzenetricarboxylates by cycloaddition of 4-hydroxycyclo-2-penten-1-one-2-carboxylates with dimethyl acetylenedicarboxylate was reported.

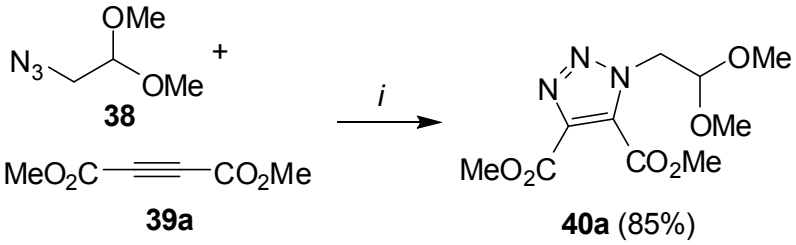
6. Regioselective synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles by copper(I)-catalyzed [3+2] cyclization of 2-azido-2,2-dimethoxyethane with alkynes

6.1 Introdution

2-Azido-1,1-dimethoxyethane (ADE) represents a small, but versatile C_2-building block containing a masked aldehyde and a masked amino group. It can be readily prepared by reaction of 1-chloro- or 1-bromo-2,2-dimethoxyethane with sodium azide.[74, 75] Despite its structural simplicity and potential synthetic usefulness, there are only a few reports related to reactions of ADE. The reaction of ADE with *p*-toluenesulfonic acid in acetone and water afforded azidoacetic aldehyde. However, no yield and procedure was reported.[76] Two pyrroles were prepared by $TiCl_4$ mediated condensation of ADE with silyl enol ethers and subsequent reductive cyclization.[77] Langer *et al*. reported the synthesis of functionalized 2-alkylidenepyrrolidines and pyrroles based on Me_3SiOTf catalyzed reactions of ADE with 1,3-bis(silyl enol ethers) and subsequent cyclization by Staudinger-aza-Wittig reactions.[75] The Staudinger-aza-Wittig reaction of 2-azido-1,1-diethoxyethane with 1,3-dicarbonyl compounds afforded 3-(1-aza-3,3-diethoxypropyl)alk-2-en-1-ones which were subsequently transformed into a variety of functionalized pyrroles.[78] The Staudinger-aza-Wittig reaction of ADE with aldehydes was reported to give iminoacetals.[74] Herein, I report what are, to the best of my knowledge, the first [3+2] cycloaddition reactions of ADE. These reactions provide a convenient approach to 1-(2,2-dimethoxyethyl)-1,2,3-triazoles. To the best of my knowledge, only one example of this type of molecule has been reported so far.[79] I believe that the triazoles reported herein will be useful synthetic building blocks in organic and medicinal chemistry. In fact, 1,2,3-triazoles are emerging as powerful pharmacophores.[80]

6.2 Results and discussion

My starting point was the reaction of ADE (**1**) with dimethyl acetylenedicarboxylate. The reaction of an ethanol solution of the starting materials in a pressure tube (2 h, 120 °C) afforded 1,2,3-triazole **40a** in excellent yield (Scheme 6-1). The structure of **40a** was independently confirmed by X-ray crystal structure analysis (Figure 6.1).[84]



Scheme 6-1: Synthesis of 1,2,3-triazole **40a**; *i*: EtOH, 2 h, 120 °C

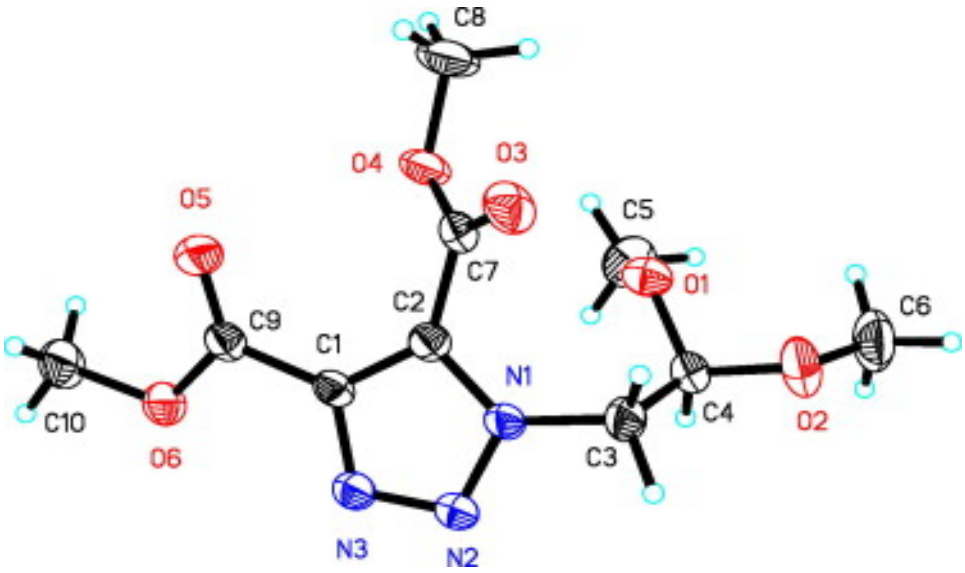
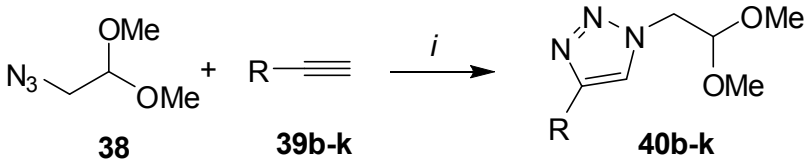


Figure 6.1: Ortep plot of **40a**

The thermal [3+2] cyclization of azides with terminal alkynes often suffers from low regioselectivities.[81] Sharpless *et al.* reported the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles by copper(I)-catalyzed [3+2] cyclization of azides with terminal alkynes.[82] The reaction of ADE (**38**) and methyl propynoate (**39b**), dissolved in a 1:1 mixture of water and *tert*-butanol (2 h, 110 °C), gave 1-(2,2-dimethoxyethyl)-1,2,3-triazole **40b** in excellent yield (Scheme 6-2, Table 6-1). Likewise, the cyclization of ADE with alkynes **39c-k** afforded the 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **40c-k**. All products were formed in excellent yields and with very good regio- and chemoselectivity. Notably, a number of different functional groups (acetal, hydroxyl, amino and trimethylsilyl groups) proved to be compatible with the reaction conditions. The structure of products **40b-k** was confirmed by 2D NMR experiments.



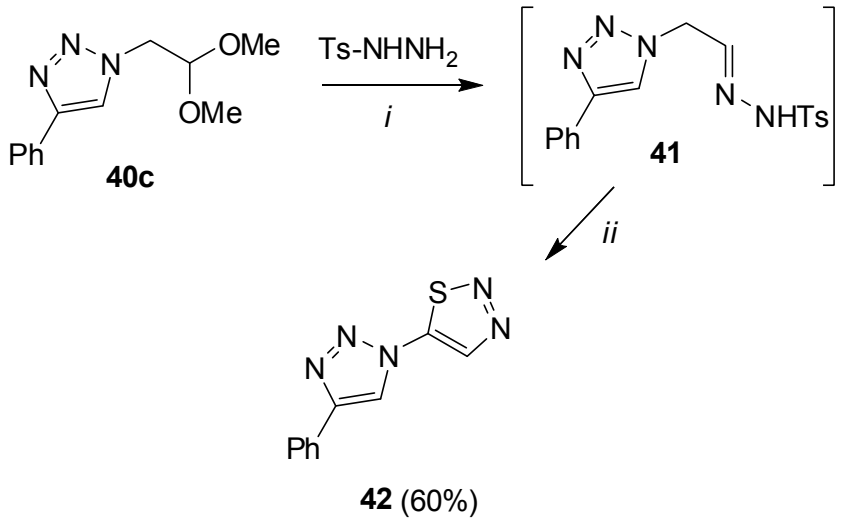
38 **39b-k** **40b-k**

Scheme 6-2: Synthesis of 1,2,3-triazoles **40b-k**; *i*: Cu/$CuSO_4$ (5 mol-%), H_2O, *t*BuOH, 2 h, 110 °C

Table 1. Products and yields

40	R^1	% [a]
b	CO_2Et	84
c	Ph	75
d	$(CH_2)_2OH$	82
e	$C(OH)Me_2$	84
f	CH(OH)Me	85
g	$CH_2N(CH_3)_2$	66
h	*n*Pet	63
i	*n*Oct	80
j	$N(Me)CH_2Ph$	72
k	$SiMe_3$	88

[a] Yields of isolated products



Scheme 6-3: Synthesis of 1,2,3-thiadiazole **42**; *i*: concd. HCl, EtOH, reflux, 12 h; *ii*: $SOCl_2$, neat, 20 °C, 2 h

The acetal group of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **40** can be further functionalized as exemplified by the following experiment. The reaction of **40c** with tosylhydrazine in the presence of hydrochloric acid and subsequent treatment with thionyl chloride[83] afforded 1,2,3-thiadiazole **42** (Scheme 6-3).

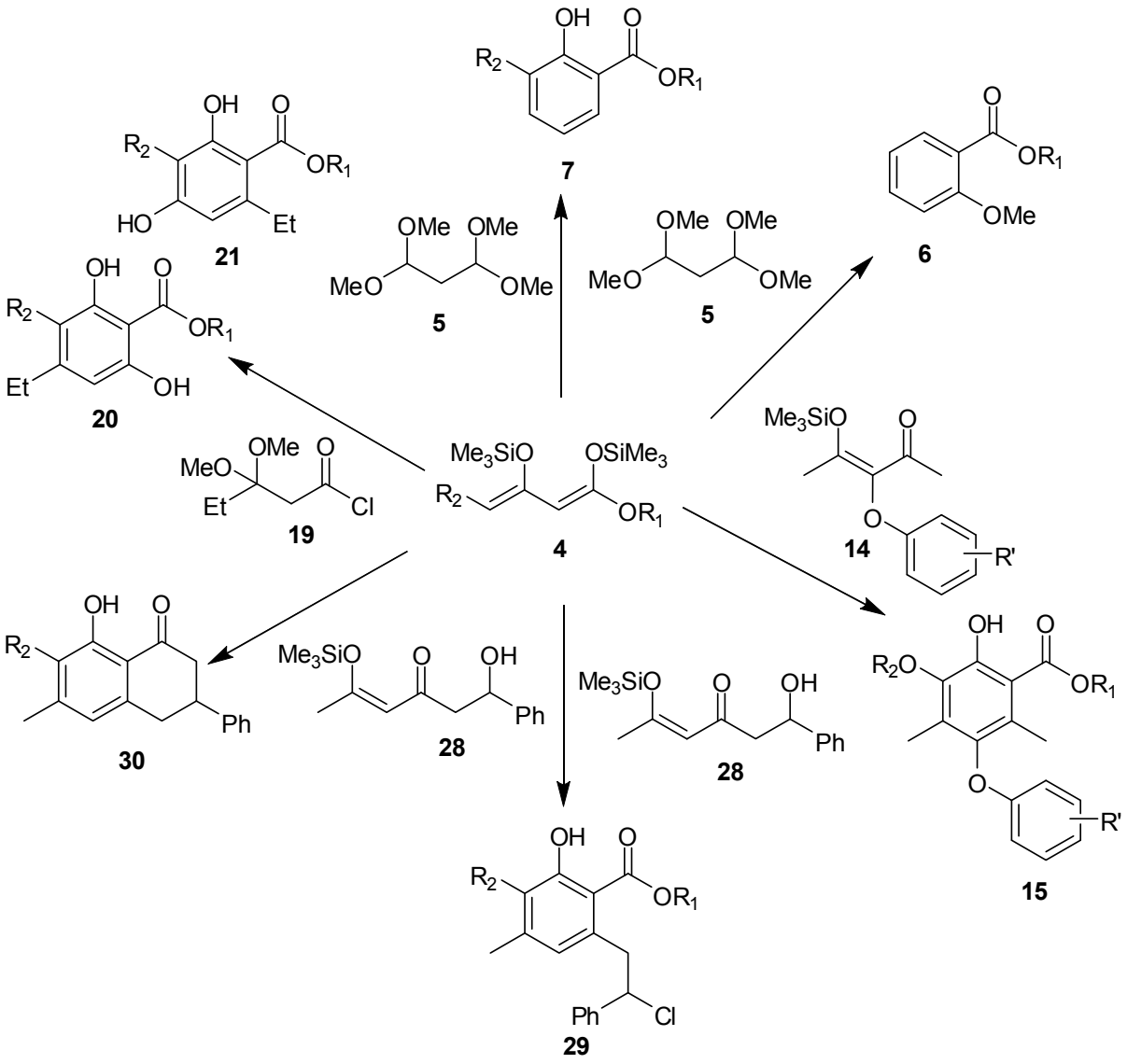
6.3 Conclusions

In conclusion, an efficiend synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles **40b-k** by copper(I) catalyzed [3+2] cyclization of 2-azido-2,2-dimethoxyethane with alkynes with very good regio- and chemoselectivity was reported.

7. Abstract

Regioselective cyclocondensation reactions of 1,3-bis(silyl enol ethers) with different mono(silyl enol ethers) provide an elegant approach for the synthesis of various complex carba- and heterocycles from simple starting materials. Salicylates, diarylethers, resorcins and 3-aryl-3,4-dihydroisocoumarins are prepared based on regioselective [3+3] cyclocondensation reactions of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane, 2-aryloxy-3-(silyloxy)alk-2-en-1-ones, 3,3-dimethoxypentanoyl chloride and 1-hydroxy-5-silyloxy-4-en-3-ones respectively. In addition, 4,5-diaryl-1,2,3-benzenetricarboxylates are prepared by reaction of 4-hydroxycyclopent-2-en-1-one-2-carboxylates with dimethyl acetylenedicarboxylate. In addition, 1-(2,2-dimethoxyethyl)-1,2,3-triazoles are prepared by regioselective copper(I)-catalyzed [3+2] cyclization of 2-azido-2,2-dimethoxyethane with alkynes.

Regioselektive Cyclokondensationsreaktionen von 1,3-Bis(silylenolethern) mit unterschiedlichen Mono(silylenolethern) ermöglichen einen eleganten Zugang zu vielen komplexen Carba- und Heterocyclen ausgehend von einfachen Startmaterialien. Salicylate, Diarylether, Resorcine und 3-Aryl-3,4-dihydroisocoumarine wurden basierend auf regioselektiven [3+3] Cyclokondensationen von 1,3-Bis(silylenolethern) mit 1,1,3,3-Tetramethoxypropan, 2-Aryloxy-3-(silyloxy)alk-2-en-1-onen, 3,3-Dimethoxypentanoylchloriden und 1-Hydroxy-5-silyloxy-4-en-3-onen hergestellt. Außerdem wurden 4,5-Diaryl-1,2,3-benzentricarboxylate durch Reaktion von 4-Hydroxycyclopent-2-en-1-on-2-carboxylaten mit Dimethylacetylendicarboxylat hergestellt. 1-(2,2-Dimethoxyethyl)-1,2,3-triazole wurden durch regioselektive Kupfer(I)-katalysierte [3+2] Cyclisierung von 2-Azido-2,2-dimethoxyethan mit Alkinen erhalten.



General Scheme: Reactions of bis(silyl enol ethers) developed in this thesis (only one substitution pattern is shown for clarity).

Reaktionen von Bis(silylenolethern) die im Rahmen dieser Arbeit entwickelt wurden (zur Klarheit wurde nur ein spezifisches Substitutionsmuster angegeben).

8. Experimental Section:

8.1 General: Equipment, chemicals and work technique

^{1}H NMR Spectroscopy:

Bruker: AM 250, Bruker ARX 300, Bruker ARX 500; δ = 0.00 ppm for Tetramethylsilane; δ = 2.04 ppm for Acetone d-6; δ = 7.26 ppm for (CDCl3); 2.50 ppm for d-6 DMSO-; Characterization of the signal fragmentations: s = singlet, d = doublet, dd = double of doublet, ddd = doublet of a double doublet, t = triplet, q = quartet, quint = quintet; sext = Sextet, sept = Septet, m = multiplet, br = broadly. Spectra were evaluated according to first order rule. All coupling constants are indicated as (*J*).

^{13}C NMR Spectroscopy:

Bruker: AM 250, (62.9 MHz); Bruker: ARX 300, (75 MHz), Bruker: ARX 500, (125 MHz) Ref: 29.84 ± 0.01 ppm and 206.26 ± 0.13 ppm for $(CD_3)_2CO$. δ = 128.00 ppm for Acetone d-6; δ = 77.00 ppm for CDCl3. The multiplicity of the carbon atoms was determined by the DEPT 135 and APT technique (APT = Attached Proton Test) and quoted as CH3, CH2, CH and C for primary, secondary, tertiary and quaternary carbon atoms. Characterization of the signal fragmentations: quart = quartet the multiplicity of the signals was determined by the DEPT recording technology and/or the APT recording technology.

Mass Spectroscopy:

AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731.

High Resolution mass spectroscopy:

Finnigan MAT 95 or Varian MAT 311; Bruker FT

CIR, AMD 402 (AMD Intectra).

Infrared spectroscopy (IR):

Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart Orbit (ATR); KBr ,KAP, Nujol, and ATR; Abbreviations for signal allocations: w = weak, m = medium, s = strong, br = broad.

Elementary analysis:

LECO CHNS-932, Thermoquest Flash EA 1112.

X-ray crystal structure analysis:

Bruker X8Apex Diffractometer with CCD-Kamera (Mo-K_a und Graphit Monochromator, $\lambda = 0.71073$ Å).

Melting points:

Micro heating table HMK 67/1825 Kuestner (Büchi apparatus); Melting points are uncorrected.

Column chromatography:

Chromatography was performed over Merck silica gel 60 (0,063 -0,200 mm, 70 - 230 mesh) as normal and/or over mesh silica gel 60 (0,040 - 0,063 mm, 200 -400 mesh) as Flash Chromatography. All solvent were distilled before use.

TLC:

Merck DC finished foils silica gel 60 F_{254} on aluminum foil and Macherey finished foils Alugram® Sil G/UV_{254}. Detection under UV light with 254 nm and/or 366 nm without dipping reagent, as well as with anisaldehyde sulfuric acid reagent (1 mL anisaldehyde consisting in 100 mL stock solution of 85% methanol, 14% acetic acid and 1% sulfuric acid).

Chemicals and work technique:

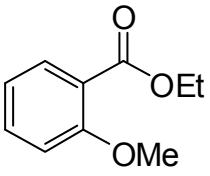
All solvents for using were distilled by standard methods. All reactions were carried out under an inert atmosphere, oxygen and humidity exclusion. All of the chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others. The order of the characterized connections effected numerically, but does not correspond to the order in the main part of dissertation.

8.2 Procedures and Spectroscopic Data:

General procedure for the synthesis of salicylates 6a-d and 7a-n:

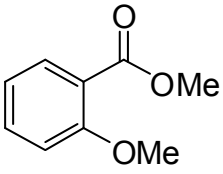
To a CH_2Cl_2 solution (100 mL) of 1,3-bis(trimethylsilyloxy)-1-ethoxy-1,3-butadiene (2.00 g, 7.28 mmol) and of 1,1,3,3-tetramethoxypropane (1.32 mL, 8.01 mmol, 1.1 equiv.) was dropwise added TMSOTf (0.11 mL, 0.73 mmol, 0.1 equiv.) at −78 °C. The reaction mixture was warmed to 20 °C during 6-12 h. After stirring for 2-6 h at 20 °C, an aqueous solution of HCl (10%, 50 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/ ethyl acetate) to give **6 a-d** and **7 a-n** .

Ethyl 2-methoxybenzoate (6a)



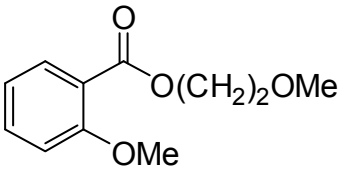
Starting with 1,3-bis(silyl enol ether), **4a** (2.00 g, 7.28 mmol), 1,1,3,3-tetramethoxypropane **5** (1.32 mL, 8.01 mmol, 1.1 equiv.) and TMSOTf (0.11 mL, 0.73 mmol, 0.1 equiv.), **6a** was obtained as a yellow oil (720 mg, 55%). ^{1}HNMR (400 MHz, $CDCl_3$): δ = 1.37 (t, ^3J = 7.1 Hz, 3H, CH_3), 3.89 (s, 3 H, OCH_3), 4.35 (q, ^3J = 7.1 Hz, 2H, OCH_2), 6.95-6.99 (m, 2H, Ar), 7.43-7.47 (m, 1H, Ar), 7.78 (dd, J = 7.8, 1.8 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3), 56.0 (OCH_3), 60.8 (OCH_2), 112.0, 120.1 (CH_{Ar}), 120.5 (C) , 131.5, 133.3 (CH_{Ar}), 159.0, 166.1 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 1725 (s), 1601 (m), 1491 (s), 1436 (s), 1302 (s), 1252 (s), 1080 (m); MS (EI, 70 eV): *m/z* (%): 180 (M^+, 24), 135 (100), 105 (20), 92 (20), 77 (38); HRMS (EI): calcd. for $C_{10}H_{12}O_3$ $[M]^+$: 180.078678; found:180.07919.

Methyl 2-methoxybenzoate (6b)



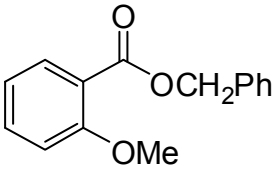
Starting with 1,3-bis(silyl enol ether), **4b** (500 mg, 1.92 mmol), 1,1,3,3-tetramethoxypropane **5** (0.32 mL, 2.11 mmol, 1.1 equiv.) and TMSOTf (0.01 mL, 0.57 mmol, 0.1 equiv.), **6b** was obtained as a yellow oil (100mg, 32%). ^{1}HNMR (400 MHz, $CDCl_3$): 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.92-6.97 (m, 2 H, ArH), 7.41-7.47 (m,1 H, ArH), 7.77 (dd, 1 H, J = 1.7, 7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.89, 55.8 (OCH_3), 111.8 (CH_{Ar}), 119.8 (C), 120.0, 131.5, 133.4 (CH_{Ar}). 158.9, 166.6 (C); GC-MS (EI, 70eV): *m/z* (%): 166.1 (M^+, 29), 135.1 (100), 105.1 (17), 92.1 (23), 77.1 (43). elemental analysis: Calcd. (%) for $C_9H_{10}O_3$ (166.17): C 65.05 H 6.07; Found C 64.88, H 6.11.

2-Methoxyethyl 2-methoxybenzoate (6c)



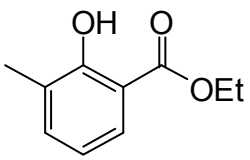
Starting with 1,3-bis(silyl enol ether), **4c** (1.50 g, 4.92 mmol), 1,1,3,3-tetramethoxypropane **5** (0.98 mL, 5.41 mmol, 1.1 equiv.) and TMSOTf (0.08 mL, 0.49 mmol, 0.1 equiv.), **6c** was obtained as a yellow oil (310 mg, 30%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.4 (s, 3 H, OCH_3), 3.71 (t, 2 H, *J* = 4.8 Hz, OCH_2), 3.89 (s, 3 H, OCH_3), 4.44 (t, 2 H, *J* = 4.8 Hz, OCH_2), 6.93-6.99 (m, 2 H, ArH), 7.42-7.48 (m, 1 H, ArH), 7.81 (dd, 1 H, *J* = 1.5, 7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 58.8 (OCH_3), 63.6, 70.3 (OCH_2), 118.8 (CH_{Ar}), 119.7 (C), 119.9, 131.5, 133.4 (C_{Ar}), 159.1, 165.8 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3430 (w), 2945 (m), 1727 (s), 1601 (m), 1492 (s), 1252 (s), 1080 (s), 1024 (m), 868 (w), 757 (s); GC-MS (EI, 70 eV): *m/z* (%): 210 (M^+, 15), 152 (100), 135 (71), 123 (56), 105 (30), 92 (41), 77 (90).

Benzyl 2-methoxybenzoate (6d)



Starting with 1,3-bis(silyl enol ether), **4d** (2.00 g, 5.96 mmol), 1,1,3,3-tetramethoxypropane **5** (1.08 mL, 6.55 mmol, 1.1 equiv.) and TMSOTf (0.11 mL, 0.59 mmol, 0.1 equiv.), **6d** was obtained as a yellow oil (566 mg, 40%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 5.34 (s, 2 H, OCH_2), 6.92-6.97 (m, 2 H, ArH), 7.33-7.46 (m, 6 H, ArH), 7.83 (dd, 1 H, *J* = 1.6, 7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8 (CH_3), 66.3 (OCH_2), 112.0 (CH_{Ar}), 119.7 (C), 119.7 (CH_{Ar}), 127.9, 128.3, 131.6, 133.5 (CH_{Ar}), 136.1, 159.2, 165.7 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3434 (w), 2946 (w), 1727 (s), 1600 (s), 1491 (s), 1436 (m), 1299 (s), 1251 (s), 1129 (m), 1073 (s), 1024 (m), 755 (s), 698 (s); GC-MS (EI, 70 eV): *m/z* (%): 242.1 (M^+, 51), 197.1 (14), 135.1 (100), 91.1 (82), 77.1 (30); HRMS (EI): Calcd. for $C_{15}H_{14}O_3$ $[M]^+$: 242.093384; found: 242.09375.

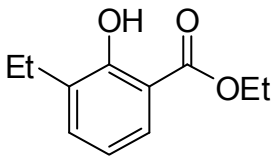
Ethyl 2-hydroxy-3-methylbenzoate (7a)



Starting with 1,3-bis(silyl enol ether), **4f** (2.00g, 6.93 mmol), 1,1,3,3-tetramethoxypropane **5** (1.20 mL, 7.62 mmol, 1.1 equiv.) and TMSOTf (0.11 mL, 0.69 mmol, 0.1 equiv.), **7a** was obtained as a yellow oil (570 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, *J* = 5.3 Hz, OCH_3), 2.13 (s, 3 H, CH_3), 4.25 (q, 2 H, *J* = 5.3 Hz, OCH_2), 6.63 (t, 1 H, *J* = 5.7 Hz, ArH), 7.16 (dd, 1 H, *J* = 1.5, 7.8 Hz, ArH), 7.56 (dd, 1 H, *J* = 1.2, 5.5 Hz, ArH); ^{13}C NMR

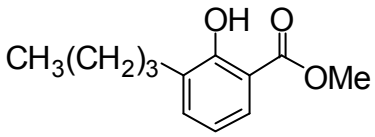
(100 MHz, $CDCl_3$): δ = 14.1, 15.5 (CH_3), 61.2 (OCH_2), 111.8 (C), 118.3 (CH_{Ar}), 126.4 (C), 127.3, 136.2, (CH_{Ar}), 160.0, 170.6 (C); IR (neat, cm^{-1}); $\tilde{\nu}$ = 3397 (m), 2985 (s), 1670 (s), 1616(m), 1435 (m), 1290 (s), 1250 (s), 1148 (s), 1083 (s), 1027 (m), 879 (w), 755 (s); GC-MS (EI, 70 eV): *m/z* (%): 180.1 (M^+, 61), 134,1 (100), 106.1 (95), 77.1 (31); HRMS (EI): Calcd. for $C_{10}H_{12}O_3$ $[M]^+$: 180.077698; found: 180.07810.

Ethyl 3-ethyl-2-hydroxybenzoate (7b)



Starting with 1,3-bis(silyl enol ether), **4g** (2.00 g, 6.61 mmol), 1,1,3,3-tetramethoxypropane **5** (1.2 mL, 7.27 mmol, 1.1 equiv.) and TMSOTf (0.11 mL, 0.66 mmol, 0.1 equiv.), **7b** was obtained as a yellow oil (520 mg, 40%). ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.61 (t, 3 H, *J* = 8.1 Hz, CH_3), 1.78 (t, 3 H, *J* = 7.0 Hz, CH_3), 3.07 (q, 2 H, *J* = 7.6 Hz, CH_2), 4.76 (q, 2 H, *J* = 4.9 Hz, OCH_2), 7.20 (t, 1 H, *J* = 7.9 Hz, ArH), 7.69 (dd, 1 H, *J* = 1.5, 7.9 Hz, ArH), 11.52 (s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.5 (CH_3), 22.8, 61.3 (OCH_2), 112.0 (C), 118.5, 127.4 (CH_{Ar}), 132.5 (C), 134.7 (CH_{Ar}), 159.8, 170.7 (C); IR (neat, cm^{-1}): 3164 (w), 2968 (m), 1669 (s), 1614 (m), 1459 (s), 1397 (w), 1246 (s), 1148 (s), 1092 (m), 1023 (m), 756 (s); GC-MS (EI, 70 eV): *m/z* (%): 194.1 (M^+, 95), 148.1 (100), 133.1 (27), 120.1 (100), 91.1 (39), 77.1 (34); HRMS (EI): Calcd. for $C_{11}H_{14}O3$ $[M]^+$: 194.09388; found: 194.09375.

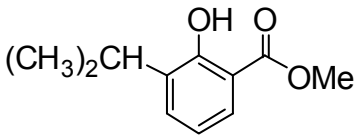
Methyl 3-butyl-2-hydroxybenzoate (7c)



Starting with 1,3-bis(silyl enol ether), **4h** (1.50 g, 4.7 mmol), 1,1,3,3-tetramethoxypropane **5** (0.86 mL, 5.21 mmol, 1.1 equiv.) and TMSOTf (0.09 mL, 0.47 mmol, 0.1 equiv.), **7c** was obtained as a yellow oil (0.59 g, 60%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.3Hz, 3H, CH_3), 1.31-1.44, 1.55-1.65 (m, 4H, $(CH_2)_2CH_3$), 2.66 (t, ^3J = 7.7 Hz, 2H, CH_2Ar), 3.93 (s, 3H, OCH_3), 6.78, 6.81 (dd, ^3J = 7.8 Hz, 1H, H-5Ar), 7.30, 7.31 (dd, ^3J = 7.4 Hz, ^4J=1.7 Hz, 1H, H-4Ar), 7.68, 7.70 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, H-6Ar), 11.03 (OH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 22.9, 29.7, 32.0 (CH_2), 52.5 (OCH_3), 112.1 (C-1), 118.8, 127.7, 136.0 (CH_{Ar}), 131.5 (C-3), 160.1 (C-2), 171.4 (C=O). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3178 (w), 2958 (s), 2929 (s), 2856 (s), 1753 (s), 1714 (s), 1676 (m), 1613 (s), 1440 (m), 1341 (m), 1307 (m), 1248 (s), 1198 (s), 1148 (s), 1103 (s), 1068 (m), 1003 (m), 842 (s), 758 (s), 646 (s), 557 (s), 441 (s). MS (EI, 70 eV): *m/z* (%) = 209 (M^+, 8), 208 (59), 177 (14), 176 (26), 165

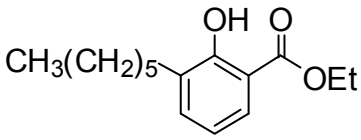
(20), 159 (10), 148 (51), 147 (26), 134 (92), 133 (100), 106 (31), 105 (23), 91 (12), 77 (25), 51(10). HRMS (EI, 70 eV): calcd for $C_{12}H_{16}O_3$ $[M]^+$: 208.1094; found: 208.1089.

Methyl 2-hydroxy-3-isobutylbenzoate (7d)



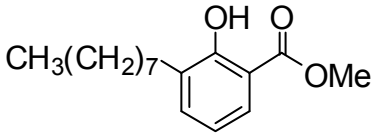
Starting with 1,3-bis(silyl enol ether), **4i** (1.50 g, 4.47 mmol), 1,1,3,3-tetramethoxypropane **5** (0.86 mL, 5.21 mmol, 1.1 equiv.) and TMSOTf (0.08 mL, 0.44 mmol, 0.1 equiv.), **7d** was obtained as a yellow oil (370 mg, 45%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.91 (d, 6 H, *J* = 6.6 Hz, CH_3), 1.91-2.03 (m, 1 H, CH), 2.52 (d, 2 H, *J* = 7.2 Hz, CH_2), 3.91 (s, 3 H, OCH_3), 6.97 (t, 1 H, *J* = 7.5 Hz, ArH), 7.27 (dd, 1 H, *J* = 1.8, 7.8 Hz, ArH), 7.68 (dd, *J* = 1.7, 8.0 Hz, 1H, ArH), 11.02 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 ($2CH_3$), 28.2 (CH_2), 38.9 (CH), 52.1 (OCH_3), 111.7 (C), 118.2, 127.5 (CH_{Ar}), 130.0 (C), 136.6 (CH_{Ar}), 159.9, 171.0 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3178 (w), 2958 (s), 2929 (s), 2856 (s), 1753 (s), 1714 (s), 1676 (m), 1613 (s), 1440 (m), 1341 (m), 1307 (m), 1248 (s), 1198 (s), 1148 (s), 1103 (s), 1068 (m), 1003 (m), 842 (s), 758 (s), 646 (s), 557 (s), 441 (s). MS (EI, 70 eV): *m/z* (%): 182.1 (M^+, 68), 150.1 (80), 122.1 (100), 107.1 (32), 92.1 (17); HRMS (EI, 70 eV): calcd. for $C_9H_{10}O_4$ $[M]^+$: 182.057383; found: 182.05736.

Ethyl 3-hexyl-2-hydroxybenzoate (7e)



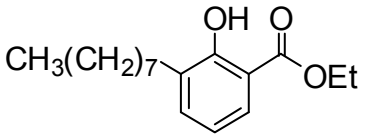
Starting with 1,3-bis(silyl enol ether), **4j** (2.00g, 5.57 mmol), 1,1,3,3-tetramethoxypropane **5** (1.01 mL, 6.13 mmol, 1.1 equiv.) and TMSOTf (0.10mL, 0.55 mmol, 0.1 equiv.), **7e** was obtained as a yellow oil (700mg, 50%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.0 Hz, CH_3), 1.23-1.41 (m, 11 H, CH_2), 2.63 (t, 2 H, *J* = 7.8 Hz, CH_2), 4.37 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.77 (dd, 1 H, *J* = 7.7 Hz, ArH), 7.28 (dd, 1 H, *J* = 1.2, 7.3 Hz, ArH), 7.69 (dd, 1 H, *J* = 1.7, 8.0 Hz, ArH), 11.09 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.10, 14.19 (CH_3), 22.6, 29.1, 29.4, 29.6, 31.7 (CH_2), 61.2 (OCH_2), 111.9 (C), 118.3, 127.3 (C_{Ar}),131.1 (C), 135.5 (C_{Ar}),159.8, 170.7 (C);); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3147 (w), 2928 (s), 2857 (m), 1670 (m), 1613 (m), 1451 (s), 1247 (s), 1147 (s), 1109 (w), 1025 (w), 757 (s); GC-MS (EI, 70 eV): *m/z* (%): 250.2 (M^+, 54), 204.1 (22), 176.1 (38), 147.1 (38), 133.1 (100), 106.1 (23), 77.1 (20); elemental analysis: Calcd. (%) for $C_{15}H_{22}O_3$ (250.33): C 71.97, H 8.86; Found C 72.44, H 9.11.

Methyl 3-heptyl-2-hydroxylbenzoate (7f)



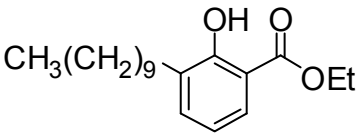
Starting with 1,3-bis(silyl enol ether), **4l** (1.50g, 4.28 mmol), 1,1,3,3-tetramethoxypropane **5** (0.76 mL, 4.61 mmol, 1.1 equiv.) and TMSOTf (0.08mL, 0.42 mmol, 0.1 equiv.), **7f** was obtained as a yellow oil (0.61 g, 59%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.86-0.91, 1.28-1.34, 1.57-1.66 (m, 13H, $(CH_2)_6CH_3$), 2.65 (t, ^{3}J=7.7Hz, 2H, CH_2Ar), 3.94 (s, 3H, OCH_3), 6.78, 6.81 (dd, ^{3}J=7.8Hz, 1H, H-5Ar), 7.30, 7.32 (dd, ^{3}J= 7.4Hz, ^{4}J=1.4Hz, 1H, H-4Ar), 7.68, 7.71 (dd, ^{3}J = 8.1Hz, ^{4}J = 1.7Hz, 1H, H-6Ar), 11.02 (OH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 23.0, 29.6, 29.8, 29.8, 30.0 (CH_2), 52.5 (OCH_3), 112.1 (C-1), 118.8, 127.7, 136.0 (CH_{Ar}), 131.6 (C-3), 160.1(C-2), 171.4 (C=O). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3174 (w), 2950 (s), 2925 (s), 2860 (s), 2369 (m), 1676 (m), 1613 (s), 1440 (m), 1341 (m), 1303 (m), 1248 (s), 1198 (s), 1148 (s), 1108 (m), 1076 (m), 996 (m), 844 (s), 757 (s), 724 (m), 647 (m), 557 (m), 441 (m). MS (EI, 70 eV): *m/z* (%) = 250 (M^+, 48), 218 (16), 190 (30), 189 (15), 175 (10), 165 (28), 161 (11), 148 (10), 147 (30), 134 (82), 133 (100), 106 (21), 105 (20), 91 (9), 77 (19), 41 (7). HRMS (EI, 70 eV): calcd. for $C_{15}H_{22}O_3$ $[M]^+$: 250.1563, found: 250.1564.

Ethyl 2-hydroxy-3-octylbenzoate (7g)



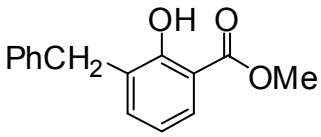
Starting with 1,3-bis(silyl enol ether), **4m** (2.00g,5.17 mmol), 1,1,3,3-tetramethoxypropane **5** (0.94 mL, 5.68 mmol, 1.1 equiv.) and TMSOTf (0.09mL, 0.52 mmol, 0.1 equiv.), **7g** was obtained as a yellow oil (700mg, 56%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.23-1.41 (m, 15 H, CH_2), 2.63 (t, 2 H, *J* = 7.8 Hz, CH_2), 4.37 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.77 (dd, 1 H, *J* = 7.7 Hz, ArH), 7.28(dd, 1 H, *J* = 1.3, 7.3 Hz, ArH), 7.69 (dd, 1 H, *J* = 1.7, 7.9 Hz, ArH), 11.09 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1 (CH_3), 22.6, 29.2, 29.43, 29.45, 29.5, 29.6, 31.8 (CH_2), 61.2 (OCH_2), 111.9 (C), 118.3, 127.3 (CH_{Ar}),131.1 (C), 135.5 (CH_{Ar}),159.8, 170.6 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3164 (w), 2926 (s), 2855 (s), 1670 (m), 1613 (m), 1451 (s), 1247 (s), 1147 (s), 1109 (w), 1025 (w), 757 (s); GC-MS (EI, 70 eV): *m/z* (%): 278.2 (M^+, 59), 232.2 (18), 204.2 (34), 179.1 (32), 147.1 (37), 134.1 (96), 133.1 (100), 106.1 (23); elemental analysis Calcd. (%) for $C_{17}H_{26}O_3$ (278.39): C 73.44, H 9.41 Found: C 73.71, H 9.92.

Ethyl 3-decyl-2-2hydroxydecylbenzoate (7h)



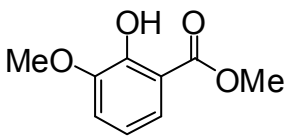
Starting with 1,3-bis(silyl enol ether), **4o** (2.00g, 4.82 mmol), 1,1,3,3-tetramethoxypropane **5** (0.88 mL, 5.31 mmol, 1.1 equiv.) and TMSOTf (0.08mL, 0.48 mmol, 0.1 equiv.), **7h** was obtained as a yellow oil (790 mg, 54%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 6.8 Hz, CH_3), 1.25-1.42 (m, 15 H, CH_2), 2.46 (t, 2 H, *J* = 7.8 Hz, CH_2), 4.39 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.78 (t, 1 H, *J* = 7.6 Hz, ArH), 7.30 (dd, 1 H, *J* = 1.5, 7.3 Hz, ArH), 7.70 (dd, 1 H, *J* = 1.7, 8.0 Hz, ArH), 11.10 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.19 (CH_3), 22.6, 29.3, 29.4, 29.5, 29.62, 29.69, 31.9 (CH_2), 61.2 (OCH_2), 11.9 (C), 118.3, 127.3 (CH_{Ar}), 131.2 (C), 135.5 (CH_{Ar}), 159.8, 170.7 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3168 (w), 2925 (s), 1670 (s), 1452 (s), 1373 (m), 1247 (s), 1148 (s), 1095 (w), 1025 (w), 757 (s); GC-MS (EI,70 eV) m/z (%) = 306 (M^+, 37), 260 (14), 203 (19), 174 (25), 147 (28), 133 (100); elemental analysis: Calcd. (%) for $C_{19}H_{30}O_3$ (306.44): C 75.21, H 8.96; Found C 75.44, H 9.03.

Methyl 3-benzyl-2-hydroxybenzoate (7k)



Starting with 1,3-bis(silyl enol ether), **4p** (1.50g, 4.35 mmol), 1,1,3,3-tetramethoxypropane **5** (0.78 mL, 4.78 mmol, 1.1 equiv.) and TMSOTf (0.08mL, 0.44 mmol, 0.1 equiv.), **7k** was obtained as a yellow oil (590mg, 57%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 4.0 (s, 2 H, CH_2), 6.77 (t, 1 H, *J* = 7.6 Hz, ArH), 6.75-7.26 (m, 6 H, ArH), 7.70 (dd, 1 H, *J* = 1.5, 8.0 Hz, ArH), 11.07 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.3 (CH_2), 52.2 (OCH_3), 112.0 (C), 118.6, 126.0, 126.4, 128.0, 128.2, 128.6, 128.8 (CH_{Ar}), 129.6, 136.2, 140.2, 159.6, 170.9 (C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3086 (s), 3062 (s), 3027 (s), 2953 (s), 2852 (s), 1945 (s), 1893 (s), 1674 (w), 1614 (s), 1494 (s), 1440 (w), 1302 (w), 1250 (m), 1198 (m), 1145 (m), 1096 (s), 1080 (s), 1030 (s), 997 (m), 843 (m), 788 (s), 759 (w), 698 (m), 611 (s), 556 (s), 546 (s), 475 (s), 455 (s), 441 (s); GC-MS (EI, 70 eV): *m/z* (%): 242.1 (M^+, 66), 210.1 (82), 182.1 (100), 152.1 (36), 105.1 (14); HRMS (EI, 70 eV): calcd. for $C_{15}H_{14}O_3$ $[M]^+$: 242.093218; found:242.09375.

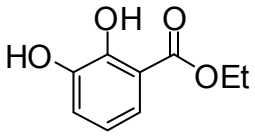
Methyl 2-hydroxy-3-methoxybenzoate (7m)



Starting with 1,3-bis(silyl enol ether), **4q** (1.50g, 5.16 mmol), 1,1,3,3-tetramethoxypropane **5** (0.94 mL, 5.67 mmol, 1.1 equiv.) and TMSOTf (0.09mL, 0.51 mmol, 0.1 equiv.), **7m** was obtained as a yellow solid (302mg, 32%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 3.93 (s, 3

H, OCH_3), 6.81 (t, 1 H, *J* = 8.0 Hz, ArH), 7.02 (dd, 1 H, *J* = 1.2, 7.9 Hz, ArH), 7.42 (dd, *J* = 8.1, 1.5 Hz, 1H, ArH), 10.99 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3, 56.1 (OCH_3), 112.5 (C), 116.4, 118.4, 120.9 (CH_{Ar}), 148.4 (C), 151.9, 170.7 (C); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3430 (s), 2885 (m), 1672 (s), 1603 (m), 1462 (s), 1376 (s), 1273 (s), 1171 (s), 1113 (m), 1069 (s), 913 (m), 847 (s), 761 (s), 641 (w), 585 (s); MS (EI, 70 eV): *m/z* (%): 182.1 (M^+, 68), 150.1 (80), 122.1 (100), 107.1 (32), 92.1 (17); HRMS (EI, 70 eV): calcd. for $C_9H_{10}O_4$ $[M]^+$: 182.057383; found: 182.05736.

Ethyl 2,3-dihydroxybenzoate (7n)

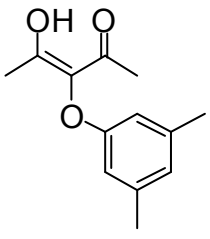


Starting with 1,3-bis(silyl enol ether), **4r** (1.50g, 4.38 mmol), 1,1,3,3-tetramethoxypropane **5** (0.78 mL, 4.761 mmol, 1.1 equiv.) and TMSOTf (0.07mL, 0.43 mmol, 0.1 equiv.), **7n** was obtained as a yellow solid (220mg, 27%). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.41 (q, 2 H, *J* = 7.1 Hz, OCH_2), 5.70 (s, 1 H, OH), 6.79 (t, 1 H, *J* = 8.0 Hz, ArH), 7.09 (dd, 1 H, *J* = 1.5, 8.0 Hz, ArH), 7.38 (dd, 1 H, *J* = 1.5, 8.1 Hz, ArH), 10.99 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 61.5 (OCH_2), 112.5 (C), 119.0, 119.6, 120.5 (C_{Ar}), 144.9, 148.8, 170.3 (C); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3472 (s), 2885 (m), 1672 (s), 1603 (m), 1462 (s), 1376 (s), 1273 (s), 1171 (s), 1113 (m), 1069 (s), 913 (m), 847 (s), 761 (s), 641 (w), 585 (s); GC-MS (EI, 70 eV): *m/z* (%): 182.2 (M^+, 28), 136.1 (100), 108.1 (15); HRMS (EI): calcd for $C_9H_{10}O_4$ $[M]^+$: 182.056870; found: 182.05736.

Synthesis of 3-(aryloxy)pentane-2,4-diones 13a-i:

3-(Phenoxy)pentane-2,4-diones **13a-i** were prepared, following a known procedure,[41] by potassium carbonate mediated reaction of phenols **11a-i** with 3-(chloro)pentane-2,4-dione (**12**).

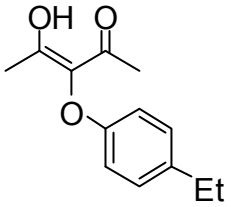
3-(3,5-dimethylphenoxy)-4-hydroxypent-3-en-2-one (13b)



Starting with **12** (10.00 g, 74.3 mmol), 3,5-dimethylphenol (12.00 g, 104.0 mmol) and K_2CO_3 (25.00 g, 185.7 mmol), **13b** was isolated as a yellow solid (3.00 g, 19%); mp. 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 6 H, CH_3), 2.28 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 6.51 (s, 2 H, ArH), 6.66 (s, 1 H, ArH), 14.41 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (2C), 21.3 (2C, CH_3), 111.9 (2C), 123.9 (CH), 130.9, 139.8 (2C), 158.0, 186.4 (2C, C); IR (KBr): $\tilde{\nu}$ = 3436 (w), 2965 (m), 1739 (m), 1610 (m), 1505 (s), 1298 (m), 1213 (m),

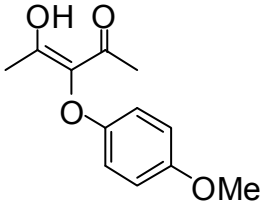
831 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 220 (M^+, 100), 178 (25), 122 (88), 107 (29), 91 (28), 77 (31), 43 (64); elemental analysis: calcd. (%) for $C_{13}H_{16}O_3$ (220.26): C 70.89, H 7.32; found: C 71.05, H 7.07.

3-(4-ethylphenoxy)-4-hydroxypent-3-en-2-one (13c)



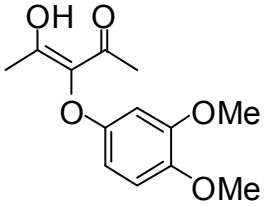
Starting with **12** (10.00 g, 74.3 mmol), 4-ethylphenol (12.90 g, 105.5 mmol) and K_2CO_3 (25.60 g, 185.7 mmol), **13c** was isolated as a colourless oil (5.30 g, 35%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.03 (s, 6 H, CH_3), 2.60 (q, 2 H, *J* = 7.8 Hz, CH_2), 6.82 (d, 2 H, *J* = 8.7 Hz, ArH), 7.12 (d, 2 H, *J* = 8.8 Hz, ArH), 14.42 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7, 20.8 (2C, CH_3), 27.9 (CH_2), 114.1 (2C), 129.1 (2C, CH), 131.0, 137.9, 156.0, 186.5 (2C, C); IR (neat): $\tilde{\nu}$ = 3436 (w), 2965 (m), 1739 (m), 1610 (m), 1505 (s), 1298 (m), 1213 (m), 831 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 220.1 (M^+, 90), 178.1 (29), 122.1 (61), 107.1 (64), 43.1 (100); HRMS (EI): calcd. for $C_{13}H_{16}O_3$ $[M]^+$: 220.1091; found: 220.1094.

3-(4-methoxyphenoxy)-4-hydroxypent-3-en-2-one (13e)



Starting with **12** (4.00 g, 29.7 mmol), 4-methoxyphenol (5.20 g, 42.2 mmol) and K_2CO_3 (10.20 g, 74.3 mmol), **13e** was isolated as a colourless oil (1.50 g, 24%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 6 H, CH_3), 3.77 (s, 3 H, OCH_3), 6.83 (s, 4 H, ArH), 14.39 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (2C), 55.6 (CH_3), 114.91 (2C), 114.95 (2C, CH), 131.2, 151.9, 154.7, 186.5 (2C, C); IR (neat): $\tilde{\nu}$ = 3085 (w), 3003 (m), 2956 (m), 2839 (w), 1607 (s), 1507 (s), 1309 (s), 1262 (s), 1228 (s), 1194 (s), 1166 (s), 1128 (s), 1026 (s), 951 (s), 740 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 222.0 (M^+, 100), 151.0 (16), 124.0 (40), 108.0 (22); HRMS (EI): calcd. for $C_{12}H_{14}O_4$ $[M]^+$: 222.0878; found: 222.0886.

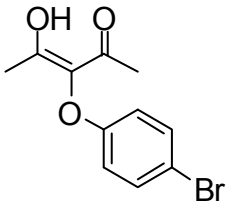
3-(3,4-dimethoxyphenoxy)-4-hydroxypent-3-en-2-one (13f)



Starting with **12** (6.00 g, 44.5 mmol), 3,4-dimethoxyphenol (9.70 g, 63.3 mmol) and K_2CO_3 (15.40 g, 111.4 mmol), **13f** was isolated as a pink solid (4.50 g, 40%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 6 H, CH_3), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.31 (dd, 1 H, *J* = 8.7, 2.8 Hz, ArH), 6.55 (d, 1 H, *J* = 2.8 Hz, ArH), 6.75 (d, 1 H, *J* = 8.7 Hz, ArH), 14.42 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (2C), 55.9, 56.3 (CH_3), 99.9, 103.6, 111.8 (CH), 131.5, 144.3, 150.2, 152.4, 186.5 (2C, C); IR (KBr): $\tilde{\nu}$ = 3085 (w), 3003 (m),

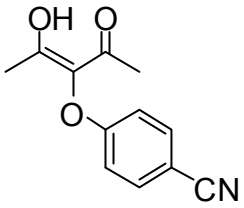
2956 (m), 2839 (w), 1607 (s), 1507 (s), 1309 (s), 1262 (s), 1228 (s), 1194 (s), 1166 (s), 1128 (s), 1026 (s), 951 (s), 740 (m) cm^{-1}; MS (CI): 253.1 (100); elemental analysis: calcd. (%) for $C_{13}H_{16}O_5$ (252.26): C 61.90, H 6.39; found: C 61.73, H 6.30.

3-(4-bromophenoxy)-4-hydroxypent-3-en-2-one (13g)



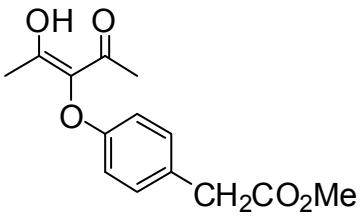
Starting with **12** (10.00 g, 74.3 mmol), 4-bromophenol (14.40 g, 105.5 mmol) and K_2CO_3 (25.60 g, 185.7 mmol), **13g** was isolated as a pink oil (5.10 g, 25%); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 6 H, CH_3), 6.81 (d, 2 H, *J* = 8.7 Hz, ArH), 7.40 (d, 2 H, *J* = 8.7 Hz, ArH), 14.39 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (2C, CH_3), 114.4 (C), 116.0 (2C, CH), 130.7 (C), 132.8 (2C, CH), 157.1, 186.3 (2C, C); IR (neat): $\tilde{\nu}$ = 2925 (w), 1593 (m), 1481 (s), 1303 (m), 1213 (m), 1165 (m), 1070 (m), 825 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 272.0 (M^+, 42), 270.0 (43), 230.0 (17), 228.0 (18), 174.0 (39), 172.0 (40), 101.1 (32); HRMS (EI): calcd. for $C_{11}H_{11}BrO_3$ $[M]^+$: 269.9890; found: 269.9886.

3-(4-Cyanophenoxy)-4-hydroxypent-3-en-2-one (13h)



Starting with **12** (10.00 g, 74.3 mmol), 4-cyanophenol (12.50 g, 105.5 mmol) and K_2CO_3 (26.50 g, 185.8 mmol), **13h** was isolated as a brown solid (4.20 g, 25%); mp. 67-68 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 6 H, CH_3), 7.02 (d, 2 H, *J* = 9.0 Hz, ArH), 7.65 (d, 2 H, *J* = 9.0 Hz, ArH), 14.42 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3), 106.0 (C), 115.2 (CH_{Ar}), 118.5, 130.4 (C), 134.5 (CH_{Ar}), 161.2, 186.0 (C); IR (KBr): $\tilde{\nu}$ = 3390 (w), 2953 (w), 1738 (s), 1611 (s), 1296 (m), 1223 (s), 1165 (m), 827 (m), 732 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 217 (M^+, 69), 175 (25), 101 (30), 43 (100); elemental analysis: calcd (%) for $C_{12}H_{11}O_3N$ (217.23): C 66.34, H 5.11, N 6.45; found: C 65.97, H 4.88, N 6.33.

Methyl 2-(4-(2,4-dioxopentane-3-yloxy)phenyl) acetate (13i)



Starting with **12** (10.00 g, 74.3 mmol), methyl 4-hydroxy acetate (17.20 g, 104.0 mmol) and K_2CO_3 (25.60 g, 185.7 mmol), **13i** was isolated as a colourless solid (4.30 g, 26%); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3), 5.29 (s, 2 H, CH_2), 6.87 (d, 2 H, *J* = 8.7 Hz, ArH), 7.22 (d, 2 H, *J* = 8.7 Hz, ArH), 14.42 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3), 40.0 (CH_2), 51.9 (OCH_3), 114.3 (CH_{Ar}), 127.6 (C), 130.6 (CH_{Ar}), 130.8, 157.0, 172.0, 186.3 (C); IR (KBr): $\tilde{\nu}$ = 3436 (w), 2965 (m), 1739 (m), 1610 (m), 1505 (s), 1298 (m), 1213

(m), 831 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 264 (M^+, 100), 222.1 (36), 205.1 (47), 166.1 (34), 107.1 (87), 43.1 (61); elemental analysis: calcd (%) for $C_{14}H_{16}O_5$ (442.56): C 63.63, H 6.10; found: C 63.26, H 5.88.

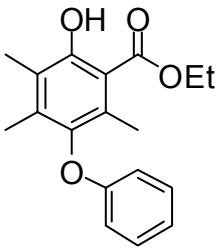
Synthesis of 2-aryloxy-3-(silyloxy)alk-2-en-1-ones 14a-i:

The reactions were carried according to a known procedure.[8c] Due to their low stability, silyl enol ethers **14a-i** were used directly after their preparation and not characterized by spectroscopy.

General procedure for the synthesis of diaryl ethers 15a-u:

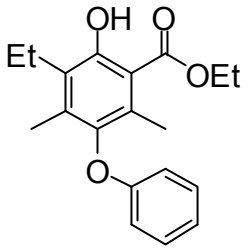
To a dichloromethane solution (2 mL/mmol) of **14** (1.0 mmol) and **4** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at –78 °C. The solution was allowed to warm to ambient temperature within 20 h. To the solution was added a saturated solution of $NaHCO_3$ (10 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 30 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silic a gel, EtOAc / *n*-heptane = 1:4).

Ethyl 3-phenoxy-6-hydroxy-2,4,5-trimethylbenzoate (15a)



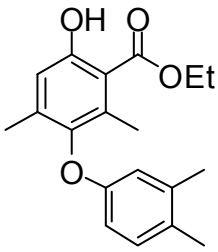
Starting with 1,3-bis(silyl enol ether), **4f** (400 mg, 1.3 mmol), 3-(siloxy)alk-2-en-1-one **14a** (367 mg, 1.3 mmol) and $TiCl_4$ (0.15 mL, 1.3 mmol), **15a** was isolated as a colourless solid (130 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 4.42 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.72-7.27 (m, 5 H, ArH), 11.51 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 12.8, 13.1, 14.3 (CH_3), 60.6 (CH_2), 109.4 (C), 113.5 (2C), 120.3 (CH), 123.0 (C), 128.6 (2C, CH), 129.2, 137.1, 142.4, 156.8, 157.2, 170.9 (C); IR (KBr): $\tilde{\nu}$ = 3438 (w), 2937 (w), 1649 (s), 1396 (s), 1293 (s), 1222 (s), 1031 (m), 810 (m), 753 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 300.0 (M^+, 88), 254.0 (100), 226.0 (72), 211.0 (17); HRMS (EI): calcd. for $C_{18}H_{20}O_4$ $[M]^+$: 300.13563; found: 300.13561.

Ethyl 5-ethyl-3-phenoxy-6-hydroxy-2,4-dimethylbenzoate (15b)



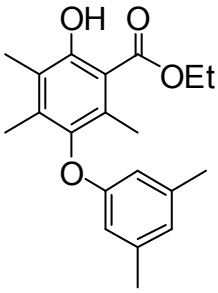
Starting with 1,3-bis(silyl enol ether), **4g** (400 mg, 1.3 mmol), 3-(siloxy)alk-2-en-1-one **14a** (349 mg, 1.3 mmol) and $TiCl_4$ (0.14 mL, 1.3 mmol), **15b** was isolated as a colourless solid (130 mg, 32%), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.38 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.70 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.40 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.69-7.23 (m, 5 H, ArH), 11.44 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 13.3, 14.1, 15.3 (CH_3), 19.7, 61.5 (CH_2), 110.6 (C), 114.5 (2C), 121.2, 129.6 (2C, CH), 130.1, 130.4, 137.4, 143.5, 157.6, 158.2, 171.9 (C); IR (KBr): $\tilde{\nu}$ = 2969 (m), 1651 (s), 1599 (m), 1492 (s), 1394 (s), 1320 (s), 1221 (s), 1052 (m), 748 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 314.1 (M^+, 46), 268.1 (100), 240.1 (10), 225.1 (2); elemental analysis: calcd. (%) for $C_{19}H_{22}O_4$ (314.37): C 72.59, H 7.05; found: C 72.65, H 6.95.

Ethyl 3-(3,5-dimethylphenoxy)-6-hydroxy-2,4-dimethylbenzoate (15c)



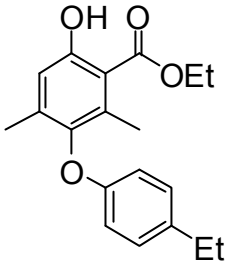
Starting with 1,3-bis(silyl enol ether), **4a** (500 mg, 1.8 mmol), 3-(siloxy)alk-2-en-1-one **14b** (533 mg, 1.8 mmol) and $TiCl_4$ (0.19 mL, 1.8 mmol), **15c** was isolated as a colourless solid (330 mg, 58%), mp. 125-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.11 (s, 3 H, CH_3), 2.24 (s, 6 H, CH_3), 2.34 (s, 3 H, CH_3), 4.43 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.35 (s, 2 H, ArH), 6.62 (s, 1 H, ArH), 6.76 (s, 1 H, ArH), 11.19 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.4, 17.3, 21.3 (2C, CH_3), 61.6 (CH_2), 111.1 (C), 112.1 (2C), 117.3, 123.3 (CH), 133.7, 139.4 (2C), 139.9, 143.9, 158.0, 159.5, 171.4 (C); IR (KBr): $\tilde{\nu}$ = 3030 (w), 2957 (m), 1660 (s), 1505 (s), 1470 (s), 1397 (s), 1373 (s), 1313 (s), 1241 (s), 1220 (s), 1077 (m), 826 (m), 799 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 314.2 (M^+, 34), 268.1 (100); elemental analysis: calcd. (%) for $C_{19}H_{22}O_4$ (314.37): C 72.59, H 7.05; found: C 72.18, H 6.88.

Ethyl 3-(3,5-dimethylphenoxy)-6-hydroxy-2,4,5-trimethylbenzoate (15d)



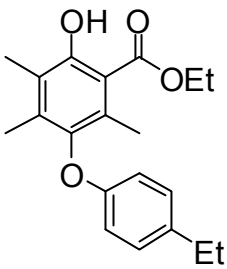
Starting with 1,3-bis(silyl enol ether), **4f** (500 mg, 1.7 mmol), 3-(siloxy)alk-2-en-1-one **14b** (506 mg, 1.7 mmol) and $TiCl_4$ (0.18 mL, 1.7 mmol), **15d** was isolated as a colourless solid (220 mg, 39%); mp. 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 2.25 (s, 6 H, CH_3), 2.33 (s, 3 H, CH_3), 4.44 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.35 (s, 2 H, ArH), 6.62 (s, 1 H, ArH), 11.54 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 13.9, 14.1, 15.3, 21.3 (2C, CH_3), 61.5 (CH_2), 110.3 (C), 112.2 (2C), 123.1 (CH), 123.8, 130.3, 138.2, 139.4 (2C), 143.5, 157.7, 158.3, 172.0 (C); IR (KBr): $\tilde{\nu}$ = 3430 (w), 2921 (m), 1647 (s), 1612 (s), 1594 (s), 1400 (s), 1378 (s), 1318 (s), 1289 (s), 1218 (s), 1142 (s), 1032 (m), 834 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 328.2 (M^+, 38), 282.2 (100), 239.2 (14); elemental analysis: calcd. (%) for $C_{20}H_{24}O_4$ (328.40): C 73.14, H 7.36; found: C 73.16, H 7.57.

Ethyl 3-(4-ethylphenoxy)-6-hydroxy-2,4-dimethylbenzoate (15e)



Starting with 1,3-bis(silyl enol ether), **4a** (500 mg, 1.8 mmol), 3-(siloxy)alk-2-en-1-one **14c** (533 mg, 1.8 mmol) and $TiCl_4$ (0.19 mL, 1.8 mmol), **15e** was isolated as a colourless solid (339 mg, 60%), mp. 52-53 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.40 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.10 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 2.58 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.42 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.65 (d, 2 H, *J* = 8.7 Hz, ArH), 6.75 (s, 1 H, ArH), 7.06 (d, 2 H, *J* = 8.7 Hz, ArH), 11.17 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 15.4, 15.7, 13.3 (CH_3), 27.9, 61.7 (CH_2), 111.2 (C), 114.3 (2C), 117.4, 129.9 (2C, CH), 133.8, 137.2, 140.0, 144.1, 156.0, 159.6, 171.5 (C); IR (KBr): $\tilde{\nu}$ = 3030 (w), 2957 (m), 1660 (s), 1505 (s), 1470 (s), 1397 (s), 1373 (s), 1313 (s), 1241 (s), 1220 (s), 1077 (m), 826 (m), 799 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 314.2 (M^+, 29), 268.2 (100); elemental analysis: calcd. (%) for $C_{19}H_{22}O_4$ (314.37): C 72.59, H 7.05; found: C 72.42, H 7.11.

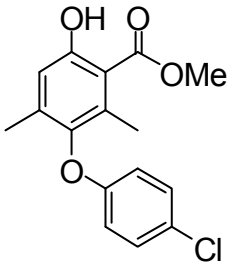
Ethyl 3-(4-ethylphenoxy)-6-hydroxy-2,4,5-trimethylbenzoate (15f)



Starting with 1,3-bis(silyl enol ether), **4f** (500 mg, 1.7 mmol), 3-(siloxy)alk-2-en-1-one **14c** (507 mg, 1.7 mmol) and $TiCl_4$ (0.18 mL, 1.7 mmol), **15f** was isolated as a colourless solid (200 mg, 36%), mp. 49-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.39 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 2.31 (s, 3

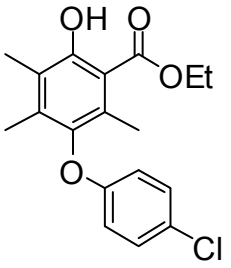
H, CH_3), 2.58 (q, 2 H, J = 7.5 Hz, CH_2), 4.41 (q, 2 H, J = 7.1 Hz, OCH_2), 6.63 (d, 2 H, J = 8.7 Hz, ArH), 7.06 (d, 2 H, J = 8.7 Hz, ArH), 11.51 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 13.9, 14.1, 15.3, 15.6 (CH_3), 27.9, 61.6 (CH_2), 110.3 (C), 114.3 (2C, CH), 123.9 (C), 128.8 (2C, CH), 130.3, 136.9, 138.2, 143.6, 156.3, 157.7, 172.0 (C); IR (KBr): $\tilde{\nu}$ = 2969 (m), 1651 (s), 1599 (m), 1492 (s), 1394 (s), 1320 (s), 1221 (s), 1052 (m), 748 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 328.2 (M^+, 31), 282.2 (100), 254.2 (13), 225.1 (8); HRMS (EI): calcd. for $C_{20}H_{24}O_4$ $[M]^+$: 328.14543; found: 328.14541.

Methyl 3-(4-chlorophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15g)



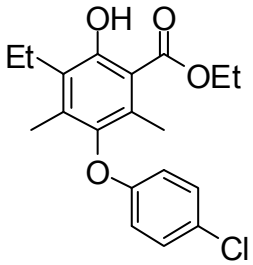
Starting with 1,3-bis(silyl enol ether), **4b** (500 mg, 1.9 mmol), 3-(siloxy)alk-2-en-1-one **14d** (574 mg, 1.9 mmol) and $TiCl_4$ (0.21 mL, 1.9 mmol), **15g** was isolated as a colourless solid (315 mg, 54%), mp. 83 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 6.67 (d, 2 H, J = 9.0 Hz, ArH), 6.76 (s, 1 H, ArH), 7.20 (d, 2 H, J = 9.0 Hz, ArH), 11.10 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 17.1, 52.2 (CH_3), 111.1 (C), 115.7 (2C), 117.6 (CH), 126.3 (C), 129.6 (2C, CH), 133.5, 139.7, 143.6, 156.5, 159.7, 171.7 (C); IR (KBr): $\tilde{\nu}$ = 3431 (m), 2959 (w), 1661 (s), 1486 (s), 1442 (m), 1361 (m), 1326 (s), 1318 (s), 1074 (m), 825 (m), 803 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 306 (M^+, 33), 274 (100), 246 (10), 163.1 (8); elemental analysis: calcd. (%) for $C_{16}H_{15}ClO_4$ (306.74): C 62.65, H 4.93; found: C 62.42, H 4.68.

Ethyl 3-(4-chlorophenoxy)-6-hydroxy-2,4,5-trimethylbenzoate (15h)



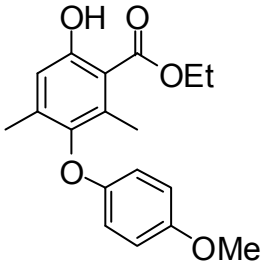
Starting with 1,3-bis(silyl enol ether), **4f** (662 mg, 2.1 mmol), 3-(siloxy)alk-2-en-1-one **14d** (654 mg, 2.1 mmol) and $TiCl_4$ (0.24 mL, 2.1 mmol), **15h** was isolated as a colourless solid (325 mg, 43%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, J = 7.1 Hz, CH_3), 2.06 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.66 (d, 2 H, J = 9.0 Hz, ArH), 7.19 (d, 2 H, J = 9.0 Hz, ArH), 11.52 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 13.7, 14.1, 15.2 (CH_3), 61.6 (CH_2), 110.4 (C), 115.8 (2C, CH), 124.2, 126.1 (C), 129.5 (2C, CH), 130.0, 137.7, 143.2, 156.9, 157.9, 171.8 (C); IR (KBr): $\tilde{\nu}$ = 2978 (w), 1650 (s), 1484 (s), 1398 (m), 1316 (s), 1221 (s), 1033 (m), 805 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 334.1 (M^+, 34), 288.1 (100), 260.1 (20); elemental analysis: calcd. (%) for $C_{18}H_{19}ClO_4$ (334.79): C 64.57, H 5.72; found: C 64.26, H 5.86.

Ethyl 5-ethyl-3-(4-chlorophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15i)



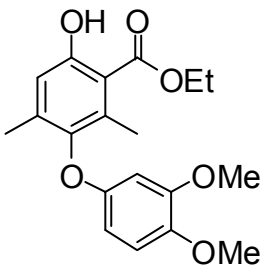
Starting with 1,3-bis(silyl enol ether), **4g** (662 mg, 2.1 mmol), 3-(siloxy)alk-2-en-1-one **14d** (654 mg, 2.1 mmol) and $TiCl_4$ (0.24 mL, 2.1 mmol), **15i** was isolated as a colourless solid (325 mg, 43%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.40 (t, 3 H, J = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.72 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.67 (d, 2 H, *J* = 9.0 Hz, ArH), 7.20 (d, 2 H, *J* = 9.0 Hz, ArH), 11.48 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 13.2, 14.1, 15.3 (CH_3), 19.7, 61.6 (CH_2), 110.6 (C), 115.8 (2C, CH), 126.1 (C), 129.5 (2C, CH), 130.2, 130.3, 137.1, 143.3, 156.8, 157.8, 171.8 (C); IR (KBr): $\tilde{\nu}$ = 2978 (w), 1650 (s), 1484 (s), 1398 (m), 1316 (s), 1221 (s), 1033 (m), 805 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 347.9 (M^+, 51), 301.9 (100), 273.9 (38); elemental analysis: calcd. (%) for $C_{19}H_{21}ClO_4$ (347.9): C 65.42, H 6.07; found: C 65.80, H 6.22.

Ethyl 3-(4-methoxyphenoxy)-6-hydroxy-2,4-dimethylbenzoate (15j)



Starting with 1,3-bis(silyl enol ether), **4a** (589 mg, 2.1 mmol), 3-(siloxy)alk-2-en-1-one **14e** (627 mg, 2.1 mmol) and $TiCl_4$ (0.23 mL, 2.1 mmol), **15j** was isolated as a colourless solid (344 mg, 52%), mp. 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.11 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.43 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.67 (d, 2 H, *J* = 9.1 Hz, ArH), 6.76 (s, 1 H, ArH), 6.80 (d, 2 H, *J* = 9.1 Hz, ArH), 11.67 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.3, 17.2, 55.6 (CH_3), 61.6 (CH_2), 111.1 (C), 114.7 (2C), 115.0 (2C), 117.4 (CH), 133.8, 139.9, 144.2, 152.0, 154.1, 159.5, 171.3 (C); IR (KBr): $\tilde{\nu}$ = 3423 (w), 2993 (m), 1659 (s), 1505 (s), 1405 (s), 1374 (m), 1316 (s), 1217 (s), 1075 (m), 824 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 316.2 (M^+, 58), 270.2 (100), 199.1 (5), 135.1 (14); elemental analysis: calcd. (%) for $C_{18}H_{20}O_5$ (316.34): C 68.34, H 6.37; found: C 68.13, H 6.67.

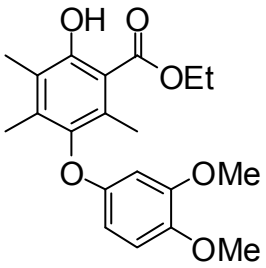
Ethyl 3-(3,4-dimethoxyphenoxy)-6-hydroxy-2,4-dimethylbenzoate (15k)



Starting with 1,3-bis(silyl enol ether), **4a** (500 mg, 1.8 mmol), 3-(siloxy)alk-2-en-1-one **14f** (590 mg, 1.8 mmol) and $TiCl_4$ (0.19 mL, 1.8 mmol), **15k** was isolated as a colourless solid (362 mg, 58%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.11 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3),

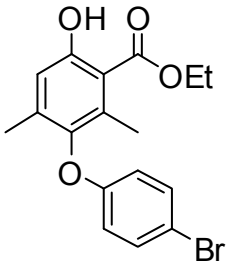
4.43 (q, 2 H, J = 7.1 Hz, OCH_2), 6.05 (dd, 1 H, J = 2.8 Hz, 8.7 Hz, ArH), 6.52 (d, 1 H, J = 2.8 Hz, ArH), 6.68 (d, 1 H, J = 8.7 Hz, ArH), 6.76 (s, 1 H, ArH), 11.17 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.3, 17.2, 55.8, 56.3 (CH_3), 61.6 (CH_2), 100.0, 104.0 (CH), 111.1 (C), 111.7, 117.4 (CH), 133.8, 139.9, 143.7, 144.0, 150.0, 152.4, 159.5, 171.3 (C); IR (KBr): $\tilde{\nu}$ = 3426 (w), 2939 (m), 1659 (s), 1512 (s), 1466 (s), 1450 (s), 1393 (m), 1260 (m), 1211 (s), 1124 (m), 1023 (m), 802 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 346.2 (M^+, 65), 300.2 (100), 285.1 (19), 150.1 (7); elemental analysis: calcd. (%) for $C_{19}H_{22}O_6$ (346.37): C 65.88, H 6.40; found: C 66.10, H 6.04.

Ethyl 3-(3,4-dimethoxyphenoxy)-6-hydroxy-2,4,5-trimethylbenzoate (15l)



Starting with 1,3-bis(silyl enol ether), **4f** (500 mg, 1.7 mmol), 3-(siloxy)alk-2-en-1-one **14f** (562 mg, 1.7 mmol) and $TiCl_4$ (0.18 mL, 1.7 mmol), **15l** was isolated as a colourless solid (215 mg, 35%), mp. 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, J = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.02 (dd, 1 H, J = 2.8 Hz, 8.7 Hz, ArH), 6.52 (d, 1 H, J = 2.8 Hz, ArH), 6.67 (d, 1 H, J = 8.7 Hz, ArH), 11.51 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 13.8, 14.1, 15.3, 55.8, 56.3 (CH_3), 61.6 (CH_2), 100.1, 104.1 (CH), 110.3 (C), 111.7 (CH), 123.9, 130.3, 138.2, 143.64, 143.69, 150.0, 152.7, 157.7, 171.9 (C); IR (KBr): $\tilde{\nu}$ = 3442 (w), 2992 (m), 1643 (s), 1510 (s), 1447 (m), 1393 (m), 1312 (s), 1260 (s), 1212 (s), 1192 (s), 1131 (m), 836 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 360.2 (M^+, 49), 314.2 (100), 215.1 (2), 138.1 (6); elemental analysis: calcd. (%) for $C_{20}H_{24}O_6$ (360.40): C 66.65, H 6.71; found: C 66.47, H 7.14.

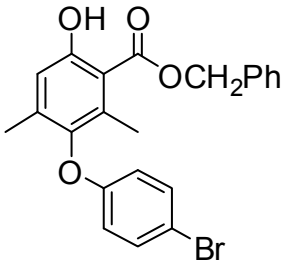
Ethyl 3-(4-bromophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15m)



Starting with 1,3-bis(silyl enol ether), **4a** (400 mg, 1.4 mmol), 3-(siloxy)alk-2-en-1-one **14g** (497 mg, 1.4 mmol) and $TiCl_4$ (0.16 mL, 1.4 mmol), **15m** was isolated as a yellow solid (305 mg, 58%), mp. 50-52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, J = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.63 (d, 2 H, J = 9.0 Hz, ArH), 6.76 (s, 1 H, ArH), 7.34 (d, 2 H, J =9.0 Hz, ArH), 11.19 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.3, 17.1 (CH_3), 61.7 (OCH_2), 111.2, 113.6 (C), 116.0 (CH_{Ar}), 117.6 (C), 132.5 (CH_{Ar}),139.5, 143.5, 157.1, 159.7, 171.2 (C); IR (KBr): $\tilde{\nu}$ = 3430 (w), 2995 (m), 1660 (s), 1483 (s), 1373 (s), 1346 (m), 1316 (s),

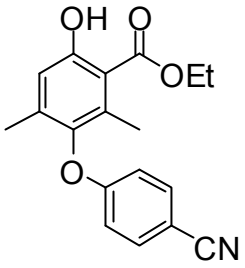
1217 (s), 1067 (m), 1058 (m), 1003 (m), 836 (s), 799 (s), 599 (m), 501 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 366 (M^+,^{81}Br 30), 364(^{79}Br, 30), 320 (100), 318 (99), 163 (8); elemental analysis: calcd. (%) for $C_{17}H_{17}O_4Br$ (365.218): C 55.91, H 4.69; found: C 56.19, H 4.33.

Benzyl 3-(4-bromophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15n)



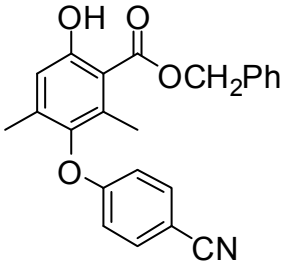
Starting with 1,3-bis(silyl enol ether), **4d** (300 mg, 0.89 mmol), 3-(siloxy)alk-2-en-1-one **14g** (306 mg, 0.89 mmol) and $TiCl_4$ (0.09 mL, 0.89 mmol), **15n** was isolated as a yellow solid (220 mg, 59%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 5.26 (s, 2 H, CH_2), 6.52 (d, 2 H, *J* = 7.1 Hz, ArH), 6.64 (s, 1 H, ArH), 6.71 (d, 2 H, *J* =7.1 Hz, ArH), 7.22-7.35 (m, 5 H, ArH), 11.21 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 17.2 (CH_3), 67.5 (OCH_2), 111.6, 113.6 (C), 116.0, 116.2, 117.6 (CH_{Ar}), 128.5, 128.6, 132.5, 132.7 (CH_{Ar}), 134.9, 139.8, 143.5, 157.0, 159.9, 171.0, 186.2 (C); IR (KBr): $\tilde{\nu}$ = 3033 (w), 2959 (w), 1662 (s), 1428 (s), 1385 (m), 1309 (s), 1229 (s), 1162 (m), 1069 (s), 1005 (m), 828 (s), 697 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 428 (M^+,^{81}Br 93), 426 (^{79}Br, 90), 320 (88), 318 (87), 91 (100); HRMS (EI): calcd. for $C_{22}H_{19Br}O_4$ $[M]^+$: 426.045476; found: 426.046612.

Ethyl 3-(4-cyanophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15o)



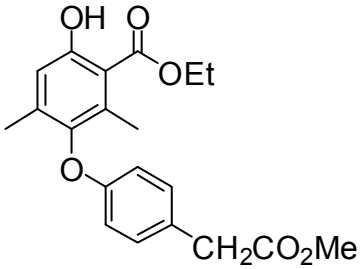
Starting with 1,3-bis(silyl enol ether), **4a** (500 mg, 1.82 mmol), 3-(siloxy)alk-2-en-1-one **14h** (530 mg, 1.82 mmol) and $TiCl_4$ (0.20 mL, 1.82 mmol), **15o** was isolated as a colourless solid (284 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 4.44(q, 2 H, *J* = 7.1 Hz, OCH_2), 6.80 (d, 2 H, *J* = 8.5 Hz, ArH), 6.84 (s, 1 H, ArH), 7.57 (d, 2 H, *J* = 8.5 Hz, ArH), 11.22 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 15.2 (CH_3), 61.8 (OCH_2), 105.1, 111.3 (C), 115.4, 117.8 (CH_{Ar}), 118.8, 133.3 (C), 134.3 (CH_{Ar}),139.0, 142.8, 143.7, 160.1, 161.3, 171.1 (C); IR (KBr): $\tilde{\nu}$ = 3390 (w), 2953 (w), 1738 (s), 1611 (s), 1296 (m), 1223 (s), 1165 (m), 827 (m), 732 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 311 (M^+, 26), 265(100), 135 (4); elemental analysis: calcd. (%) for $C_{18}H_{17}O_4N$ (311.34): C 69.44, H 4.49; found: C 69.32, H 4.35.

Benzyl 3-(4-cyanophenoxy)-6-hydroxy-2,4-dimethylbenzoate (15p)



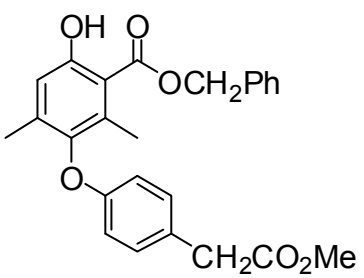
Starting with 1,3-bis(silyl enol ether), **4d** (400 mg, 1.19 mmol), 3-(siloxy)alk-2-en-1-one **14h** (340 mg, 1.19 mmol) and $TiCl_4$ (0.13 mL, 1.19 mmol), **15p** was isolated as a yellow oil (292 mg, 54%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3), 2.22 (s, 3 H, CH3), 5.35 (s, 2 H, OCH_2), 6.76 (d, 2 H, *J* = 9.0 Hz, ArH), 7.20 (s, 1 H, ArH), 7.30-7.37 (m, 5 H, Ph), 7.50 (d, 2 H, *J* = 9.0 Hz, ArH), 11.11 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 15.7 (CH3), 67.5 (CH_2), 105.0, 111.1 (C), 115.3, 118.8 (CH_{Ar}), 118.7 (C), 125.1, 128.1, (CH_{Ar}), 128.6 (C), 133.2 (CH_{Ar}), 134.7, 139.3, 142.7, 160.1, 161.1, 170.8 (C); MS (EI, 70 eV): *m/z* (%): 373 (M^+, 34), 265 (13), 91 (100); elemental analysis: calcd. (%) for $C_{23}H_{19N}O_4$ (373.40): C 73.98, H 5.13, N 3.75; found: C 73.51, H 4.98, N 3.72

Ethyl 3-(4-methylacetatephenoxy)-6-hydroxy-2,4-dimethylbenzoate (15q)



Starting with 1,3-bis(silyl enol ether), **4a** (400 mg, 1.45 mmol), 3-(siloxy)alk-2-en-1-one **14i** (480 mg, 1.45 mmol) and $TiCl_4$ (0.16 mL, 1.45 mmol), **15q** was isolated as a colourless solid (259 mg, 50%), mp. 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.55 (s, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 4.42 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.69 (d, 2 H, *J* = 8.7 Hz, ArH), 6.75 (s, 1 H, ArH), 7.15 (d, 2 H, *J* =8.7 Hz, ArH), 11.17 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 15.3, 17.2 (CH_3), 40.1 (CH_2), 51.9 (OCH_3), 61.6 (OCH_2), 111.1 (C), 114.5, 117.4 (CH_{Ar}), 126.8 (C) 130.4 (CH_{Ar}),136.6, 139.7, 143.7, 157.6, 159.5, 171.3, 172.1 (C); IR (KBr): $\tilde{\nu}$ = 3438 (w), 2987 (s), 1740 (s), 1605 (s), 1505 (s), 1318 (s), 1216 (s), 1143 (s) 1012 (m), 874 (m), 802 (s), 642 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 358 (M^+, 28), 312(100), 253 (13); elemental analysis: calcd. (%) for $C_{20}H_{22}O_6$ (358.39): C 67.03, H 6.19; found: C 67.38, H 6.37.

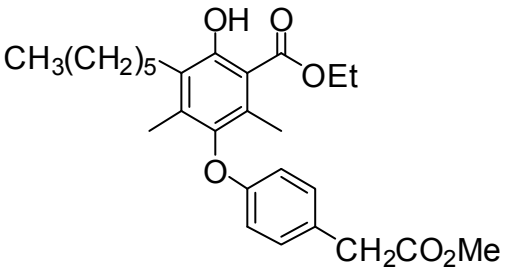
Benzyl 6-hydroxy 3-(4-(2-methoxy-2-oxoethyl)phenoxy)-2,4-dimethylbenzoate (15r)



Starting with 1,3-bis(silyl enol ether), **4d** (500 mg, 1.49 mmol), 3-(siloxy)alk-2-en-1-one **14i** (500 mg, 1.49 mmol) and $TiCl_4$ (0.16 mL, 1.49 mmol), **15r** was isolated as a yellow solid (292 mg, 54%); mp. 66-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.54 (s, 2 H, CH_2),

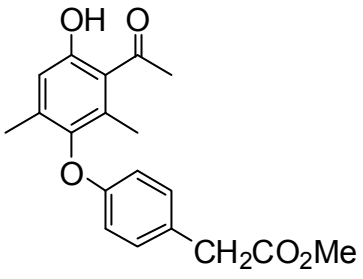
3.68 (s, 3 H, OCH_3), 5.39 (s, 2 H, OCH_2), 6.67 (d, 2 H, J = 8.7 Hz, ArH), 6.76 (s, 1 H, ArH), 7.25 (d, 2 H, J = 8.7 Hz, ArH), 7.35-7.43 (m, 5 H, Ph), 11.11 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 17.2 (CH_3), 40.1 (CH_2), 67.5 (CH_2), 110.9 (C), 114.4, 114.5, 117.5 (CH_{Ar}), 126.9 (C), 128.3, 128.5, 128.6, 130.5, 130.7 (CH_{Ar}), 133.7 134.9, 140.1, 143.7, 157.0, 159.7, 171.1, 172.2; IR (KBr): $\tilde{\nu}$ = 3441 (w), 2955 (m), 1736 (s), 1655 (s), 1612 (m), 1509 (s), 1435 (m), 1387 (s), 1313 (s), 1231 (s), 1161 (s), 1055 (m), 908 (m), 803 (s), 751 (s), 695 (s), 585 (m); elemental analysis: calcd. (%) for $C_{25}H_{24}O_6$ (420.45): C 71.41, H 5.75; found: C 71.51, H 5.38.

Ethyl 3-(4-(2-methoxy-2-oxoethyl)phenoxy)-5-hydroxy-4-nhexyl-2,4-dimethylbenzoate (15s)



Starting with 1,3-bis(silyl enol ether), **4j** (500 mg, 1.39 mmol), 3-(siloxy)alk-2-en-1-one **14i** (460 mg, 1.39 mmol) and $TiCl_4$ (0.15 mL, 1.39 mmol), **15s** was isolated as a yellow oil (292 mg, 54%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, J = 6.9 Hz, CH_3), 1.28-1.32 (m, 8 H, CH_2), 1.39 (t, 3 H, J = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.67 (t, 2 H, J = 8.2 Hz, CH_2), 3.56 (s, 2 H, OCH_2), 3.69 (s, 2 H, CH_2), 4.11(q, 2 H, J = 7.1 Hz, OCH_2), 6.67 (d, 2 H, J = 8.7 Hz, ArH), 7.15 (d, 2 H, J = 8.7 Hz, ArH), 11.42 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 14.0, 15.3 (CH_3), 22.6, 26.5, 29.0, 29.6, 31.7, 40.2 (CH_2), 52.0 (OCH_3), 61.5 (CH_2) , 110.5 (C), 114.6 (CH_{Ar}), 126.7, 128.9, 130.3 (C), 130.4 (CH_{Ar}),137.6, 143.4, 157.3, 157.8, 171.9, 172.3 (C); IR (neat): $\tilde{\nu}$ = 2954 (s), 2928 (s), 1742 (s), 1655 (s), 1609 (m), 1373 (m), 1315 (s), 1222 (s), 1159 (m),1052 (s), 1014 (m), 806 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 442 (M^+, 100), 396(63), 367 (46), 353 (34), 326 (90), 233 (33); elemental analysis: calcd. (%) for $C_{28}H_{34}O_6$ (442.56): C 70.56, H 7.74; found: C 70.21, H 7.30.

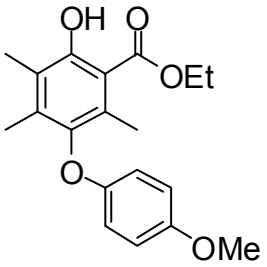
Methyl 2-(4-(3-acetyl-4-hydroxy-2,4-dimethylphenoxy)phenyacetate (15t)



Starting with 1,3-bis(silyl enol ether), **4x** (400 mg, 1.63 mmol), 3-(siloxy)alk-2-en-1-one **14i** (540 mg, 1.63 mmol) and $TiCl_4$ (0.17 mL, 1.6 mmol), **15t** was isolated as a yellow oil (280 mg, 55%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.62 (s, 3 H, CH_3), 3.57 (s, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 6.71 (d, 2 H, J = 8.6 Hz, ArH), 6.75 (s, 1

H, ArH), 7.17 (d, 2 H, J = 8.6 Hz, ArH), 11.91 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 17.2, 33.0 (CH_3), 40.0 (CH_2) 51.9 (OCH_3), 114.4, 118.4 (CH_{Ar}), 120.8, 127.0 (C), 130.5 (CH_{Ar}),131.7, 140.3, 143.7, 156.8, 157.0, 172.0, 186.3, 205.3 (C); IR (neat): $\tilde{\nu}$ = 3390 (w), 2953 (w), 1738 (s), 1611 (s), 1296 (m), 1223 (s), 1165 (m), 827 (m), 732 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 311 (M^+, 26), 265(100), 135 (4); elemental analysis: calcd. (%) for $C_{19}H_{22}O_4$ (314.38): C 72.59, H 7.05; found: C 72.23, H 7.06.

Ethyl 3-(4-methoxyphenoxy)-6-hydroxy-2,4,5-trimethylbenzoate (15u)

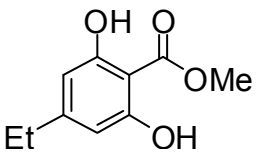


Starting with 1,3-bis(silyl enol ether), **4f** (341 mg, 1.2 mmol), 3-(siloxy)alk-2-en-1-one **14e** (353 mg, 1.2 mmol) and $TiCl_4$ (0.13 mL, 1.2 mmol), **15u** was isolated as a colourless solid (120 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, J = 7.1 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.65 (d, 2 H, J = 9.1 Hz, ArH), 6.78 (d, 2 H, J = 9.1 Hz, ArH), 11.51 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 12.8, 13.1, 14.3, 54.6 (CH_3), 60.5 (CH_2), 109.3 (C), 113.7 (2C), 114.1 (2C, CH), 122.9, 129.3, 137.2, 142.8, 151.3, 153.0, 156.7, 170.9 (C); IR (KBr): $\tilde{\nu}$ = 2969 (m), 1651 (s), 1599 (m), 1492 (s), 1394 (s), 1320 (s), 1221 (s), 1052 (m), 748 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 330.2 (M^+, 44), 284.2 (100); HRMS (EI): calcd. for $C_{19}H_{22}O_5$ $[M]^+$: 330.14618; found: 330.14616.

General procedure for the synthesis of Resorcins a-m:

To a CH_2Cl_2 solution (8 mL) of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene **4a** (860 mg, 3.32 mmol) and of **19** (660 mg, 3.65 mmol) was dropwise added TMSOTf (0.3 mL, 1.66 mmol, 0.5 equiv.) at −78 °C. The reaction mixture was allowed to warm to 20 °C during 6–12 h. After stirring for additional 2–6 h at 20 °C, hydrochloric acid (10%, 25 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($NaSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, heptanes/EtOAc) to give **20a-m.**

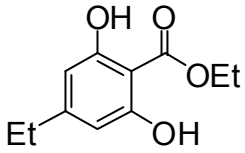
Methyl 4-ethyl-2,6-dihydroxybenzoate (20a)



Starting with 1,3-bis(silyl enol ether), **4b** (880 mg, 3.32 mmol), 3,3-dimethoxypentanoyl chloride **19** (660 mg, 3.65 mmol, 1.2 equiv.) and TMSOTf (0.3 mL, 1.66 mmol, 0.5 equiv.), **20a** was isolated as

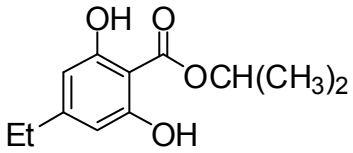
yellow solid (280 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, *J* = 7.6 Hz, CH_3), 2.48 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.99 (s, 3 H, OCH_3), 6.28 (s, 2 H, CH_{Ar}), 9.54 (s, 2 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.2 (CH_2), 52.7 (OCH_3), 97.7 (C), 107.8 (CH), 154.6, 164.5, 169.8 (C); IR (KBr): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 196.0 (M^+, 35), 164.0 (100), 136.0 (21), 121.0 (27); elemental analysis: calcd. (%) for $C_{10}H_{12}O_4$ (196.07): C 61.22, H 6.16; found: C 61.32, H 6.11.

Ethyl 4-ethyl-2,6-dihydroxybenzoate (20b)



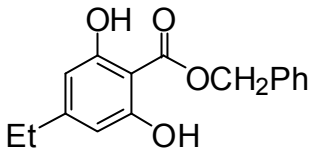
Starting with 1,3-bis(silyl enol ether), **4a** (1.0g, 3.64 mmol), 3,3-dimethoxypentanoyl chloride **19** (650 mg, 4.01 mmol, 1.2 equiv.) and TMSOTf (0.3 mL, 1.82 mmol, 0.5 equiv.), **20b** was isolated as yellow oil (360 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.62 Hz, CH_3), 1.47 (t, 3 H, *J* = 7.14 Hz, 3 H, CH_3), 2.54 (q, 2 H, *J* = 7.59 Hz, CH_2), 4.55 (q, 2 H, *J* = 7.41 Hz, CH_2), 6.34 (s, 2 H, CH_{Ar}), 9.75 (s, 2 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.7 (CH_3), 29.2, 62.4 (CH_2), 97.6 (C), 107.7 (CH_{Ar}), 155.6, 160.6, 172.4 (C); IR (neat): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 210 (M^+, 8%), 164 (100), 141 (56), 97 (12), 75 (24), 43 (21); elemental analysis: calcd. (%) for $C_{11}H_{14}O_4$ (210.09): C 62.85, H 6.71; found: C 62.32, H 6.11.

Isopropyl 4-ethyl-2,6-dihydroxybenzoate (20c)



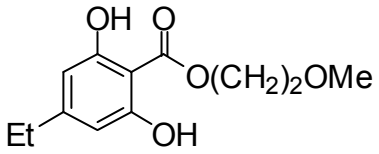
Starting with 1,3-bis(silyl enol ether), **4e** (600 mg, 2.04 mmol), 3,3-dimethoxypentanoyl chloride **19** (450 mg, 2.49 mmol, 1.2 equiv.) and TMSOTf (0.4 mL, 1.02 mmol, 0.5 equiv.), **20c** was isolated as yellow oil (260 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, 3 H, *J* = 7.65 Hz, CH_3), 1.45 (d, 6 H, *J* = 6.27 Hz,, $(CH_3)_2$), 2.53 (q, 2 H, *J* = 7.59 Hz, CH_2), 5.39-5.47 (m, 1 H, CH), 6.32 (s, 1 H, CH_{Ar}) 9.81 (s, 2 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 22.0 (CH_3), 29.6 (CH_2), 71.1 (CH), 98.0 (C), 107.7 (CH_{Ar}) 154.2, 160.8, 169.3 (C); IR (neat): $\tilde{\nu}$ = 3439 (s), 3149 (w), 2978 (s), 1669 (s), 1571 (s), 1378 (m), 1284 (m), 1189 (s), 1088 (s), 1040 (w), 844 (m), 706 (m), 530 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 224 (M^+, 16%), 182 (13), 164 (100), 136 (13), 121 (21); HRMS (EI): calcd. for $C_{12}H_{16}O_4$ $[M]^+$: 224.104661; found: 224.10431.

Benzyl 4-ethyl-2,6-dihydroxybenzoate (20d)



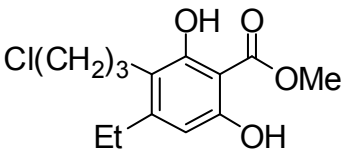
Starting with 1,3-bis(silyl enol ether), **4d** (700 mg, 2.07 mmol), 3,3-dimethoxypentanoyl chloride **19** (450 mg, 2.49 mmol, 1.2 equiv.) and TMSOTf (0.18 mL, 1.03 mmol, 0.5 equiv.), **20d** was isolated as yellow oil (285 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 3 H, *J* = 7.62 Hz, CH_3), 2.52 (q, 2 H, *J* = 7.56 Hz, CH_2), 5.46 (s, 2 H, CH_2), 6.32 (s, 2 H, CH_{Ar}), 7.38-7.41 (m, 5 H, Ph), 9.64 (s, 2 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.1, 67.9 (CH_2), 97.7 (C), 107.8 (CH_{Ar}), 125.1, (C), 126.9, 129.2, 129.2 (CH_{Ar}), 134.0, 154.6, 160.7, 169.3 (C); IR (neat): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; EI-MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 44%), 165 (9), 135 (12), 91 (100), 65 (14), 57 (6); HRMS (EI): calcd. for $C_{16}H_{16}O_4$ $[M]^+$: 272.104117; Found: 272.10431.

2-Methoxyethyl 4-ethyl-2,6-dihydroxybenzoate (20e)



Starting with 1,3-bis(silyl enol ether), **4c** (600 mg, 1.97 mmol), 3,3-dimethoxypentanoyl chloride **19** (425 mg, 2.36 mmol, 1.2 equiv.) and TMSOTf (0.18 mL, 0.98 mmol, 0.5 equiv.), **20e** was isolated as yellow oil (180 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.62 Hz, CH_3), 2.55 (q, 2 H, *J* = 7.56 Hz, CH_2), 3.43 (s, 3 H, OCH_3), 3.72 (t, 2 H, *J* = 4.62 Hz, CH_2), 4.58 (t, 2 H, *J* = 4.68 Hz, CH_2), 6.34 (s, 2 H, CH_{Ar}), 9.66 (s, 2 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.2 (CH_2), 59.0 (OCH_3), 64.4, 69.6 (CH_2), 97.8 (C), 107.8 (CH_{Ar}), 154.6, 160.8, 169.3 (C); IR (neat): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 8%), 225 (100), 207 (8), 183 (21), 141 (56), 97 (12), 75 (24), 43 (21); HRMS (EI): calcd. for $C_{12}H_{16}O_5$ $[M]^+$: 240.09923; found: 240.09954.

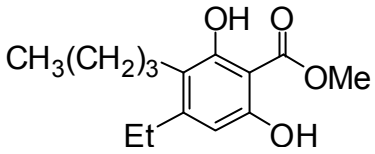
Methyl 3-(3-chloropropyl)-4-ethyl-2,6-dihydrobenzoate (20g)



Starting with 1,3-bis(silyl enol ether), **4u** (600 mg, 1.78 mmol), 3,3-dimethoxypentanoyl chloride **19** (385 mg, 2.13 mmol, 1.2 eq) and $TiCl_4$ (0.19 mL, 1.78 mmol), **20g** was isolated as yellow solid (195 mg, 40 %). mp. 73-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.4 Hz, CH_3), 2.04 (q, 2 H, *J* = 6.7 Hz), 2.76-2.88 (m, 4 H, -CH_2-CH_2-), 3.52 (t, 2 H, *J* =

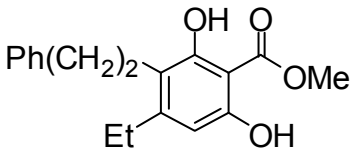
6.6 Hz), 3.93 (s, 3 H, OCH_3), 5.62 (s, 1 H, OH), 6.2 (s, 1 H, CH_{Ar}), 11.99 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ =15.7 (CH_3), 20.0, 29.6, 31.3, (CH_2), 51.9 (OCH_3), 104.7 (C), 109.4 (CH_{Ar}), 111.5, 147.2, 158.5, 163.1, 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3371 (w), 2959 (w), 1612 (s), 1453 (m), 1416 (m), 1262 (s), 1198 (s), 1151 (s), 1098 (w), 983 (m), 856 (m) 765 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 272 (M^+,^{35}Cl, 65%), 274 (^{37}Cl, 6), 240 (6), 209 (77), 205 (100), 178 (32), 77 (6). elemental analysis.: calcd. (%) for $C_{13}H_{17}ClO_4$ (272.72): C 57.25, H 6.28; found: C 57.39, H 6.34.

Methay 3-butyl-4-ethyl-2,6-dihydroxybezoate (20i)



Starting with 1,3-bis(silyl enol ether), **4h** (600 mg, 1.89 mmol), 3,3-dimethoxypentanoyl chloride **19** (409 mg, 2.26 mmol, 1.2 equiv.) and TMSOTf (0.17 mL, 0.94 mmol, 0.5 equiv.), **20i** was isolated as yellow solid (240 mg, 50 %). mp. 66-68 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.17 Hz, CH_3), 1.15 (t, 3 H, *J* = 7.41 Hz, CH_3), 1.13-1.56 (m, 4 H, -CH_2-CH_2-), 2.61 (t, 2 H, *J* = 7.8 Hz, CH_2), 2.83 (q, 2 H, *J* = 7.4 Hz, CH_2), 3.91 (s, 3 H, OCH_3), 5.37 (s, 1 H, OH), 6.22 (s, 1 H, CH_{Ar}) 11.94 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 15.7 (CH_3), 22.6, 22.8, 29.6, 30.9 (CH_2), 51.8 (OCH_3), 104.6 (C), 109.3 (CH_{Ar}), 113.6, 146.5, 158.2, 163.0, 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3410 (w), 2934 (w), 1647 (s), 1575 (s), 1421 (s), 1321 (s), 1284 (m), 1235 (s), 1175 (s), 1151 (s), 1120 (s), 1018 (m), 971 (s), 935 (w), 810 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 27%), 220 (13), 203 (27), 191 (15), 178 (100), 150 (12); elemental analysis: calcd. (%) for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99; found: C 66.73, H 8.11.

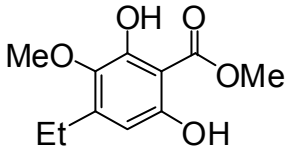
Methyl 4-ethyl-2,6-dihydroxy-3-phenethylbenzoate (20j)



Starting with 1,3-bis(silyl enol ether), **4s** (600 mg, 1.65 mmol), 3,3-dimethoxypentanoyl chloride **19** (360 mg, 1.97 mmol, 1.2 equiv.) and TMSOTf (0.14 mL, 0.82 mmol, 0.5 equiv.), **20j** was isolated as yellow solid (260 mg, 52 %). mp. 116-118 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, 3 H, *J* = 7.44 Hz, CH_3), 2.83 (q, 2 H, *J* = 7.4 Hz, CH_2), 2.88-2.93 (m, 4 H, $(CH_2)_2$), 3.91 (s, 3 H, OCH_3), 6.15 (s, 1 H, CH_{Ar}), 7.18-7.27 (m, 5 H, Ph), 11.98 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ =15.7 (CH_3), 22.5, 29.6, 34.8, (CH_2), 51.9 (OCH_3), 104.7 (C), 109.4 (CH_{Ar}), 112.7 (C), 125.9, 128.4, (CH_{Ph}), 142.5, 146.9, 158.2, 163.1, 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3385 (w), 2974 (w), 1609 (s), 1431 (m), 1272 (s), 1195 (s), 1155 (s), 1101 (m), 1035 (m), 839 (s) 751 (s), 698 (s) cm^{-1}; EI-MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 65%),

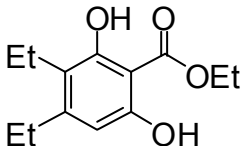
269 (6), 209 (77), 177 (100), 91 (53); elemental analysis: calcd. (%) for $C_{18}H_{20}O_4$ (300.34): C 71.98, H 6.71; found: C 72.01, H 6.87.

Methyl 4-ethyl-2,6-dihyroxy-3-methoxybenzoate (20k)



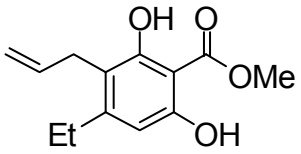
Starting with 1,3-bis(silyl enol ether), **4q** (600 mg, 2.06 mmol), 3,3-dimethoxypentanoyl chloride **19** (440 mg, 2.47 mmol, 1.2 equiv.) and TMSOTf (0.28 mL, 1.03 mmol, 0.5 equiv.), **20k** was isolated as yellow oil (160 mg, 34 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.55 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.77 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.22 (s, 1 H, CH_{Ar}), 11.35 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6 (CH_3), 34.4 (CH_2), 52.6, 60.2 (OCH_3), 113.3 (CH_{Ar}), 119.9, 145.3, 153.4, 168.4, 169.3, 175.9 (C); IR (neat): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 226 (M^+, 71 %), 193 (42), 179(26), 167 (62), 153 (100), 138 (64), 125 (23), 99 (15), 69 (25), 57 (24); HRMS (EI): calcd. for $C_{11}H_{14}O_5$ $[M]^+$: 226.083590; found: 226.08358.

Ethyl 3,4-diethyl-2,6-dihydroxybenzoate (20l)



Starting with 1,3-bis(silyl enol ether), **4g** (500 mg, 1.65 mmol), 3,3-dimethoxypentanoyl chloride **19** (350 mg, 1.98 mmol, 1.2 equiv.) and TMSOTf (0.12 mL, 0.82 mmol, 0.5 equiv.), **20l** was isolated as white solid (237 mg, 60 %); mp. 80-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.17 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.40 (t, 3 H, *J* = 7.14 Hz, CH_3), 2.63 (q, 2 H, *J* = 7.5 Hz, CH_2), 2.85 (q, 2 H, *J* = 7.41 Hz, CH_2), 4.39 (q, 2 H, *J* = 7.14 Hz, CH_2), 5.09 (s, 1 H, OH), 6.20 (s, 1 H, CH_{Ar}), 12.02 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.0, 16.0 (CH_3), 16.1, 29.6, 61.2 (CH_2), 104.8 (C), 109.3 (CH_{Ar}), 114.8, 146.6, 157.7, 162.9, 171.9 (C); IR (KBr): $\tilde{\nu}$ = 3464 (s), 2978 (s), 1612 (s), 1499 (w), 1479 (m), 1424 (s), 1322 (s), 1273 (s), 1179 (s), 1113 (s), 1072 (m), 1007 (s), 841 (s), 764 (s), 622 (m), 581 (w) cm^{-1}; MS (CI, isobutane): 239 $[(M+1)^+]$; elemental analysis: calcd. (%) for $C_{13}H_{18}O_4$ (238.28): C 65.53, H 7.61; found: C 65.54, H 7.49.

Methyl 3-allyl-4-ethyl-2,6-dihydroxybenzoate (20m)

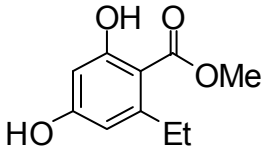


Starting with 1,3-bis(silyl enol ether), **4w** (500 mg, 1.66 mmol), 3,3-dimethoxypentanoyl chloride **19** (360 mg, 1.99 mmol, 1.2 equiv.) and TMSOTf (0.14 mL, 0.83 mmol, 0.5 equiv.), **20m** was isolated as yellow oil (140 mg, 36 %).^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.4 Hz, CH_3), 2.85 (q, 2 H, *J* = 7.4 Hz, CH_2), 3.45 (d, 2 H, *J* = 6.1 Hz, CH_2), 3.93 (s, 3 H, OCH_3), 5.06-5.11 (m, 2 H, CH_2), 5.94-6.05 (m,1 H, CH), 6.27 (s, 1 H, ArH), 12.03 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (CH_3), 27.1, 29.6 (CH_2), 51.9 (OCH_3), 104.6 (C), 109.7 (CH), 110.2 (C), 115.6 (CH_2), 135.9 CH_{Ar}), 147.4, 159.1,162.6, 172.4 (C); IR (neat): $\tilde{\nu}$ = 3408 (w), 2976 (w), 1615 (s), 1414 (s), 1266 (s), 1194 (m), 1154 (s), 1116 (m), 1028 (w), 983 (s), 910 (w), 812 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 236 (M^+, 47), 204 (57), 189 (75), 161 (100), 91 (14), 77 (12); elemental analysis: calcd. (%) for $C_{13}H_{16}O_4$ (236.26): C 66.09, H 6.83; found: C 66.02, H 6.75.

General procedure for the synthesis of Resorsin 21a-l:

To a CH_2Cl_2 solution (5 mL) of 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-butadiene **4b** (500 mg, 1.91 mmol) and of **19** (385 mg, 2.11 mmol) was dropwise added $TiCl_4$ (0.21 mL, 1.91 mmol) at −78 °C. The reaction mixture was allowed to warm to 20 °C during 6–12 h. After stirring for additional 2–6 h at 20 °C, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried ($NaSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/ ethyl acetate) to give **21a**.

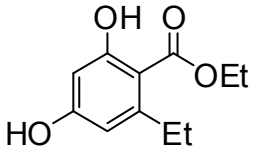
Methyl 2-ethyl-4,6-dihydrobenzoate (21a)



Starting with 1,3-bis(silyl enol ether), **4b** (500 mg, 1.91 mmol), 3,3-dimethoxypentanoyl chloride **19** (385 mg, 2.11 mmol, 1.2 eq) and $TiCl_4$ (0.21 mL, 1.91 mmol), **21a** was isolated as yellow solid (230 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, 3 H, *J* = 7.5 Hz, CH_3), 3.28 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.01 (s, 3 H, OCH_3), 6.08 (s, 1 H, CH_{Ar}), 6.78 (s, 1 H, CH_{Ar}), 12.06 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 28.8 (CH_2), 52.7 (OCH_3), 110.5, 116.0, 155.0, 166.0, 167.6, 170.5, 179.9 (C); IR (KBr): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS

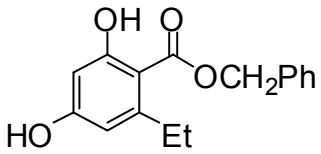
(EI, 70 eV): *m/z* (%) = 196.0 (M^+, 37), 164.0 (100), 136.0 (26), 121.0 (27). HRMS (EI): calcd. for $C_{10}H_{12}O_4$ $[M]^+$: 196.072572; found: 196.07301.

Ethyl 2-ethyl-4,6-dihydrobenzoate (21b)



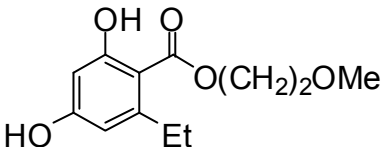
Starting with 1,3-bis(silyl enol ether), **4a** (700 mg, 2.55 mmol), 3,3-dimethoxypentanoyl chloride **19** (550 mg, 3.06 mmol, 1.2 eq) and $TiCl_4$ (0.27 mL, 2.55 mmol), **21b** was isolated as yellow solid (215 mg, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.47 (t, 3 H, *J* = 7.1 Hz, 3 H, CH_3), 2.61 (q, 2 H, *J* = 7.5 Hz, CH_2), 4.49 (q, 2 H, *J* = 7.1 Hz, CH_2), 6.08 (s, 1 H, CH_{Ar}), 6.78 (s, 1 H, ArH), 12.17 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 26.8 (CH_3), 28.8, 62.1 (CH_2), 100.1 (C), 110.1 (CH_{Ar}), 115.1 (C), 116.0 (CH_{Ar}), 154.8, 166.1, 170.1 (C); IR (KBr): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 210 (M^+, 8%), 164 (100), 141 (56), 97 (12), 75 (24), 43 (21); elemental analysis: calcd (%) for $C_{11}H_{14}O_4$ (210.09): C 62.85, H 6.71; found: C 62.32, H 6.11.

Benzyl 2-ethyl-4,6-dihydrobenzoate (21c)



Starting with 1,3-bis(silyl enol ether), **4d** (600 mg, 1.78 mmol), 3,3-dimethoxypentanoyl chloride **19** (390 mg, 2.13 mmol, 1.2 eq) and $TiCl_4$ (0.19 mL, 1.78 mmol), **21c** was isolated as yellow solid (185 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 3 H, *J* = 7.6 Hz, CH_3), 2.25 (s, 2 H, CH_2), 2.84 (q, 2 H, *J* = 7.4 Hz, CH_2), 6.23 (s, 1 H, CH_{Ar}), 6.27 (s, 1 H, CH_{Ar}), 7.25-7.41 (m, 5 H, Ph), 11.70 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 29.1, 67.9 (CH_2), 99.1 (C), 107.8, 128.7 (CH_{Ar}), 125.1, (C), 126.9, 129.2, 129.2 (CH_{Ar}), 134.0, 154.6, 160.7, 169.3 (C); EI-MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 44%), 165 (9), 135 (12), 91 (100), 65 (14), 57 (6). HRMS (EI): calcd. for $C_{168}H_{16}O_4$ $[M]^+$: 272.104117, Found; 272.10431.

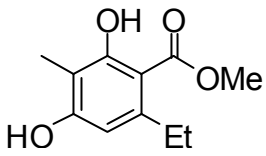
2-Methoxyethyl 2-ethyl-2,6-dihydrobenzoate (21d)



Starting with 1,3-bis(silyl enol ether), **4c** (600 mg, 1.97 mmol), 3,3-dimethoxypentanoyl chloride **19** (430 mg, 2.36 mmol, 1.2 eq) and $TiCl_4$ (0.21 mL, 1.97 mmol), **21d** was isolated as yellow solid (190 mg, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.56 Hz, CH_3), 2.74 (q, 2 H, *J* = 7.5 Hz, CH_2), 3.56 (s, 3 H,

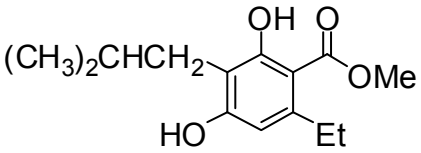
OCH_3), 4.29 (t, 2 H, J = 4.56 Hz, CH_2), 4.57 (t, 2 H, J = 4.59 Hz, CH_2), 6.09 (s, 1 H, CH_{Ar}), 6.78 (s, 1 H, CH_{Ar}), 11.97 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (CH_3), 28.8 (CH_2), 55.7 (OCH_3), 64.5, 70.1 (CH_2), 97.1, 102.0 (C), 110.5, 111.0 (CH), 155.0, 165.9, 169.9 (C); IR (KBr): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 8%), 225 (100), 207 (8), 183 (21), 141 (56), 97 (12), 75 (24), 43 (21); elemental anylysis: calcd (%) for $C_{12}H_{16}O_5$ (240.25): C 59.99, H 6.71; found: C 60.47, H 6.73.

Methyl 6-ethyl-2,4-dihydro-3-methylbenzoate (21e)



Starting with 1,3-bis(silyl enol ether), **4f** (500 mg, 1.82 mmol), 3,3-dimethoxypentanoyl chloride **19** (390 mg, 2.18 mmol, 1.2 eq) and $TiCl_4$ (0.20 mL, 1.82 mmol), **21e** was isolated as yellow solid (250 mg, 65 %). mp. 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, J = 7.44 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.82 (q, 2 H, J = 7.4 Hz, CH_2), 3.90 (s, 3 H, OCH_3), 5.45 (s, 1 H, OH), 6.22 (s, 1 H, CH_{Ar}) 11.97 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.5, 15.6 (CH_3), 29.6 (CH_2), 51.6 (OCH_3), 104.3, 108.5 (C), 109.0 (CH_{Ar}) 146.2, 158.1, 162.2, 172.2 (C); IR (KBr): $\tilde{\nu}$ = 3334 (w), 2960 (w), 1623 (s), 1438 (s), 1263 (s), 1194 (s), 1159 (s), 1109 (s), 1053 (m), 944 (w), 873 (s), 803 (s), 787 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 210 (M^+, 42%), 178 (100), 160 (10), 150 (40), 135 (11), 107 (10), 77 (13); elemental analysis: calcd. (%) for $C_{11}H_{14}O_4$ (210.09): C 62.85, H 6.71; found: C 62.47, H 6.73.

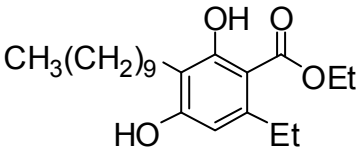
Methyl 6-ethyl-2,4-dihydro-3-isobutylbenzoate (21f)



Starting with 1,3-bis(silyl enol ether), **4i** (600 mg, 1.89 mmol), 3,3-dimethoxypentanoyl chloride **19** (400 mg, 2.26 mmol, 1.2 eq) and $TiCl_4$ (0.21 mL, 1.89 mmol), **21f** was isolated as yellow solid (315 mg, 66 %). mp. 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 6 H, J = 6.63 Hz, $(CH_3)_2$), 1.16 (t, 3 H, J = 7.44 Hz, CH_3), 2.48 (d, 2 H, J = 7.35 Hz, CH_2), 2.85 (q, 2 H, J = 7.41 Hz, CH_2), 3.92 (s, 3 H, OCH_3), 5.08 (s, 1 H, OH), 6.23 (s, 1 H, CH_{Ar}) 11.93 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7, 22.6, 28.1 (CH_3), 29.6, 31.9 (CH_2), 51.8 (OCH_3), 104.6 (C), 109.2 (CH_{Ar}), 112.5, 146.6, 158.3, 163.3, 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3469 (m), 2949 (m), 1643 (s), 1595 (s), 1435 (m), 1411 (m), 1294 (s), 1270 (S), 1194 (m), 1155 (s), 1112 (s), 1022 (m), 982 (s), 824 (s), 740 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 17%), 220 (12), 209 (11), 177

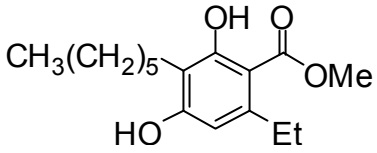
(100), 91 (6), 77 (6); elemental analysis: calcd (%) for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99; found: C 66.20, H 7.79.

Ethyl 6-ethyl-2,4-dihydro-3-octylbenzoate (21g)



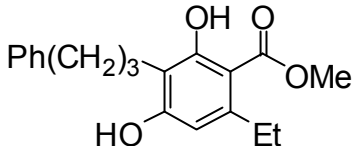
Starting with 1,3-bis(silyl enol ether), **4m** (600 mg, 1.55 mmol), 3,3-dimethoxypentanoyl chloride **19** (330 mg, 1.86 mmol, 1.2 eq) and $TiCl_4$ (0.17 mL, 1.55 mmol), **21g** was isolated as yellow oil (265 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 6.93 Hz, CH_3), 1.17 (t, 3 H, *J* = 7.4 Hz, CH_2), 1.25-1.30 (m, 14 H, $(CH_2)_7$), 1.41 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.86 (q, 2 H, *J* = 7.11 Hz, CH_2), 4.40 (q, 2 H, *J* = 7.14 Hz, CH_2), 5.75 (s, 1 H, OH), 6.21 (s, 1 H, CH_{Ar}), 12.03 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1, 16.0 (CH_3), 22.6, 22.9, 28.8, 29.3, 29.5, 29.7, 29.8, 31.9, 61.2 (CH_2), 104.7 (C), 109.3 (CH_{Ar}), 113.7, 146.5, 158.1, 163.0, 172.0 (C); IR (neat): $\tilde{\nu}$ = 3407 (w), 2972 (m), 1615 (m), 1414 (s), 1266 (s), 1156 (s), 1117 (s), 1029 (w), 810 (m)m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 322 (M^+, 19), 276 (18), 259 (19), 178 (100), 151 (51); elemental analysis: calcd (%) for $C_{19}H_{30}O_4$ (322.44): C 70.77, H 9.38; found: C 71.02, H 9.44.

Methyl 6-ethyl-3-hexyl-2,4-dihydrobenzoate (21i)



Starting with 1,3-bis(silyl enol ether), **4k** (500 mg, 1.45 mmol), 3,3-dimethoxypentanoyl chloride 19 (320 mg, 1.74 mmol, 1.2 eq) and $TiCl_4$ (0.16 mL, 1.45 mmol), **21i** was isolated as yellow oil (220 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.11 Hz, CH_3), 1.15 (t, 3 H, *J* = 7.44 Hz, CH_3), 1.26-1.33 (m, 8 H, $(CH_2)_4$), 2.61 (t, 2 H, *J* = 7.86 Hz, CH_2), 2.83 (q, 2 H, *J* = 7.41 Hz, CH_2), 5.75 (s, 1 H, OH), 6.22 (s, 1 H, CH_{Ar}), 11.95 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.7 (CH_3), 22.6, 22.9, 28.8, 29.5, 29.6, 31.8, 61.2 (CH_2), 104.7 (C), 109.3 (CH_{Ar}), 113.8, 146.5, 158.3, 162.9, 172.5 (C); IR (neat): $\tilde{\nu}$ = 3407 (w), 2972 (m), 1615 (m), 1414 (s), 1266 (s), 1156 (s), 1117 (s), 1029 (w), 810 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 280 (M^+, 25%), 248 (21), 231 (21), 191 (14), 178 (100), 150 (11); elemental analysis: calcd (%) for $C_{16}H_{24}O_4$ (280.36): C 69.36, H 8.90; found: C 69.31, H 8.89.

Methyl 6-ethyl-2,4-dihydroxy-3-(phenylpropyl)benzoate (21j)

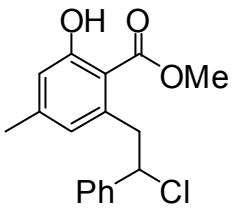


Starting with 1,3-bis(silyl enol ether), **4t** (600 mg, 1.58 mmol), 3,3-dimethoxypentanoyl chloride **19** (340 mg, 1.90 mmol, 1.2 eq) and $TiCl_4$ (0.17 mL, 1.58 mmol), **21j** was isolated as yellow solid (230 mg, 46 %). mp. 69-71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, 3 H, *J* = 7.4 Hz, CH_3), 1.80-1.90 (m, 2 H, CH_2), 2.61-2.69 (m, 4 H, $(CH_2)_2$), 2.81 (q, 2 H, *J* = 7.3 Hz, CH_2), 3.89 (s, 3 H, OCH_3), 5.01 (s, 1 H, OH), 6.17 (s, 1 H, CH_{Ar}), 7.13-7.24 (m, 5 H, Ph), 11.92 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (CH_3), 22.5, 29.5, 30.1, 35.7 (CH_2), 51.8 (OCH_3), 104.7 (C), 109.3 (CH_{Ar}), 113.3 (C), 125.6, 128.2, 128.3, (CH_{Ph}), 142.4, 146.7, 158.1, 163.0, 172.4 (C); IR (KBr): $\tilde{\nu}$ = 3427 (s), 2960 (s), 1670 (s), 1571 (s), 1377 (m), 1257 (s), 1103 (s), 1040 (m), 949 (m), 846 (s) 799 (s), 738 (s), 613 (s), 531 (m) cm^{-1}; EI-MS (EI, 70 eV): *m/z* (%) = 314 (M^+, 25), 282 (6), 216 (3), 178 (100), 150 (6), 91 (15); elemental analysis: calcd (%) for $C_{19}H_{22}O_4$ (314.38): C 72.59, H 7.01; found: C 73.01, H 6.83.

General procedure for the synthesis of salicylates 29a-g and Dihydroisocoumarins:

To a CH_2Cl_2 solution (5 mL) of 1,3-bis(silyl enol ether) **4** (1.0 eq.) and **28** (1.0 eq.) was dropwise added $TiCl_4$ (1.0 eq.) at −78 °C. The reaction mixture was allowed to warm to 20 °C during 6−12 h. After stirring for additional 2−6 h at 20 °C, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried ($NaSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane/ ethyl acetate) to give **29a-g**, **30b-d**, **30j** and **30k**.

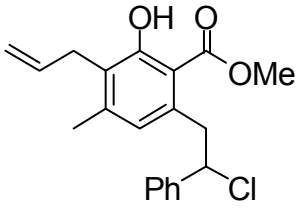
Methyl 2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (29a)



Starting with 1,3-bis(silyl enol ether), **4b** (500 mg, 2.07 mmol), 1-Hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (490 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **29a** was obtained as colourless solid (302 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 3.61 (dd, 2 H, *J* = 7.4, 2.9 Hz, CH_2), 3.93 (s, 3 H, OCH_3), 5.02 (dd, 1 H, *J* = 7.4, 6.2 Hz), 6.41 (s, 1 H, ArH), 6.72 (s, 1 H, ArH), 7.29-7.35 (m, 5 H, Ph), 11.23 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 46.7 (CH_2), 52.3 (OCH_3), 64.1 (CH), 109.5 (C), 117.3, 125.9, 126.9, 128.3, 128.5 (CH_{Ar}), 139.4, 141.6, 145.3, 163.0, 171.3 (C); IR (KBr): $\tilde{\nu}$ = 2955 (w), 1653 (s), 1568 (m), 1452 (s), 1317 (s), 1261 (s), 1207 (s), 1092 (s), 955 (m), 855 (m) 728 (s), 691 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 304 (M^+,

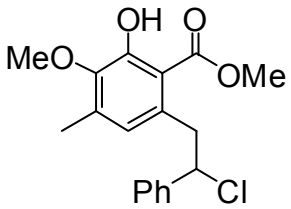
^{35}Cl, 35), 306 (M^+, ^{37}Cl, 13), 268 (32), 237 (86), 208 (24), 179 (100), 165 (31), 125 (45), 119 (21), 89 (15), 77 (13); HRMS (EI): calcd. for $C_{17}H_{17}O_3Cl$ $[M]^+$: 304.087148; found: 304.08607.

Methyl 3-allyl-6-(2chloro-2-phenylethyl)-2-hydroxy-4-methylbenzoate (29b)



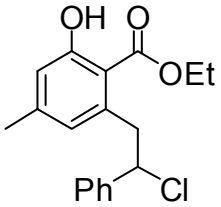
Starting with 1,3-bis(silyl enol ether), **4w** (500 mg, 2.07 mmol), 1-Hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (490 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **29b** was obtained as slight yellow oil (240 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3), 3.41 (d, 2 H, J = 2.5 Hz, CH_2), 3.57 (dd, 2 H, J = 7.6, 5.2 Hz, CH_2), 3.94 (s, 3 H, OCH_3), 4.98- 5.03 (m, 3 H), 5.91 (dd, 1 H, J = 12.4, 3.4 Hz, CH), 6.43 (s, 1 H, ArH), 7.24-7.34 (m, 5 H, Ph), 11.59 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 (CH_3), 30.0, 46.5 (CH_2), 52.1 (OCH_3), 64.0, 80.8 (CH), 108.8 (C), 114.3 (CH), 125.2 (C), 126.1, 126.7, 128.0, 128.5 (CH_{Ar}), 135.1, 136.7, 141.5, 143.6, 160.7, 171.6 (C); IR (neat): $\tilde{\nu}$ = 2920 (m), 2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s) 717 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 344 (M^+, ^{35}Cl, 43), 346 (15), 308 (26), 276 (67), 261 (39), 219 (100), 178 (15), 159 (22), 91 (23); elmental analysis: calcd. (%) for $C_{20}H_{21}O_3Cl$ (344.83): C 69.66, H 6.14; Found: C 69.61, H 6.41.

Methyl 2-(2-chloro-2-phenylethyl)-2-hydroxy-3-methoxy-4-methylbenzoate (29c)



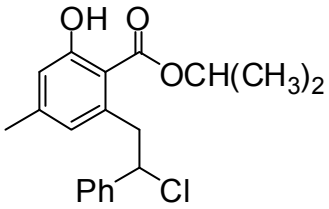
Starting with 1,3-bis(silyl enol ether), **4q** (700 mg, 2.40 mmol), 1-Hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (670 mg, 2.40 mmol) and $TiCl_4$ (0.26 mL, 2.40 mmol), **29c** was obtained as slight yellow oil (350 mg, 44 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (dd, 2 H, J = 7.6, 5.8 Hz, CH_2), 3.70 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.87 (dd, J = 7.6, 5.9 Hz, CH), 6.28 (s, 1 H, ArH), 7.12-7.21 (m, 5 H, Ph), 11.24 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (CH_3), 46.4 (CH_2), 52.4, 59.8 (OCH_3), 64.2 (CH), 110.5 (C), 125.9, 126.9 (CH_{Ar}), 128.2 (C), 128.4 (CH_{Ar}), 133.8, 137.2, 141.6, 145.7, 156.3, 171.4 (C). IR (neat): $\tilde{\nu}$ = 2953 (w), 1658 (s), 1440 (m), 1309 (w), 1252 (s), 1199 (m), 107 (m), 805 (w), 696 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 334 (M^+, ^{35}Cl, 6), 336 (M^+, ^{37}Cl, 2), 284 (59), 266 (100), 208 (27), 251 (20), 236 (30), 165 (23), 77 (20); HRMS (EI) calcd. for $C_{18}H_{19}O_4Cl$ $[M]^+$: 334.096744; Found: 334.09664.

Ethyl 2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (29d)



Starting with 1,3-bis(silyl enol ether), **4a** (600 mg, 2.18 mmol), 1-Hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (610 mg, 2.18 mmol) and $TiCl_4$ (0.24 mL, 2.18 mmol), **29d** was obtained as slight yellow oil (255 mg, 37 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.55 (dd, 1 H, *J* = 13.2, 6.7 Hz, CH_2), 3.75 (dd, 1 H, *J* = 13.2, 7.3 Hz, CH_2), 4.41 (q, 2 H, *J* = 7.1 Hz, OCH_2CH_3), 6.27 (s,1 H, ArH), 6.68 (s, 1 H, ArH), 7.27-7.30 (m, 5 H, Ph), 11.45 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.3 (CH_3), 46.3, 61.8 (CH_2), 63.7 (CH), 109.5 (C), 117.2 (CH_{Ar}), 125.7, 127.0 (CH_{Ar}), 128.2 (C), 128.3 (CH_{Ar}), 139.2, 141.2, 145.0, 163.0, 170.9 (C); IR (neat): $\tilde{\nu}$ = 2980 (w), 1654 (s), 1620 (m), 1570 (w), 1452 (m), 1314 (s), 1258 (s), 1212 (s), 1095 (s), 1014 (w), 852 (w), 738 (m), 696 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 318 (M^+, ^{35}Cl, 27), 320 (M^+, ^{37}Cl, 9), 282 (28), 237 (79), 208 (27), 165 (100), 125 (29), 91 (12), 77 (10). HRMS (EI) calcd. for $C_{18}H_{19}O_3Cl$ $[M]^+$: 318.102296; Found 318.10172.

Isopropyl 2-(2-chloro-2-phenylethyl)-6-hydroxy-4-methylbenzoate (29e)

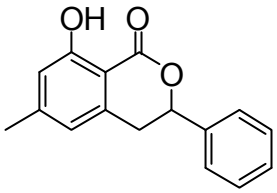


Starting with 1,3-bis(silyl enol ether), **4e** (600 mg, 2.07 mmol), 1-Hydroxy-1-phenyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (570 mg, 2.07 mmol) and $TiCl_4$ (0.22 mL, 2.07 mmol), **29e** was obtained as slight yellow oil (260 mg, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, 6 H, *J* = 6.3 Hz, $(CH_3)_2$), 2.11 (s, 3 H, CH_3), 3.48 (dd, 1 H, *J* = 13.0, 7.5 Hz, CH_2), 3.87 (dd, 1 H, *J* = 13.0, 6.8 Hz, CH_2), 5.04 (t, 1 H, *J* = 7.0 Hz, CH), 5.32-5.40 (m, 1 H, $CH(CH_3)_2$), 6.16 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), 7.24-7.30 (m, 5 H, Ph), 11.45 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 21.9 (CH_3), 46.1 (CH_2), 63.6, 70.1 (CH), 109.5 (C), 117.2, 125.8, 127.3, 128.2 (CH_{Ar}), 128.3, 139.1, 141.0, 144.8, 163.1, 170.5 (C); IR (neat): $\tilde{\nu}$ = 2981 (w), 1650 (s), 1618 (m), 1571 (w), 1452 (m), 1367 (m), 1310 (m), 1259 (s), 1214 (s), 1090 (s), 1041 (w), 1090 (s), 909 (w), 852 (m), 738 (m), 695 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 332 (M^+, ^{35}Cl, 27), 334 (M^+, ^{37}Cl, 9) 296 (15), 254 (25), 237 (92), 208 (28), 179 (19), 165 (100), 125 (64), 91 (17); HRMS (EI): calcd. for $C_{19}H_{21}O_3$ Cl $[M]^+$: 332.117594; found: 332.117337.

General procdure for the synthesis of 3-aryl-3,4-dihydroisocoumarins 30a and 30e-f:

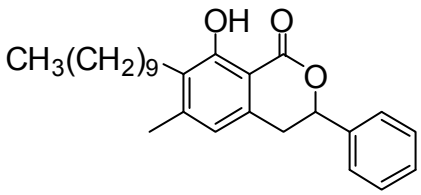
To a THF solution of **29a** (190 mg, 0.62 mmol) silica gel (Merck silica gel 60, 0.063-0.200 mm, 70-230 mesh, 1.5 g) was added and the mixture was stirred at room temperature for 6-14 h. After completion of the reaction (tlc control), THF was removed in *vacuo*. The residue was purified by chromatography (silica gel, heptane / ethyl acetate) to give **30a**. 3-aryl-3,4-dihydroisocoumarins, **30b-d**, **30g-j** and **30k** were formed by [3+3] cyclization to give 6-(2-phenyl-2-chloroethyl)salicylates which subsequently hydrolyzed and underwent a lactonization during the aqueous work-up or silica gel chromatography. This process can be regarded as a domino ′[3+3] cyclization / lactonization′ reaction.

8-Hydroxy-6-methyl-3-phenylisochroman-1-one (30a)



Starting with **29a** (190 mg, 0.62 mmol) and silica gel (Merck silica gel 60, 0.063-0.200 mm, 70-230 mesh, 1.5 g), **30a** was obtained as white solid (110 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 3.07 (dd, 1 H, *J* = 16.5, 3.3 Hz, CH_2), 3.27 (dd, 1 H, *J* = 16.3, 3.3 Hz, CH_2), 5.56 (dd, 1 H, *J* = 12.0, 3.3 Hz), 6.56 (s, 1 H, ArH), 6.74 (s, 1 H, ArH), 7.39-7.45 (m, 5 H, Ph), 10.92 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0 (CH_3), 35.2 (CH_2), 80.7 (CH), 105.9 (C), 116.5, 119.1, 126.1, 128.7, 128.8 (CH_{Ar}), 138.0, 139.0, 148.1, 1662.2, 169.7 (C); IR (KBr): *v* = 3089 (w), 1652 (s), 1455 (m), 1277 (m), 1097 (s), 1060 (s), 912 (w), 845 (s), 798 (s), 699 (s) cm^{-1} ; GC-MS (EI, 70 eV): *m/z* (%) = 254 (M^+, 100), 236 (69), 208 (61), 179 (40), 165 (51), 148 (31), 91 (28), 77 (22); elmental analysis: calcd. (%) for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55; Found: C 75.11, H 5.56.

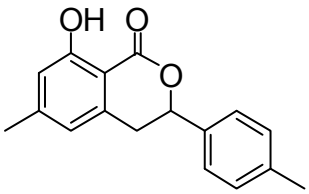
7-Decyl-8-hydroxy-6-methyl-3-phenylisocoroman-1-one (30d)



Starting with 1,3-bis(silyl enol ether), **4o** (700 mg, 1.81 mmol), 1-Hydroxy-1-p-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **28a** (500 mg, 1.81 mmol) and $TiCl_4$ (0.19 mL, 1.81 mmol), **30d** was obtained as colouless solid (320 mg, 54 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.24-1.36 (m, 16 H, $(CH_2)_8$), 2.32 (s, 3 H, CH_3), 2.65 (t, 2 H, *J* = 8.2 Hz, CH_2), 3.02 (dd, 1 H, *J* = 16.5, 3.2 Hz, CH_2), 3.23 (dd, 1 H, *J* = 12.5, 3.2 Hz, CH_2), 5.54 (dd, 1 H, *J* = 12.1, 3.3 Hz, CH), 6.51 (s, 1 H, ArH), 7.25-7.46 (m, 5 H, Ph), 11.21 (s, 1 H, OH).); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.1 (CH_3), 22.6, 28.8, 29.3, 29.5, 29.6, 29.9, 31.8 (CH_2), 80.8 (CH), 105.7, (C), 119.5, 126.0, 128.5, 128.6 (CH_{Ar}), 135.5, 138.2, 145.5, 160.3, 170.2(C); IR (KBr): $\tilde{\nu}$ = 2920 (m),

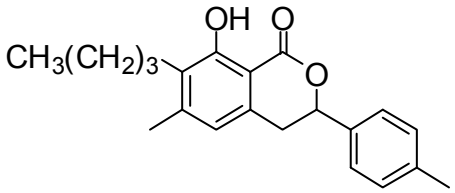
2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s) 717 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 394 (M^+, 67), 306 (46), 291 (18), 264 (100), 249 (15), 192 (19), 91 (11); HRMS (EI): calcd. for $C_{26}H_{34}O_3$ $[M]^+$: 394.171172; found: 394.17200.

8-Hydroxy-6-methyl-3-p-tolylisochroman-1-one (30g)



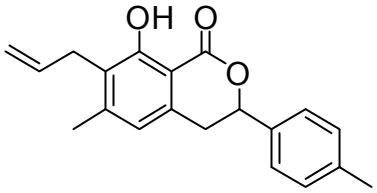
Starting with 1,3-bis(silyl enol ether), **4b** (600 mg, 2.30 mmol), 1-Hydroxy-1-p-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **28b** (670 mg, 2.30 mmol) and $TiCl_4$ (0.25 mL, 2.30 mmol), **30g** was obtained as colouless solid (250 mg, 41 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.03 (dd, 1 H, *J* = 16.5, 3.2 Hz, CH_2), 3.24 (dd, 1 H, *J* = 12.2, 3.4 Hz, CH_2), 5.51 (dd, 1 H, *J* = 12.0, 3.3 Hz, CH), 6.55 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 7.24 (d, 2 H, *J* = 8.1 Hz, ArH), 7.33 (s, 1 H, *J* = 8.1 Hz, ArH), 10.93 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 22.0 (CH_3), 35.1 (CH_2), 80.7 (CH), 105.9 (C), 116.5, 119.1, 127.9, 129.6 (CH_{Ar}), 135.1, 138.7, 139.1, 147.9, 147.9, 162.2, 169.8 (C); IR (KBr): $\tilde{\nu}$ = 2919 (w), 1660 (s), 1628 (s), 1578 (m), 1516 (w), 1349 (m), 1268 (m), 1230 (s), 1202 (s), 1157 (m), 1095 (s), 1058 (s), 975 (m), 854 (s), 814 (s), 732 (m), 695 (s) cm^{-1}; EI-MS (EI, 70 eV): *m/z* (%) = 268 (M^+, 100), 250 (75), 222 (78), 179 (23), 148 (17) 91 (15); elmental analysis: calcd (%) for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; Found: C 75.98, H 6.32.

7-Butyl-8-hydroxy-6-methyl-3-p-tolylisochroman-1-one (30i)



Starting with 1,3-bis(silyl enol ether), **4h** (700 mg, 2.21 mmol), 1-hydroxy-1-p-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **28b** (650 mg, 2.21 mmol) and $TiCl_4$ (0.24 mL, 2.21 mmol), **30i** was obtained as yellow solid (452 mg, 62 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.30 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 2.63 (t, 2 H, *J* = 8.1 Hz, CH_2), 2.97 (dd, 1H, *J* = 16.5, 3.2 Hz,CH_2), 3.20 (dd, 1 H, *J* = 12.1, 3.4 Hz, CH), 5.48 (dd, 1 H, *J* = 12.1, 3.2 Hz, CH), 6.51 (s, 1 H, ArH), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.31 (d, 2 H, *J* = 8.1 Hz, ArH), 11.21 (s, 1 H, OH).); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.1, 21.2 (CH_3), 23.0, 25.6, 31.0, 35.0 (CH_2), 80.8 (CH), 105.8, (C), 119.5, 126.1 (CH_{Ar}), 128.5, (C), 129.3 (CH_{Ar}), 135.3, 135.7, 138.6, 145.5, 160.3, 170.3 (C); IR (KBr): $\tilde{\nu}$ = 2920 (m), 2856 (w), 1665 (s), 1625 (m), 1414 (w), 1290 (s), 1246 (s), 1159 (s), 1115 (m), 1038 (w), 806 (s), 750 (s) 717 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 324 (M^+, 67), 306 (46), 291 (18), 264 (100), 249 (15), 192 (19), 91 (11); HRMS (EI): calcd. for $C_{21}H_{24}O_3$ $[M]^+$: 324.171172; found: 324.17200.

7-Allyl-8-hydroxy-6-methyl-3-p-tolylisochroman-1-one (30j)

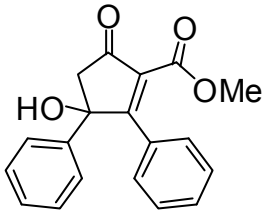


Starting with 1,3-bis(silyl enol ether), **4w** (600 mg, 1.99 mmol), 1-hydroxy-1-p-tolyl-5-(trimethylsilyloxy)hex-4-en-3-one **28b** (581 mg, 1.99 mmol) and $TiCl_4$ (0.22 mL, 1.99 mmol), **30j** was obtained as yellow solid (210 mg, 35 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.99 (dd, 1 H, *J* = 16.6, 3.3 Hz, CH), 3.21 (dd, 1 H, *J* = 12.2, 3.3 Hz, CH), ,3.42 (d, 2 H, *J* = 5.9 Hz, CH_2), 4.81-5.11 (m, 2 H, CH_2), 5.49 (dd, 1 H, *J* = 12.0, 3.3 Hz, CH), 5.84-5.97 (m, 1 H, CH), 6.54 (s, 1 H, CH_{Ar}), 7.19 (d, 2 H, *J* = 7.9 Hz, CH_{Ar}), 7.31 (d, 2 H, *J* = 8.1 Hz, CH_{Ar}), 11.25 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 21.2 (CH_3), 29.8, 34.9 (CH_2), 80.8 (CH), 105.9 (C), 114.8 (CH_2), 119.6 (CH_{Ar}), 123.3 (C), 125.0, 129.6 (CH_{Ar}), 135.1 (CH), 135.2, 136.5, 138.6, 146.3, 160.1, 170.2 (C); IR (KBr): $\tilde{\nu}$ = 3061 (w), 2904 (w), 1659 (s), 1432 (m), 1352 (m), 1271 (s), 1239 (s), 1153 (s), 1070 (m), 1008 (m), 912 (m), 824 (s) 756 (s), 720 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 100), 290 (82), 275 (86), 247 (28), 203 (19), 173 (14), 115 (21), 91 (22); HRMS (EI) calcd. for $C_{20}H_{20}O_3$ $[M]^+$: 308.141298; Found: 308.14070.

General procedure for the synthesis of functionalized 4-hydroxycyclopent-2-en-1-one-2-carboxylates 3a-i and 6:

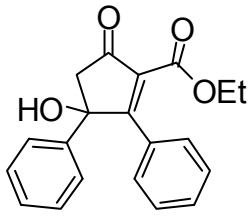
A THF solution (2.5 mL/ mmol of LDA) of diisopropylamine (2.5 equiv.) and *n*-butyllithium (2.5 equiv., solution in *n*-hexane) was stirred at 0 °C for 30 min. The 1,3-dicarbonyl compound was added (1.1 equiv.) and the mixture was stirred for 1 h. To the solution was added the 1,2-diketone (1.0 equiv.) at −78 °C. The solution was stirred for 1 h and was then slowly warmed to 20 °C with stirring. To the solution was added silica gel (0.5 g / mmol of 1,2-diketone) and the mixture was heated to reflux (tlc control). After cooling of the mixture to 20 °C, hydrochloric acid (5 mL, 10%), a saturated aqueous solution of sodium chloride (10 mL), and diethyl ether (50 mL) were added. The organic and the aqueous layer were separated and the latter was repeatedly extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc, heptane).

Methyl 3-hydroxy-5-oxo-2,3-diphenyl-1-ene-1-carboxylate (33a)



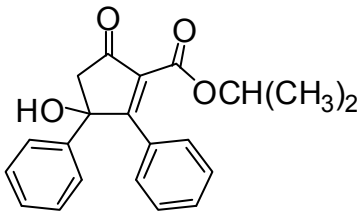
Starting with methyl acetoacetate **31a** (1.12 mL, 10.46 mmol, 1.1 equiv.), diisopropylamine (3.21 mL, 22.82 mmol, 2.5 equiv.), *n*-butyllithium (8.74 mL, 22.82 mmol, 2.5 equiv.) and benzyl **32a** (2.00 g, 9.51 mmol), **33a** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (1.50 g, 51%). Reaction time: 24 h; mp. 129-130 ^{o}C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.98 (d, 1 H, ^{2}J = 18 Hz, HCH-CO), 3.11 (d, 1 H, J = 18 Hz, HCH-CO), 3.76 (s, 3 H, OCH_3), 7.17-7.44 (m, 10 H, Ph); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.4 (CH_3), 55.0 (CH_2-CO), 80.7 (COH), 124.5 ($2CH_{Ph}$), 128.6 (CH_{Ph}), 128.2 ($2CH_{Ph}$), 128.6 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 130.5 (CH_{Ph}), 131.2, 134.3, 142.3, 164.7, 174.1, 200.0 (C); IR (KBr): $\tilde{\nu}$ = 3357 (w), 3060 (w), 2951 (m), 1735 (s), 1686 (s), 1434 (m), 1343 (s), 1229 (s), 1059 (m), 779 (s), 704 (s), 513 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 308.1 (M^+, 22), 276.1 (100), 208 (18), 129 (27), 105 (56); elemental analysis: calcd. (%) for $C_{19}H_{16}O_4$ (308.327): C 74.01, H 5.23; found: C 73.90, H 5.23.

Ethyl 3-hydroxy-5-oxo-2,3-diphenyl-1-ene-1-carboxylate (33b)



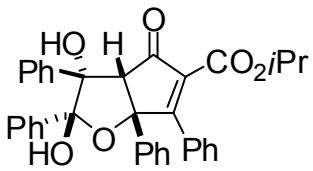
Starting with ethyl acetoacetate **31b** (1.32 mL, 10.46 mmol, 1.1 equiv.), diisopropylamine (3.35 mL, 23.77 mmol, 2.5 equiv.), *n*-butyllithium (9.51 mL, 23.77 mmol, 2.5 equiv.) and benzyl **32a** (2.00 g, 9.51 mmol), **33b** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (1.82 g, 60%). Reaction time: 26 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, 3 H, ^{3}J = 7.1 Hz, CH_3), 2.95 (d, 1 H, ^{2}J = 18.4 Hz, HCH-CO), 3.07 (d, 1 H, ^{2}J = 18.4 Hz, HCH-CO), 4.19 (q, 2 H, ^{3}J = 7.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 55.0 (CO-CH_2), 61.6 (OCH_2), 80.8 (COH), 124.5 ($2CH_{Ph}$), 127.7 (CH_{Ph}), 128.3 ($2CH_{Ph}$), 128.6 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 130.4 (CH_{Ph}), 131.2, 134.2, 142.5, 163.8, 173.9, 199.9 (C); IR (KBr): $\tilde{\nu}$ = 3463 (s), 3062 (w), 2979 (m), 1737 (s), 1712 (s), 1618 (m), 1447 (m), 1461 (m), 1373 (m), 1336 (s), 1211 (s), 1102 (m), 772 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 322 (M^+, 59), 276 (100), 105 (59); elemental analysis: calcd. (%) for $C_{20}H_{18}O_4$ (322.36): C 74.52, H 5.63; found: C 74.43, H 5.36.

Isopropyl 3-hydroxy-5-oxo-2,3-diphenyl-1-ene-1-carboxylate (33c)



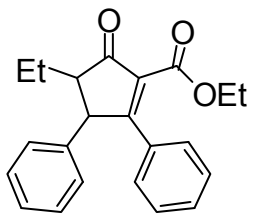
Starting with isopropyl acetoacetate **31c** (1.14 mL, 7.84 mmol, 1.1 equiv.), diisopropylamine (2.51 mL, 17.82 mmol, 2.5 equiv.), *n*-butyllithium (7.13 mL, 17.82 mmol, 2.5 equiv.) and benzyl **32a** (1.50 g, 7.13 mmol), **33c** was isolated by chromatography (heptane/ethyl acetate) as a yellow solid (0.97 g, 41%). Besides, a small amount of **5** (10 mg) was isolated. Reaction time: 20 h; mp. 110-111 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (d, 3 H, J = 6.7 Hz, CH_3), 1.16 (d, 3 H, J = 6.7 Hz, CH_3), 2.98 (d, 1 H, J = 18 Hz, HCH-CO), 3.10 (d, 1 H, J = 18 Hz , HCH-CO), 5.11 (sept, 1 H, J = 6.7 Hz, OCH), 5.30 (s, 1 H, OH), 7.10-7.24 (m, 10 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): 21.2, 21.4 (CH_3), 55.0 (CH_2), 69.5 (CH), 80.7 (COH), 124.5 ($2CH_{Ph}$), 127.7 (CH_{Ph}), 128.2 ($2CH_{Ph}$), 128.6 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 130.2 (CH_{Ph}), 131.2, 134.3, 142.5, 163.4, 173.5, 199.8 (C); IR (KBr): $\tilde{\nu}$ = 3373 (w), 2983 (m), 1718 (s), 1679 (s), 1610 (s), 1450 (m), 1371 (s), 1323 (s), 1228 (m), 1095 (s), 1005 (s), 773 (m), 510 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 336.2 (M^+, 24), 276.1 (100), 129.1 (33), 105.1 (76), 77.1 (26); HRMS (EI): calcd. for $C_{21}H_{20}O_4$ $[M]^+$: 336.135023; found: 336.13561.

35: Compound 5 was isolated as a side-product during the synthesis of (33c)



Formed as side with **33c**. ^{1}H NMR (300 MHz, $CDCl_3$): 1.12 (d, 3 H, ^{3}J = 6.2 Hz, CH3), 1.14 (d, 3 H, ^{3}J = 6.2 Hz, CH3), 2.11 (s, 1 H, OH), 2.75 (s, 1 H, CH), 4.37 (s, 1 H, OH), 5.11 (sept, 1 H, ^{3}J = 6.2 Hz, CH), 7.29-7.52 (m, 20 H, Ph); MS (CI, isobutane): 547.3 ($[M+1]^+$); elemental analysis: calcd (%) for $C_{35}H_{30}O_6$ (546.619): C 76.90, H 5.54; found: C 76.81, H 5.49.

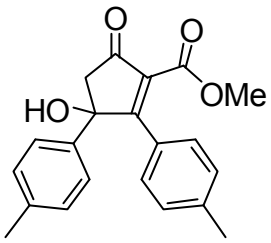
Ethyl 4-ethyl-5-oxo-2,3-diphenylcyclopent-1-enecarboxylate (33d)



Starting with ethyl 3-oxohexanoate **31d** (1.68 mL, 10.46 mmol, 1.1 equiv.), diisopropylamine (3.35 mL, 23.77 mmol, 2.5 equiv.), *n*-butyllithium (9.51 mL, 23.77 mmol, 2.5 equiv.) and benzil **32a** (2.00 g, 9.51 mmol), **33d** was isolated by chromatography (heptane/ethyl acetate) as a colourless solid (1.82 g, 55%). Reaction time: 24 h; mp. 97-98 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, 3 H, ^{3}J = 8.2 Hz, CH_3), 1.18 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 1.81 (m, 2 H, CH_2), 2.68 (t, 1 H, ^{3}J = 7.9 Hz, CH), 4.25 (q, 2 H, ^{3}J = 6.1 Hz, OCH_2), 7.22-7.27 (m, 10 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.5 (CH_3), 19.8

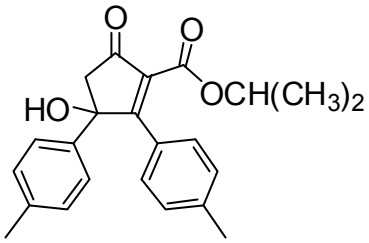
(CH_2), 61.9 (CH_2), 64.2 (CH), 84.9 (COH), 126.0 ($2CH_{Ph}$), 128.5 (CH_{Ph}), 128.7 ($2CH_{Ph}$), 129.1 ($2CH_{Ar}$), 129.2 ($2CH_{Ph}$), 130.8 (CH_{Ph}), 131.4, 134.0, 143.8, 164.6, 173.1, 201.1 (C); IR (KBr): $\tilde{\nu}$ = 3390 (w), 2978 (m), 1719 (s), 1687 (s), 1629 (m), 1447 (s), 1373 (s), 1341 (s), 1247 (s),1183 (m), 1019 (s), 963 (m), 699 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 350.2, (M^+, 7), 321.1 (31), 304.1 (100), 275.1 (38), 129.1 (24), 105.1 (54), 77 (23); HRMS (EI): calcd. for $C_{22}H_{22}O_4$ $[M]^+$: 350.150583; found: 350.15126.

Methyl 3-hydroxy-5-oxo-2,3-di(p-methylphenyl)-1-ene-1-carboxylate (33e)



Starting with methyl acetoacetate **31a** (0.74 mL, 6.92 mmol, 1.1 equiv.), diisopropylamine (2.21 mL, 15.72 mmol, 2.5 equiv.), *n*-butyllithium (6.29 mL, 15.72 mmol, 2.5 equiv.) and 4,4-dimethylbenzil **32b** (1.50 g, 6.29 mmol), **33e** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (0.75 g, 36%). Reaction time: 20 h; mp. 41-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 2.94 (d, 1 H, ^2J = 18 Hz, HCH-CO), 3.07 (d, 1 H, ^2J = 18 Hz, HCH-CO), 3.78 (s, 3 H, OCH_3), 7.07 (d, 2 H, ^3J = 8.5 Hz, ArH), 7.10 (d, 2 H, ^3J = 8.5 Hz, ArH), 7.17 (d, 2 H, ^3J = 8.0 Hz, ArH), 7.30 (d, 2 H, ^3J = 8.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.4 (CH_3), 52.5 (OCH_3), 55.3 (OCH_2), 80.8 (COH), 124.3 ($2CH_{Ar}$), 128.1 (C), 128.8 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 133.4, 137.6, 139.9, 141.3, 164.5, 173.9, 199.6 (C); IR (KBr): $\tilde{\nu}$ = 1739 (s), 1608 (s), 1511 (m), 1435 (m), 1341 (s), 1216 (s), 1015 (m), 820 (s); MS (EI, 70 eV): *m/z* (%): 336 (M^+, 44), 304 (98), 236 (37), 206 (48), 143 (40), 119 (100), 91 (38); elemental analysis: calcd. (%) for $C_{21}H_{20}O_4$ (360.387): C 74.94, H 5.99; found: C 74.56, H 6.08.

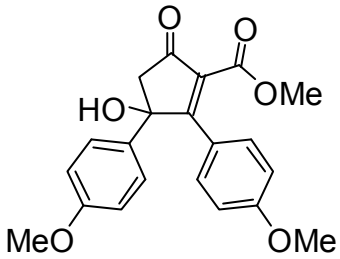
Isopropyl 3-hydroxy-5-oxo-2,3-di(p-methylphenyl)-1-ene-1-carboxylate (33f)



Starting with isopropyl acetoacetate **31c** (1.0 mL, 6.92 mmol, 1.1 equiv.), diisopropyamine (2.44 mL, 17.31 mmol, 2.5 equiv.), *n*-butyllithium (6.92 mL, 17.31 mmol, 2.5 equiv.) and 4,4-dimethylbenzil **32b** (1.50 g, 6.29 mmol), **33f** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (1.20 g, 53%). Reaction time: 22 h; mp. 118-119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, 3 H, ^3J = 7.6 Hz, CH_3), 1.20 (d, 3 H, ^3J = 6.2 Hz, CH_3), 2.29 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.92 (d, 1 H, ^2J = 18.4 Hz, HCH-CO), 3.04 (d, 1 H, ^2J = 18.4 Hz, HCH-CO), 5.11-5.18 (m, 1 H, OCH), 7.05 (d, 2 H, ^3J = 7.7 Hz, ArH), 7.12 (d, 2 H, ^3J = 8.3 Hz, ArH), 7.15 (d,

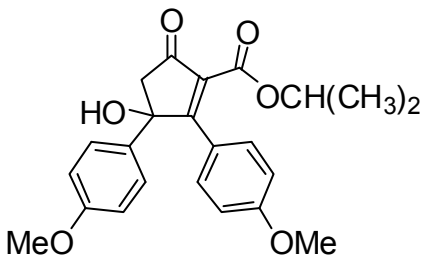
2 H, ^{3}J = 8.0 Hz, ArH), 7.29 (d, 2 H, ^{3}J = 8.3 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.44, 21.48, 21.6 (CH_3), 55.3 (CH2), 69.4 (CH), 80.7 (COH), 124.4 ($2CH_{Ar}$), 128.3 (C), 128.8 ($2CH_{Ar}$), 129.0 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 134.1, 137.3, 140.0, 140.9, 163.7, 172.9, 199.9 (C); IR (KBr): $\tilde{\nu}$ = 3428 (w), 2978 (m), 1727 (s), 1693 (s), 1601 (s), 1512 (m), 1326 (s), 1224 (s), 1100 (s); GC-MS (EI, 70 eV): *m/z* (%): 364.2 (M^+, 36), 304.1 (98), 236.1 (35), 206.1 (48), 119.1 (100), 91.1 (39); elemental analysis: calcd. (%) for $C_{23}H_{24}O_4$ (364.44): C 75.80, H 6.63; found: C 75.74, H 6.74.

Methyl 3-hydroxy-5-oxo-2,3-di(p-methoxyphenyl)-1-ene-1-carboxylate (33g)



Starting with methyl acetoacetate **31a** (0.87 mL, 8.13 mmol, 1.1 equiv.), diisopropylamine (2.60 mL, 18.47 mmol, 2.5 equiv.), *n*-butyllithium (7.38 mL, 18.47 mmol, 2.5 equiv.) and 4,4-dimethoxybenzil **32c** (2.00 g, 7.39 mmol), **33g** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (0.85 g, 32%). Reaction time: 20 h; mp. 50-52 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.91 (d, 1 H, *J* = 18 Hz, HCH-CO), 3.06 (d, 1 H, *J* = 18 Hz , HCH-CO), 3.77 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.78 (d, 2 H, *J* = 8.8 Hz, ArH), 6.88 (d, 2 H, *J* = 9.1 Hz, ArH), 7.24 (d, 2 H, *J* = 8.2 Hz, ArH), 7.34 (d, 2 H, *J* = 9.1 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.4 (OCH_3), 55.2 (2C, OCH_3), 55.5 (CH_2-CO), 80.6 (COH), 114.0 ($2CH_{Ar}$), 114.2 ($2CH_{Ar}$), 123.2 (C), 125.6 ($2CH_{Ar}$), 131.1, 132.1 (CH_{Ar}) ($2CH_{Ar}$), 135.3, 158.6, 161.6, 164.9, 173.1, 199.5 (C); IR (KBr): $\tilde{\nu}$ = 3451 (w), 2839 (m), 1735 (s), 1603 (s), 1437 (m), 1137 (s), 1029 (s), 835 (s), 779 (m); MS (EI, 70 eV): *m/z* (%): 368.1 (M^+, 22), 336.1 (27), 219.0 (21), 152.0 (78), 135 (100), 77 (29); HRMS (EI): calcd. for $C_{21}H_{20}O_6$ $[M]^+$: 368.125102; found: 368.12544.

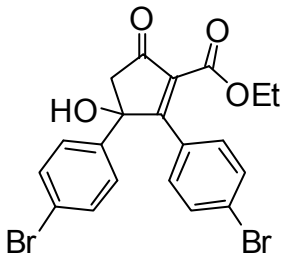
Isopropyl 3-hydroxy-5-oxo-2,3-di(p-methoxyphenyl)-1-ene-1-carboxylate (33h)



Starting with isopropyl acetoacetate **31c** (1.18 mL, 8.13 mmol, 1.1 equiv.), diisopropylamine (2.60 mL, 18.47 mmol, 2.5 equiv.), *n*-butyllithium (7.38 mL, 18.47 mmol, 2.5 equiv.) and 4,4-dimethoxybenzil **32c** (2.00 g, 7.39 mmol), **33h** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (1.36 g, 47%). Reaction time: 20 h; mp. 117-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, 3 H, ^{3}J = 6.2 Hz, CH_3), 1.17 (d, ^{3}J = 6.2 Hz, 3 H, CH_3), 2.82 (d, 1 H, ^{2}J = 18.4 Hz, HCH-CO), 2.95 (d, 1 H, ^{2}J = 18.4 Hz, HCH-CO), 3.68

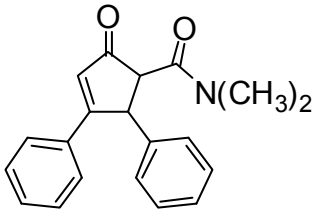
(s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 5.07-5.14 (m, 1 H), 6.68 (d, 2 H, ^3J = 9.0 Hz, ArH), 6.79 (d, 2 H, ^3J =8.9 Hz, ArH), 7.19 (d, 2 H, ^3J = 9.0 Hz, ArH), 7.26 (d, 2 H, ^3J = 8.9 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.6 (CH_3), 55.2, 55.3 (OCH_3), 55.4 (CH_2), 69.4 (OCH), 80.5 COH), 113.8 (2CHAr), 114..1 (2CHAr),123.4 (C),125.7 (2CHAr), 131.19 (2CHAr), 133.2, 135.3, 158.9, 161.4, 164.2, 171.8, 199.8 (C); IR (KBr): $\tilde{\nu}$ = 3431 (w), 2984 (m), 1740 (s), 1724 (s), 1516 (m), 1264 (s), 1242 (s), 1108 (s), 1063 (m), 817 (s), 788 (m), cm^{-1}; MS (CI, isobutene): 397 [$(M+1)^+$]; elemental analysis: calcd (%) for $C_{23}H_{24}O_6$ (396.439): C 69.68, H 6.10; found: C 59.56, H 6.29.

Ethyl 3-hydroxy-5-oxo-2,3-di(p-bromophenyl)-1-ene-1-carboxylate (33i)



Starting with ethyl acetoacetate **31b** (583 mg, 4.48 mmol, 1.1 equiv.), diisopropyamine (1.43 mL, 10.2 mmol, 2.5 equiv.), *n*-butyllithium (4.1 mL, 10.2 mmol, 2.5 equiv.) and 4,4-dibromobenzil **32d** (1.50 g, 4.1 mmol), **33i** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (810 mg, 42%). Reaction time: 24 h; mp. 139-149 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, ^3J = 7.6 Hz, CH_3), 2.97 (d, 1 H,^{2} J = 18 Hz, HCH-CO), 3.07 (d, 1 H, ^2J = 18 Hz, HCH-CO), 4.25 (q, 2 H, ^3J = 7.6 Hz, CH_2), 7.13 (d, 2 H, ^3J = 9.1 Hz , ArH), 7.26 (d, 2 H, ^3J = 8.5 Hz, ArH), 7.41 (d, 2 H, ^3J = 8.5 Hz, ArH), 7.48 (d, 2 H, ^3J = 8.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 55.3 (CH_2), 62.4 (OCH_2), 80.9 (COH), 122.4, 125.8 (C), 126.8 ($2CH_{Ar}$), 130.3 (C), 130.6 ($2CH_{Ar}$), 132.1 ($2CH_{Ar}$), 132.4 ($2CH_{Ar}$), 134.9, 141.7, 164.1, 199.8 (C)); IR (KBr): $\tilde{\nu}$ = 3481 (w), 1744 (s), 1486 (m), 1336 (s), 1217 (m), 1072 (s), 1010 (s), 825 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 482 (M^+, ^{81}Br, 10), 479.9 (M^+, ^{79}Br, 17), 433.9 (57), 281.1 (42), 207 (100), 185 (49); elemental analysis: calcd (%) for $C_{20}H_{16}O_4Br_2$ (479.95): C 50.01, H 3.36; found: C 49.67, H 3.40.

N,N-Dimethyl-5-oxo-2,3-diphenylcyclopent-3-enecarboxamide (36)



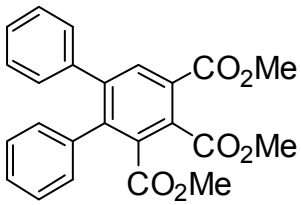
Starting with *N,N*-diethylacetamide (0.82 mL, 5.22 mmol, 1.1 equiv.), diisopropylamine (1.61 mL, 11.41 mmol, 2.5 equiv.), *n*-butyllithium (4.36 mL, 11.4 mmol, 2.5 equiv.) and benzil (1.00 g, 4.75 mmol), **6** was isolated by chromatography (heptane/ethyl acetate) as a slightly yellow solid (725 mg, 43%). Reaction time: 17 h; mp. 117-118 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00 (t, 3 H, ^3J = 6.4 Hz, CH_3), 1.16

(t, 3 H, ^3J = 7.3 Hz, CH_3), 3.11-3.50 (m, 2 H), 3.55-3.85 (m, 2 H). 3.85 (s, 1 H, CH-C=O), 6.77 (s, 1 H, CH=C), 7.25-7.68 (m, 10 H, Ph); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.9, 14.3 (CH_3), 41.3, 42.7 (CH_2), 63.4 (CH), 82.3 (COH), 124.6 ($2CH_{Ph}$), 127.5 (CH_{Ph}), 127.8 (CH_{Ph}), 128.4 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 129.7 ($2CH_{Ph}$), 130.9 (CH_{Ph}), 131.2 (CH), 144.2, 167.7, 176.6, 199.7 (C); IR (KBr): $\tilde{\nu}$ = 3399 (w), 2978 (m), 1691 (s), 1624 (s), 1571 (m), 1449 (s), 1309 (s), 1223 (s), 1339 (m), 772 (s), 6004 (s) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 349.2 (M^+, 33), 331.1 (23), 249.1 (100), 105.0 (43), 72.1 (26); HRMS (EI): calcd. for $C_{22}H_{23}O_3N_1$ $[M]^+$: 349.166663; found: 349.16725.

General procedure for the cyclization of functionalized 4-hydroxycyclopent-2-en-1-ones with dimethyl acetylenedicarboxylate (DMAD):

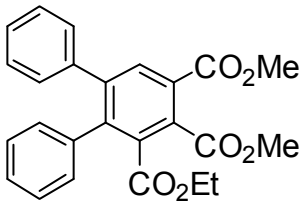
To a toluene solution (25 mL) of the 4-hydroxycyclopent-2-en-1-one (1.0 equiv.) was added dimethyl acetylenedicarboxylate (DMAD, 8.0 equiv.) and *p*-toluenesulfonic acid (PTSA, 5 mol-%). The mixture was heated at reflux (tlc control). After cooling of the reaction mixture to 20 °C, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc, heptane) to give **34a-i**.

1,2,3-trimethyl-4,5-diphenylbenzene-1,2,3-tricarboxylate (34a)



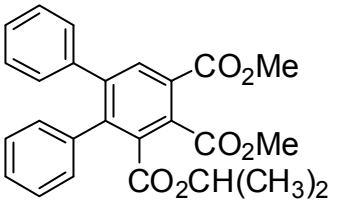
Starting with **33a** (500 mg, 1.62 mmol), DMAD (1.60 mL, 12.96 mmol) and PTSA (12 mg, 5 mol-%), **34a** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (302 mg, 46%); mp. 143-144 °C. Reflux time: 8h; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 7.0-7.21 (m, 10 H, Ph), 8.03 (s, 1 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.8, 50.9, 51.0 (OCH_3), 125.9, 126.0 (CH_{Ph}), 126.1 ($2CH_{Ph}$), 126.6 ($2CH_{Ph}$), 126.7 ($2CH_{Ph}$), 127.6 ($2CH_{Ph}$), 130.1, 130.8 (C), 132.3 (CH_{Ph}), 135.4, 137.0, 139.1, 140.6, 141.7, 163.9, 165.8, 166.9 (C); IR (KBr): $\tilde{\nu}$ = 1743 (s), 1728 (s), 1588 (m), 1429 (s), 1299 (s), 1244 (s), 1156 (m), 1008 (s), 765 (m), 703 (s); MS (EI, 70 eV): *m/z* (%): 404.1 (M^+, 68), 373.1 (100), 226.0 (11), 105 (22); HRMS (EI): calcd. for $C_{24}H_{20}O_6$ $[M]^+$: 404.125328; found: 404.12544.

3-Ethyl-1,2-dimethyl-4,5-diphenylbenzene-1,2,3-tricarboxylate (34b)



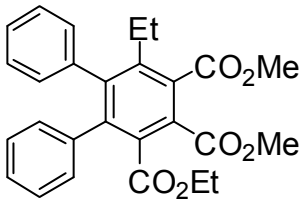
Starting with **33b** (400 mg, 1.24 mmol), DMAD (1.21 mL, 11.84 mmol, 8 equiv.) and PTSA (5 mol-%), **34b** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (293 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, ^{3}J = 7.1 Hz), 3.92 (s, 6 H, OCH_3), 3.95 (q, 2 H, ^{3}J = 7.1 Hz), 7.01-7.21 (m, 10 H, Ph), 8.03 (s, 1 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3 (CH_3), 52.7, 52.8 (OCH_3), 61.6 (OCH_2), 127.2, 127.5 (CH_{Ph}), 127.7 ($2CH_{Ph}$), 127.8 ($2CH_{Ph}$), 128.3 (C), 129.4 ($2CH_{Ph}$), 125.5 ($2CH_{Ph}$), 132.1 (CH_{Ph}), 132.6, 134.3, 137.4, 138.9, 142.5, 143.5, 165.7, 167.3, 167.8 (C); IR (KBr): $\tilde{\nu}$ = 1745 (s), 1726 (s), 1429 (m), 1337 (m), 1243 (s), 1161 (m), 1022 (m), 765 (m), 703 (s); MS (EI, 70 eV): *m/z* (%): 418 (M^+, 100), 373 (73), 327 (63), 306 (26), 226 (38), 133 (59), 57 (33); elemental analysis: calcd (%) for $C_{25}H_{22}O_6$ (418.445): C 71.75, H 5.29; found: C 71.64, H 5.04.

3-Isopropyl-1,2-dimethyl-4,5-diphenylbenzene-1,2,3-tricarboxylate (34c)



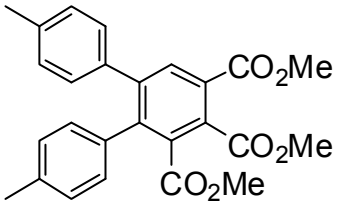
Starting with **33c** (500 mg, 1.48 mmol), DMAD (1.23 mL, 11.84 mmol) and PTSA (5 mol-%), **34c** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (293 mg, 46%). Reflux time: 12 h; mp. 160-161 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (d, 6 H, ^{3}J = 5.8 Hz), 3.92 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.83 (sept, 1 H, ^{3}J = 7.6 Hz), 6.99-7.20 (m, 10 H, Ph), 8.02 (s, 1 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.1 (2C, CH_3), 52.7, 52.8, (OCH_3), 69.5 (CH), 127.2 ($2CH_{Ph}$), 127.5(CH_{Ph}), 127.7 (C), 127.8 ($2CH_{Ph}$), 128.3 (CH_{Ph}), 129.4 ($2CH_{Ph}$), 129.7 ($2CH_{Ph}$), 129.9 (C), 132.5 (CH_{Ph}), 134.5, 137.6, 139.1, 142.1, 143.8, 165.7, 167.0, 168.0 (C); IR (KBr): $\tilde{\nu}$ = 1740 (s), 1723 (s), 1550 (m), 1499 (m), 1429 (s),1326 (s), 1241 (s), 1109 (s), 1000 (s), 910 (m), 700 (s), 552 (m); GC-MS (EI, 70 eV): *m/z* (%): 432.2 (M^+, 100), 373.1 (54), 359.1 (28), 327.1 (55), 256.1 (35), 226.1 (62); elemental analysis: calcd (%) for $C_{26}H_{24}O_6$ (432.47): C 72.20, H 5.59; found: C 72.21, H 5.56.

3-Ethyl-6-ethyl-1,2-dimethyl-4,5-diphenylbenzene-1,2,3-tricarboxylate (34d)



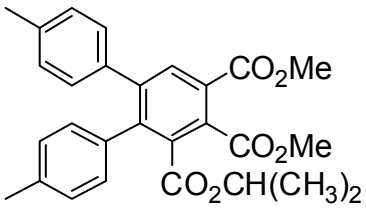
Starting with **33d** (400 mg, 1.14 mmol), DMAD (0.95 mL, 9.13 mmol) and PTSA (5%), **34d** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (165 mg, 33%). Reflux time: 11 h. A small amount of impurity could not be separated. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, ^{3}J = 7.6 Hz, CH_3), 1.17 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 2.53 (q, 2 H, ^{3}J = 6.4 Hz, CH_2), 3.86 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.24 (q, 2 H, ^{3}J = 6.5 Hz, OCH_2), 6.95-7.18 (m, 10 H, Ph); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.2, 13.9 (CH_3), 19.1 (CH_2), 52.6, 52.9 (OCH_3), 61.5 (OCH_2), 125.5 ($2CH_{Ph}$),126.9 (CH_{Ph}), 127.5 (C), 128.0 ($2CH_{Ph}$), 128.8 ($2CH_{Ph}$), 129.6 ($2CH_{Ph}$), 129.7 (C), 130.4 (CH_{Ph}), 131.0, 133.3, 133.7, 137.6, 139.4, 141.8, 163.8, 166.5, 171.8 (C); IR (KBr): $\tilde{\nu}$ = 2950 (m), 1797 (s), 1646 (m), 1541 (s), 1331 (s), 1282 (w), 1232 (s), 1171 (m), 1062 (s), 966 (m), 778 (m), 698 (s); GC-MS (EI, 70 eV): *m/z* (%): 446.2 (M^+, 7), 400.1 (46), 353.1 (100), 239.1 (28).

1,2,3-trimethyl-4,5-di(p-methylphenyl)-benzene-1,2,3-tricarboxylate (34e)



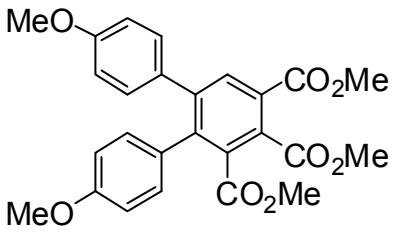
Starting with **33e** (400 mg, 1.18 mmol), DMAD (1.16 mL, 9.51 mmol, 8 equiv.) and PTSA (12 mg, 5 mol-%), **34e** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (340 mg, 86%); mp. 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.49 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH3), 3.91 (s, 3 H, OCH_3), 6.90 (d, 2 H, ^{3}J = 8.2 Hz, ArH), 6.91 (d, 2 H, ^{3}J = 8.2 Hz, ArH), 6.98 (d, 2 H, ^{3}J = 7.8 Hz, ArH), 6.99 (d, 2 H, ^{3}J = 7.8 Hz, ArH), 7.24 (s, 1 H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.2 (CH_3), 52.3, 52.7, 52.9 (OCH_3), 128.3 (C), 128.5 (2CHAr), 128.6 (2CHAr), 129.4 (4CHAr), 131.6 (C), 132.7 (CH_{Ar}), 134.3, 134.4, 136.1, 137.0, 137.2, 142.5, 143.6, 165.9, 167.9, 167.0; IR (KBr): $\tilde{\nu}$ = 1738 (s), 1515 (m), 1433 (s), 1297 (s), 1265 (s), 1222 (s), 1159 (m), 1065 (m), 1000 (s), 779 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 432 (M^+, 100), 401 (82), 385 (21); elemental analysis: calcd (%) for $C_{26}H_{24}O_6$ (432.46): C 72.21, H 5.59; found: C 72.25, H 6.00.

3-Isopropyl-1,2-dimethyl-4,5-di(p-methylphenyl)-benzene-1,2,3-tricarboxylate (34f)



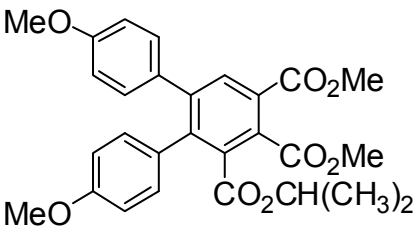
Starting with **33f** (500 mg, 1.37 mmol), DMAD (1.34 mL, 10.97 mmol, 8 equiv.) and PTSA (5 mol-%), **34f** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (250 mg, 40%); mp. 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 6 H, ^{3}J = 6.2 Hz, CH_3), 2.27 (s, 6 H, CH_3), 3.90 (s, 3 H, OCH_3), 3.91 (s, 3H, OCH3), 4.80-4.87 (m, 1 H, OCH), 6.46 (d, 2 H, ^{3}J = 8.2 Hz, ArH), 6.94 (d, 2 H, ^{3}J = 8.2 Hz, ArH), 6.98 (d, 2 H, ^{3}J = 7.8 Hz, ArH), 7.99 (d, 2 H, ^{3}J = 7.8 Hz, ArH), 7.98 (s,1 H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.08 (2C, CH_3), 20.09 (CH_3), 20.16 (CH_3), 51.7 (OCH_3), 51.8 (OCH_3), 68.3 (CH), 127.1, 127.5, 127.6 (C), 128.4 (2CHAr), 128.6 (2CHAr), 130.6 (2CHAr), 131.5 (2CHAr), 133.5 (CHAr), 133.7, 135.2, 135.9, 136.2, 141.3, 142.5, 164.9, 166.0, 166.9 (C); IR (KBr): $\tilde{\nu}$ = 2980 (m), 1725 (s), 1687 (s), 1598 (s), 1513 (S), 1457 (m), 1327 (m), 1251 (s), 835 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 460.2 (M^+, 100), 401.1 (24), 355.1 (35), 239.1 (20), 131 (26), 69 (75); elemental analysis: calcd (%) for $C_{28}H_{28}O_6$ (460.526): C 73.62, H 6.12; found: C 73.73, H 6.34.

1,2,3-trimethyl-4,5-di(p-methoxyphenyl)-benzene-1,2,3-tricarboxylate (34g)



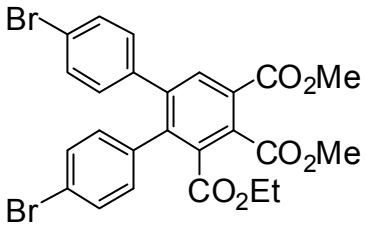
Starting with **33g** (500 mg, 1.35 mmol), DMAD (1.13 mL, 10.85 mmol, 8 equiv.) and PTSA (5 mol-%), **34g** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (250 mg, 40%); mp. = 143-144 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.52 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.92 (s, 6 H, OCH_3), 6.72 (d, 2 H, ^{3}J = 9.1 Hz, ArH), 6.74 (d, 2 H, ^{3}J = 8.8 Hz, ArH), 6.95 (d, 2 H, ^{3}J = 8.5 Hz, ArH), 6.96 (d, 2H, ^{3}J = 8.5 Hz, ArH), 7.98 (s, 1 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 52.7, 52.9, 55.0, 55.1 (OCH3), 113.3 ($2CH_{Ar}$), 113.4 ($2CH_{Ar}$), 128.3, 129.6 (C), 130.7 ($2CH_{Ar}$), 131.4 (2C), 132.6 (CH_{Ar}), 134.4, 142.0, 143.3, 158.8, 158.9, 165.9, 167.8, 168.0 (C); IR (KBr): $\tilde{\nu}$ = 1745 (s), 1608 (s), 1575 (m), 1516 (s), 1458 (m), 1435 (s), 1339 (s), 1248 (s), 1067 (m), 843 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 464.2, (M^+, 100), 433.1 (16), 401.1 (11)); elemental analysis: calcd (%) for $C_{26}H_{24}O_8$ (464.47): C 67.23, H 5.21; found: C 66.89, H 5.20.

3-Isopropyl-1,2-dimethyl-4,5-di(p-methoxyphenyl)-benzene-1,2,3-tricarboxylate (34h)



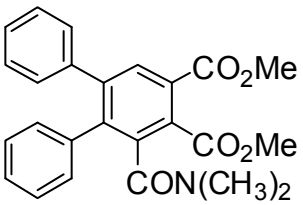
Starting with **33h** (500 mg, 1.26 mmol), DMAD (1.23 mL, 10.08 mmol, 8 equiv.) and PTSA (5%), **34h** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (290 mg, 46%); mp. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, 6 H, ^{3}J = 6.2 Hz, CH_3), 3.74 (s, 6 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.89 (sept, 1 H, ^{3}J = 6.2 Hz, OCH), 6.70 (d, 2 H, ^{3}J = 6.4 Hz, ArH), 6.72 (d, 2 H, ^{3}J = 6.3 Hz, ArH), 6.92 (d, 2 H, ^{3}J = 8.8 Hz, ArH), 6.95 (d, 2H, ^{3}J = 8.8 Hz, ArH), 7.24 (s, 1 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 ($2CH_3$), 51.7, 51.8, 54.1,, 54.2 (OCH_3), 68.3 (CH),112.3 ($2CH_{Ar}$), 112.4 ($2CH_{Ar}$), 127.1, 128.9, 129.9, 130.4 (C), 130.5 ($2CH_{Ar}$), 131.3 ($2CH_{Ar}$), 133.9 (CH_{Ar}), 140.8, 142.3, 157.7, 158.0, 164.9, 166.0, 166.9 (C); IR (KBr): $\tilde{\nu}$ = 1741 (s), 1727 (s), 1608 (s), 1516 (s), 1461 (m), 1351 (m), 1251 (m), 1160 (s), 1065 (s), 833 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 492 (M+, 100), 450 (20), 418 (25), 387 (19); HRMS (EI): calcd. for $C_{28}H_{28}O_8$ $[M]^+$: 492.177507; found: 492.17787.

3-Ethyl-1,2-dimethyl-4,5-di(p-bromophenyl)-benzene-1,2,3-tricarboxylate (34i)



Starting with **33i** (400 mg, 0.83 mmol), DMAD (0.81 mL, 6.66 mmol, 8 equiv.) and PTSA (5 mol-%), **34i** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (325 mg, 68%); mp. 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, ^{3}J = 7.1 Hz, CH_3), 3.92 (s, 6 H, OCH_3), 3.99 (q, 2 H, ^{3}J = 7.1 Hz, OCH_2CH_3), 6.88 (d, 2 H, ^{3}J = 8.4 Hz, ArH), 6.92 (d, 2 H, ^{3}J = 8.4 Hz , ArH), 7.35 (d, 2 H, ^{3}J = 8.4 Hz, ArH), 7.36 (d, 2 H, ^{3}J = 8.4 Hz, ArH), 7.98 (s, 1 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 (CH_3), 52.8, 52.9 (OCH3), 61.4 (OCH_2), 122.0, 122.2, 128.9 (C) 131.0 ($2CH_{Ar}$), 131.1 ($2CH_{Ar}$), 131.2 ($2CH_{Ar}$), 131.3 ($2CH_{Ar}$), 132.5 (CH_{Ar}), 132.6, 136.0, 137.5, 141.0, 142.2, 165.4, 166.8, 167.5 (C); IR (KBr): $\tilde{\nu}$ = 2950 (m), 1742 (s), 1493 (m), 1249 (s), 1202 (s), 1073 (m), 835 (m), 701 (m), cm^{-1}; MS (EI, 70 eV): *m/z* (%): 578.9 (M^+, ^{81}Br, 12), 575.9 (M^+, ^{79}Br, 100), 530.9 (37), 484.9 (33), 229 (31), 121.1 (36) 91 (29); elemental analysis: calcd (%) for $C_{25}H_{20}O_6Br_2$ (576.237): C 52.11, H 3.52; found: C 52.16, H 3.54.

Compound (37)

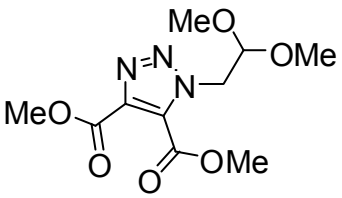


Starting with **36** (200 mg, 0.57 mmol), DMAD (0.65 mL, 4.58 mmol) and PTSA (5 mol-%), **37** was isolated by chromatography (heptane/ ethyl acetate) as a yellow solid (165 mg, 65%); mp. 143-144 °C. Reflux time: 10 h. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.68 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 0.84 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 2.51-2.65 (1 H), 2.90-3.06 (2 H), 3.40-3.49 (1 H). 3.88 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.01-7.60 (m, 10 H, Ph), 8.02 (s, 1 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 11.5, 12.5 (CH_3), 37.6, 42.5 (CH_2), 52.73, 52.75 (OCH_3), 127.2, 127.3 (C), 127.6 ($2CH_{Ph}$), 127.9 (CH_{Ph}), 128.5 ($2CH_{Ph}$), 129.6 ($2CH_{Ph}$), 130.1 ($2CH_{Ph}$), 131.7 (CH_{Ph}), 131.8 (CH_{Ar}), 136.6, 137.2, 139.4, 140.7, 143.2, 166.0, 167.0, 168.1 (C); IR (KBr): $\tilde{\nu}$ = 2951 (w), 1731 (s), 1628 (s), 1437 (m), 1267 (s), 1163 (m), 1092 (m), 761 (s), 702 (s); cm^{-1}; MS (EI, 70 eV): *m/z* (%): 445.1 (M^+, 2), 386.1 (91), 373.0 (100), 342.0 (17), 226.0 (33), 72.0 (54); HRMS (EI): calcd. for $C_{27}H_{27}O_5N_1$ $[M]^+$: 445.188455; found: 445.18837.

General procedure for the synthesis of 1,2,3-triazoles:

Mixture of acetyle (1.0 eq) and 2-azido-1,1-dimethoxyethane (1.2 eq) were suspended in a 1:1 mixture of water and *t*-butanol (5 mL each). To this mixture was added copper turning (50 mg) and an aqueous copper sulphate solution (1 M, 5 mol-%) and the mixture was heated at 110 °C for two hours. After cooling, the reaction mixture was diluted with water (20 mL), and precipitated product was filtered off and washed with cold water (20 mL) and subsequently with petroleum ether to give the **40a** and **40c** as a colourless solid. In case of oil products, the mixture was extracted with EtoAc. The organic layers were combined and dried by $NaSO_4$ and solvent was removed on *vacu.*

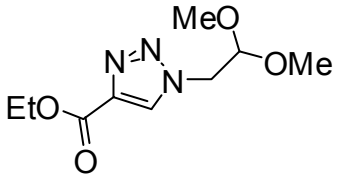
Dimethyl 1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (40a)



Starting with DMAD **39a** (600mg, 4.22 mmol) and 2-azido-1,1-dimethoxyethane **38** (664 mg, 5.06 mmol), **40a** was obtained as colourless solid (875 mg, 85 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 6 H , OCH_3), 3.96 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.61 (t, 1 H, *J* = 5.63 Hz, CH), 4.73 (d, 2 H, *J* = 5.3 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.2 (CH_2), 52.6, 53.3, 55.1 (OCH_3), 102.3 (CH), 131.7, 139.3, 159.1, 160.3 (C); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2992 (w), 1728 (s), 1570 (w), 1471 (m), 1331 (m), 1277 (s), 1156 (s), 1102 (m), 1063 (s), 1045 (s), 962 (m), 780 (w), 704 (w) . GC-MS (EI 70 eV): *m/z*

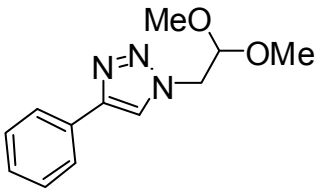
(%) = 242 (M^+, 3 %), 213 (2), 150 (3), 75 (100); elemental alalysis: Calcd (%) for $C_{10}H_{15}N_3O_6$ (273.23): C 43.93, H 5.53, N 15.38; Found: C 44.31, H 5.50, N 15.25.

Ethyl 1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-carboxylate (40b)



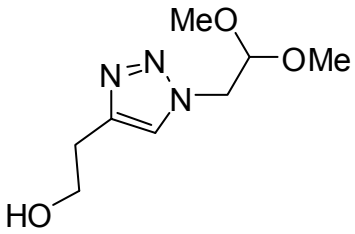
Starting with Ethyl propiolate (500 mg, 5.09 mmol) and 2-azido-1,1-dimethoxyethane **38** (739 mg, 5.60 mmol), **40b** was obtained as slight yallow oil (985 mg, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 140 (t, 3 H, *J* = 5.40, CH_3), 3.41 (s, 6 H, OCH_3), 4.41 (q, 2 H, *J* = 6.75 Hz, CH_2), 4.52 (d, 2 H, *J* = 4.83 Hz, CH_2), 4.67 (t, 1H, *J* = 5.53 Hz, CH), 8.19 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3), 51.8 (CH_2), 55.0 (OCH_3), 61.0 (CH_2), 102.0, 128.6 (CH), 140.0, 160.5 (C); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2963 (w), 1721 (s), 1463 (w), 1375 (m), 1198 (s), 1124 (s), 1072 (s), 1037 (s), 839 (m), 776 (s), 697 (w); MS (CI, isobutane): 230 ($[M+1]^+$); elemental analysis: Calcd. for $C_9H_{15}N_3O_4$ (229.23); C 47.16, H 6.60, N 18.33; Found: C 47.6, H 6.62, N 18.17.

1-(2,2-dimethoxyethyl)-4-phenyl-1H-1,2,3-triazole (40c)



Starting with Phenyl acetylene (500 mg, 4.89 mmol) and 2-azido-1,1-dimethoxyethane **38** (705 mg, 5.38 mmol), **40c** was obtained as colourless solid (851 mg, 75 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (s, 6 H, OCH_3), 4.06 (d, *J* = 5.2 Hz, CH_2), 4.24 (t, *J* = 5.2 Hz, CH), 6.81-7.01 (m, 3 H, Ph), 7.31-7.40 (m, 2 H, Ph), 7.41 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.9 (CH_2), 55.1 (OCH_3), 102.7 (CH), 120.8, 15.6, 128.0, 130.5 (CH_{Ph}), 132.3, 147.8 (C). IR (KBr): $\tilde{\nu}$ = 3126 (s), 2996 (m), 2894 (s), 1466 (s), 1364 (m), 1222 (s), 1124 (s), 1079 (s), 1018 (s), 924 (s), 772 (s), 836 (s), 768 (s), 693 (s), 542 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 233 (M^+, 16), 173 (13), 116 (19), 75 (100), 47 (18); elemental analysis: calcd. (%) for $C_{12}H_{15}N_3O_2$ (233.27): C 61.79, H 6.48, N 18.03; found: C 61.75, H 6.44, N 17.78.

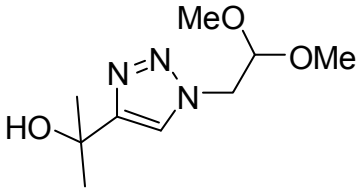
2-(1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-yl)ethanol (40d)



Starting with But-3-yn-1-ol (500 mg, 7.13 mmol) and 2-azido-1,1-dimethoxyethane **38** (995 mg, 7.84 mmol), **40d** was obtained as slight yallow oil (1.17 g, 82 %).^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.94 (t, 2 H, *J* = 5.7 Hz, CH_2), 3.40 (s, 6 H, OCH_3), 3.60 (t, 2 H, *J* = 5.7Hz, CH_2), 3.94 (s, 1 H, OH), 4.43 (d,

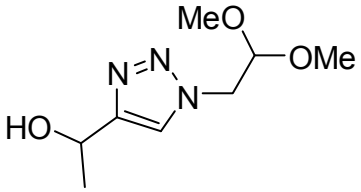
2 H, J = 5.22 Hz, CH_2), 4.64 (t, 1 H, J = 5.16 Hz, CH), 7.52 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 51.7 (CH_2), 54.9 (OCH_3), 61.5 (CH_2), 102.6, 122.8 (CH), 137.6 (C); IR (neat): $\tilde{\nu}$ = 3373 (w), 2938 (w), 1458 (w), 1124 (s), 1049 (s), 979 (m), 819 (w) cm^{-1}; MS (CI, isobutane): 202 ($[M+1]^+$); elemental analysis calcd (%) for $C_8H_{15}N_3O_3$ (201.2): C 47.15, H 7.51, N 20.88; Found: C 46.96, H 7.32, N 19.25.

2-(1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-yl)propan-2-ol (40e)



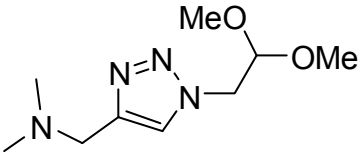
Starting with 2-Methylbut-3-yn-2-ol (500 mg, 5.94 mmol) and 2-azido-1,1-dimethoxyethane **38** (933 mg, 7.12 mmol), **40e** was obtained as slight yallow oil (1.08 g, 84 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 6 H, CH_3), 3.36 (s, 6 H, OCH_3), 3.38(d, 2 H, J = 5.28 Hz, CH_2), 4.59 (t, 1 H, J = 5.22 Hz, CH), 7.50 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3 (CH_3), 51.6 (CH_2), 54.8 (OCH_3), 102.5, 120.3 (CH), 155.5 (C); IR (neat): $\tilde{\nu}$ = 3392 (w), 2935 (w), 1375 (w), 1168 (m), 1125 (s), 105 (s), 958 (m), 856 (m), 820 (w), 672 (w) cm^{-1}; MS (CI, isobutane): 216 ($[M+1]^+$); 2216; elemental analysis Calcd. (%) for $C_9H_{17}N_3O_3$ (215.25): C 50.22, H 7.96, N 19.52; Found: C 50.55, H 7.99, N 17.90.

1-(1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-yl)ethanol (40f)



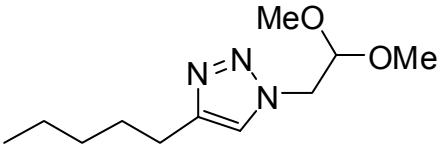
Starting with But-3-yn-2-ol (600 mg, 8.56 mmol) and 2-azido-1,1-dimethoxyethane **38** (1.34 g, 10.27 mmol), **40f** was obtained as slight yallow oil (1.46 g, 85 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (d, 3 H, J = 6.51 Hz, CH_3), 3.44 (s, 6 H, OCH_3), 4.47 (d, 2 H, J = 5.22 Hz, CH_2), 4.69 (t, 1 H, J = 5.4 Hz, CH), 5.12 (s, 1 H, OH), 7.60 (s, H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (CH_3), 51.7 (CH_2), 54.9 (OCH_3), 62.9, 102.5, 121.2 (CH), 142.2 (C); IR (neat): $\tilde{\nu}$ = 3374 (w), 2973 (w), 1224 (m), 1124 (s), 1053 (s), 979 (m), 892 (m), 820 (m), 778 (m) cm^{-1}; GC-MS (EI 70 eV): *m/z* (%) = 201 (M^+, 2%) 170 (2), 158 (1), 141 (6), 98 (2), 75 (100), 47 (11); elemental analysis: calcd. (%) for $C_8H_{15}N_3O_3$ (201.22): C 47.75, H 7.51, N 20.88; found: C 47.51, H 7.11, N 20.77.

2-(1-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-yl)-N,N-dimethylmethanamine (40g)



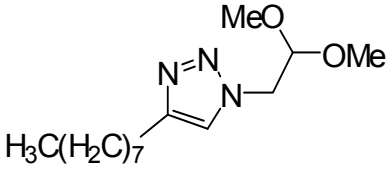
Starting with N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol) and 2-azido-1,1-dimethoxyethane **38** (870 mg, 6.61 mmol), **40g** was obtained as slight yallow oil (850 mg, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 6 H, CH_3), 3.39 (s, 6 H, OCH_3), 3.60 (s, 2 H, CH_2), 4.44 (d, 2 H, *J* = 5.19 Hz, CH_2), 4.64 (t, 1 H, *J* = 5.4 Hz, CH), 7.58 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.9 (CH_3), 51.6, 54.1 (CH_2), 54.7 (OCH_3), 102.6, 123.5 (CH), 144.8 (C); IR (neat): $\tilde{\nu}$ = 3392 (w), 2935 (w), 1375 (w), 1168 (m), 1125 (s), 105 (s), 958 (m), 856 (m), 820 (w), 672 (w) cm^{-1}; GC-MS (EI 70 eV): *m/z* (%) = 214 (M^+, 6 %) 171 (100), 89 (19), 75 (29), 58 (20); HRMS (EI): calcd. for $C_9H_{18}N_4O_2$ $[M]^+$: 214.142232; found: 214.14243.

1-(2,2-dimethoxyethyl)-4-pentyl-1H-1,2,3-triazole (40h)



Starting with 1-heptyne (500 mg, 5.19 mmol) and 2-azido-1,1-dimethoxyethane **38** (750 mg, 5.72 mmol), **40h** was obtained as slight yallow oil (740 mg, 63 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 5.3 Hz, CH_3), 1.21-1.36 (m, 4 H, $(CH_2)_2$), 1.59 (m, 2 H, CH_2), 2.71 (t, 2 H, *J* = 7.8 Hz, CH_2), 3.40 (s, 6 H, OCH_3), 4.42 (d, 2 H, *J* = 5.2 Hz, CH_2), 4.63 (t, 1 H, *J* = 5.2 Hz, CH), 7.36 (s, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.4, 23.0, 25.6, 31.1, 51.6 (CH_2), 55.1 (OCH_3), 102.5, 121.9 (CH), 155.5 (C); IR (neat): $\tilde{\nu}$ = 3392 (w), 2935 (w), 1375 (w), 1168 (m), 1125 (s), 105 (s), 958 (m), 856 (m), 820 (w), 672 (w) cm^{-1}; GC-MS (EI 70 eV): *m/z* (%) = 227 (M^+, 2), 196 (3), 167 (100); elemental analysis calcd (%) for $C_{11}H_{21}N_3O_2$ (227.30): C 58.12, H 9.31, N 18.49; Found: C 57.55, H 9.55, N 18.90.

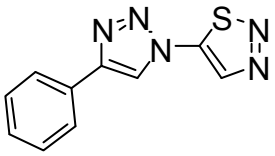
1-(2,2-dimethoxyethyl)-4-octyl-1H-1,2,3-triazole (40i)



Starting with 1-Decyne (500 mg, 3.01 mmol) and 2-azido-1,1-dimethoxyethane **38** (472 mg, 3.61 mmol), **40i** was obtained as slight yallow oil (650 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.26-1.32 (m, 10 H, $(CH_2)_5$), 1.59-1.62 (m, 2 H, CH_2), 2.70 (t, 2 H, *J* = 7.3 Hz, CH_2), 3.39 (s, 6 H, OCH_3), 4.42 (d, 2 H, *J* = 5.2 Hz, CH_2), 4.64 (t, 1 H, *J* = 5.1 Hz, CH), 7.41

(s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 25.6, 29.0, 29.1, 29.3, 31.4, 31.7, 51.7 (CH_2), 55.4 (OCH_3), 102.7, 122.7 (CH), 149.5 (C).

5-(4-phenyl-1H-1,2,3-triazole-1-yel)-1,2,3-thiadiazole (42)



Starting with **41** (500 mg, 1.40 mmol) and thionyl chloride (10 mL), **42** was obtain as white solid (190 mg, 60%); ^{1}H NMR (300 MHz, DMSO): δ = 7.36-5.51 (m, 3 H, Ph), 7.85-7.88 (m, 2 H, Ph), 9.44 (s, 1 H, CH), 9.44 (s, 1 H, CH); ^{13}C NMR (100 MHz, DMSO): δ = 121.3 (CH), 125.5 (CH_{Ph}), 128.9 (C), 129.0 (CH_{Ph}), 129.1 (C), 129.2, (CH_{Ph}), 138.7 (CH), 147.9 (C); IR (KBr): $\tilde{\nu}$ = 2996 (m), 2894 (s), 1466 (s), 1364 (m), 1222 (s), 1124 (s), 1079 (s), 1018 (s), 924 (s), 772 (s), 836 (s), 768 (s), 693 (s), 542 (m) cm^{-1}; elemental analysis: calcd (%) for $C_{10}H_7N_5S$ (229.26): C 52.39, H 3.08, N 30.50; found: C 52.67, H 3.44, N 30.11.

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X-Ray Crystals Data

Data for compound 15o Chapter 2:

Identification code	15o	
Empirical formula	$C_{18}H_{17}NO_4$	
Formula weight	311.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 16.1123(4) Å	α= 90°.
	b = 10.4002(2) Å	β= 92.6710(10)°.
	c = 9.5600(2) Å	γ = 90°.
Volume	1600.24(6) $Å^3$	
Z	4	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	656	
Crystal size	0.40 x 0.39 x 0.32 mm^3	
Θ range for data collection	2.33 to 29.00°.	
Index ranges	$-21\leq h\leq 21$, $-14\leq k\leq 12$, $-13\leq l\leq 11$	
Reflections collected	17495	
Independent reflections	4237 [R(int) = 0.0209]	
Completeness to Θ = 29.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9712 and 0.9642	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4237 / 0 / 230	
Goodness-of-fit on F^2	1.048	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0636, wR2 = 0.1602	
R indices (all data)	R1 = 0.0968, wR2 = 0.1979	
Largest diff. peak and hole	0.459 and -0.383 $e.Å^{-3}$	

Data for compound 21a Chapter 3:

Identification code	21a	
Empirical formula	$C_{10}H_{12}O_4$	
Formula weight	196.20	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	Pbcm	
Space group (Hall)	-P 2c 2b	
Unit cell dimensions	a = 8.5016(3) Å	α= 90°.
	b = 16.2098(5) Å	β= 90°.
	c = 6.6887(2) Å	γ = 90°.
Volume	921.76(5) $Å^3$	
Z	4	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	
F(000)	416	
Crystal size	0.72 x 0.27 x 0.11 mm^3	
Θ range for data collection	2.51 to 29.99°.	
Index ranges	$-11 \leq h \leq 11$, $-13 \leq k \leq 22$, $-9 \leq l \leq 9$	
Reflections collected	5372	
Independent reflections	1448 [R(int) = 0.0212]	
Completeness to Θ = 29.99°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9880 and 0.9253	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1448 / 0 / 91	
Goodness-of-fit on F^2	1.058	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0376, wR2 = 0.1031	
R indices (all data)	R1 = 0.0441, wR2 = 0.1096	
Largest diff. peak and hole	0.478 and -0.217 $e.Å^{-3}$	

Data for compound 29a Chapter 4:

Identification code	29a	
Empirical formula	$C_{17}H_{17}ClO_3$	
Formula weight	304.76	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.5794(2) Å	α= 101.665(2)°.
	b = 8.5472(3) Å	β= 93.335(2)°.
	c = 11.9123(4) Å	γ = 92.402(2)°.
Volume	753.35(4) $Å^3$	
Z	2	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.261 mm^{-1}	
F(000)	320	
Crystal size	0.64 x 0.25 x 0.06 mm^3	
Θ range for data collection	2.44 to 29.83°.	
Index ranges	$-10\leq h\leq 10$, $-11\leq k\leq 11$, $-16\leq l\leq 16$	
Reflections collected	18761	
Independent reflections	4268 [R(int) = 0.0773]	
Completeness to Θ = 29.83°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9845 and 0.8510	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4268 / 0 / 196	
Goodness-of-fit on F^2	0.958	
Final R indices [I>2σ(I)]	R1 = 0.0412, wR2 = 0.0976	
R indices (all data)	R1 = 0.0639, wR2 = 0.1064	
Largest diff. peak and hole	0.300 and -0.282 $e.Å^{-3}$	

Data for compound 33b Chapter 5:

Identification code	33b	
Empirical formula	$C_{20}H_{18}O_4$	
Formula weight	322.34	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 10.9545(4) Å	α= 90°.
	b = 9.7930(3) Å	β= 90.357(2)°.
	c = 15.5740(5) Å	γ = 90°.
Volume	1670.71(10) $Å^3$	
Z	4	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	680	
Crystal size	0.85 x 0.75 x 0.45 mm^3	
Θ range for data collection	2.46 to 28.00°.	
Index ranges	$-13\leq h\leq 14$, $-12\leq k\leq 12$, $-18\leq l\leq 19$	
Reflections collected	18208	
Independent reflections	3954 [R(int) = 0.0754]	
Completeness to Θ = 28.00°	97.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3954 / 0 / 246	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2σ(I)]	R1 = 0.0501, wR2 = 0.1305	
R indices (all data)	R1 = 0.0594, wR2 = 0.1461	
Largest diff. peak and hole	0.348 and -0.242 $e.Å^{-3}$	

Data for compound 33j Chapter 5:

Empirical formula	C22 H22 O4	
Formula weight	350.40	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.5959(5) Å	α= 109.329(3)°.
	b = 10.9449(8) Å	β= 92.053(4)°.
	c = 14.947(1) Å	γ = 107.283(4)°.
Volume	961.4(1) $Å^3$	
Z	2	
Density (calculated)	1.210 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	372	
Crystal size	0.6 x 0.12 x 0.12 mm^3	
Theta range for data collection	2.08 to 33.31°.	
Index ranges	-10<=h<=9, -16<=k<=16, -22<=l<=22	
Reflections collected	26480	
Independent reflections	7147 [R(int) = 0.0253]	
Completeness to theta = 33.31°	96.4 %	
Absorption correction	Multiscan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7147 / 0 / 235	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0533, wR2 = 0.1445	
R indices (all data)	R1 = 0.0916, wR2 = 0.1667	
Largest diff. peak and hole	0.359 and -0.177 $e.Å^{-3}$	

Data for compound 34a Chapter 5:

Empirical formula	C24 H20 O6	
Formula weight	404.40	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.2895(2) Å	α= 90°.
	b = 20.2579(3) Å	β= 107.703(1)°.
	c = 10.3277(2) Å	γ = 90°.
Volume	2050.80(6) $Å^3$	
Z	4	
Density (calculated)	1.310 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	848	
Crystal size	0.41 x 0.32 x 0.2 mm^3	
Theta range for data collection	3.17 to 32.28°.	
Index ranges	-15<=h<=13, -29<=k<=30, -15<=l<=15	
Reflections collected	29524	
Independent reflections	7174 [R(int) = 0.0228]	
Completeness to theta = 32.28°	98.2 %	
Absorption correction	multiscan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7174 / 0 / 271	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0484, wR2 = 0.1415	
R indices (all data)	R1 = 0.0658, wR2 = 0.1568	
Largest diff. peak and hole	0.279 and -0.227 $e.Å^{-3}$	

Data for compound 34c Chapter 5:

Identification code	34c	
Empirical formula	C_{28} H_{28} O_6	
Formula weight	460.50	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 10.6294(3) Å	α= 82.7240(10)°.
	b = 10.9743(3) Å	β= 63.9770(10)°.
	c = 12.0168(3) Å	γ = 74.9550(10)°.
Volume	1216.34(6) $Å^3$	
Z	2	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	488	
Crystal size	0.83 x 0.56 x 0.36 mm^3	
Θ range for data collection	2.55 to 27.50°.	
Index ranges	-13≤h≤13, -14≤k≤14, -15≤l≤15	
Reflections collected	35793	
Independent reflections	5498 [R(int) = 0.0209]	
Completeness to Θ = 27.50°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9691 and 0.9306	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5498 / 0 / 314	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2σ(I)]	R1 = 0.0382, wR2 = 0.1033	
R indices (all data)	R1 = 0.0408, wR2 = 0.1072	
Extinction coefficient	0.037(3)	
Largest diff. peak and hole	0.365 and -0.195 $e.Å^{-3}$	

Data for compound 35 Chapter 5:

Identification code	35	
Empirical formula	$C_{35}H_{30}O_6$	
Formula weight	546.59	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	Pbca	
Space group (Hall)	-P 2ac 2ab	
Unit cell dimensions	a = 17.2693(9) Å	α= 90°.
	b = 16.3400(8) Å	β= 90°.
	c = 20.1333(10) Å	γ = 90°.
Volume	5681.2(5) $Å^3$	
Z	8	
Density (calculated)	1.278 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	2304	
Crystal size	0.50 x 0.26 x 0.03 mm^3	
Θ range for data collection	2.65 to 21.47°.	
Index ranges	$-17\leq h\leq 17$, $-16\leq k\leq 16$, $-19\leq l\leq 20$	
Reflections collected	36426	
Independent reflections	3247 [R(int) = 0.0967]	
Completeness to Θ = 21.47°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9974 and 0.9579	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3247 / 0 / 372	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2σ(I)]	R1 = 0.0398, wR2 = 0.0826	
R indices (all data)	R1 = 0.0793, wR2 = 0.0967	
Largest diff. peak and hole	0.279 and -0.218 $e.Å^{-3}$	

Data for compound 40a Chapter 6:

Identification code	40a	
Empirical formula	$C_{10}H_{15}N_3O_6$	
Formula weight	273.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	$Pna2_1$	
Space group (Hall)	P 2c -2n	
Unit cell dimensions	a = 14.9011(6) Å	α= 90°.
	b = 7.3659(3) Å	β= 90°.
	c = 23.7379(10) Å	γ = 90°.
Volume	2605.47(19) $Å^3$	
Z	8	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	1152	
Crystal size	0.77 x 0.76 x 0.20 mm^3	
Θ range for data collection	2.73 to 27.99°.	
Index ranges	-19≤h≤19, -9≤k≤8, -31≤l≤30	
Reflections collected	24464	
Independent reflections	5905 [R(int) = 0.0248]	
Completeness to Θ = 27.99°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9771 and 0.9159	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5905 / 1 / 351	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2σ(I)]	R1 = 0.0330, wR2 = 0.0891	
R indices (all data)	R1 = 0.0374, wR2 = 0.0939	
Absolute structure parameter	-0.2(7)	
Largest diff. peak and hole	0.233 and -0.203 $e.Å^{-3}$	

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Publications:

1. **Muhammad Sher**, Zafar Ahmed, Muhammad A. Rashid, Christine Fischer, Peter Langer*, *J. Org. Chem.* **2007**, *72*, 6284-6286.
"Efficient Synthesis of Salicylates by Catalytic [3+3] Cyclizations of 1,3-Bis(Silyl Enol Ethers) with 1,1,3,3-Tetramethoxypropane".

2. **Muhammad Sher**, Helmut Reinke, Peter Langer*, *Tetrahedron* **2007**, *63*, 4080-4086.
"Synthesis of 4,5-Diaryl-1,2,3-benzenetricarboxylates by Reaction of 4-Hydroxycyclopent-2-en-1-one-2-carboxylates with Dimethyl Acetylenedicarboxylate".

3. **Muhammad Sher**, Zafar Ahmad, Muhammad A. Rashid, Christine Fisher, Anke Spannenberg, Peter Langer*, *Tetrahedron* **2007**, *63*, 4929-4936.
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4. **Muhammad Sher**, Helmut Reinke, Peter Langer*, *Tetrahedron Lett.* **2007**, *48*, 7923-7925.
"Regioselective synthesis of 1-(2,2-dimethoxyethyl)-1,2,3-triazoles by copper(I)-catalyzed [3+2] cyclization of 2-azido-1,1-dimethoxyethane with alkynes".

5. **Muhammad Sher**, Peter Langer*, *Synlett* **2008**, 1050-1053.
"Regioselective synthesis of functionalized resorcins by cyclization of 1,3-bis(trimethylsilyloxy)-1,3butadienes with 3,3-dimethoxypentanoyl chloride".

6. **Muhammad Sher**, Asad Ali, Peter Langer*, *Tetrahedron Lett.* **2008** *In print*.
"Synthesis of 3-Aryl-3,4-dihydroisocoumarins by Regio-selective Domino '[3+3] Cyclization / Lactonization' Reactions of 1,3-Bis(silyloxy)-1,3-butadienes with 1-Hydroxy-5-silyloxy-4-en-3-ones".

7. Mathias Lubbe, Alina Bunescu, **Muhammad Sher**, Alexander Villinger, Peter Langer*, *Synlett* **2008**, accepted.
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8. Ibrar Hussain, Mirza A. Yawer, Bettina Appel, **Muhammad Sher**, Ahmed Mahal, Alexander Villinger, Peter Langer*, *Tetrahedron* **2008**, accepted.
"Synthesis of 4-Hydroxy- and 2,4-Dihydroxy-homophthalates by [4+2] Cycloaddition of 1,3Bis(trimethylsilyloxy)-1,3-butadienes with Dimethyl Allene-1,3-dicarboxylate".

9. Aurangzeg Hasan*, Khalid M.Khan*, **Muhammad Sher**, Ghulam M. MAharvi, Sarfraz A.Nawaz,, M. I. Choudhary, Atta-Ur-Rehman, Claudiu T.Supuran. *Journal of Enzyme Inhibition and medicinal Chemistry*, **2005**, 41-47.
"Synthesis and inhibitory potential towards acetylcholinesterase, butyrylcholisterase and lipoxygenase of some variably substituted chalcones".

Declaration/Erklärung

Here by I declare that this work has so for neither submitted to the Faculty of Mathematics and Natural Sciences at the University of Rostock nor to any other scientific Institution for the purpose of doctorate. Further more, I declare that I have written this work by myself and that I have not used any other sources, other than mentioned earlier in this work.

Hiermit erkläre ich, daß diese Arbeit bisher von mir weder an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock noch einer anderen wissenschaftlichen Einrichtung zum Zwecke der Promotion eingereicht wurde.

Ferner erkläre ich, dass ich diese Arbeit selbständig verfasst und keine anderen als die darin angegebenen Hilfsmittel benutzt habe

I hereby apply irrevocably to take oral examination in the form of a private viva voce and a public presentation.

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Muhammad Sher