Bis-silyl-enol ethers as convenient building blocks for the design and synthesis of Salicylates, Pyrones, Cyclohexenones, Pyridones and Benzophenones

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Declaration

Hereby I declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Erklärung

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Alina Bunescu

Rostock, June 2011

Abstract

The present thesis describes the synthetic potential of 1,3-bis-silyl-enol ethers. They undergo regioselective cyclocondensation reactions with simple substrates providing various complex carba- and heterocycles. The $TiCl_4$-mediated cyclocondensation with functionalized butenones afforded a variety of halogen-substituted salicylates, while the Me_3SiOTf-mediated cyclocondensation afforded halogen-substituted *γ*-pyrones and cyclohexenones. A new type of formal [3+3]-cyclization reaction with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine has been discovered. It provided a convenient approach to functionalized 2,6-bis(trifluoromethyl)pyridones. The mechanism was studied by the isolation of an unusual bicyclic intermediate. The reactions with 3-methoxalylchromones and their derivatives afford a great variety of functionalised 2,4-dihydroxybenzophenones *via* isolation of an uncommon tricyclic intermediate. The products are promising candidates for novel UV-A/B filters.

Kurzbeschreibung

Die vorliegende Arbeit beschreibt das synthetische Potential von 1,3-Bis-silyl-enolethern. Sie durchlaufen regioselektive Cyclokondensationsreaktionen mit einfachen Substraten, um verschiedene komplexere Carbo- und Heterocyclen zu liefern. Die $TiCl_4$-vermittelte Cyclokondensation mit funktionalizierten Butenonen lieferte eine Vielzahl von halogensubstituierten Salicylaten und Phenolen, während die Me_3SiOTf-vermittelte Cyclokondensation halogensubstituierte *γ*-Pyrone und Cyclohexenone lieferte. Ein neuer Typ von formalen [3+3]-Cyclisierungen mit 2,4,6-Tris(trifluormethyl)-1,3,5-triazin ist entdeckt worden. Die Methode bietet einen bequemen Zugang zu funktionalisierten 2,6-Bis(trifluormethyl)pyridonen. Der Mechanismus wurde durch die Isolierung eines ungewöhnlichen bicyclischen Zwischenprodukts untersucht. Die Reaktionen mit 3-Methoxalylchromon und dessen Derivaten ergaben eine Vielzahl von funktionalisierten 2,4-Dihydroxybenzophenonen und verlaufen über die Isolierung einer ungewöhnlichen tricyclischen Zwischenstufe. Die Produkte sind vielversprechende Kandidaten für neuartige UV-A/B Filter.

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Alina Bunescu, Rostock 24.06.2011

Contents

Chapter 1

Preface

1.1 Task and Motivation

“Organic chemistry” is the science that shapes the life, it is everything we see, feel and odour. Initially, it was said that organic compounds exist only in living organism and cannot be synthesized. Therefore, scientists at that time named these compounds "organic".

However, in 1828 the first organic substance, namely urea was synthesized by Friedrich Wöhler. This was the revolution of organic chemistry, followed later by the breakthrough of the concept of chemical structure. It was then clear that the “organic” compounds mainly contain the “inorganic” carbon and hydrogen atoms.

Since then, millions of organic compounds have been synthesized. Organic chemistry is now not only creating the life but also supporting it. It is the chemistry that makes possible the manufacture of clothing, perfumes, soaps, creams, plastics, fibers, medications, insecticides and other products which make life more convenient.

The last decade of the 19th century represented the breakthrough of the pharmaceutical chemistry with the first synthesis and manufacture of Aspirin® by Bayer. The beginning of the 20th century symbolized the progress of organic chemistry on highly complex molecules and natural compounds. In 1907 the total synthesis of camphor was realized, followed by the synthesis of human hormones. Biochemistry, the chemistry of living organisms, revolutionizes the end of the 20th century, beginning of the 21th century and the organic chemistry.

The focus of the pharmaceutical industry is nowadays the construction of novel complex molecules with various functional groups and stereogenic centers that must be synthesized selectively with asymmetric synthesis.

Therefore, the concept of building up biomolecules with pharmacological and biological activity has become a huge interest for organic chemists. Consequently, the present thesis relays on the synthesis, characterisation and optimisation of different heterocyclic substances, wich are understood to be pharmaceutical active.

Biomolecules with fluorine-containing functional groups often show different physiologically activity than non-fluorinated analogues. The reason is the high electronegativity of the fluorine atom, compared for example to that of a hydrogen atom. This results in a noticeable change of the reactivity that can afford new drug-receptor interactions or restrict undesirable metabolic transformations. Some of the compounds in this thesis contain fluorine, like R^F-substituted salicylates, *γ*-pyrones or benzophenones.

1.2 State of the art

It is well known that simple cyclic and heterocyclic compounds are, for example, approachable by several cyclisation, condensation and Diels-Alder reactions. Though, it has to be taken into consideration that the synthesis of R^F-substituted arenes and hetarenes is often a difficult task. Trifluoromethyl-substituted compounds have been prepared, for example, by the reaction of aryl halides with *in situ* generated trifluoromethylcopper [1] or by transformation of carboxylic acids [2] and C-halides [3] into CF_3-groups. These reactions are often applicable only to specific substrates.

Not more than a handful of organofluorine compounds occur in nature and even those occur just in small amounts. Consequently, any fluorine-containing substance selected for fundamental studies or promoted as a pharmaceutical, agrochemical or advanced material has to be hand-made. [4] Therefore, the development of new strategies for the synthesis of functionalized benzenes and heterocycles with polifluoralkyl groups located at specific positions is of considerable current interest. The new reported strategies are based on the use of R^F-containing building blocks. [5]

The research group of Prof. Langer accounted already new pathways for the synthesis of R^F-substituted salicylates based on [3+3]-cyclizations of 1,3-bis-silyl enol ethers [6] with R^F-containing building blocks like: 4-ethoxy and 4-silyloxy-1,1,1-trifluoroalk-3-en-2-ones [7] or α,β-unsaturated trifluoromethyl and perfluoroalkyl ketones [8]. The products were not readily available by other methods. Recently new routes have been reported for the synthesis of fluorine-containing derivatives of heterocycles like coumarines [9] and pyranones [10]. Though, the scope of this method is limited to products containing less or no functional group besides the R^F-group.

Electron deficient heterocyclic azadienes have proven to be useful reagents for Inverse Electron Demand Diels-Alder (IEDDA) reactions with electron-rich dienophiles, providing a rapid access to a wide range of highly substituted heterocyclic systems. [11] The IEDDA reaction of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (a masked azadiene) with electron excessive aromatic and heteroaromatic amines and enamines has been reported. [12] Therefore, this triazine is an interesting substrate for the chemistry of 1,3-bis-silyl enol ethers. [13]

Therefore, reactions of new functionalized substrates with the 1,3-bis-silyl enol ether building blocks have been investigated. Additionally, the present thesis describes for the first time the influence of different Lewis acids on the product distribution of [3+3]-reactions involving 1,3-bis-silyl enol ethers.

Chapter 2

1,3-Bis-silyl enol ethers as masked dianions for cyclization reactions

2.1 Introduction

The formation of carbon-carbon bonds is nowadays an important task for the modern organic chemist. Essential chemical reactions are carried up by the formation of carbon-carbon bonds, producing many fundamental chemicals for industry and medicine, such as pharmaceuticals, plastic materials, dyes and cosmetics.

Various reactions like polymerization, cycloaddition or metathesis use dienes or dianions **A** (**Figure 2.1**) as precursors for the regioselective formation of the C-C-bond. [14] Though, their high reactivity can also lead to undesired side products. To overcome this limitation, particular dienes, like the Danishefsky`s diene **B** (**Figure 2.1**) were developed. They are electron rich dienes, therefore very reactive reagents for the Diels-Alder reaction. A variety of aromatics and heterocycles are available by [4+2]-cyclisation of Danishefsky`s diene. [15]

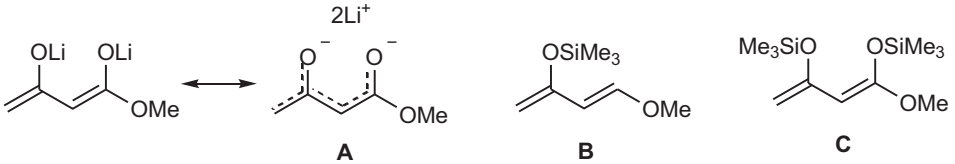
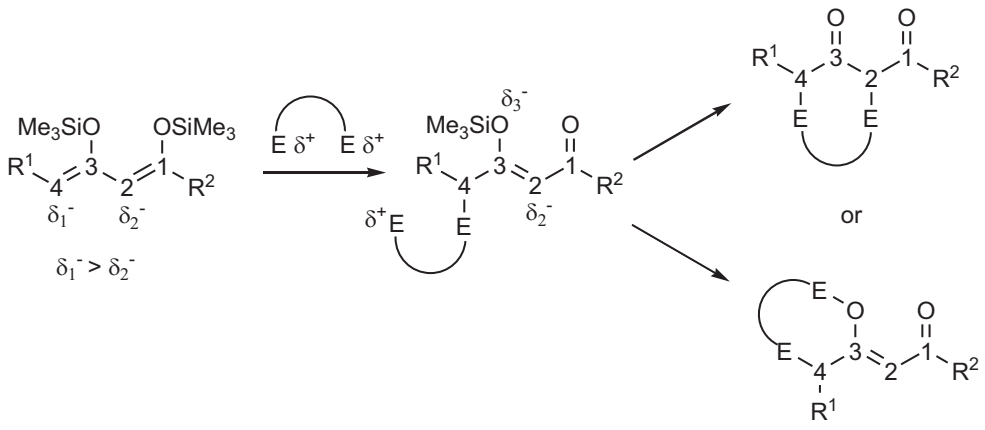


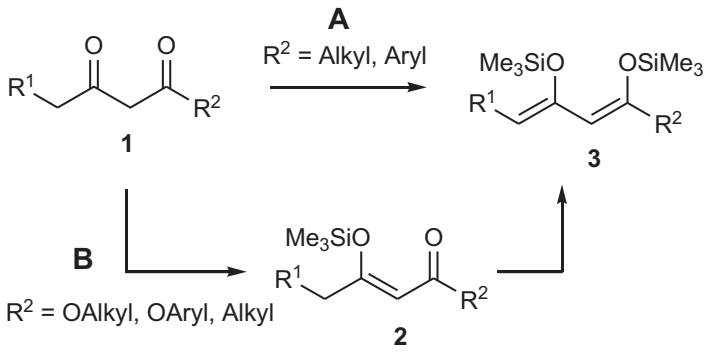
Figure 2.1: Dianions (**A**), Danishefsky`s diene (**B**) and Chan's diene (**C**)

The present thesis reveals the 1,3-bis-silyl enol ethers, like Chan's diene **C** (**Figure 2.1**), as equivalents of 1,3-dicarbonyl dianions (masked dianions) for cyclization reactions. [16] They react with electrophiles after a typical mechanistic pathway, beginning with the attack at the more nucleophilic carbon atom of the diene (terminal C-4 atom). These reactions are mediated by Lewis acids. Depending on the Lewis acid and the substitution pattern, the electrophile attacks at the central carbon (C-2) or at the oxygen atom of the diene (**Scheme 2.1**).



Scheme 2.1: Cyclization reactions of masked dianions with dielectrophiles. E = electrophilic centre.

The 1,3-bis-silyl enol ethers **3** can be prepared from the respective 1,3-dicarbonyl compounds in one or two steps. Simchen et al. reported the one step synthesis of **3** starting from the respective diketone, dissolved in ether and treatment with NEt_3 and Me_3SiOTf (**Method A, Scheme 2.2**). [17] Following Chan and Molander ester-derived 1,3-bis-silyl enol ethers **3** were prepared in two steps over mono-silyl enol ethers **2**. The respective *β*-ketoester is treated with NEt_3 and Me_3SiCl to give **2**, deprotonation with LDA and subsequent addition of Me_3SiCl gave **3** (**Method B, Scheme 2.2**). [18]



Scheme 2.2: Methods for the synthesis of bis-silyl enol ethers **3**: *Simchen* (**A**); *i*) NEt_3 (2 equiv.), Me_3SiOTf (2 equiv.), Et_2O, 0 - 20°C and *Molander* (**B**); *i*) 1) NEt_3 (1.6 equiv.), C_6H_6, 20°C, 2 h; 2) Me_3SiCl (1.8 equiv.), 20°C, 3 d; *ii*) 1) LDA (1.5 equiv.), THF, -78°C, 1 h; 2) Me_3SiCl (1.8 equiv.), –78 - 20 °C, 12 h.

2.2 Results and discussions

The following chapters describe the reactions of masked dianions **3** with different substrates. Each reaction was well tested by control experiments with various R^1 and R^2. Variation of R^2 was easier due to the commercial availability of *β*-ketoesters. Variation of R^1 requires first of all the synthesis of the respective *β*-ketoesters **1**. Therefore, different *β*-ketoesters were prepared by alkylation of 1,3-dicarbonyl dianions with alkyl halides after a known procedure. [19] The formation of a dianion as intermediate was necessary, due to the fact that monoanions are generally alkylated at the central carbon or at the oxygen atom, but not at the terminal carbon atom. They can be generated by reaction of the 1,3-dicarbonyl compounds in the presence of strong base, such as LDA. [20]

The synthesized and the commercially available *β*-ketoesters were transformed, after the known procedure of Molander, into the 1,3-bis-silyl enol ethers **3** (**Scheme 2.2**). Reactions occurred with yields according to the literature and all products were already reported.

The 1,3-bis-silyl enol ethers **3** used for control experiments are listed in the following table.

Table 2.1: 1,3-bis silyl enol ethers **3**

3	R^1	R^2	**3**	R^1	R^2
a	H	OMe	**s**	*n*Bu	OEt
b	H	OEt	**t**	*n*Pent	OMe
c	H	OBn	**u**	*i*Pent	OMe
d	H	O*i*Pr	**v**	*n*Hex	OMe
e	H	O*n*Bu	**w**	*n*Hept	OEt
f	H	O*i*Bu	**x**	*n*Oct	OMe
g	H	O*i*Pent	**y**	*n*Non	OMe
h	H	O*n*Oct	**z**	*n*Undec	OMe
i	H	$O(CH_2)_2OMe$	**aa**	*n*Dodec	OMe
j	Me	OMe	**ab**	*n*Tetradec	OMe
k	Et	OMe	**ac**	*n*Hexadec	OMe
l	Et	OEt	**ad**	$(CH_2)_2Ph$	OMe
m	OMe	OMe	**ae**	$(CH_2)_3Ph$	OMe
n	Cl	OMe	**af**	$(CH_2)_3Ph$	OEt
o	Allyl	OMe	**ag**	$(CH_2)_3Cl$	OMe
p	*n*Pr	OMe	**ah**	$(CH_2)_4Cl$	OMe
q	*i*Pr	OEt	**ai**	$(4\text{-}FC_6H_4)CH_2$	OMe
r	*n*Bu	OMe	**aj**	H	Ph

All prepared *β*-ketoesters were stable at room temperature. 1,3-Bis-silyl enol ethers were stored at -20°C under dry and inert gas atmosphere for several months without decomposition.

2.3 Conclusions

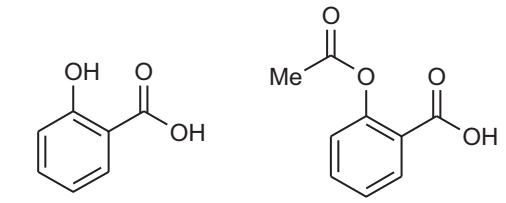
The described procedure allows the synthesis of 1,3-bis-silyl enol ethers as electroneutral 1,3-dicarbonyl dianions equivalents. These masked dianions can be used as reagent for cyclization reactions. The option of changing the alkyl rest and their high reactivity with many substrates containing key functional groups, gave the possibility to reach new heterocycles and aromatic rings for the natural product synthesis. This matter will be elaborated in the next chapters.

Chapter 3

Salicylates vs. Pyrones vs. Cyclohexenones

3.1 Introduction

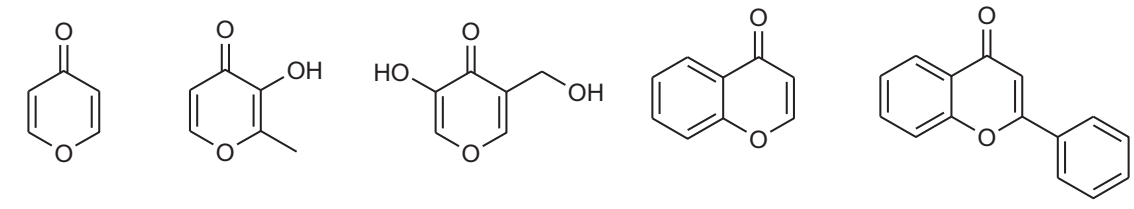
Acetylsalicylic acid (**Figure 3.1)**, also known as Aspirin®, is the most spread drug of the group of salicylates. They and their precursor the salicylic acid (**Figure 3.1)** possess analgesic, antipyretic and anti-inflammatory properties. Aspirin® was the first discovered member of the class of non-steroidal anti-inflammatory drugs. Other prominent members of this group are Ibuprofen and Naproxen. They have the same mechanism of action by inhibition of the enzyme cyclooxygenase. The broad therapeutic uses and the minor side effects make Aspirin® today one of the most used medications in the world.



Salicylic acid Acetylsalicylic acid

Figure 3.1: The most known salicylates.

The *γ*-pyrone forms the central core of several natural compounds like maltol and kojic acid and of complex structures like chromones and flavones (**Figure 3.2)**. Maltol is the natural organic compound that gives malt its sweet flavor. It is used as essence for fragrances and flavor enhancer for foods (E 636). Kojic acid, produced by some species of fungi, is a well-known tyrosinase (monophenol monooxygenase) inhibitor. Though, simple Kojic acid has insufficient inhibitory activity and stability and has low cell permeability. To enhance this, metal coordination compounds were prepared, since it is known that maltol and kojic acid are good chelation agents, binding to metal centers. [21]



γ-Pyrone Maltol Kojic acid Chromone scaffold Flavone scaffold

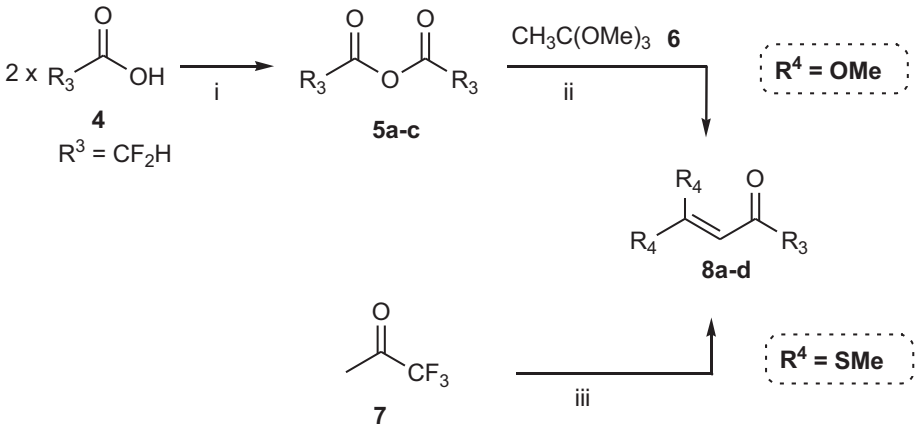
Figure 3.2: Natural compounds with *γ*-pyrone core.

3.2 Results and discussions

Recently, we have reported the $TiCl_4$-mediated cyclocondensation of 1,3-bis-silyl enol ethers **3** with 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one. These reactions provide a convenient and regioselective approach to 4-methoxy-6-(trifluoromethyl)salicylates. [22] In the present thesis, the influence of the Lewis acid on the product distribution of this reaction is discussed. To our surprise, the Me_3SiOTf-mediated cyclization of **3** resulted in the formation of various *γ*-pyrones or cyclohexenoenes, depending on the substrates involved in the reaction. As a result, the reaction afforded the synthesis of different halogen-substituted salicylates, pyrones and cyclohexenones starting from same building blocks but using different Lewis acids.

3.2.1 Preparation of the starting materials

1,3-Bis-silyl enol ethers **3** were prepared in two steps starting from the corresponding *β*-ketoesters, after the description in chapter 2. Changing their substitution pattern and bringing them together with different substrates afforded various functionalized salicylates. Therefore, different butenones **8a-d** (**Scheme 3.1**, **Table 3.1**) were synthesized. The 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one (**8a**), 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) and the 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) were prepared by reaction of the respective acetic acid anhydride **5a-c** with 1,1,1-trimethoxyethane **6** after a known procedure. [23] Anhydride **5a** and **5b** are commercially available. Only anhydride **5c** required a one-step synthesis, starting from 2,2-difluoroacetic acid **4**. [24] The synthesis of 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one **8d** followed an alternative procedure starting from the commercially available 1,1,1-trifluoroacetone **7**. [25]



Scheme 3.1: Synthesis of **5c**: i) P_2O_5, 140°C, 2 h. Synthesis of **8a-c**: ii) pyridine, CH_2Cl_2, 0 - 20°C, 12 h. Synthesis of **8d**: iii) 1) NaH, CS_2, DMF, 0 - 20°C, 1 h; 2) MeI 0 - 20°C, 18 h.

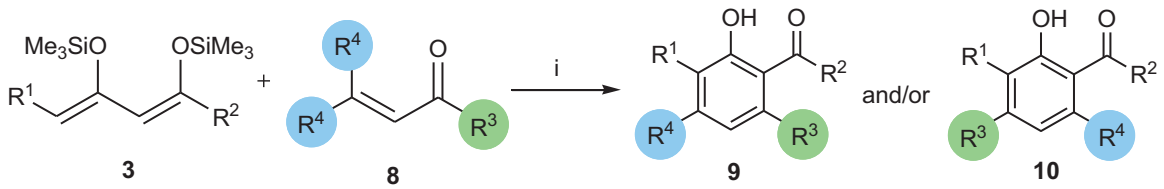
Table 3.1: Synthesis of **8a-d**.

8	R^3	R^4	Yield [a] %
a	CF_3	OMe	75
b	CF_2H	OMe	76
c	CCl_3	OMe	60
d	CF_3	SMe	44

[a] Yields of isolated products.

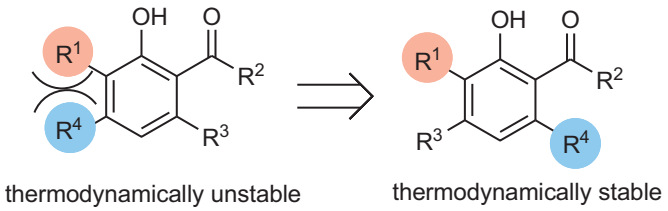
3.2.2 $TiCl_4$-mediated cyclocondensation

The $TiCl_4$-mediated reaction of the dielektrophile **8** and the dinucleophile **3** afforded the salicylates **9** respectively **10** and the phenol **10ak** in moderate yields (**Scheme 3.2**, **Table 3.2**).



Scheme 3.2: Synthesis of **9** and **10**: i) $TiCl_4$, CH_2Cl_2, -78 - 20°C, 12 - 14 h.

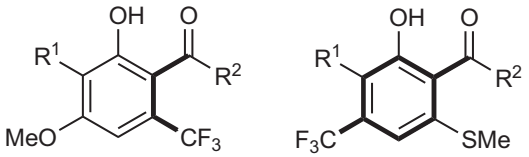
The most reactions proceeded with very good regioselectivities, though, there are special cases were the regioselctivity was influenced by the steric effects of the substituents. The reaction of dienes **3j,u,ah,ad** with enone **8c** and the reaction of enone **8d** with all 1,3-bis-silyl enol ethers **3**, containing a terminal substituent ($R^1 \neq H$), afforded mixtures of regioisomers. Obviously the larger the terminal substituents R^1 and R^4 are the less regioselectivity is observed, which can be explained by the increased steric effects of bigger substituents (**Scheme 3.3**, **Table 3.2**).



Scheme 3.3: Regioisomer formation due to steric effects.

The CF_3-group of salicylates **9a-q** is located on *ortho* position to the ester group, while for salicylates **10aj-10aq** the CF_3-group is on *para* position to the ester group (**Scheme 3.4**). Obviously, the change in the regioselectivity is a result of the replacement of the methoxy group by methylthio group in the 1,1,1-trifluorobut-3-en-2-one. This fact proposes different

mechanistic pathways. Apparently, the addition of 1,3-bis-silyl enol ethers to keteneacetals proceeds by a 1,4-pathway, while the addition to thioketeneacetals occurs by 1,2-addition. [26] Another reason might be the fact that the thio group is larger than the methoxy group.



ortho — **9a-q** | *para* — **10aj-10aq**

Scheme 3.4: OMe vs. SMe substitution pattern.

Table 3.2: Synthesis of **9** and **10**.

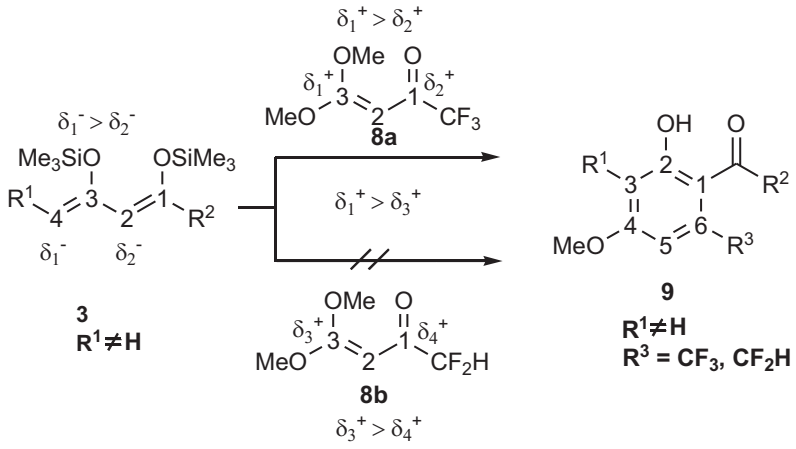
3	8	R^1	R^2	R^3	R^4	9/10	9:10	Yield [a] %
a	**a**	H	OMe	CF_3	OMe	**9a**	-	47[b]
b	**a**	H	OEt	CF_3	OMe	**9b**	-	34[b]
c	**a**	H	OBn	CF_3	OMe	**9c**	-	32[b]
d	**a**	H	O*i*Pr	CF_3	OMe	**9d**	-	36[b]
i	**a**	H	$O(CH_2)_2OMe$	CF_3	OMe	**9e**	-	35[b]
j	**a**	Me	OMe	CF_3	OMe	**9f**	-	34[b]
l	**a**	Et	OEt	CF_3	OMe	**9g**	-	44[b]
o	**a**	Allyl	OMe	CF_3	OMe	**9h**	-	42[b]
p	**a**	*n*Pr	OMe	CF_3	OMe	**9i**	-	41[b]
r	**a**	*n*Bu	OMe	CF_3	OMe	**9j**	-	40[b]
v	**a**	*n*Hex	OMe	CF_3	OMe	**9k**	-	30[b]
x	**a**	*n*Oct	OMe	CF_3	OMe	**9l**	-	30[b]
z	**a**	*n*Undec	OMe	CF_3	OMe	**9m**	-	30[b]
ad	**a**	$(CH_2)_2Ph$	OMe	CF_3	OMe	**9n**	-	38[b]
ae	**a**	$(CH_2)_3Ph$	OMe	CF_3	OMe	**9o**	-	43[b]
m	**a**	OMe	OMe	CF_3	OMe	**9p**	-	50[b]
ag	**a**	$(CH_2)_3Cl$	OMe	CF_3	OMe	**9q**	-	57[b]
a	**b**	H	OMe	CF_2H	OMe	**9r**	-	35
b	**b**	H	OEt	CF_2H	OMe	**9s**	-	33
c	**b**	H	OBn	CF_2H	OMe	**9t**	-	30
d	**b**	H	O*i*Pr	CF_2H	OMe	**9u**	-	58
e	**b**	H	O*n*Bu	CF_2H	OMe	**9v**	-	37
g	**b**	H	O*i*Pent	CF_2H	OMe	**9w**		24
i	**b**	H	$O(CH_2)_2OMe$	CF_2H	OMe	**9x**	-	30
j	**b**	Me	OMe	CF_2H	OMe	**9y**	-	10

a	**c**	H	OMe	CCl_3	OMe	**9z**	-	30
c	**c**	H	OBn	CCl_3	OMe	**9aa**	-	30
j	**c**	Me	OMe	CCl_3	OMe	**9ab + 10ab**	1:0.1	42
k	**c**	Et	OMe	CCl_3	OMe	**9ac**	-	46
o	**c**	Allyl	OMe	CCl_3	OMe	**9ad**	-	32
u	**c**	*i*Pent	OMe	CCl_3	OMe	**9ae + 10ae**	1:0.3	41
ag	**c**	$(CH_2)_3Cl$	OMe	CCl_3	OMe	**9af**	-	45
ah	**c**	$(CH_2)_4Cl$	OMe	CCl_3	OMe	**9ag + 10ag**	1:0.2	35
ad	**c**	$(CH_2)_2Ph$	OMe	CCl_3	OMe	**9ah + 10ah**	1:0.2	60
ai	**c**	$(4\text{-}FC_6H_4)CH_2$	OMe	CCl_3	OMe	**9ai**	-	20
a	**d**	H	OMe	CF_3	SMe	**10aj**	-	52[c]
b	**d**	H	OEt	CF_3	SMe	**10ak**	-	51[c]
c	**d**	H	OBn	CF_3	SMe	**10al**	-	51[c]
d	**d**	H	O*i*Pr	CF_3	SMe	**10am**	-	56[c]
f	**d**	H	O*i*Bu	CF_3	SMe	**10an**	-	49[c]
g	**d**	H	O*i*Pent	CF_3	SMe	**10ao**	-	56[c]
h	**d**	H	O*n*Oct	CF_3	SMe	**10ap**	-	55[c]
aj	**d**	H	Ph	CF_3	SMe	**10aq**	-	39[c]
j	**d**	Me	OMe	CF_3	SMe	**9ar +10ar**	0.1:1	69[c]
k	**d**	Et	OMe	CF_3	SMe	**9as +10as**	0.1:1	54[c]
p	**d**	*n*Pr	OMe	CF_3	SMe	**9at + 10at**	0.1:1	39[c]
q	**d**	*i*Pr	OEt	CF_3	SMe	**9au +10au**	0.4:1	50[c]
r	**d**	*n*Bu	OEt	CF_3	SMe	**9av+10av**	0.5:1	30[c]
t	**d**	*n*Pent	OEt	CF_3	SMe	**9aw + 10aw**	1:1	36[c]
w	**d**	*n*Hep	OEt	CF_3	SMe	**9ax+ 10ax**	0.7:1	34[c]
x	**d**	*n*Oct	OMe	CF_3	SMe	**9ay + 10ay**	0.7:1	50[c]
o	**d**	Allyl	OMe	CF_3	SMe	**9az + 10az**	0.5:1	44[c]
ag	**d**	$(CH_2)_3Cl$	OMe	CF_3	SMe	**9ba + 10ba**	0.4:1	54[c]
ae	**d**	$(CH_2)_3Ph$	OEt	CF_3	SMe	**9bb + 10bb**	1:1	23[c]

[a] Yields of isolated products.
[b] Yields already reported. [27]
[c] Yields obtained during master thesis support. [28]

Having established the 1,2-addition as the major mechanistic pathway for the reaction of dithioketeneacetal **8d**, it was interesting to study the reaction of **8d** with 1,3-bis-silyl enol ethers **3** containing a terminal substituent. As described, the regioselectivity of the nucleophilic attack depends on the steric effects of the substituents. In fact, the regioselectivity dropped, allthough the 1,2-attack was still dominant. The reactions afforded a mixture of salicylates **9ar-9bb** (1,4-addition) and salicylates **10ar–10bb** (1,2-addition) in variable conversions (23–69%) and proportions (**Table 3.2**). Additionally, the less reactive benzoyl acetone derived diene **3aj** gave the benzophenone **10aq** with 39% yield.

The reaction of enone **8b** with terminal substituted diene **3** did not take place. Therefore the synthesis of C-3 substituted CF_2H-salicylates ($R^1 \neq H$) was not possible (**Scheme 3.5**). The terminal carbon atom C-4 of the 1,3-bis-silyl enol ethers **3** has the highest electron density and the C-3 carbon atom of butenones **8** has the lowest electron density. The substituents R^1-R^4 have strong influence on the electronic state of these molecules and on the product distribution. For instance, replacing the CF_3-group with the CF_2H-group leads to a weaker electron withdrawing effect and to a higher electron density at the C-3 atom of the butenone. This leads to a reduced electropilicity of the butenone. This fact and the steric hindrance of R^1, could explain why the synthesis C-3 substituted 6-difluoromethyl-4-methoxysalicylates ($R^1 \neq H$) failed.



Scheme 3.5: CF_3 vs. CF_2H; inductive effect on the electronic state of the enone **8**.

The optimization of the reaction showed that the temperature and the stoichiometry play an important role. Best yields were obtained when the reaction took place under cooling conditions (-78 - 20°C), with excess of silyl enol ether **3** (2.0 equiv) and high concentrated solution (**Table 3.3**). The optimization of **9a** has been already reported. [29]

The moderate yields can be explained by a possible hydrolysis or $TiCl_4$-mediated oxidative dimerization of diene **3**. This type of process has been previously reported. [30] The reaction control by TLC-method shows a small amount of *β*-ketoester formed by hydrolysis of the remaining excess of diene **3**. Its chromatographic separation from the product was difficult in some cases. Therefore, practical problems during the chromatographic purification also influenced the yields.

The products are stable at 20 °C for several months without decomposition. No sensitivity against air or water was observed.

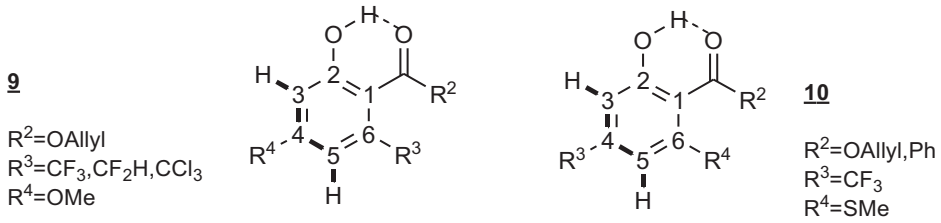
Table 3.3: Optimization of the synthesis of **9u**, **9z** and **10am**.

	Ratio of 8:3 (mmol)	CH_2Cl_2 (mL)	Yield [a] (%)
9u	1:2	2	48
	1:1	5	38
	1:2	5	58
	1:3	5	42
	1:2	10	55
9z	1:2	1	28
	1:1	2	10
	1:2	2	30
	1:3	2	25
	1:2	5	27
10am	1:1	0	26
	1:1	1	33
	1:2	1	56
	1:3	1	21
	1:2	2	38
	1:2	5	39

[a] Yields of isolated products.

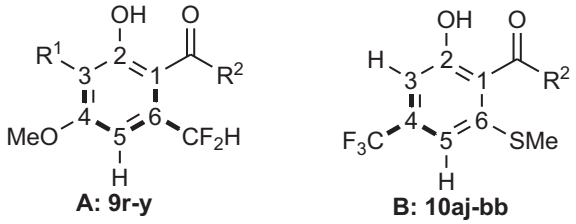
3.2.2.1 Structure identification

All structures were confirmed by spectroscopic methods NMR, IR, mass spectrometry and elemental analysis. The hydroxyl protons showed low field ^{1}H-NMR shifts (12 ppm), indicating that the protons were involved in intramolecular hydrogen bond with the ester group (**Scheme 3.6**). This seemed not to be the case for the benzophenone **10aq.** The shift to a higher field (8 ppm) indicated the absence or weakness of the hydrogen bond. In addition, long-range couplings were observed between protons H-3 and H-5 of C-3-unsubstituted salicylates ($^4J_{H,H}$ ~ 3 Hz). The CF_2H-group appeared as a triplet at ca. 7 ppm ($^2J_{H,F}$ ~ 56 Hz).



Scheme 3.6: Observations from ^{1}H-NMR spectra.

The ^{13}C-NMR Spectroscopy confirmed the structures of R^F-substituted salicylates **10** and **9**. Long-run ^{13}C-NMR analysis gave spectra with typical triplets and quartets and expected $^{1}J_{C,F}$ $^{2}J_{C,F}$, $^{3}J_{C,F}$ coupling constants. The CF_2H moiety appears as a triplet at ca. 112 ppm with a coupling constant $^{1}J_{C,F}$ ~ 238 Hz. A triplet with $^{3}J_{C,F}$ = 4.0 Hz was observed for carbon atom C-1 clearly showing that the CF_2H-group is located *ortho* to the ester group (**A, Scheme 3.7**). There is no proof that the CF_2H-group is located at carbon atom C-4, since there is no $^{3}J_{C\text{-}F}$–coupling to C-3. In fact, there exists a $^{5}J_{C\text{-}F}$-long-range-coupling to C-3 of ca. 2 Hz.

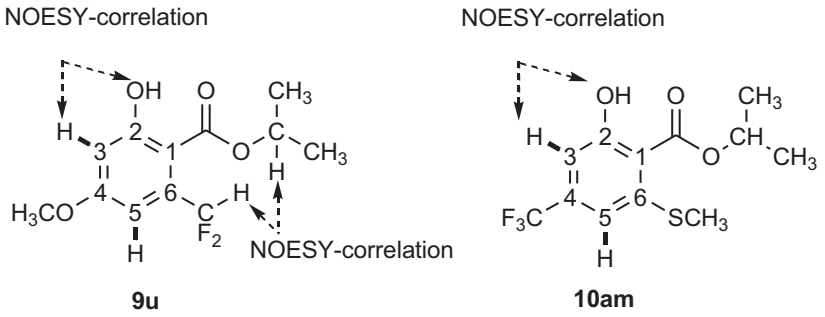


Scheme 3.7: Observations from ^{13}C-NMR spectra.

Quartets of a quaternary carbon were observed at 123 ppm, with $^{1}J_{C\text{-}F}$ coupling constants of approximately 273 Hz, indicating the CF_3-group. Long-run ^{13}C-NMR spectra of compounds **10aj-bb** show no couplings to carbon atom C-1. According to DEPT-experiments there are two quartets ($^{3}J_{C\text{-}F}$ = 4 Hz) of two tertiary C-atoms that match to C-3 and C-5. Conclusively, C-3 unsubstituted thiosalicylates have the CF_3-group on *para* position to the ester group (**B, Scheme 3.6**).

Furthermore, the structures of **9u** and **10am** were confirmed by 2D NMR experiments (NOESY and HMQC). The correlations are shown in **Scheme 3.8**. The NOESY-experiment shows a weak correlation between the proton of the CF_2H-group and the CH-group of the ester moiety (**9u**). NOESY-correlations were also observed between proton H-3 and the hydroxyl proton. In the HMQC-experiment, proton H-3 gives cross-peaks with carbon atom C-3, which appears as a broad singlet due to the C-F-long-range-coupling (**9u**) or as a

quartet (**10am**), respectively. Proton H-5 correlates with carbon atom C-5, which appears as a triplet resp. quartet.



Scheme 3.8: Observations from NOESY and HMQC experiments.

The ^{19}F-NMR spectra show duplets for the CF_2H-group that appear at ca. -113 ppm ($^2J_{F,H}$ ~ 56 Hz). The CF_3-group appears as a singlet at ca. -60 ppm. The theoretical shifts for CF_3 attached to aromatics are at -64 ppm. [31]

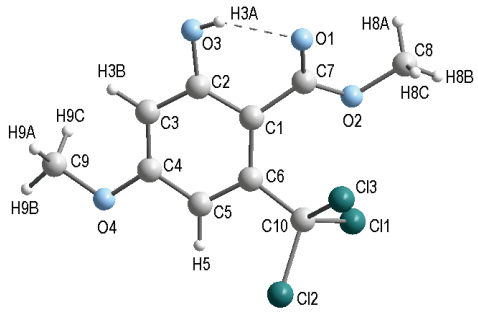
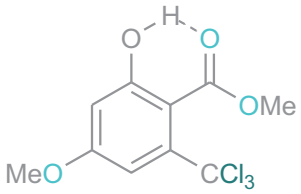
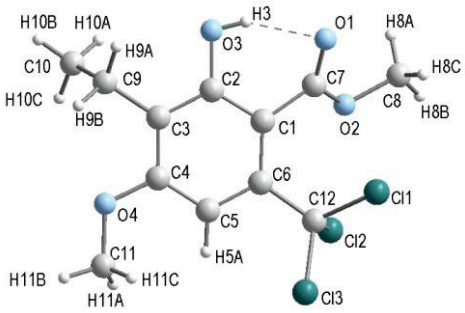
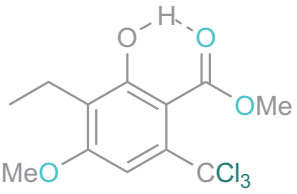
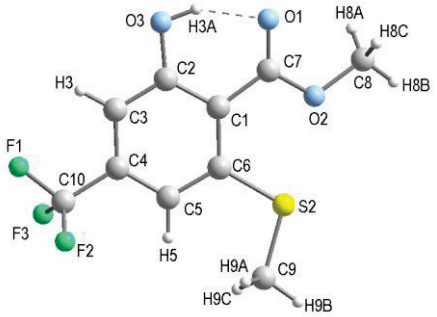
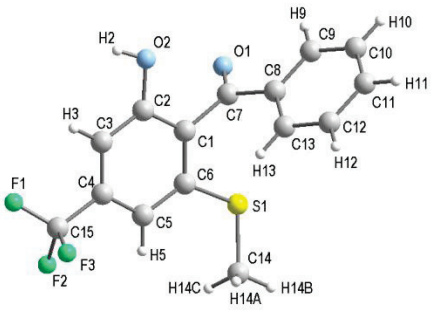
IR spectra confirm the presence of the OH and aromatic CH-groups, showing weak to middle intensive bands at ~ 3000 cm^{-1}. Strong C=O stretching bands are observed at 1650 – 1730 cm^{-1}.

The structures of **9z, 9ac, 10aj** and **10aq** were independently confirmed by X-ray crystal structure analysis (**Table 3.4**). [32] The lengths of the aromatic double bonds are as expected ca. 1.39 Å and the aromatic angles 118 - 120° reach the theoretical value. Interesting are the values of the torsion angle O1-C7-C1-C2 between the oxygen atom of the ester group and the aromatic ring. While for compounds **9z**, **9ac** and **10aj** the torsion angle of 12 - 37° allows the formation of H-bonds O3H3···O1 with lengths from 1.72 - 1.94 (near to theoretical length), for **10aq** the 81° torsion angle makes the O1-H2 distance too long for a H-bond (**Table 3.3**). This remark matches with the observations from the ^{1}H-NMR experiment.

Table 3.3: Torsion angle and H-bond length.

	9z	**9ac**	**10aj**	**10aq**
Torsion angle (°)	34	37	12	81
H-bond (Å)	1.94	1.88	1.72	3.81

Table 3.4: Crystal structures of salicylates **9z, 9ac, 10aj, 10aq**.

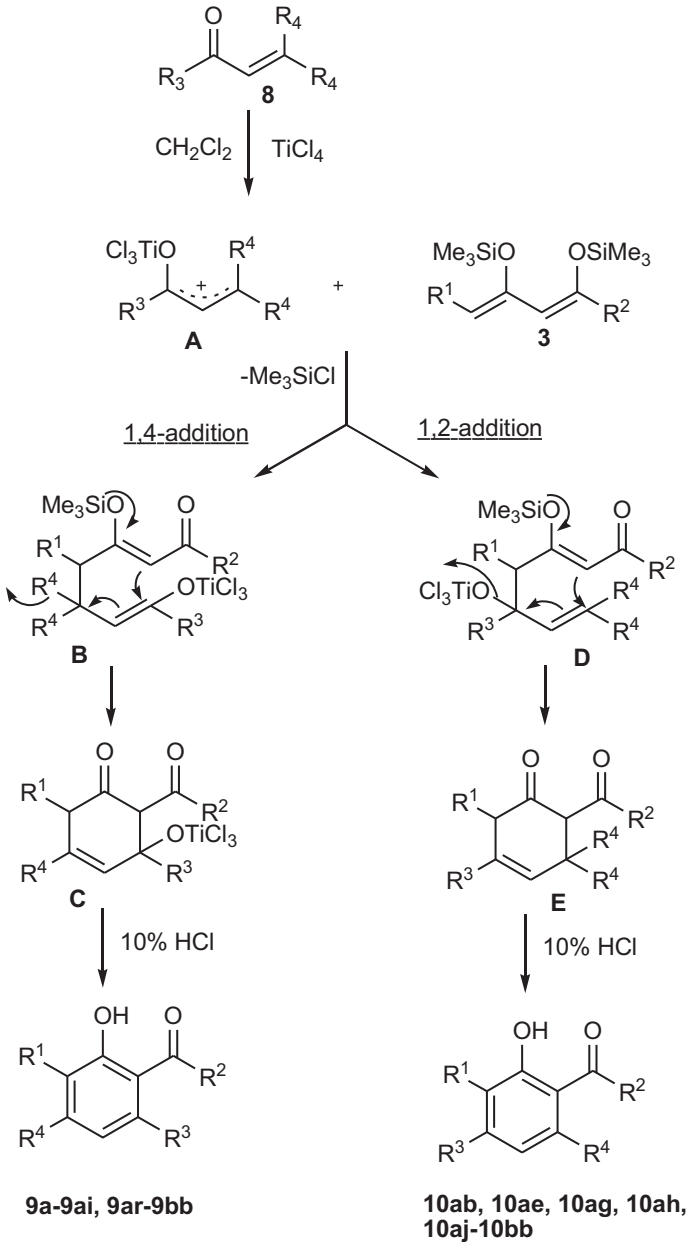
Crystal structure	Compound	Structure
	**9z**	
	**9ac**	
	**10aj**	
	**10aq**	

3.2.2.2 Mechanistic pathway

The addition of 1,3-bis-silyl enol ethers to keteneacetals proceeds by a 1,4-pathway, while the addition to thioketeneacetals occurs by 1,2-addition.

The regioselective formation of salicylates **9** can be explained by reaction of **8** with $TiCl_4$ as a Lewis acid, to give cation **A** containing an allylic carbon unit, followed by 1,4-addition of the terminal carbon atom of **3** onto the *β*-carbon atom of **A** (intermediate **B**) and

subsequent cyclization by attack of the central carbon atom of the bis-silyl enol ether onto the activated carbonyl group of **8** giving intermediate **C**. Aromatization follows giving **9** (**Scheme 3.9**).

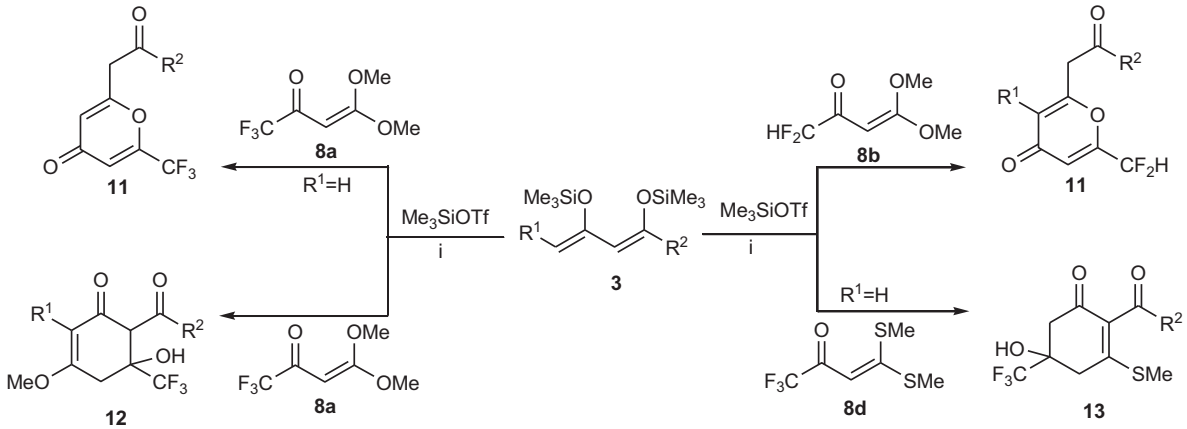


Scheme 3.9: Possible mechanism of the formation of **9** and **10**.

The formation of the other regioisomer **10**, proceeds by 1,2-addition of the terminal carbon atom of **3** onto the activated carbonyl group of **A** (intermediate **D**), cyclization (intermediate **E**), and subsequent aromatization under mild acidic conditions.

3.2.3 Me_3SiOTf-mediated cyclocondensation

The reaction of butenones **8** with 1,3-bis-silyl enol ethers **3**, carried out in the presence of Me_3SiOTf, instead of $TiCl_4$, resulted in the formation of *γ*-pyrones **11** or cyclohexenones **12** and **13**, depending on the substituents R^1, R^3 and R^4 (**Scheme 3.10**, **Table 3.5**).



Scheme 3.10: Synthesis of **11**, **12** and **13**: i) Me_3SiOTf, CH_2Cl_2, -78 - 20°C, 12-14 h.

The Me_3SiOTf-mediated reactions of **8a,b** with 1,3-bis-silyl enol ethers containing no terminal substituent (R^1 = H), provided *γ*-pyrones **11a-g**. The reaction conditions were optimized for the synthesis of derivatives **11d** and **11g** (**Table 3.6**). The yield could be significantly improved when the reaction was carried out in a more dilute solution, on the contrary to the $TiCl_4$-mediated syntheses of salicylates **3**, that was carried out in a highly concentrated solution.

Table 3.6: Optimization of the synthesis of **11d,g,i** and **12i**.

	Ratio of 8:3 (mmol)	CH_2Cl_2 (mL)	Yield [a](%) 11	12
11d	1:2	1	42	0
	1:2	2	50	0
	1:2	10	64	0
	1:2	15	60	0
	1:1	15	31	0
11g	1:2	5	34	0
	1:2	10	60	0
	1:2	15	55	0
11i/12i	1:1	2	10	15
	1:2	5	24	19
	1:1	10	9	20
	1:2	10	12	38
	1:3	10	10	12
	1:2	15	12	26

[a] Yields of isolated products

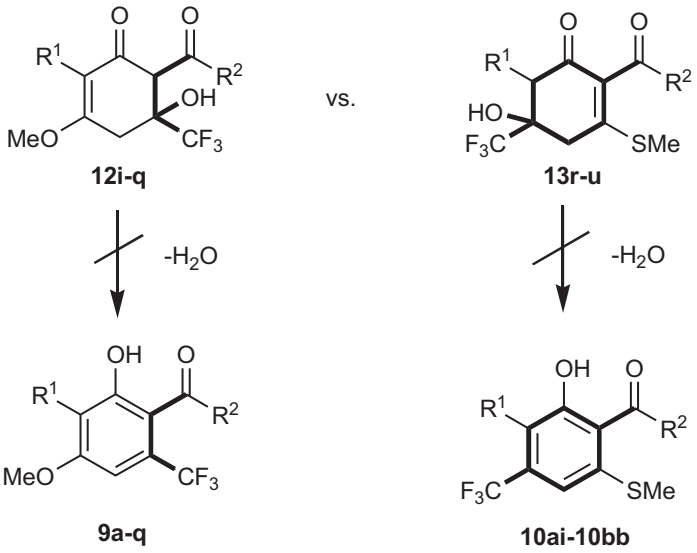
On the one hand, the Me_3SiOTf-mediated reactions of **8b** with 1,3-bis-silyl enol ethers that contain an alkyl group located at carbon C-4 of the diene moiety ($R^1 \neq H$), afforded also the *γ*-pyrone **11h**. On the other hand, the reaction of **8a** under same conditions provided the cyclohexenones **12i-q**. Alone the cyclization of **8a** with diene **3j** was of special interest because both *γ*-pyrone **11i** (12%) and cyclohexenone **12i** (38%) could be isolated. This can be explained by the fact that the steric influence of the methyl group (R^1 = Me) is relatively small. The influence of the reaction conditions on the product distribution was studied also for this reaction (**Table 3.6**). The best yield for **12i** was observed when 2.0 equiv of diene **3j** was used and when the cyclization was carried out in a relatively dilute solution.

Table 3.5: Synthesis of **11**, **12** and **13**.

3	**8**	**11/12/13**	R^1	R^2	R^3	R^4	Yield [a] %		
							11	**12**	**13**
a	**a**	**a**	H	OMe	CF_3	OMe	63	0	0
b	**a**	**b**	H	OEt	CF_3	OMe	69	0	0
c	**a**	**c**	H	OBn	CF_3	OMe	32	0	0
d	**a**	**d**	H	O*i*Pr	CF_3	OMe	64	0	0
f	**a**	**e**	H	O*i*Bu	CF_3	OMe	64	0	0
i	**a**	**f**	H	$O(CH_2)_2OMe$	CF_3	OMe	40	0	0
b	**b**	**g**	H	OEt	CF_2H	OMe	60	0	0
p	**b**	**h**	*n*Pr	OMe	CF_2H	OMe	32	0	0
j	**a**	**i**	Me	OMe	CF_3	OMe	12	38	0
k	**a**	**j**	Et	OMe	CF_3	OMe	0	50	0
t	**a**	**k**	*n*Pent	OEt	CF_3	OMe	0	39	0
u	**a**	**l**	*i*Pent	OMe	CF_3	OMe	0	55	0
w	**a**	**m**	*n*Hep	OEt	CF_3	OMe	0	35	0
x	**a**	**n**	*n*Oct	OMe	CF_3	OMe	0	62	0
y	**a**	**o**	*n*Non	OMe	CF_3	OMe	0	57	0
aa	**a**	**p**	*n*Dodec	OMe	CF_3	OMe	0	58	0
ab	**a**	**q**	*n*Hexdec	OMe	CF_3	OMe	0	54	0
a	**d**	**r**	H	OMe	CF_3	SMe	0	0	39
e	**d**	**s**	H	O*n*Bu	CF_3	SMe	0	0	52
g	**d**	**t**	H	O*i*Pent	CF_3	SMe	0	0	36
h	**d**	**u**	H	O*n*Oct	CF_3	SMe	0	0	34

[a] Yields of isolated products

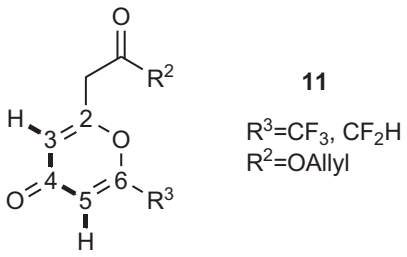
Starting with **8d** and dienes **3a,e,g,h**, which do not contain a terminal substituent (R^1 = H), the CF_3-substituted cyclohexenones **13r-u**, which are regioisomeric to **12i-q**, were obtained. Obviously, the change in the regioselectivity was again a result of the replacement of the methoxy group by methylthio group and the 1,4-addition vs. 1,2-addition in the mechanistic pathways. In contrast to the formation of products **9** and **10**, no elimination of the hydroxyl group and aromatization occured when the Me_3SiOTf was used (**Scheme 3.11**).



Scheme 3.11: Regioselctivity of **12** vs. **13**.

3.2.3.1 Structure identification

The structures were confirmed by modern analytic methods like NMR, IR, mass spectrometry and elemental analysis. Characteristic for *γ*-pyrones are the ^{1}H-NMR signals of H-3 and H-5 protons (**Scheme 3.12**), which appear as doublets in the range of δ ~ 6 ppm with $^4J_{H,H}$ ~ 3 Hz. The CF_2H-group appears as a triplet at ca. 6 ppm.



Scheme 3.12: Observations from ^{1}H-NMR spectra.

Long-run ^{13}C-NMR-Spectroscopy showed typical quartets for the CF_3–substituent and triplets for the CF_2H-substituent with expected $^1J_{C,F}$, $^2J_{C,F}$, $^3J_{C,F}$ coupling constants. Quartets of a quaternary carbon were observed at 118 - 120 ppm, with $^1J_{C,F}$ coupling constants of

approximately 272 Hz and triplets of a tertiary carbon at 108 ppm, with $^{1}J_{C,F}$ coupling constants of approximately 241 Hz, indicating the CF_3 and CF_2H-group, respectivly. The presence of the *α*-CH_2-group was clearly confirmed by DEPT experiments.

While the ^{19}F-NMR signals of salicylates appear at ca. -60 ppm for CF_3-substitution and at 113 ppm for CF_2H-substitution, the signals of *γ*-pyrones appear at ca. -70 resp. -123 ppm. This shift to lower field can be explained by the fact that the CF_3 and CF_2H-group of the *γ*-pyrones are located in the neighbourhood of the ring oxygen atom.

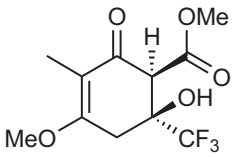
Cyclohexenones **12i-q** showed interesting ^{1}H-NMR spectra with two characteristic dublets in the range of δ = 2.80 - 3.10 ppm for protons H-5 ($^{2}J_{H,H}$ ~ 17 Hz) (**Scheme 3.13**). Their regioisomers, the C-3 unsubstituted thiocyclohexenones **13r-u**, showed multiples for the two protons of H-5 due to the ^{1}H,^{1}H-long-range-couplings to proton H-3. The proton of the OH-group appeared as a singlet at δ ~ 5.6 ppm. The chemical shift suggests that there is a weaker or no intramolecular hydrogen bond to the keto group.

12i-q **13r-u**

Scheme 3.13: Observations from ^{1}H-NMR spectra.

The structures of **11a, 12i,** and **13r** were independently confirmed by X-ray crystal structure analysis (**Table 3.4**). [32] As expected, the cyclohexoneone ring is not planar and the double bonds are 1.35 Å long, shorter than the aromatic double bonds.

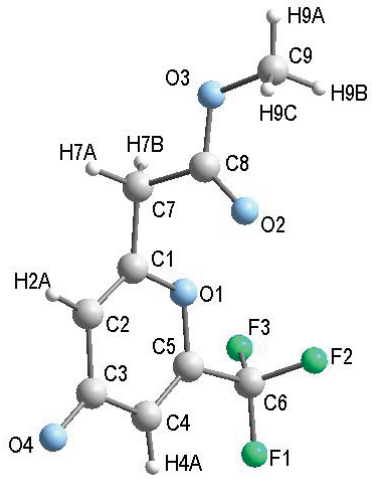
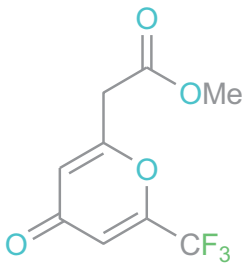
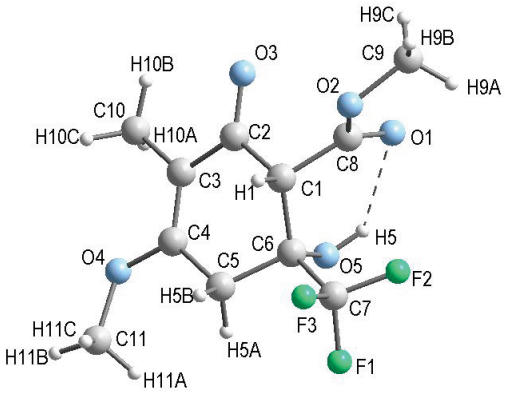
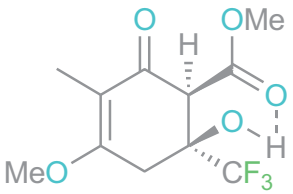
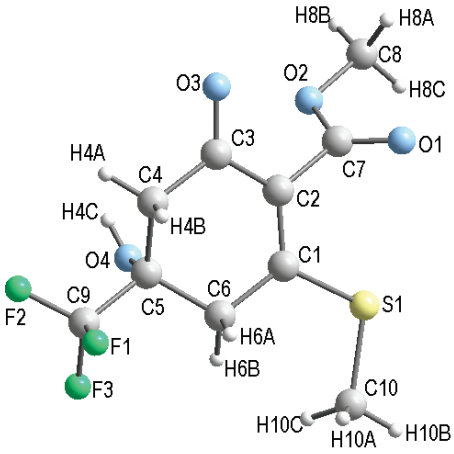
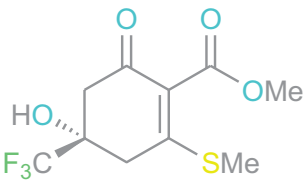
The X-ray structure of **12i** clearly proved the relative configuration of this molecule. The hydroxyl and the ester group are located *cis* to each other and the distance O5H5····O1 is 2.2 Å long (**Scheme 3.14**). The theoretical weak intramolecular hydrogen bond corresponds to the NMR observations.



12i

Scheme 3.14: Relative configuration of **12i**.

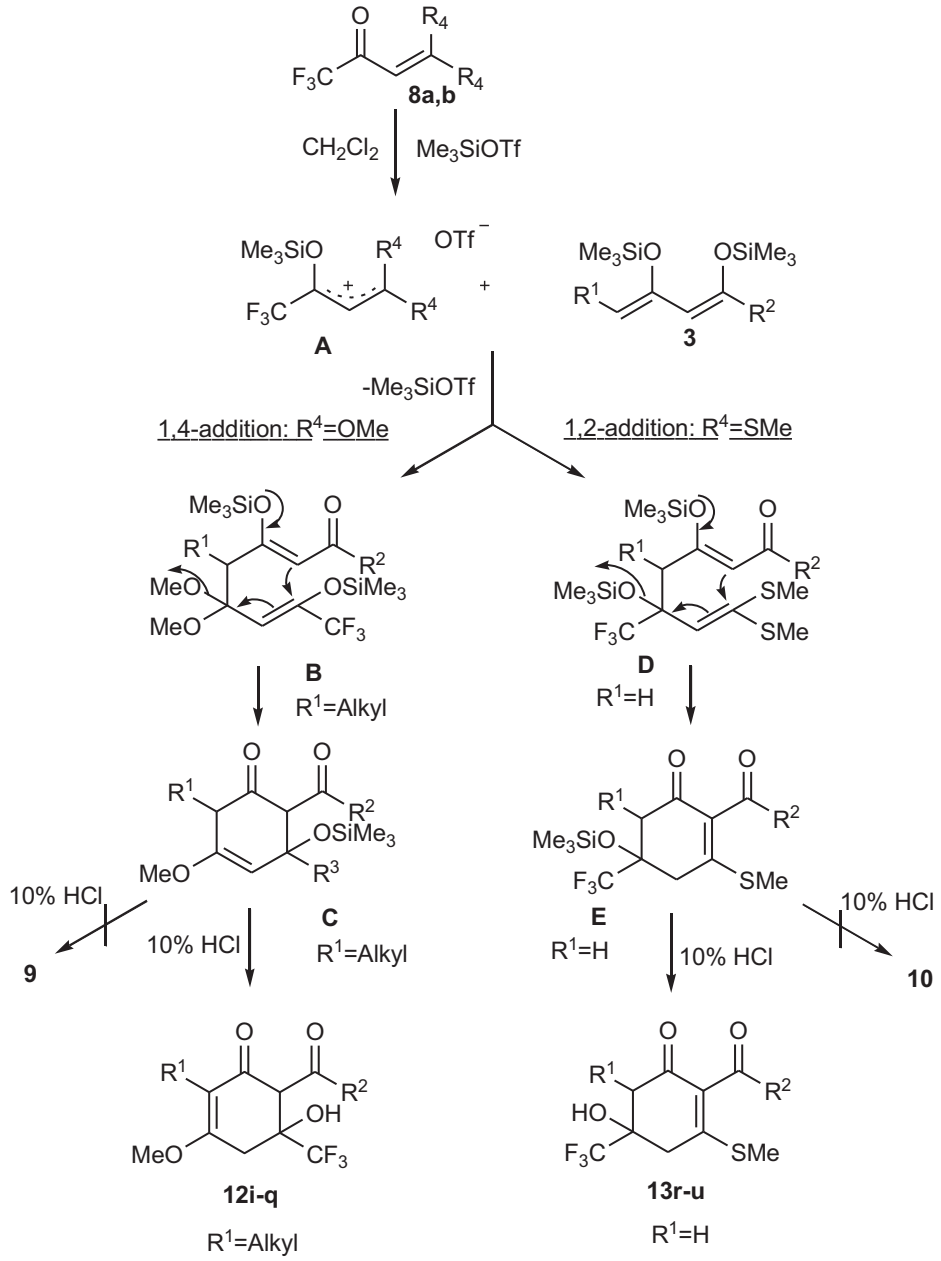
Table 3.7: Crystal structures of **11a, 12i, 13r**.

Crystal structure	Compound	Structure
	**11a**	
	**12i**	
	**13r**	

Under the conditions of GC-MS, elimination of water from cyclohexenones **12** and **13** was observed and only the molecular ions of the aromatized products could be detected. The correct molecular ions were observed when the measurements were carried out using the milder EI (electron ionization) or ESI technique (electrospray ionization).

3.2.3.2 Mechanistic pathway

The formation of cyclohexenones **12i-q** and **13r-u** can be explained by a mechanism related to the one suggested for the formation of products **9** and **10** (**Scheme 3.9** and **Scheme 3.15**).



Scheme 3.15: Possible mechanism for the formation of **12** and **13**.

Activated diene **8a** (Intermediate **A**) reacts with **3** by 1,4-addition on the terminal carbon atom giving intermediate **B**. Cyclization follows, by attack of the central carbon atom of the 1,3-bis-silyl enol ethers onto the activated carbonyl group of **8a** giving intermediate **C**. In contrast to the formation of salicylates **9**, no elimination of the hydroxyl group and aromatization occurs. This result is surprising since the aromatization should be a facile

process. It is assumed that intermediate **C** (**Scheme 3.9**), containing a titanium alkoxide moiety, readily undergoes an elimination of $TiCl_3OH$ and aromatization. On the other side, the intermediate **C** (**Scheme 3.15**) containins a Me_3Si protecting group, which is more stable. Accordingly, the addition of hydrochloric acid (10%), during the aqueous work up, resulted in the cleavage of Si-O bond giving **12i-q**. No cleaveage of C-O bond and no aromatization occurred. Salicylates **9** were not observed.

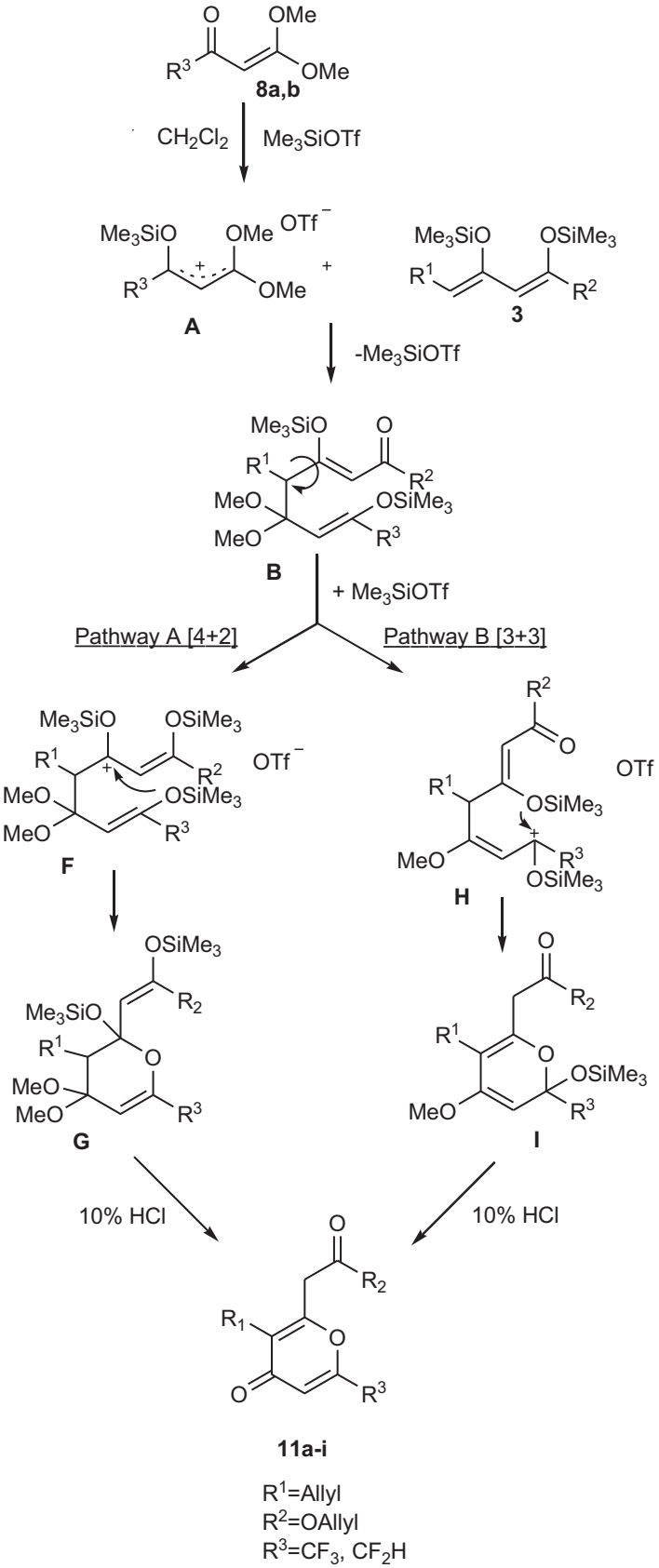
The formation of the other regioisomer **13r-u**, proceeds by 1,2-addition of the terminal carbon atom of **3** onto the activated carbonyl group of **A** (intermediate **D**), cyclization (intermediate **E**) and once more no elimination to **10**.

Due to the novelty of the described reactions, further investigations are necessary in order to establish a mechanistic pathway. For the formation of *γ*-pyrones there are also two assumed mechanisms (**Scheme 3.16**).

Pathway A: The reaction follows the mechanistic type of a formal and sequential [4+2] cyclization. Accordingly, the regioselective formation of the product can be explained by the attack of the terminal carbon atom of **8** onto **A** (intermediate **B**), followed by the activation of the electrophiliic center of the butenone (intermediate **F**) and the subsequent attack of the oxygen atom of **8**. Elimination follows under mild acidic conditions giving **11a-i**.

Pathway B: The reaction follows the mechanistic type of [3+3]-cyclization reactions. It is assumed that the C3-C4-bond of the diene in intermediate **B** rotates, making possible the cyclization via the oxygen of the 1,3-bis-silyl enol ethers (intermediate **H**). The elimination of silanol results in the formation of *γ*-pyrone **11a-i**.

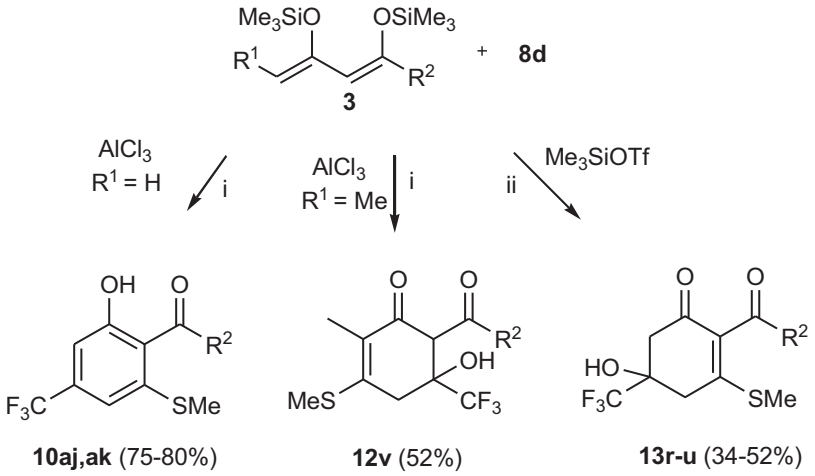
The formation of cyclohexenones **12i-q** rather than *γ*-pyrones can be explained by the steric influence of the R^1 substituent (R^1 = Allyl), leading to a change of the conformation of the intermediate **H** with regard to **B**. As mentioned before, the influence of the methyl group (R^1 = Me) is relatively small making the isolation of both cyclohexenone and pyrone possible.



Scheme 3.16: Possible mechanism of the formation of **11a-i**.

3.2.4 Other Lewis Acids

The influence of different Lewis acids on the product distribution and mechanism of the 1,3-bis-silyl enol ether reactions is now under intensive investigation, including calculations an *in situ* IR-Spectroscopy. The first efforts toward increasing the yields, regisoselectivities and chemoselectivities were tried on the substrate **8d**. When the reaction of **8d** with **3a,b** was mediated by $AlCl_3$ (1.0 equiv) in CH_2Cl_2, salicylates **10aj,ak** were isolated with higher yields (75–80%). Unfortunately the reaction with other 1,3-bis-silyl enol ether gave no results. Only the terminal substituted diene **3j** (R^1 = Me) under $AlCl_3$ conditions provided the stable cyclohexenone **12v** with 52% yield. The structure was similar to the one observed for the other cyclohexenones **12** and so regioselective to **13** (**Scheme 3.17**). Attempts to synthesize other derivatives **12** in the presence of $AlCl_3$/THF as well as salicylates **10** using BF_3/DCM or $ZnCl_2$/THF failed.

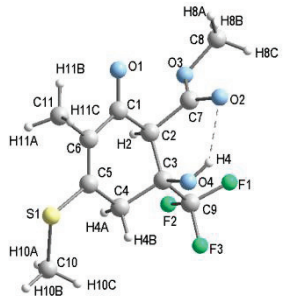
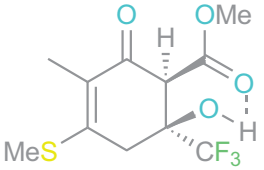


10aj,ak (75-80%) **12v** (52%) **13r-u** (34-52%)

Scheme 3.17: $AlCl_3$ vs. Me_3SiOTf: i) $AlCl_3$, CH_2Cl_2, -78 - 20°C, 14 h. ii) Me_3SiOTf, CH_2Cl_2, -78 - 20°C, 12-14 h.

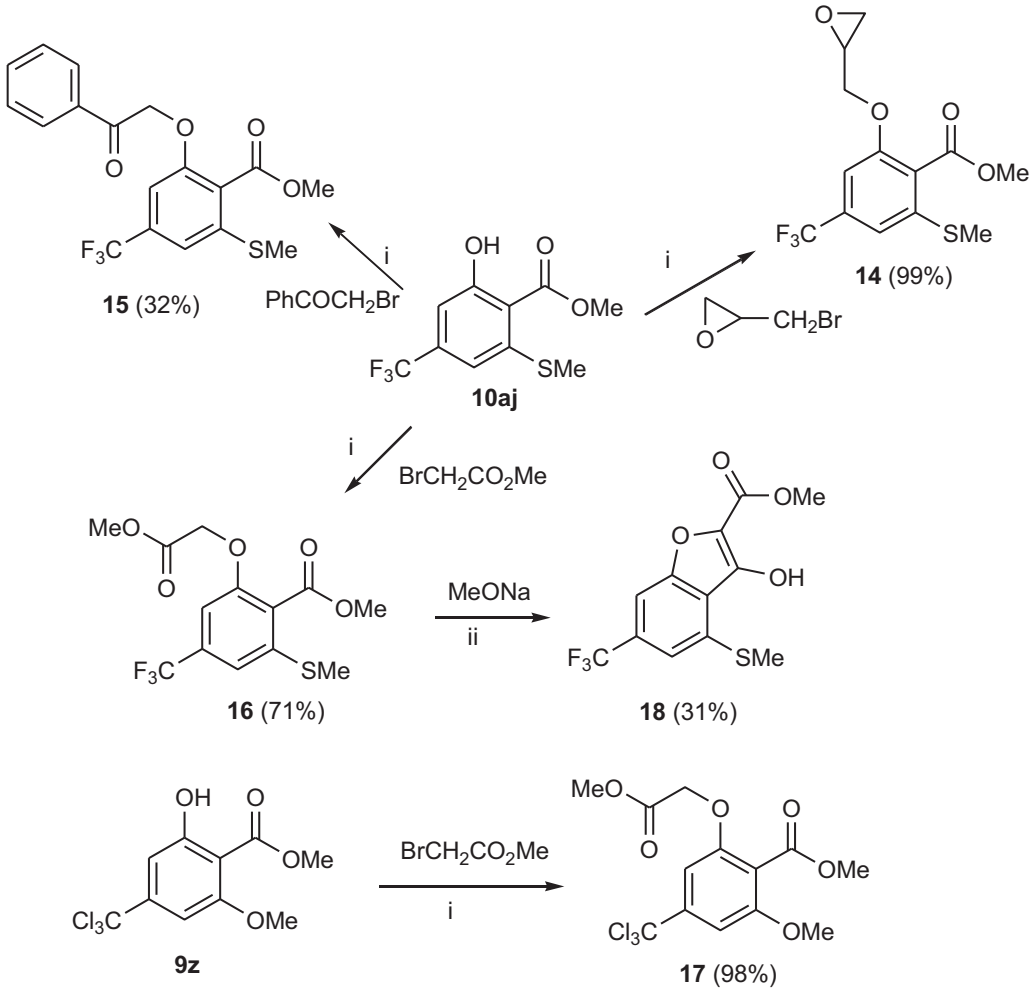
The X-ray crystal structure analysis of **12v** [32] attested the relative configuration of the molecule. The hydroxyl and the ester group are located *cis* to each other and an intramolecular hydrogen bond O4H4···O2 (2.1 Å) is present (**Table 3.8**). The mechanism follows the 1,4-addition pathway like **12i-q**. The change of the reaction route can be explained by the steric influence of the methyl group.

Table 3.8: Crystal structure of **12v**.

Crystal structure	Compound	Structure
	**12v**	

3.3 Applications

The large diversity of products offers a broad follow up chemistry. For example, the methoxy group can be deprotected (BBr_3) and subsequently functionalized (via the corresponding triflate) by palladium(0)-catalyzed cross-coupling reactions. Alkylation or coupling reactions of OH-group could provide interesting building block for the synthesis of more complex compounds. Derivates **10aj** and **9z** were alkylated with 2-bromoacetophenone, 2-(bromomethyl)oxirane or methyl bromoacetate, after a known procedure [33], to give ether derivatives **14–17** with 31–99% yields (**Scheme 3.18**).



Scheme 3.18: Applications of **9z** and **10aj**: i) K_2CO_3 , acetone, 55°C, 8 h; ii) MeONa, MeOH / CH_2Cl_2, 50°C, 6 h.

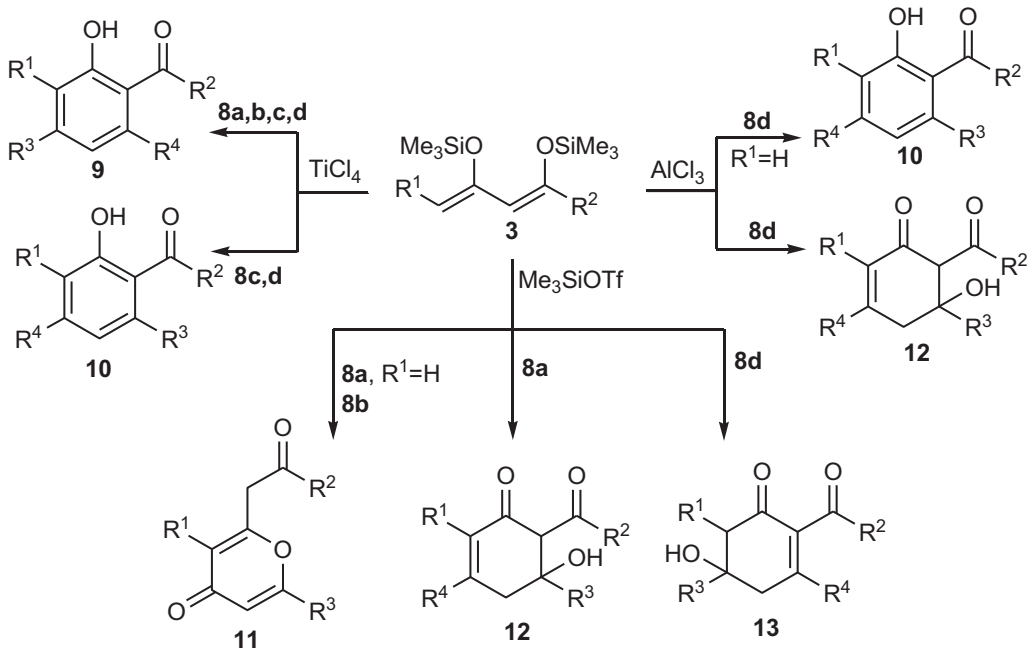
Recently, derivatives of *ortho*-acylated phenols and thiophenols were used for the synthesis of benzofurans and benzothiophenes. [34] Therefore derivate **16** represented an interesting building block for the formation of a benzofuran. Cyclization took place after 6 h heating in methanol in the presence of sodium methoxide giving bezofuran **18** with 31% yield.

3.4 Conclusions

The influence of different Lewis acids on the formal [3+3]-cyclocondensation of 1,3-bis-silyl enol ethers with different halogenated butenones was described for the first time. The $TiCl_4$-mediated reaction afforded a variety of functionalized salicylates (**9** and **10**, **Scheme 3.20**). Depending on the substituents of the butenone and diene the regioselectivity was either very good or droped at all.

The Me_3SiOTf-mediated reaction was also influenced by the steric or the inductive effect of the substituents. Cyclization via the oxygen atom of the diene formed *γ*-pyrones (**11**), while cyclization via carbon atom afforded cyclohexenones (**12**, **13**). Allthough some butenones afforded regioisomers, the reactions took place mostly with very good regioselectivities. The influence of the $AlCl_3$ on the regioselectivity of the cyclization remains unclear. Deeper investigations with these and other lewis acids are in progress.

The products constitute an important structural subunit of a variety of biologically active compounds, which are not readily available by other methods. They could serve as versatile and useful building blocks in the construction of functionalized heterocycles bearing a trifluoromethyl group.



Scheme 3.20: $TiCl_3$ vs. $AlCl_3$ vs. Me_3SiOTf

Chapter 4

1,3-Bis-silyl enol ethers as dienophiles for a novel type of reaction

4.1 Introduction

By virtue of its excellent chemo-, regio- and diastereoselectivity, the Diels-Alder (DA) reaction is one of the most important and elegant methods for the construction of six membered ring compounds. Diels-Alder reactions can be classified into three types: (I) Normal $HOMO_{diene}$-controlled, (II) Neutral and (III) $LUMO_{diene}$-controlled or inverse electron demand Diels-Alder (IEDDA) reactions. [35]

Nitrogen containing compounds are one of the most spread in nature, like for example the alkaloids. Therefore, they are important building blocks for the synthesis of potential medicinally active substances or natural compounds. Electron-deficient azadienes proved to be useful reagents for IEDDA reactions with electron-rich dienophiles, giving a rapid access to a wide range of highly substituted nitrogen containing heterocyclic systems. [36] Therfore, IEDDA reactions gained a wide popularity as synthetic tool for the assembly of complex carbocyclic and heterocyclic products [37] as well as natural products [38] and drug-like scaffolds [39]

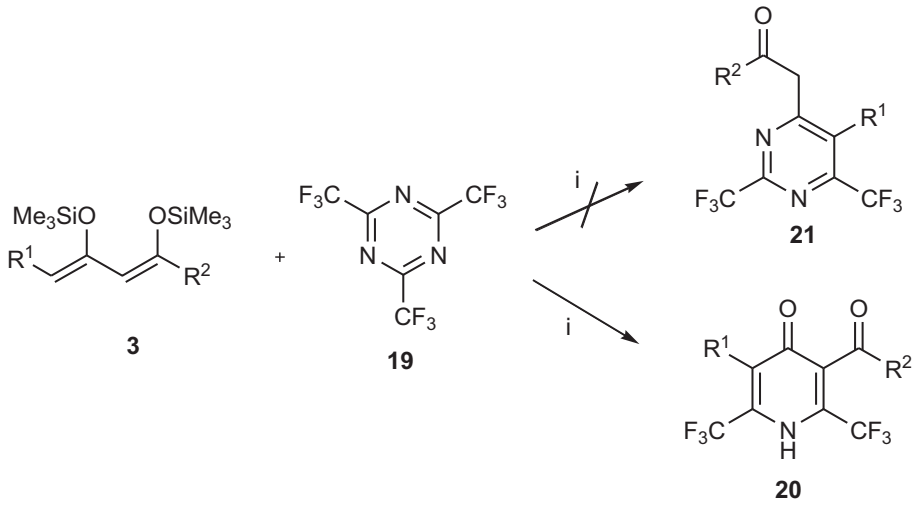
It is known that the Diels-Alder reaction accelerates when the energy separation between HOMO (Highest occupied molecule orbital) and LUMO (Lowes unoccupied molecule orbital) decreases. The electronic influence of the substituents of the diene and dienophile affects the molecule orbital energy separation. In the normal Diels-Alder reaction (type I), electron-donating groups on the diene and electron-withdrawing groups on the dienophile increase the reaction rate. In type III, namely the IEDDA reactions, the electronic effect of the substituents is the reverse of those of type I.

Therefore, several strategies were investigated to accelerate the participation of electron-deficient heterocyclic azadienes in IEDDA reactions. For example, additional substitution of the heterocyclic azadiene system with electron withdrawing groups increase the electron-deficient nature of the diene and permits the use of electron-rich, strained, or even simple olefins as dienophiles. [40] For example, CF_3-containing electron poor heterocyclic masked azadienes, such as 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine and 3,6-bis(trifluoromethyl)-1,2,4-triazine, were recently explored for the assembly of heterocyclic and carbocyclic frameworks. [41] It was also reported that the IEDDA reaction of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine with electron-excessive heteroaromatic amines, anilines, and enamines gave annulated 2,6-bis(trifluoromethyl)pyrimidines including important purine scaffolds. [42] Their reactions with dienophiles generally involved the formation of a bridged intermediate.

Based on these results and on the experience with the chemistry of 1,3-bis-silyl enol ethers, it was motivating to study the reaction with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine. This reaction can produce a novel synthetic access to 2-(2,6-bis(trifluoromethyl)pyrimidin-4-yl)acetate derivatives (**21**, **Scheme 4.1**), which was not yet reported in the literature.

4.2 Results and discussions

Surprisingly, the reaction of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine **19** with 1,3-bis-silyl enol ethers **3** followed an unusual pathway and led to the formation of *γ*-pyridone **20** instead of expected pyrimidine **21**. Encouraged by this finding, the scope, the limitations and the mechanism of the new cyclization reaction were investigated.



Scheme 4.1: Synthesis of **20**: i) 1) Me_3SiOTf, CH_2Cl_2, -78 - 20°C, 12 h; 2) 10% HCl; 3) EtOH, 50 -60°C, 10-25 h

The reaction was carried out in three steps to give 2,6-bis(trifluoromethyl)-1,4-dihydro-4-oxopyridines **20a–j** in good yields and with very good chemoselectivity (**Table 4.2**). The yield was significantly improved when in the first step, a CH_2Cl_2 solution of the reaction mixture was stirred in the presence of Me_3SiOTf with slow warming from -78 to 20 °C during 12-14 h. In the third step, an ethanol solution of the crude product was heated at 50-60 °C. The reflux at 80°C instead of only heating resulted in a dramatic decrease of the yield and the formation of several unidentified products. The use of Me_3SiOTf proved to be important; the yield decreased to 30% when the reaction was carried out in the absence of Me_3SiOTf (**Table 4.1**).

Table 4.1: Optimization of the synthesis of **20a**.

Ratio 19 : 3 : Me_3SiOTf	% (**20a**)[a]
1 : 2 : 0	30
1 : 2 : 1	78

[a] Yields of isolated products

Table 4.2: Yields of 2,6-bis(trifluoromethyl)-1,4-dihydro-4-oxopyridines **20a-n**.

20	**3**	R^1	R^2	% (**20**) [a]
a	**a**	H	OMe	78
b	**b**	H	OEt	95
c	**c**	H	OBn	57
d	**d**	H	O*i*Pr	64
e	**f**	H	O*i*Bu	69
f	**g**	H	O*i*Pent	40
g	**h**	H	O*n*Oct	54
h	**i**	H	$O(CH_2)_2OMe$	77
i	**j**	Me	OMe	35
j	**k**	Et	OMe	23
k	**n**	Cl	OMe	0
l	**ad**	$(CH_2)_2Ph$	OMe	0
m	**ag**	$(CH_2)_3Cl$	OMe	0
n	**ah**	$(CH_2)_4Cl$	OMe	0

[a] Yields of isolated products.

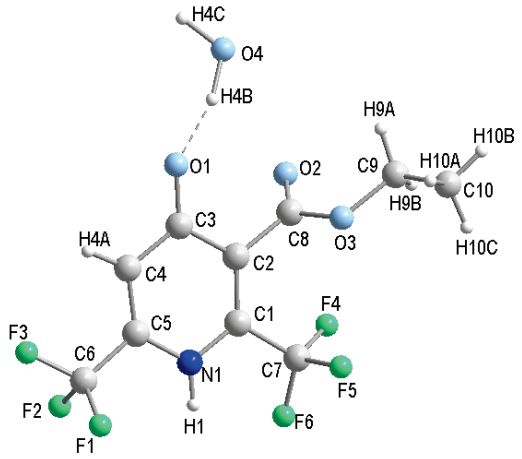
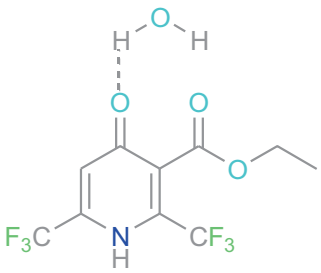
The reactions of dienes containing no substituent located at carbon C-4 proceeded with very good yields (**20a-j**). The yields decreased for dienes **3j** and **3k** having a methyl or an ethyl group at carbon C-4 of the diene. No product could be isolated when dienes **20k-n** or C-2 substituted 1,3-bis-silyl enol ethers were employed. The reaction resulted in the formation of a complex mixture. This could be explained by the steric influence of the substituents that will be described later on.

4.2.1 Structure identification

All structures were confirmed by NMR, IR, mass spectrometry and elemental analysis. Long-run ^{13}C-NMR-experiments showed typical quartets and expected $^1J_{C\text{-}F}$ and $^2J_{C\text{-}F}$ coupling constants. Two quartets with coupling constants $^1J_{C\text{-}F}$ ~ 274 Hz at about 122 ppm characterize the two CF_3-groups. The ^{19}F-NMR spectra show two singlets at ca. -60 ppm, which confirm the aromatic structure of the molecule.

The structure of product **20b** was certified by X-ray crystal structure analysis (**Table 4.3**). [43] The compound crystallized as a monohydrate and its structure is as expected planar, due to the aromatic ring. The lengths of the aromatic C-C bonds are 1.36-1.42 Å while the C-N bonds are ca. 1.32 Å long and as expected shorter. A torsion angle O2-C8-C2-C3 of 64° is present between the ester-group and the aromatic ring.

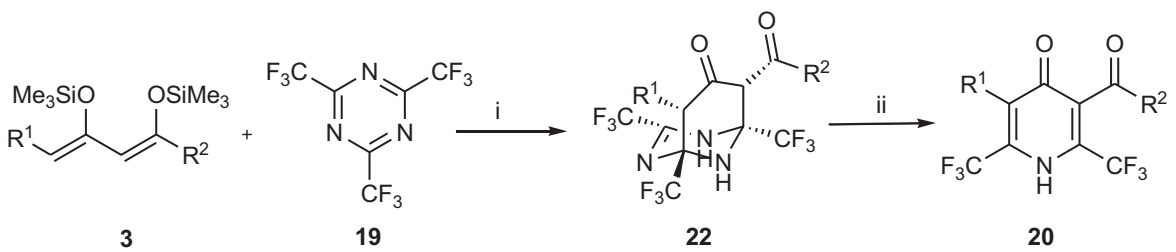
Table 4.3: Crystal structure of **20b**.

Crystal structure	Compound	Structure
	**20b**	

4.2.2. Mechanistic investigations

Consequently, the mechanism of this new reaction needed to be investigated. It was assumed that the first step was mainly responsible for the reaction pathway. Therefore, this step was then carried out in the absence of Me_3SiOTf and followed by TLC. A weak spot of a product that was not identical to **20** was observed at the beginning of the reaction. Once the temperature slowly reached 20°C, the intensity of this spot increased and the intensity of the starting material **19** decreased until it disappeared. Work-up with 10% HCl was necessary to eliminate the Me_3Si-groups. The new products were isolated by using flash chromatography and their structural elucidation revealed that the bridged heterocycles **22** were formed (**Scheme 4.2**, **Table 4.4**). The moderate yields can be explained by the fact that the products seemed to be unstable on the silica gel and in solution under normal atmosphere.

The fact that many reactions of masked azadienes involved the formation of a bridge intermediate supports these outcomes. As a result, a new type of formal [3+3]-cyclization reaction of 1,3-bis-silyl enol ethers was discovered.



3 **19** **22** **20**

Scheme 4.2: Reagents and conditions: i) a) CH_2Cl_2, -78 - 20°C, 12 h; 2) 10% HCl; ii) EtOH, 50-60 °C, 10-25 h.

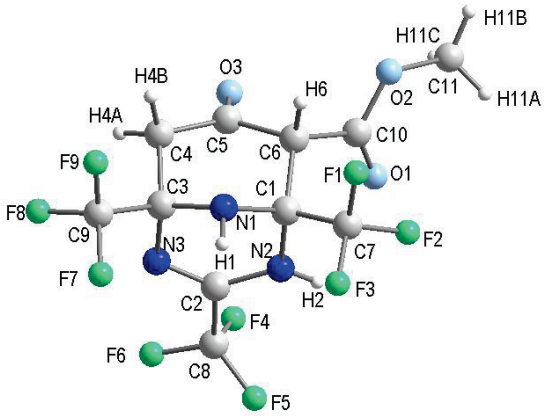
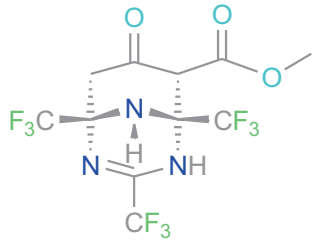
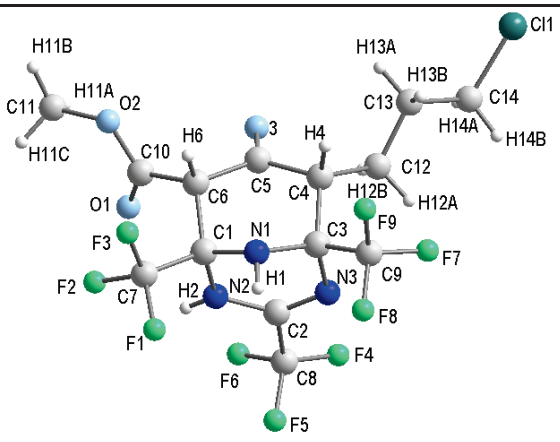
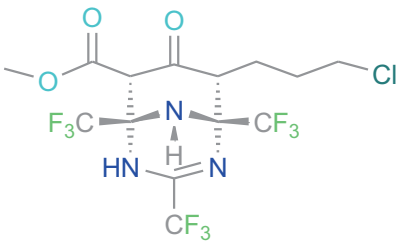
Table 4.4: Yields of compounds **22a-e**

22	3	R^1	R^2	% (22)[a]
a	**a**	H	OMe	43
b	**j**	Me	OMe	54
c	**ad**	$(CH_2)_2Ph$	OMe	42
d	**ag**	$(CH_2)_3Cl$	OMe	71
e	**ah**	$(CH_2)_4Cl$	OMe	48

[a] Yields of isolated products

The structures of **22a** and **22d** were independently confirmed by X-ray crystal structure analysis [43]. Both crystalized in a monoclinic system with the space group C_{2h}^5 (P 21/n and P 21/c). The piperidinone ring is in *chair* conformation and the tetrahydrotriazine ring is in *half-chair* conformation and the overall configuration is *endo* with a C6-C1-N2 angle of 112° resp. 110° for C4-C3-N3. The C=N bonds are ca. 1.27 Å long while the C-N bonds are 1.36-1.40 Å long. The ester-groups are in both cases on the opposite site to the C=N bond, this means on the same side with the cyclic NH-group, with a distance C=O···H of 2.50 Å. Therefore no hydrogen bond formation was observed.

Table 4.5: Crystal structures of **22a** and **22d**.

Crystal structure	Compound	Structure
	**22a**	
	**22d**	

^{1}H-NMR spectroscopy confirmed the presence of only two NH-groups with broad singlets at ca. 3 ppm resp. 7 ppm. The three singlets of the CF_3-groups appeared in ^{19}F-NMR spectra at ca. -73, -79 and -83 ppm. The correct molecular ions were observed when the measurements were carried out using the milder EI or ESI technique, but not using GC-MS.

The pure compounds **22a** and **22b** could be successfully transformed to pyridone **20a** resp. **20i** by simple heating in ethanol at 50–60 °C (see **Table 4.6**, **Scheme 4.2**). However, the thermal transformation of **22c-e** into **20l-n** failed. The transformation to **20a** occurred with 62% yield, which is lower than the yield obtained when Me_3SiOTf was involved. As described before, the use of Me_3SiOTf resulted in an increase of the yield (**Table 4.1**). However, the two step transformation, with isolation of the pure intermediate, proceeded with higher yield than the direct reaction without Me_3SiOTf (62% vs. 30%). This could be a consequence of a different method of purification. The intermediate could be isolated by column chromatography and then transformed into pyridone with no further need of purification. In the direct reaction, pyridone **20** could only be isolated by washing with CH_2Cl_2, since the Rf = 0 made the isolation over column chromatography difficult. Unfortunately this method has a higher systematic error since the product can dissolve in CH_2Cl_2. This can explain also the higher yield of **20i** (77% vs. 35%) obtained in two steps without Me_3SiOTf.

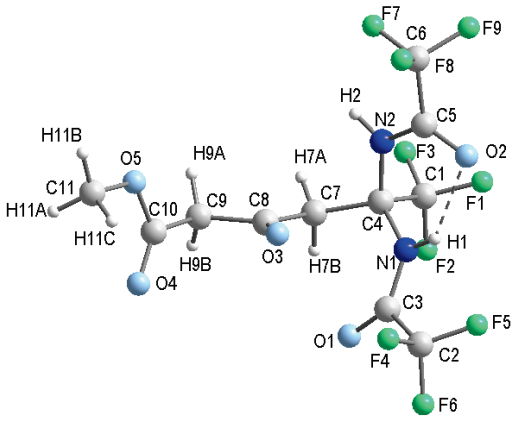
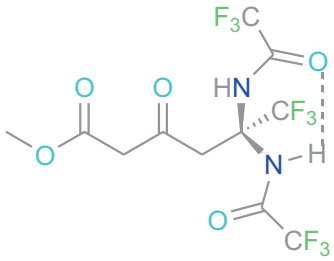
Table 4.6: Synthesis of **20** starting from **22a-e**.

22	20	R^1	R^2	% (20)[a]
a	**a**	H	OMe	62
b	**i**	Me	OMe	77
c	**l**	$(CH_2)_2Ph$	OMe	0
d	**m**	$(CH_2)_3Cl$	OMe	0
e	**n**	$(CH_2)_4Cl$	OMe	0

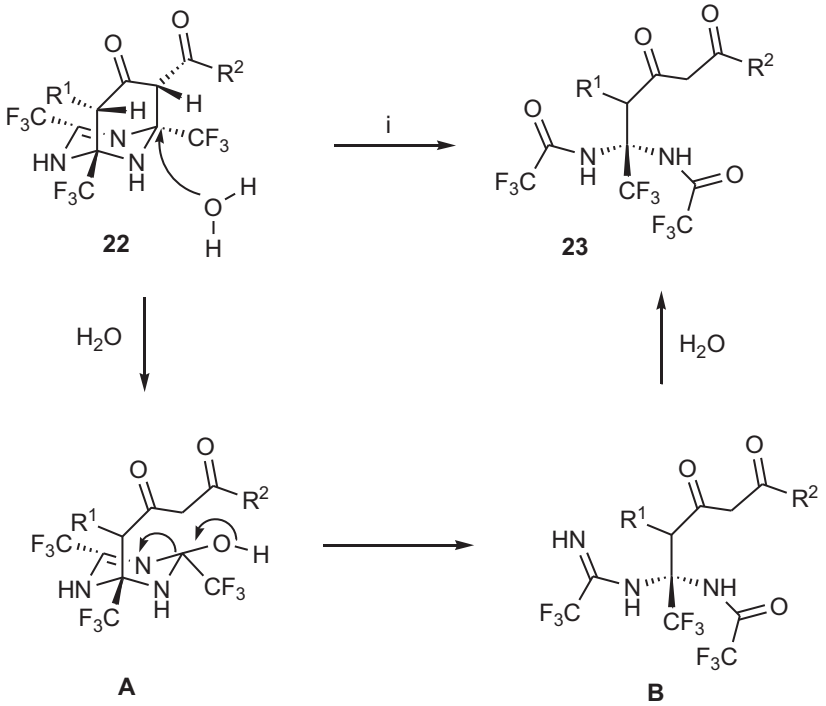
[a] Yields of isolated products

However, extending the heating time and increasing the temperature (90°C) of the reaction gave a mixture of products and byproducts. The ^{19}F-NMR spectra of the reaction mixture showed strong signals in the range of δ =-72, -75, and -80 ppm, with integral ratio of 1:1:1. These signals do not belong to the pyridone **20**. These results suggested that a major byproduct was formed. The efforts to isolate this product proved to be successful only in case of **22a**. The structure of the product, methyl 5,5-bis(2,2,2-trifluoroacetamido)-6,6,6-trifluoro-3-oxohexanoate **23a**, could be identified by X-ray crystal structure analysis [43] (**Table 4.7**).

Table 4.7: Crystal structure of **23**.

Crystal structure	Compound	Structure
	**23a**	

Mechanistically, this transformation can proceed by attack of a water molecule onto **22** to give intermediate **A** (**Scheme 4.3**), followed by C-C bond cleavage of the pyridone ring and C-N bond cleavage of the triazine ring. This tandem transformation leads to intermediate **B**, which is transformed by hydrolysis into **23**.



Scheme 4.3: Possible mechanism for the formation of **23**: i) 1) 10% HCl; 2) EtOH, 90°C, >30 h.

These transformations could explain why compounds **20l-m** could not be isolated. It seems that the larger the rest R^1 is, the more likely the cleavage of the C-C bond takes place, making impossible the isolation of the intact pyridone ring. Unfortunately, these byproducts could not be isolated. Though, ^{19}F-NMR spectroscopic analysis of the reaction mixture revealed that, besides unidentified products, pyridones **20** and compounds **23** were present in the ratio given in **Table 4.8**.

Table 4.8: Ratio of **20** to **23** in the reaction mixture (by ^{19}F-NMR).

22	R^1	R^2	(20):(23)
a	H	Me	4 : 1
b	Me	Me	7 : 1
c	$(CH_2)_2Ph$	Me	1 : 23
d	$(CH_2)_3Cl$	Me	1 : 21
e	$(CH_2)_4Cl$	Me	1 : 25

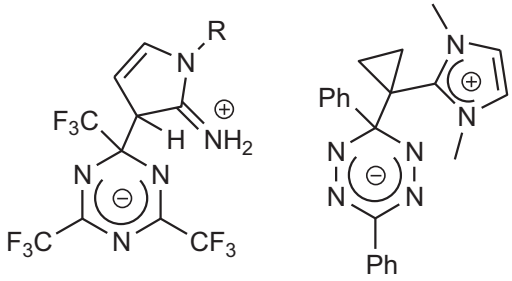
4.2.3. Mechanistic pathway

Based on the results discussed above, there are two proposed pathways for the one-pot synthesis of pyridones **20**. Both ways start with the reaction of dienes **3** with triazine **19** to give intermediate **F**, which can be regarded as a silylated analogue of **22** (**Scheme 4.4**).

Pathway A follows a sequential process by nucleophilic attack. First the triazine **19** is probably activated by interaction with Me_3SiOTf to give the highly electrophilic 1,3,5-triazonium triflate (Intermediate **A**). This fact can explain the increased yield for the Lewis acid mediated reaction. Intermediate **B**, which can exist in equilibrium with intermediate **C**, is formed by nucleophilic attack of the terminal carbon atom of diene **3** on the C=N bond of **A**. Attack of the central carbon atom of the bis-silyl enol ether follows giving intermediate **F**.

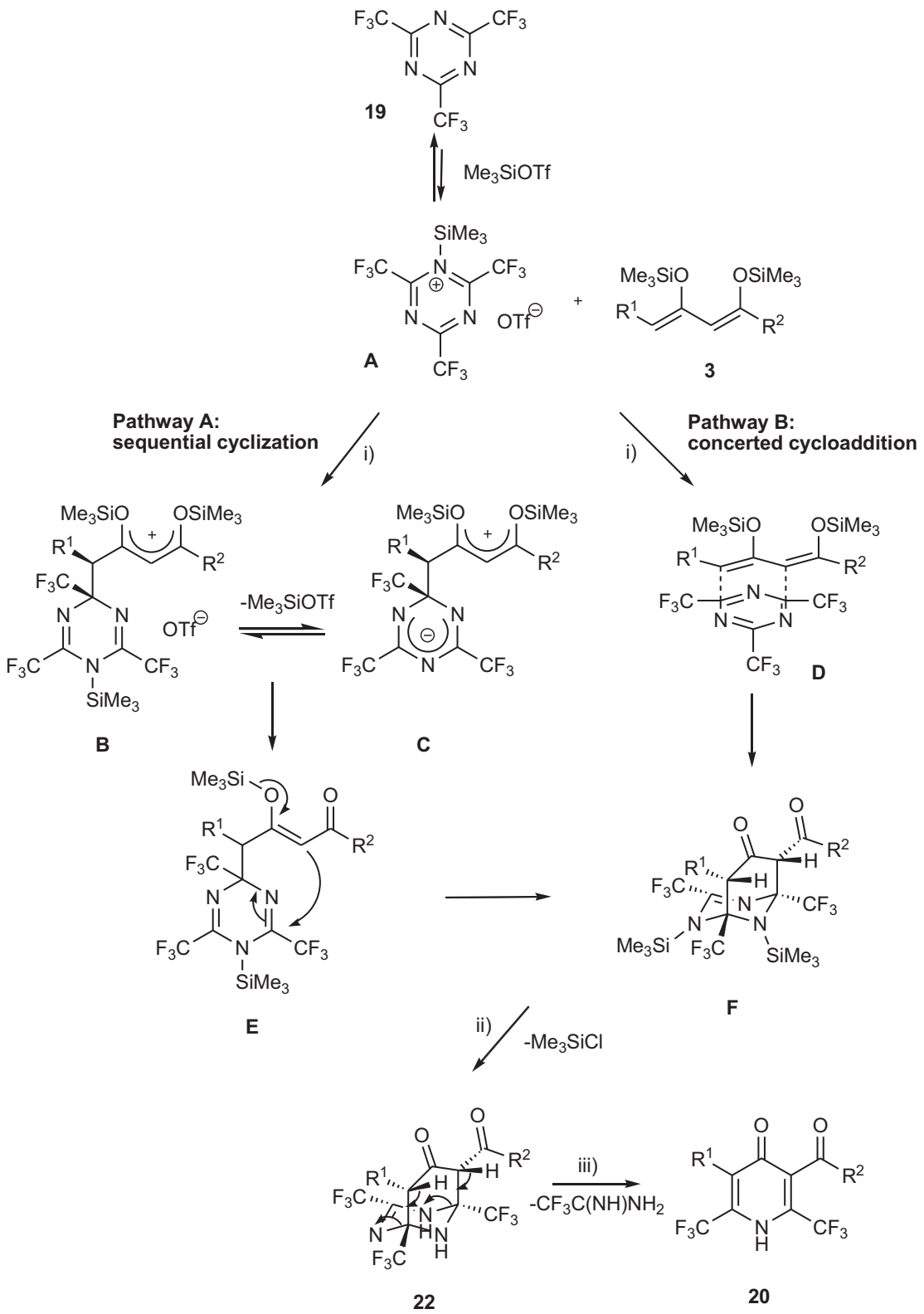
The alternative, *pathway B*, is similar to a pericyclic cycloaddition via transition state **D**, which implies the simultaneous migration of the Me_3Si-groups to the nitrogen atoms to give intermediate **F**. Intermediate **F** undergoes then subsequent desilylation to give **22** and extrusion of 2,2,2-trifluoroacetamidine to give **20**.

As mentioned above, products of type **22** were exclusively formed as *endo* isomers. Therefore it can be, that the reaction followed *pathway B*, a concerted type of reaction like the Diels-Alder reaction where the *endo* rule is dominating. Though, it is worth noting that zwitterions **24** and **25** have been previously isolated and characterized [44] (**Figure 4.1**), fact which supports the intermediates **B** and **C** and the *pathway A*. In fact, the sequential cyclization is a typical mechanism for the reactions of bis-silyl enol ethers.



24 **25**

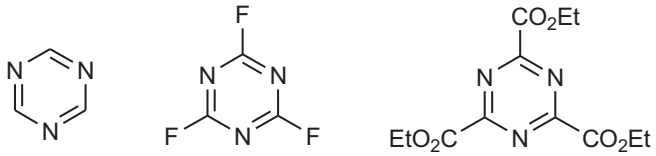
Figure 4.1: Zwitterions previously isolated and characterized.



Scheme 4.4: Possible mechanism of the formation of 20: i) CH_2Cl_2, -78 - 20°C, 12 h; ii) 10% HCl; iii) EtOH, 50-60°C, 10-25 h.

4.3 Unsuccessful trials

The conditions described for **20** and **22** have been also tested for the implementation of other 1,3,5-triazine derivatives.



A **B** **C**

Unfortunately the test reactions with other derivatives were unsuccessful. The reaction of 1,3-bis-silyl enol ether with simple 1,3,5-triazin (**A**) afforded a product according to TLC, but the isolation was not possible since this product was highly volatile. Same difficulties occurred when triethyl 1,3,5-triazine-2,4,6-tricarboxylate (**C**) was involved. The reaction with 2,4,6-trifluoro-1,3,5-triazine (**B**) afforded a complex mixture of products which could not be separated, but according to TLC small amounts of pyridone were formed.

4.4 Conclusions

In conclusion, the [3+3]-reaction reported herein is different to known modes of cycloadditions and constitutes a novel type of reaction for the bis-silyl enol ether chemistry. The products are not readily available by other methods. The reaction mechanism was studied by the isolation of an unusual tricyclic intermediate.

Chapter 5

1,3-Bis-silyl enol ethers as building blocks for potential UV-filters

5.1 Introduction

Organisms are using nucleic acids (RNA and DNA) for storage of their genetic information encoded in the sequences of the four nucleobases adenine, cytosine, guanine and thymine (uracil in RNA). The damage of the DNA and RNA matrix causes mistakes during the replication and transcription. In many cases this leads to mutations in the genetic material causing cancer. For example, the sunlight ultraviolet radiation (UV) can cause damages of nucleic acids, leading to skin cancer.

The electromagnetic spectrum of the ultraviolet light is divided into UV-A (400-320 nm), UV-B (320-280 nm) and UV-C (280−200 nm) bands. The most dangerous radiation of sunlight lies in the range of UV-C bands. However this UV light is absorbed by ozone in the upper parts of the atmosphere. Only the less energetic UV-B and UV-A radiations reach the Earth`s surface and contribute significantly to the negative effects of sun radiation like sunburn and cancer. [45]

Though, there are not only risks but also benefits of sun exposure. For example, UV radiation is used as medical treatment for skin disorders such as psoriasis. Although, this treatment is less used since it has side effects like skin cancer. UV light with wavelength of 311 nm proved to be the middle way for an effective treatment. [46] Sunlight is necessary for the production of vitamin D in the human body. Too little UV radiation causes a lack of vitamin D. Too much UV radiation causes DNA damage, sunburn and skin cancer. An appropriate amount of UV light is needed.

To control the amount of UV radiation and to protect the skin from negative effects, a variety of personal care products have been investigated and produced. They contain organic substances that can absorb the UV radiation and reduce the negative effects. These chemicals are generally called UV filters and they are fundamental for the sunscreen industry. Ultraviolet filters can be broadly classified into two types:

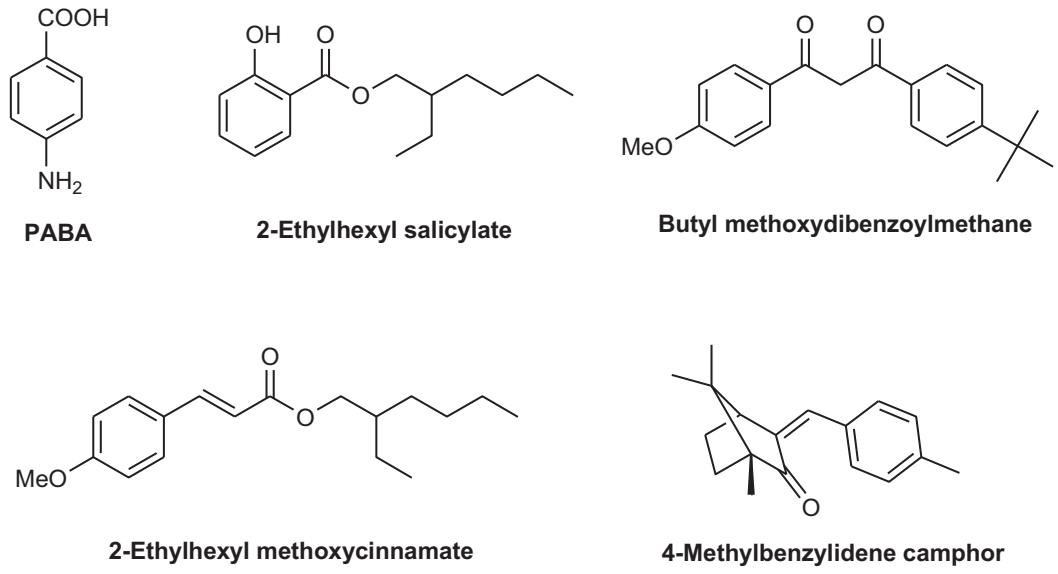
1) UV absorbers, which are mostly organic compounds that absorb the UV light. They are classified as either UV-B or UV-A filters or both (UV-A/B filters).

2) Inorganic particulates that may absorb reflect and scatter the UV light. There are only two inorganic particulates approved (zinc oxide and titanium dioxide). Both ingredients are considered to have a broad spectrum since they absorb, scatter and reflect UV-B and UV-A bands. [47]

There are about fifty five ultraviolet filters that are approved for use in sunscreen products. [47] These are not sufficient to fully protect us against the sunrays.

Optimal sun-creams should have a broad and strong absorption of UV-A (400–320 nm) and UV-B radiation (320–280 nm), since the UV-C radiation does not reach the skin. They should be stable against light, temperature and water and have a moderate lipophilicity.

Para-amino benzoates (e.g. 4-aminobenzoic acid / PABA) and salicylates (e.g. 2-ethylhexyl salicylate) were one of the first used UV-B and UV-A filters, respectively. Dibenzoyl methanes (so called avobenzone, e.g. butyl methoxydibenzoylmethane), cinnamates (e.g 2-ethylhexyl methoxycinnamate) and camphor derivatives (e.g. 4-methylbenzylidene camphor) are also widely used because of their exceptionally high absorption coefficients (**Figure 5.1**). However, these compounds are still investigated since they are thought to be toxic or carcinogenic. Other are not perfect suitable since they are too aggressive and discolor the cloths or they are not stable against light and need photostabilisers. [47]

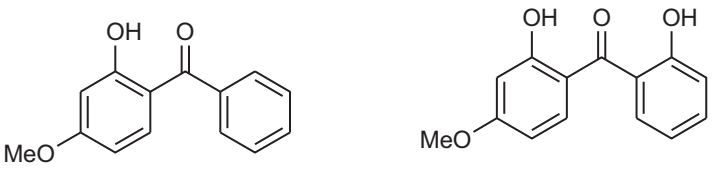


PABA **2-Ethylhexyl salicylate** **Butyl methoxydibenzoylmethane**

2-Ethylhexyl methoxycinnamate **4-Methylbenzylidene camphor**

Figure 5.1: Some approved UV-A or UV-B filters.

Sun-creams often contain a mixture of UV-A and UV-B filters or they are UV-A/B broad spectrum filters, which combine a UV-A and UV-B filter in one molecule. Functionalised benzophenones, such as benzophenone-3 (oxybenzone) or benzophenone-8 (dioxybenzone), are widely used UV-A/B filters in sun-creams [48] (**Figure 5.2**).



Benzophenone-3 **Benzophenone-8**

Figure 5.2: Some approved UV-A/B broad spectrum filters.

The ability of benzophenones to absorb UV radiation is due to the completely conjugated system, consisting of the two phenyl rings which can interact with the π-bond of the C=O-group. The π-electron delocalization results in two λ_{max} at 286 nm (UV-B) and at 324 nm (UV-A).

Unluckily, benzophenone-3 has been reported to act as photosensitizer, increasing the production of free radicals under illumination, fact which possibly makes this UV filter photocarcinogenic. [49] Therefore, the EU requires that cosmetic companies label the presence of more than 0.5 % of benzophenone-3 on their products with “contains oxybenzone”. [50] Consequently, the development of new UV-A/B filters is of considerable interest.

At the same time, functionalized benzophenones have found various medicinal and technical applications. They represent important core structures for the development of pharmaceuticals. [51]

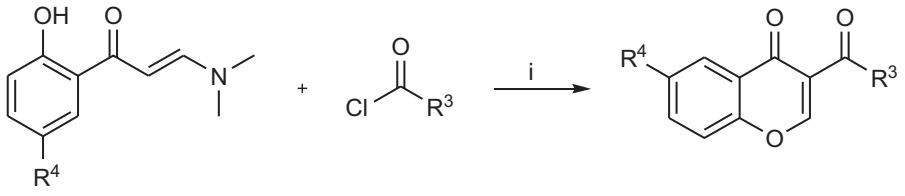
The group of Prof. Dr. Peter Langer has previously reported that 3-formylchromones react with 1,3-bis-silyl enol ethers to give 2,4-dihydroxybenzophenones. [52] Recently, it has been reported the synthesis of 3-methoxalylchromone and its reactions with electron-rich nitrogen heterocycles. [53] Hence, the reaction of 3-methoxalylchromone and related derivatives with 1,3-bis-silyl enol ethers needed to be investigated.

5.2 Results and discussions

The reaction of 1,3-bis-silyl enol ethers with different chromones and thiochromones afforded a great variety of functionalized benzophenones and xanthene derivatives. These are interesting substrates for the C-C coupling reactions and can be a novel UV-A/B filter.

5.2.1 Preparation of the starting materials

The chromones [53] and the thiochromones [54] have been prepared in collaboration with group colleagues after already reported literature procedures.



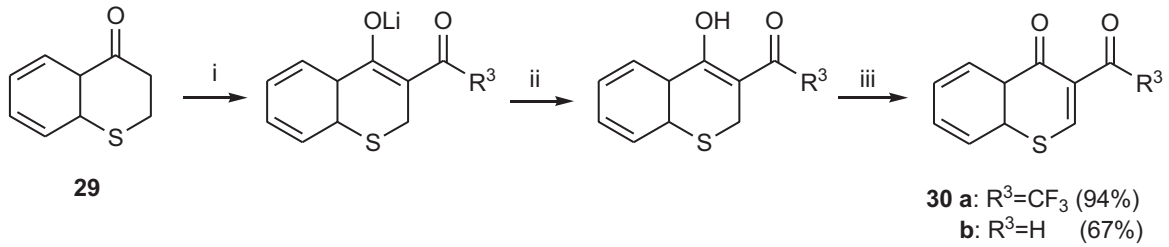
26 a: R^4=H
b: R^4=Br
c: R^4=CH_3

27 a: R^3=CO_2CH_3
b: R^3=$CHCl_2$

28 a: R^3=CO_2CH_3, R^4=H (82%)
b: R^3=CO_2CH_3, R^4=Br (80%)
c: R^3=CO_2CH_3, R^4=CH_3 (78%)
d: R^3=$CHCl_2$, R^4=H (75%)

Scheme 5.1: Synthesis of chromones **28**: i) pyridine, CH_2Cl_2, 20°C, 8 h.

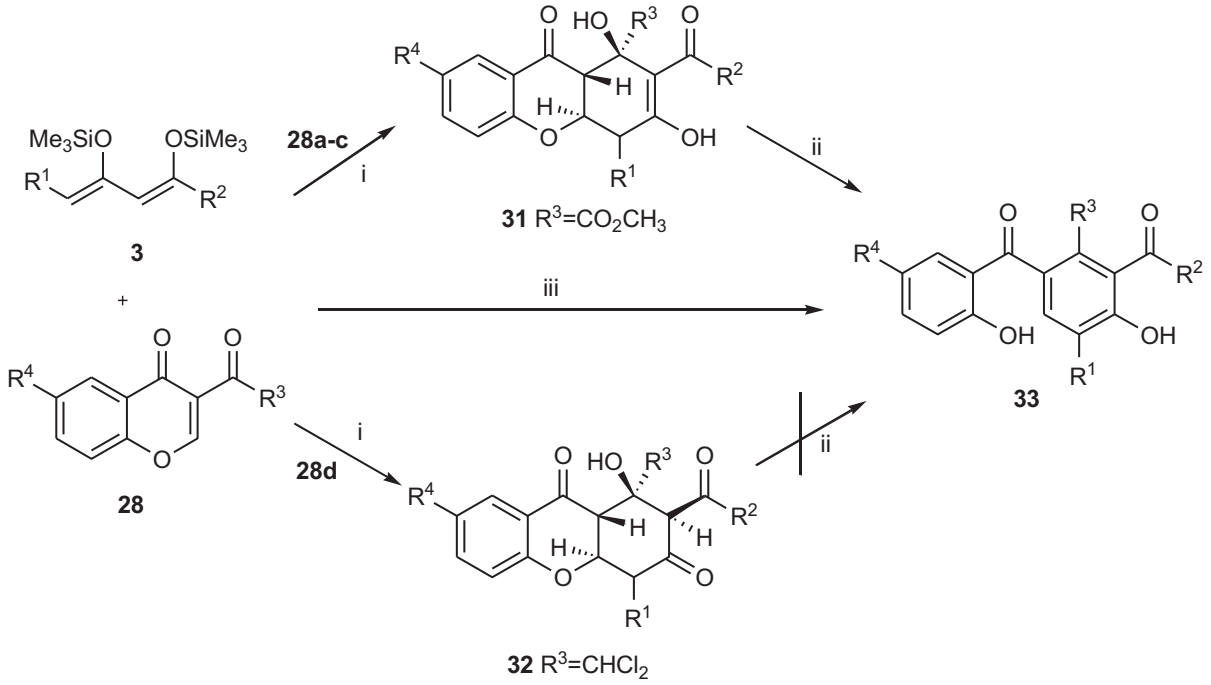
The 3-methoxalylchromone and derivatives (**28a-c**) could be prepared in good yields by reaction of **26a-c** with methyl 2-chloro-2-oxoacetate **27a** (**Scheme 5.1**). The 3-(dichloromethylcarbonyl)-chromone **28d**, containing a $CHCl_2$-group as a masked formyl-group, has been synthesized after the same procedure starting with **26a** and 2,2-dichlorocetyl chloride **27b**. Thiochromones **30a,b** could be prepared in three steps, starting from commercially available thiochromenone **29** (**Scheme 5.2**).



Scheme 5.2: Synthesis of thiochromones **30**: i) LiH, R_3CO_2Et, benzene, bp, 20 h; ii) 10% H_2SO_4, CH_2Cl_2, 20°C, 16 h; iii) SO_2Cl_2, $CHCl_3$, 20°C, 20 h.

5.2.2 Reactions of chromones

The reactions of 3-methoxalylchromone and derivatives **28a-d** with 1,3-bis-silyl enol ethers **3** resulted in the formation of highly functionalized xanthene derivatives **31** and **32** instead of the expected benzophenones. However, only the tetrahydroxanthones **31** could be transformed into functionalized benzophenones **33** by treatment with *p*-toluenesulfonic acid (**Scheme 5.3**).



Scheme 5.3: Synthesis of **33**: *via isolation of **31** and **32***: i)1) Me_3SiOTf, 20°C, 1 h; 2) CH_2Cl_2, 0 - 20°C, 12-14 h; 3) 10% HCl. ii) *p*-TsOH (3 mol%), EtOH, reflux, 5-10 h. *Two-step one pot*: iii) 1) Me_3SiOTf, 20°C, 1 h; 2) CH_2Cl_2, 0 - 20°C, 12-14 h; 3) 10% HCl; 4) p-TsOH (3 mol%), EtOH, reflux, 5-10 h.

Studying the scope and limitation of the reaction, it was obvious that 1,3-bis-silyl enol ethers **3** readily reacted with chromones **28** to give the correspondent polycyclic products **31** and **32** with 41-80% yield and excellent regio and diastereoselectivity (**Table 5.1**). The variation of the substituents had a dramatic influence on the yields. The highest yield was obtained for R^3 = *i*Bu and R^2 = Br. In general, it seemed that the Br-substituted chromone **28b** attained higher yields in compare to the unsubstituted one (e. g **31d** vs. **31h**). Large substituents at the terminal position of **3** ($R^1 \neq H$) made the isolation of the pure compounds **31** difficult.

The chemical behaviour of chromone **28d** seemed not to be similar with that of chromones **28a-c**. The resulted derivatives **31** exist in enole-form, which can be because of the support of an intramolecular hydrogen bond with the R^2=CO_2CH_3. In case of compound **32**, where such bonding is not possible, the keto-form predominates. It should be also mentioned that starting with same 1,3-bis-silyl enol ether **3j**, the product **32** was formed with a higher yield than **31f**. However, product **32** was formed as a mixture of diastereomers and so the NMR methods were not sufficient to verify the structure obtained.

Table 5.1: Synthesis of intermediates **31** and **32.**

	28	3	R^1	R^2	R^3	R^4	Yield [a] %
31a	**a**	**a**	H	OMe	CO_2Me	H	52
31b	**a**	**b**	H	OEt	CO_2Me	H	47
31c	**a**	**c**	H	OBn	CO_2Me	H	41
31d	**a**	**f**	H	O*i*Bu	CO_2Me	H	43
31e	**a**	**g**	H	O*i*Pent	CO_2Me	H	52
31f	**a**	**j**	Me	OMe	CO_2Me	H	42
31g	**b**	**a**	H	OMe	CO_2Me	Br	51
31h	**b**	**f**	H	O*i*Bu	CO_2Me	Br	80
31i	**c**	**a**	H	OMe	CO_2Me	Me	71
31j	**c**	**d**	H	O*i*Pr	CO_2Me	Me	45
32	**d**	**j**	Me	OMe	CCl_2H	H	54[b]

[a] Yields of isolated products.
[b] Mixture of diastereomers

The optimization of the reaction conditions showed that the use of a Lewis acid for the activation of the substrate played an important role. The highest yield was obtained when the substrate was mixed with the Me_3SiOTf and stirred for at least 1 h, at room temperature,

before the solvent and the 1,3-bis-silyl enol ether were added. The reaction temperature and the stoichiometry had also significant influence on the conversion. All optimizations were carried out only for the reaction to **31f** (**Table 5.2**).

Table 5.2: Optimization of the synthesis of **31f**

28:3:Me_3SiOTf	activation time	reaction temperature	Yield [a] % 31f
1 : 2 : 1	1 h	0°C	16
1 : 2 : 2	1 h	0°C	42
1 : 2 : 3	1 h	0°C	38
1 : 4 : 2	1 h	0°C	22
1 : 2 : 2	15 min	0°C	0[b]
1 : 2 : 2	1 h	-78°C	0[b]

[a] Yields of isolated products.
[b] No conversion (by TLC).

To perform the ring-open reaction of **31** to give the desired benzophenone **33**, acidic media was taken into consideration. The substrate **31a** was taken as a model for the conditions optimization. At first the substrate was refluxed in the presence of TFA or acetic acid. Both experiments underwent the desired ring-open reaction but with a disappointing yield of ca. 20%. These conditions seemed to be drastic for the substrate. The best yield (63%) was obtained when a catalytic amount of *para*-toluenesulfonic acid (PTSA) in ethanol was employed (**Scheme 5.3**).

Knowing this, it was now possible to apply a two-step one pot reaction of 1,3-bis-silyl enol ether **3** and chromone **28** to directly reach benzophenone **33**, without the isolation of the polycyclic intermediate **31**. The yields in this case were significantly higher (63% vs. 50%, **Table 5.3**). This is expected since there might be loss of intermediate during its purification.

However, the ring opening reaction, followed by aromatization did not take place for intermediate **32**. Both acidic media (PTSA/ethanol) and basic media (KOH/methanol) have been tried without success.

The synthesis of **33j** took place in only one step, without PTSA/ethanol reflux, after which the product precipitated with no need of further purification. This could also be observed in case of **33k**, unfortunately the aromatization in one step took place with only 32% yield, so that the second step was needed to get 56% yield.

The small yield of **33i** can be explained by observation and isolation of **33a** as byproduct with 41% yield. It can be that the reflux with PTSA/ethanol causes the elimination of the ethylbenzene-group.

The formation of benzophenones **33** with very good selectivity confirmed the excellent regio and diastereoselectivity of the intermediate **31**. The presence of other regiosiomers was not observed.

Table 5.3: Synthesis of benzophenones **33**

33	**28**	**3**	R^1	R^2	R^3	R^4	Yield [a] % **33**
a	**a**	**a**	H	OMe	CO_2Me	H	63[b] (50[c])
b	**a**	**e**	H	O*n*Bu	CO_2Me	H	84[b]
c	**a**	**h**	H	O*n*Oct	CO_2Me	H	80[b]
d	**a**	**j**	Me	OMe	CO_2Me	H	67[b] (45[c])
e	**a**	**k**	Et	OMe	CO_2Me	H	66[b]
f	**a**	**y**	*n*Non	OMe	CO_2Me	H	70[b]
g	**a**	**ab**	*n*Tetradec	OMe	CO_2Me	H	74[b]
h	**a**	**ac**	*n*Hexadec	OMe	CO_2Me	H	72[b]
i	**a**	**ad**	$(CH_2)_2Ph$	OMe	CO_2Me	H	37[b]
j	**a**	**ag**	$(CH_2)_3Cl$	OMe	CO_2Me	H	53[d]
k	**a**	**ah**	$(CH_2)_4Cl$	OMe	CO_2Me	H	56[b] (32[d])
l	**b**	**a**	H	OMe	CO_2Me	Br	49[b] (45[c])
m	**b**	**f**	H	O*i*Bu	CO_2Me	Br	72[b] (63[c])
n	**b**	**j**	Me	OMe	CO_2Me	Br	75[b]
o	**b**	**y**	*n*Non	OMe	CO_2Me	Br	77[b]
p	**b**	**ac**	*n*Hexadec	OMe	CO_2Me	Br	54[b]
q	**b**	**ah**	$(CH_2)_4Cl$	OMe	CO_2Me	Br	82[b]
r	**c**	**a**	H	OMe	CO_2Me	Me	60[b] (58[c])
s	**c**	**d**	H	O*i*Pr	CO_2Me	Me	63[b]
t	**c**	**j**	Me	OMe	CO_2Me	Me	74[b]
v	**c**	**y**	*n*Non	OMe	CO_2Me	Me	63[b]
w	**c**	**ac**	*n*Hexadec	OMe	CO_2Me	Me	72[b]

[a] Yields of isolated products.

[b] Two-step one pot path.

[c] The yield *via* the isolation of **31.**

[d] Product isolated after the first step.

5.2.2.1 Structure identification

The structures were confirmed by spectroscopic methods. The ring CH_2-group of the polycyclic intermediate was obviously confirmed by NMR spectra. The typical ^{1}H-NMR multiplet of this group disappeared after the PTSA/ethanol reflux, which indicateed the aromatization. Significant was also the OH-singulet at ca. 4 ppm for the non-aromatic intermediate **31**. The shift of the second OH-peak at ca. 13 ppm suggested an O-H····H hydrogen bond to the ester-group. This was observed also for the OH-groups of the benzophenones **33**. Both peaks were shifted to 11 ppm due to assumed hydrogen bonds formation to the neighboured keto or ester-groups. A coupling constant $^3J_{H,H}$ ~ 13 Hz between the bridgehead hydrogen atoms of **31** was observed that indicated a *trans* relationship between these protons (**Figure 5.3**).

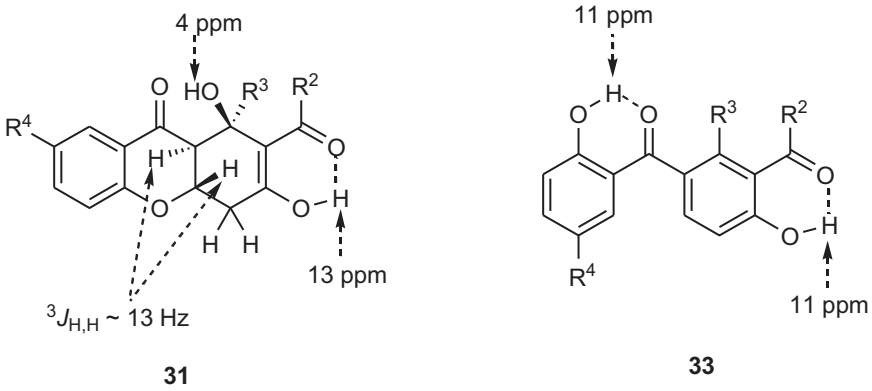


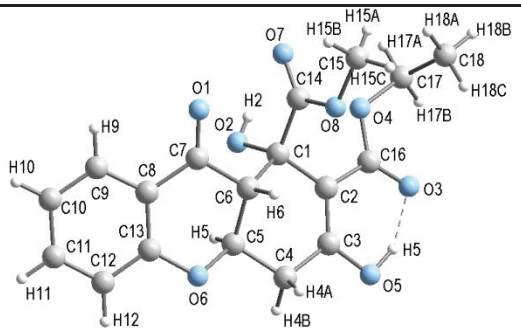
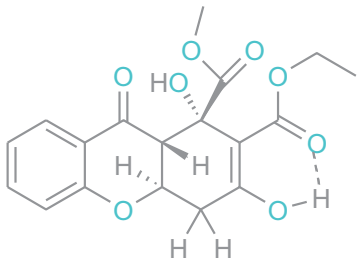
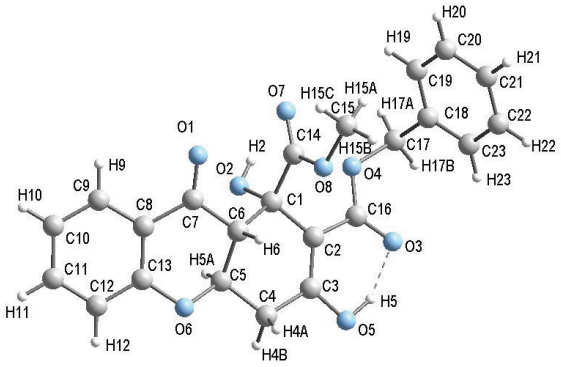
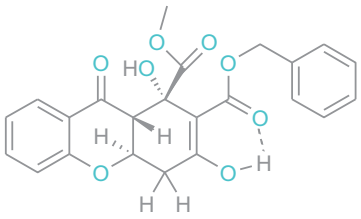
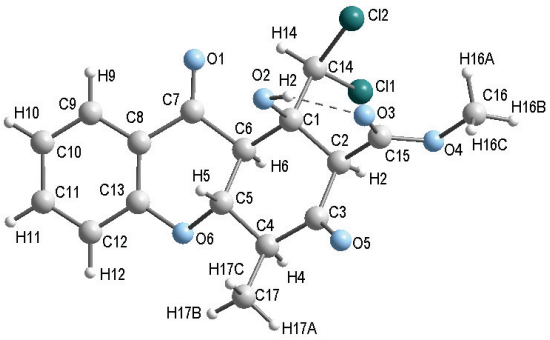
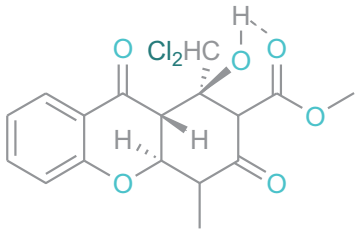
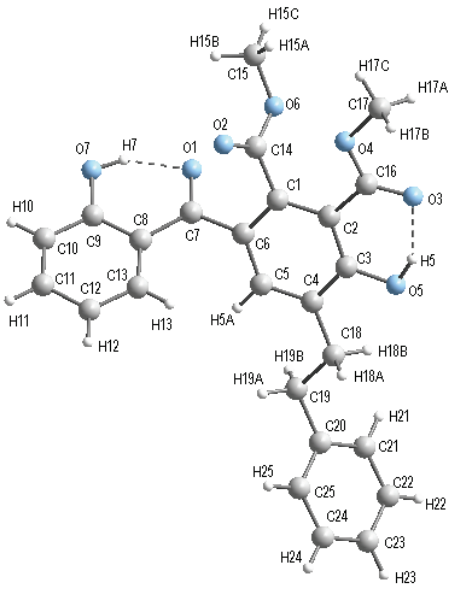
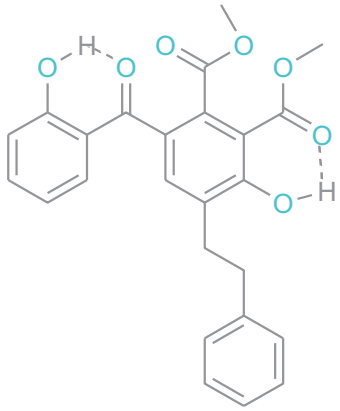
Figure 5.3: Observations from NMR experiments.

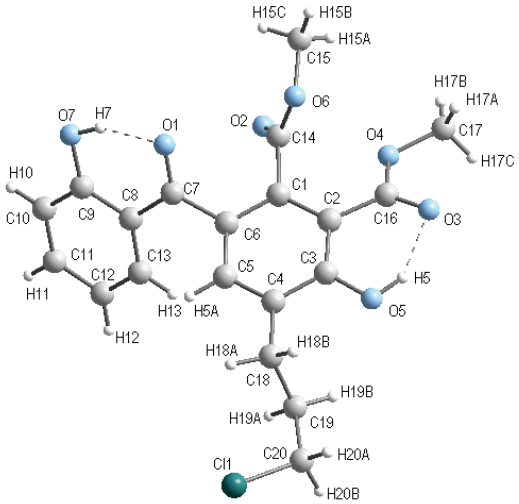
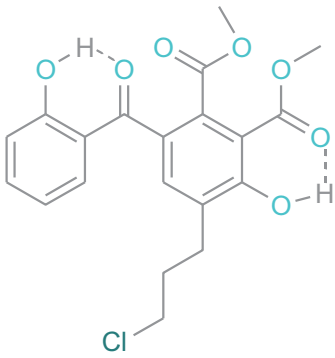
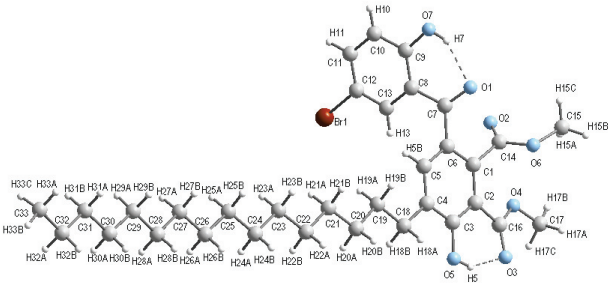
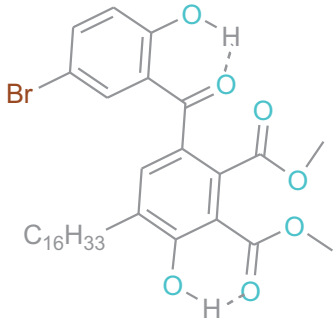
The correct molecular ions for polycyclic compounds **31** were only observed with the milder EI (electron ionization) or ESI technique (electrospray ionization). Under the conditions of GC-MS, elimination took place so that only the molecular ions of the aromatized products **33** could be detected.

Similar to salicylates **9** and **11**, the IR spectra confirmed the presence of the OH and aromatic CH-groups, showing weak to middle intensive bands at ~ 3000 cm^{-1}. Strong C=O stretching bands were observed at 1580-1680 cm^{-1}.

The structures of intermediates **31b,c**, **32** and benzophenones **33i,j,p** were independently confirmed by X-ray crystal structure analysis. Intermediates **31** crystalized in a triclinic system with the space group C_i (P-1). The crystal structure confirmed that these compounds exist in enol-form at C-3 (**Table 5.4**) and a hydrogen bond with the neighbor ester-group (O5H5···O2 is ca. 1.6 Å long) maintains its form. For that, the ester-group at C-2 made a 180° rotation away from the C1-C2-bond. The OH at the asymmetric center C-1 is too far-off to be involved in a hydrogen bond. Both non-aromatic rings are in *half-chair* conformation.

Table 5.4: Crystal structures.

Crystal structure	Compound	Structure
	**31b**	
	**31c**	
	**32**	
	**33i**	

	**33j**	
	**33p**	

Intermediate **32,** in comparison, crystalized in a monoclinic system with the space group C_{2h} (C 2/c). This compound exists in keto-form at C-3, since there is no possible hydrogen bond which can stabilize the enol-form. The ester-group at C-2 rotated with only 52° away from C1-C2-bond and created a hydrogen bond with the OH-group at C-1 (O2H2 O3 is 1.9 Å long). The cyclohexane ring is in *chair* conformation and the pyran ring is in *half-chair* conformation.

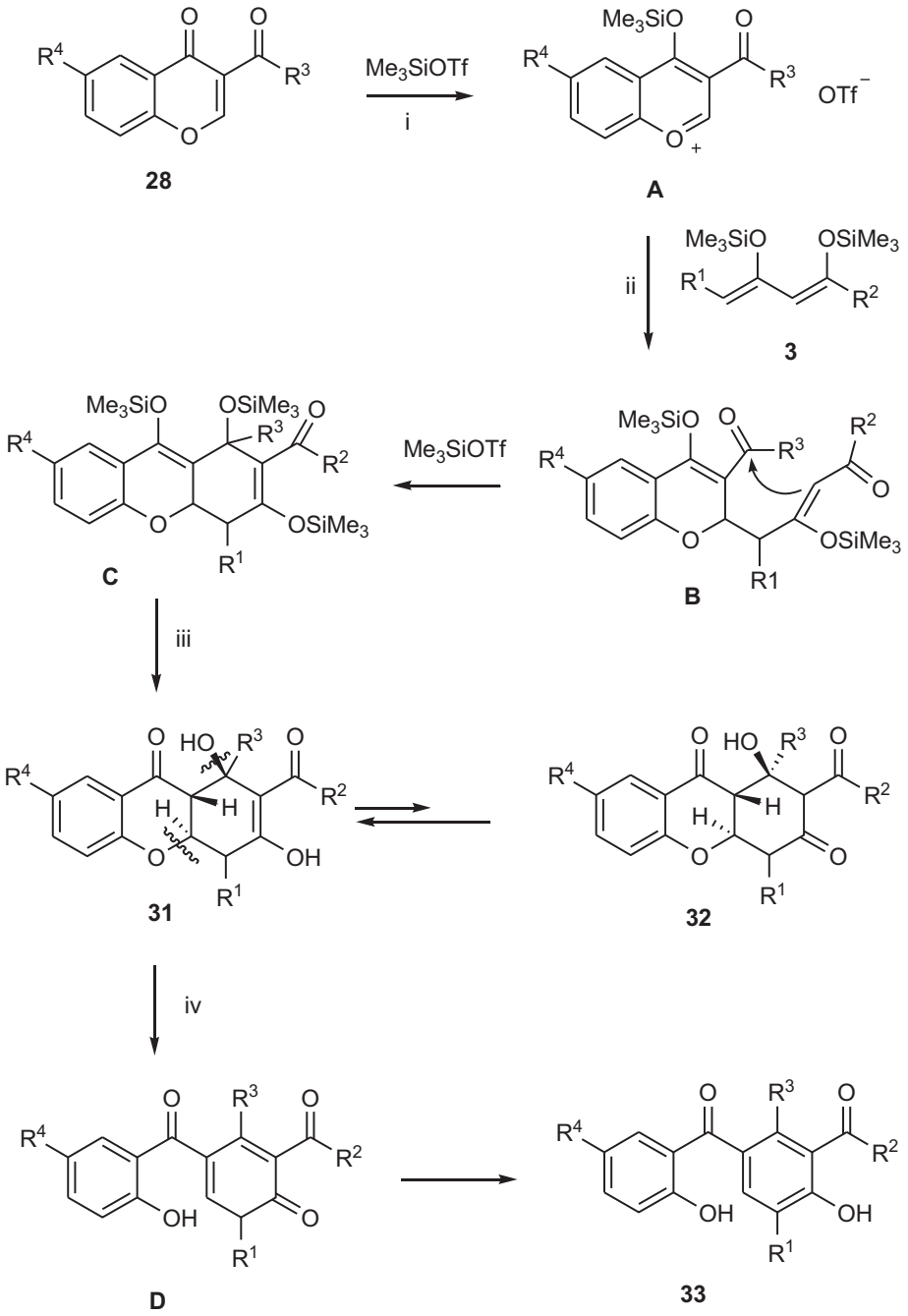
All observation agreed with the results of the NMR experiments. The supposed hydrogen bonds, the keto/enol-forms and also the *trans* relationship of the bridge hydrogen atoms H-5 and H-6 were confirmed.

Benzophenones **33i** and **33j** crystalized in a monoclinic system with the space group C_2 (P 21) resp. C_{2h} (P 21/n), while benzophenone **33p** crystalized in a triclinic system with the space group C_i (P-1). All benzophenones showed, as expected, two hydrogen bonds (O5H5···O3 and O7H7···O1 ca. 1.8 Å long), one for each OH-group. Therefore, the ester-group at C-2 rotates with an angle O3-C16-C2-C1 of 160-180° anti-periplanar to C1-C2-bond and the unsubstituted phenol ring is in one plane with the linking CO-group. This plane makes a torsion angle C8-C7-C6-C5 of 50-60° to the additional ring.

Compounds like **33p** are of great interest. The long hydrophobic chain and the hydrophilic head are good qualities for surfactants. The products are not readily available by other methods.

5.2.2.2 Mechanistic pathway

The proposed mechanism of this unusual domino reaction is outlined in the following scheme and relies on four main steps.



Scheme 5.4: Possible mechanism for the formation of **31**, **32** and **33**: i) Me_3SiOTf, 20°C, 1h; ii) CH_2Cl_2, 0 - 20°C, 12-14 h; iii) 10% HCl; iv) p-TsOH (3 mol%), EtOH, reflux, 5-10 h.

The initial formation of the pyrylium salt **A** is followed by attack of the carbon atom C-4 of diene **3** at the activated carbon atom of **A** to give intermediate **B**. Subsequent Me_3SiOTf-mediated intramolecular aldol reaction delivers intermediate **C**.

The addition of hydrochloric acid (10%) resulted in cleavage of the Me_3Si-groups and the intermediates **31,** which can exist in the keto-form **32,** were isolated. The isolation of these intermediates is unusual, since up to date, the proposed mechanism for this type of reaction should undergo first a retro-Michael reaction [52], followed by intramolecular aldol reaction. These kinds of products were not reported before.

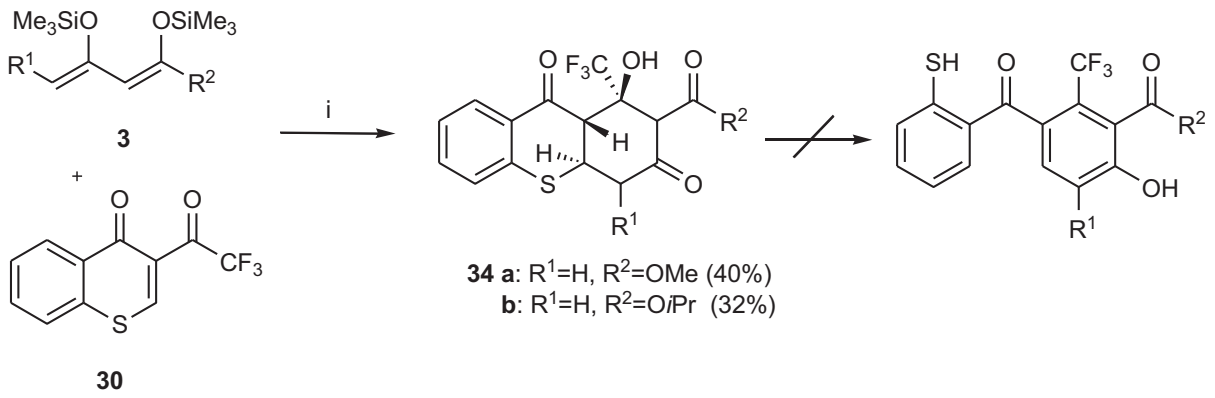
In the fourth step (heating in ethanol with catalytic amount of PTSA) the reaction probably proceeds via a ring-open cascade with the formation of intermediate **D**, followed by aromatization.

5.2.3 Reactions of thiochromones

While chromones have been broadly investigated, few reports can be found regarding the chemical behavior of thiochromones. A reason can be the difficult preparation of these compounds. It was reported that 3-trifluoroacylthiochromone **30** (**Scheme 5.5**) reacted with a number of 1,3-NCN-dinucleophiles, such as amidines or guanidines over the thiopyrone ring opening cascade, to give tihophenol scaffolds. [55] Also, some reactions of 3-formylthiochromone with N-nucleophiles, such as hydroxylamine, hydrazine, ethylenediamine and primary aromatic amines, have been described. [56] Nevertheless, these reactions mostly gave substituted thiochromones where the thiopyrone ring was not opened.

For that reason and because of the results achieved with the chromones, it was interesting to investigate the reaction of 3-trifluoroacylthiochromone with 1,3-bis-silyl enol ethers. Note that 3-trifluoroacylthiochromone readily reacts with water to form stable hydrates (*gem*-diols).

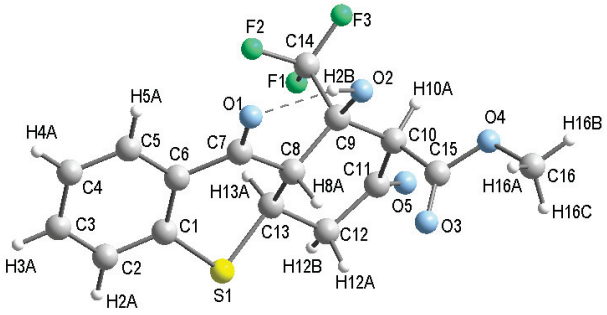
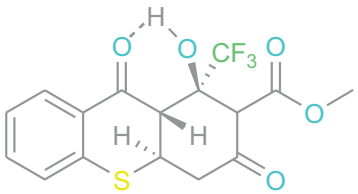
Unfortunately, these substrates were not as active as the chromones. The reaction of 3-trifluoroacylthiochromone **30** afforded the polycyclic intermediate analogous to intermediate **32**. The optimization tests showed that the reaction works if the activation with Me_3SiOTf is carried out in the presence of CH_2Cl_2 (1.5 mL / mmol), unlike the activation of chromones **28**. The ring opening reaction, followed by aromatization did not take place. Both acidic media (PTSA/ethanol) and basic media (KOH/methanol) and different 1,3-bis-silyl enol ethers **3** have been tried without success. The same behaviour was observed for compound **32**. It looks like the keto-form of these polycyclic compounds is stable against elimination and aromatization. (**Scheme 5.5**)



Scheme 5.5: Synthesis of **34**: i)1) Me_3SiOTf, CH_2Cl_2, 20°C, 1 h; 2) CH_2Cl_2, 0 - 20°C, 12-14 h; 3) 10% HCl.

It was possible to obtain a single crystal for compound **34a**. The crystal structure showed similar characteristics to **32** (**Table 5.5**). It crystalized in a monoclinic system with the space group C_{2h} (P 2/n). Surprisingly, the OH-group at C-9 was this time involved in a hydrogen bond with the keto-group at C-7 instead of the ester-group at C-10 (O2H2B···O1 of 1.9 Å long). This can be the consequence of the torsion angle O3-C15-C10-C9 of 68° made by the ester-group. These parameters should actually support a possible enol-form at C-11, but the *chair* conformation of the cyclohexane ring hindered the formation of a thinkable hydrogen bond (distance O3-O5 of ca. 3.8 Å). The bridge hydrogen atoms H-8A and H-13A are located *trans* to each other.

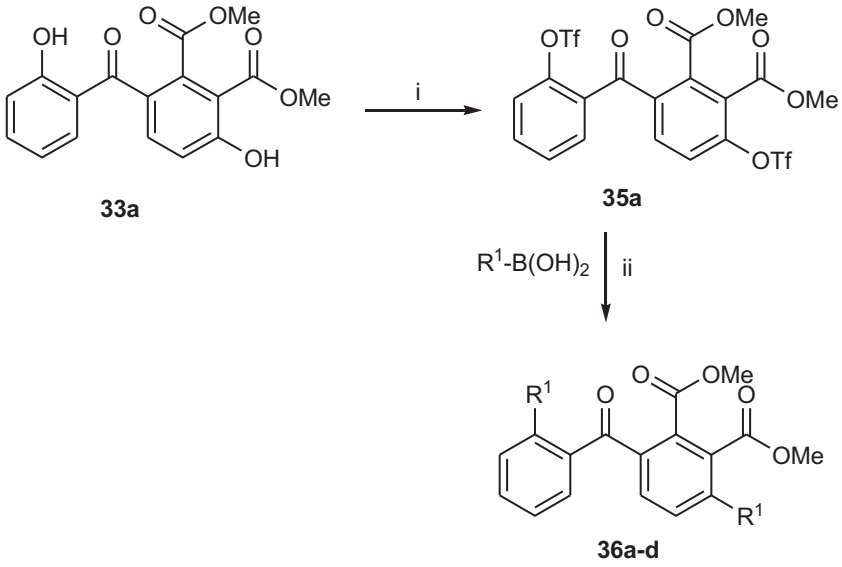
Table 5.5: Crystal structure of **34a**.

Ortep plot	Compound	Structure
	**34a**	

5.3 Applications

Modification of benzophenones **33** is of great interest, since these scaffolds have high potential for a novel UV-filter. A proper UV-filter should absorb as much UV light as possible. The insertion of aryl substituents increases the conjugated system of the benzophenone which should increas the absorption of UV light. Following this purpose, the Pd-mediated C-C Suzuki coupling of **33** was investigated.

Therefore, benzophenone **33a** was transformed into the respective bis-triflate derivative **35a**, which performed as a substrate for the reactions with different arylboronic acids. The double Suzuki reaction of **33a** with arylboronic acids afforded the novel benzophenones derivatives **36a–d** in good yields (**Scheme 5.6, Table 5.6**).



33a **35a** **36a-d**

Scheme 5.6: Synthesis of **36a-d***:* i) CH_2Cl_2, pyridine, -78 - 0 °C, inert atmosphere, 4 h; ii) K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 90°C, 4 h.

The reactions were carried out in 1,4-dioxane using $Pd(PPh_3)_4$ (6 mol%) as catalyst and potassium phosphate (K_3PO_4) as base. The employment of $CsCO_3$ as base resulted in a decreased overall yield, because its basicity could be to strong for the substrate. All products were isolated by chromatographic purification. A small amount of the corresponding biphenyls could be detected (by ^1H NMR and GC-MS) in the crude product.

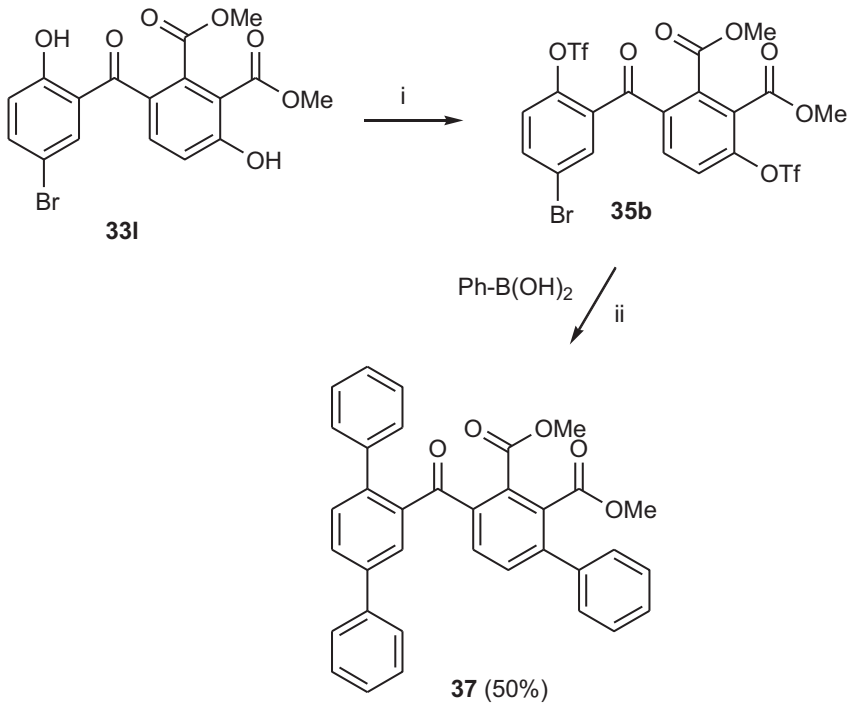
The position of the aryl substituents had a dramatic influence on the yields. The best yields were obtained when *para*-substituted arylboronic acids were used (**36a-c**). This can explain the small yield of **36d,** where the *metha*-trifluoromethylboronic acid was employed. The Suzuki reaction with *ortho*-substituted boronic acids (2,5-substitution) was not successful. The reason can be the steric hindrance of the substituents and the electronic effects.

Table 5.6: Synthesis of benzophenones **36**.

36	R^1	Yield [a] %
a	$(4\text{-}OCH_3)C_6H_4$	60
b	$(4\text{-}C_2H_5)C_6H_4$	60
c	$(4\text{-}Cl)C_6H_4$	70
d	$(3\text{-}CF_3)C_6H_4$	39

[a] Yields of isolated products

Following the same procedure, benzophenone **33l** with R_2 = Br was successfully transformed into the bis-triflate derivative **35b**. The subsequent coupling with phenyl boronic acid afforded the triple Suzuki reaction. Though, the optimal reaction conditions used for the synthesis of **36** failed, providing an inseparable mixture of mono, bi and tri-substituted products. Change of the base by using KF instead of K_3PO_4 afforded the benzophenone **37** (**Scheme 5.7**).

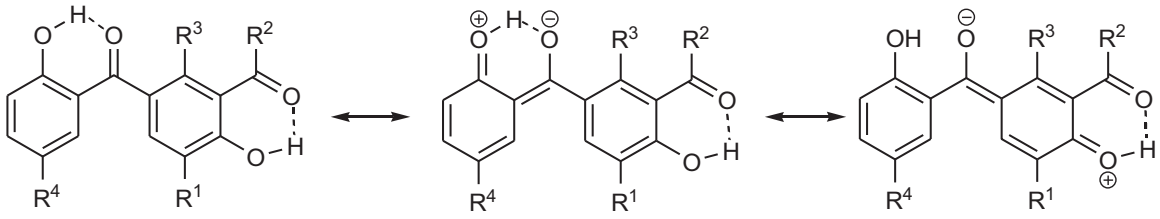


Scheme 5.7: Synthesis of **37***:* i) CH_2Cl_2, pyridine, -78 - 0 °C, inert atmosphere, 4 h; ii) KF, $Pd(PPh_3)_4$, 1,4-dioxane, 90°C, 4 h.

Of particular interest is also the study of the site-selective (mono) Suzuki reaction of the substrates **35**. Though, this is a problematic task since the substrates are prepared after a multistep method. Besides that, similar selective reactions have been broadly investigated on simple benzophenones. [57]

5.4 UV measurements

It is known that highly conjugated systems absorb light in the UV wavelength without decomposition. According to the structure of benzophenones, both phenyls can interact with the C=O-group through the σ-electrons (inductive effect) and the π-electrons (mesomeric effect). The π-electron delocalization stabilizes the system relocating the electronic deficiency through the molecule. (**Figure 5.4**) At the same time one or more internal hydrogen bonds of *ortho*-substituted molecules lower the energy requirements for the π→π* resp. n→π* excitations and increase the wavelength of the UV absorbance. This has been successfully used in the design of many new UV-filters that have appeared on the market. [47]



33

Figure 5.4: The electron delocalization in the benzophenone molecule.

To develop a new UV-A/B filter, the UV absorptions of the polycyclic system **31** and of the benzophenones **33**, **36** and **37** were studied. Electron transfers (π→π* resp. n→π*) in the benzophenones **33a-v** resulted in tree λ_{max} at ca. 230 nm (UV-C), 240-280 nm (UV-C) and 315-380 nm (UV-A/UV-B). (**Table 5.7, Figure 5.5**)

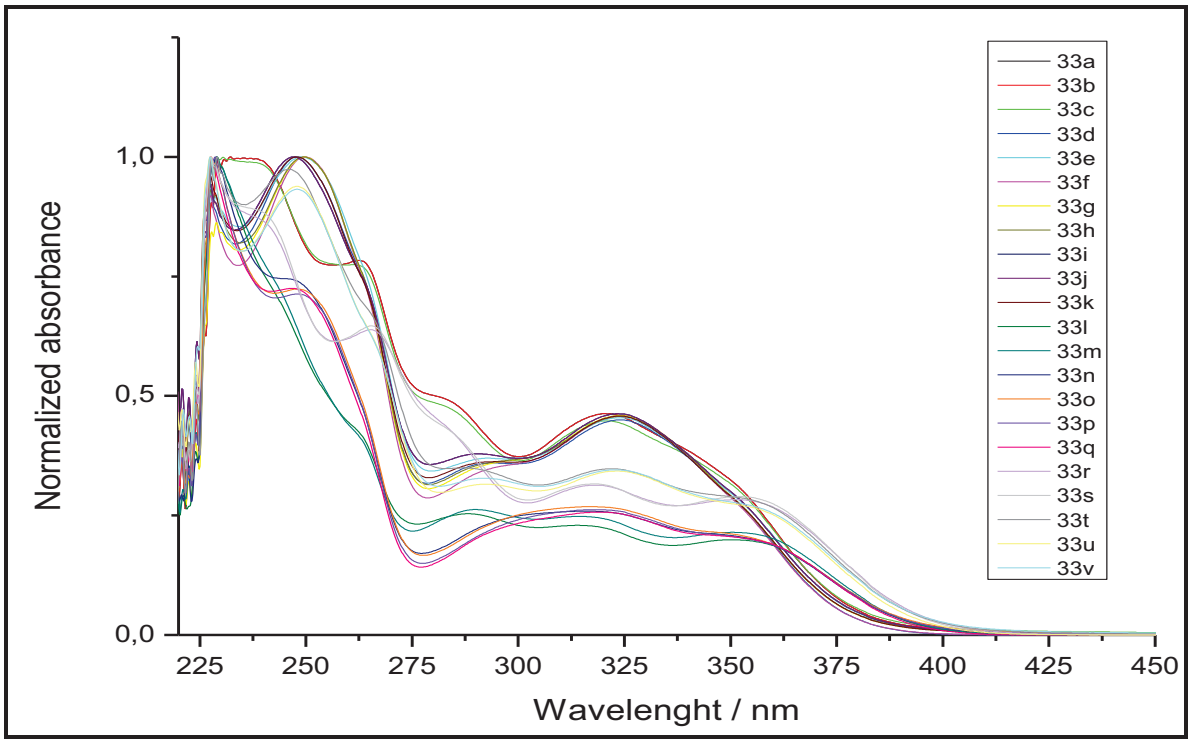


Figure 5.5: UV absorbance spectra of **33** in CH_2Cl_2.

Table 5.7: The UV properties of **33**.

33[a]	λ_{max} (nm)	E[b]	ε[c] ($cm^{-1}mol^{-1}l$)	logε	33[a]	λ_{max} (nm)	E[b]	ε[c] ($cm^{-1}mol^{-1}l$)	logε
33a	229	1,25	22644	4,35	**33l**	229	1,34	24364	4,39
	262	0,99	18013	4,26		288	0,34	6182	3,79
	321	0,56	10267	4,01		350	0,26	4727	3,67
33b	232	1,83	18290	4,26	**33m**	229	1,41	25636	4,41
	262	1,43	14336	4,16		289	0,37	6727	3,83
	320	0,85	8470	3,93		350	0,30	5455	3,74
33c	229	1,18	11821	4,07	**33n**	229	1,41	25636	4,41
	321	0,53	5311	3,73		315	0,36	6545	3,82
33d	227	0,92	16733	4,22	**33o**	227	1,26	22909	4,36
	247	0,99	18082	4,26		247	0,92	16727	4,22
	323	0,45	8125	3,91		315	0,33	6000	3,78
33e	227	0,97	17658	4,25	**33p**	228	1,32	24000	4,38
	248	1,03	18753	4,27		247	0,94	17091	4,23
	323	0,48	8644	3,94		318	0,34	6182	3,79
33f	227	0,87	15855	4,20	**33q**	227	0,65	11818	4,07
	249	0,95	17240	4,24		246	0,47	8545	3,93
	324	0,44	7929	3,90		318	0,16	2909	3,46
33g	228	1,63	16263	4,21	**33r**	227	0,83	15091	4,18
	249	1,88	18848	4,28		265	0,53	9636	3,98
	323	0,87	8653	3,94		318	0,26	4727	3,67
33h	227	1,10	10955	4,04	**33s**	227	0,80	14545	4,16
	249	1,18	11765	4,07		265	0,51	9273	3,97
	324	0,54	5380	3,73		352	0,23	4182	3,62
33i	227	1,33	13325	4,12	**33t**	229	1,70	17000	4,23
	249	1,43	14280	4,15		246	1,66	16600	4,22
	324	0,65	6490	3,81		321	0,59	5900	3,77
33j	227	1,16	21060	4,32	**33u**	227	0,84	15273	4,18
	246	1,23	22322	4,35		247	0,79	14364	4,16
	323	0,57	10340	4,01		323	0,29	5273	3,72
33k	227	0,88	16042	4,21	**33v**	227	0,75	13636	4,13
	247	0,92	16707	4,22		247	0,70	12727	4,10
	324	0,42	7636	3,88		323	0,26	4727	3,67

[a] Dissolved in CH_2Cl_2.

[b] E = Extinction

[c] ε = Extinction coefficient

As expected, the best absorptions were observed for high conjugated systems like benzophenones **36** and **37** with absorption coefficients ε = 25000-37000 $cm^{-1}mol^{-1}l$, which are very high in contrast to other known UV-A/UV-B filters. [47] Surprisingly, the expected bathochromic shift to UV-A area was not witnessed. They showed strong absorptions only in the range of λ_{max} = 230 nm (UV-C) and 300 nm (UV-B). This can be explained by the absence of hydrogen bonding. (**Figure 5.6, Table 5.8**)

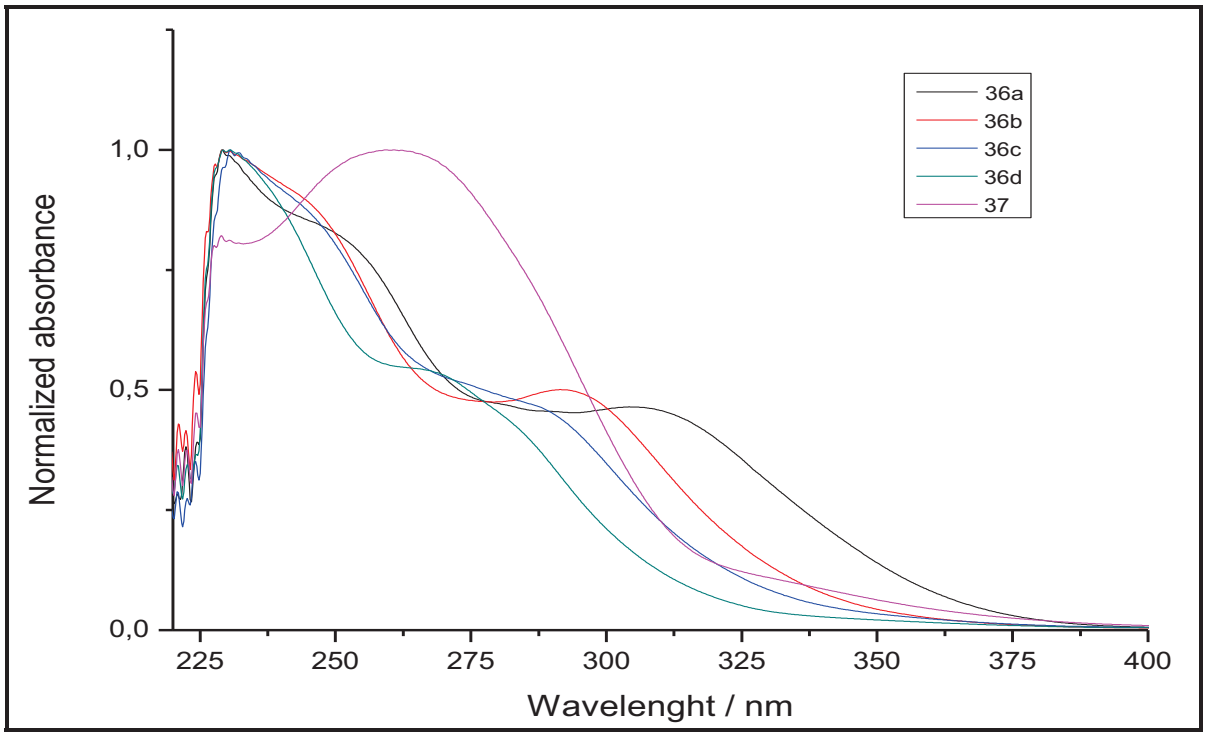


Figure 5.6: UV absorbance spectra of **36** and **37** in CH_2Cl_2.

Table 5.8: The UV properties of **36** and **37**.

Compound[a]	$\lambda_{max,1}$ (nm)	E_1[b]	ε_1[c] ($cm^{-1}mol^{-1}l$)	$\log\varepsilon_1$	$\lambda_{max,2}$ (nm)	E_2[b]	ε_2[c] ($cm^{-1}mol^{-1}l$)	$\log\varepsilon_2$
36a	229	1,52	27636	4,44	304	0,70	12727	4,10
36b	229	1,44	26182	4,42	291	0,72	13091	4,12
36c	230	2,03	36909	4,57	-	-	-	-
36d	230	1,38	25091	4,40	-	-	-	-
37	228	1,26	28000	4,45	259	1,54	34222	4,53

[a] Dissolved in CH_2Cl_2.

[b] E = Extinction

[c] ε = Extinction coefficient

Weaker absorption coefficients were observed for the polycyclic system **31** at wavelengths similar to the ones of benzophenones **33**, making them to a less promising UV-A/UV-B filter. (**Table 5.9, Figure 5.7**)

In general**,** electron-donor groups led to a slight blue shift, while electron-acceptor groups (Br, Cl, CF_3) led to a slight red shift. This result is not in agreement with the theory, because the energy of the HOMO decreases with electron-acceptor substituents and the energy required to afford the $\pi\rightarrow\pi^*$ electron excitation is therefore higher, and the wavelength that provides this energy is decreased correspondingly. This can only be explained by the presence of the $n\rightarrow\pi^*$ absorption of the C-X-group.

Table 5.9: The UV properties of **31**.

31[a]	λ_{max} (nm)	E[b]	ε[c] ($cm^{-1}mol^{-1}l$)	logε	32	λ_{max} (nm)	E[b]	ε[c] ($cm^{-1}mol^{-1}l$)	logε
31a	229	1,10	10976	4,04	**31f**	227	0,66	6553	3,82
	252	2,10	21016	4,32		252	1,14	11428	4,06
	321	0,59	5862	3,77		323	0,34	3388	3,53
31b	228	0,70	6994	3,84	**31g**	232	1,87	18671	4,27
	251	1,19	11862	4,07		334	0,35	3491	3,54
	321	0,35	3513	3,55					
31c	228	0,85	8476	3,93	**31h**	232	2,00	19982	4,30
	252	1,56	15608	4,19		334	0,39	3879	3,59
	321	0,39	3929	3,59					
31d	228	0,87	8673	3,94	**31i**	229	1,00	9993	4,00
	251	1,66	16576	4,22		255	0,82	8151	3,91
	321	0,44	4351	3,64		331	0,38	3821	3,58
31e	228	0,74	7428	3,87	**31j**	230	1,45	14496	4,16
	251	1,39	13890	4,14		254	1,86	18614	4,27
	321	0,38	3822	3,58		331	0,53	5311	3,73

[a] Dissolved in CH_2Cl_2.

[b] E = Extinction

[c] ε = Extinction coefficient

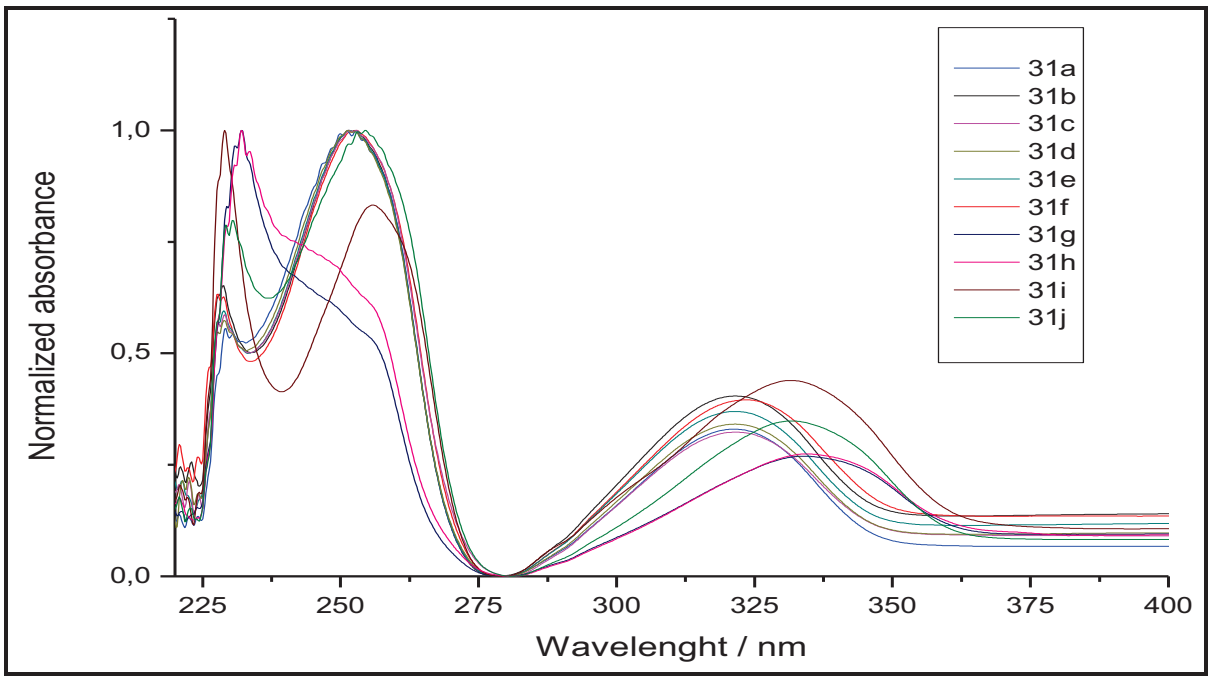
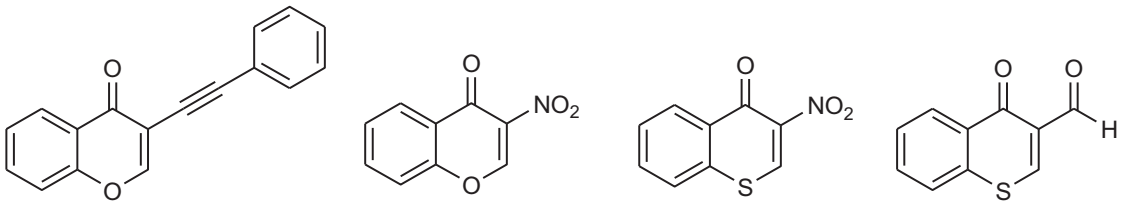


Figure 5.7: UV absorbance spectra of **31** in CH_2Cl_2

5.5 Unsuccessful trials

The described method is convenient for the synthesis of different benzophenones which are potential UV filters. Consequently, other chromones derivatives have been tested for this domino-cascade reaction with 1,3-bis-silyl enol ethers under the same conditions.



A **B** **C** **D**

Unfortunately not all chromones led to the desired benzophenones. In fact, the reaction of 3-nitrochromone (**B**) and 3-nitrothiochromone (**C**) did not work at all. Only starting materials were obtained after the known procedure. Different 1,3-bis-silyl enol ethers and reaction conditions have been tried without succes. The 3-formylthiochromone (**D**) and the 3-(2-phenylethynyl)chromone (**A**) afforded a mixture of inseparable products and no formation of benzophenone was observed.

5.5 Conclusions

In summary, the domino-cascade reaction of high functionalized chromones with 1,3-bis-silyl enol ethers is a novel two-step synthetic strategy for the assembling of new benzophenones derivatives. The isolation of the polycyclic intermediate changed the theoretical mechanism reported before, which assumed a domino Michael/retro-Michael/Mukaiyama-aldol reaction pathway. Unfortunately, this new method is limited to 3-methoxalylchromone and derivatives only.

Functionalization of the benzophenones was explored by Suzuki C-C-coupling reaction. The triple cross-coupling reaction on benzophenones has not been reported before. These methods afforded a wide range of novel UV absorbers with good UV absorbing properties.

Chapter 6

Summary

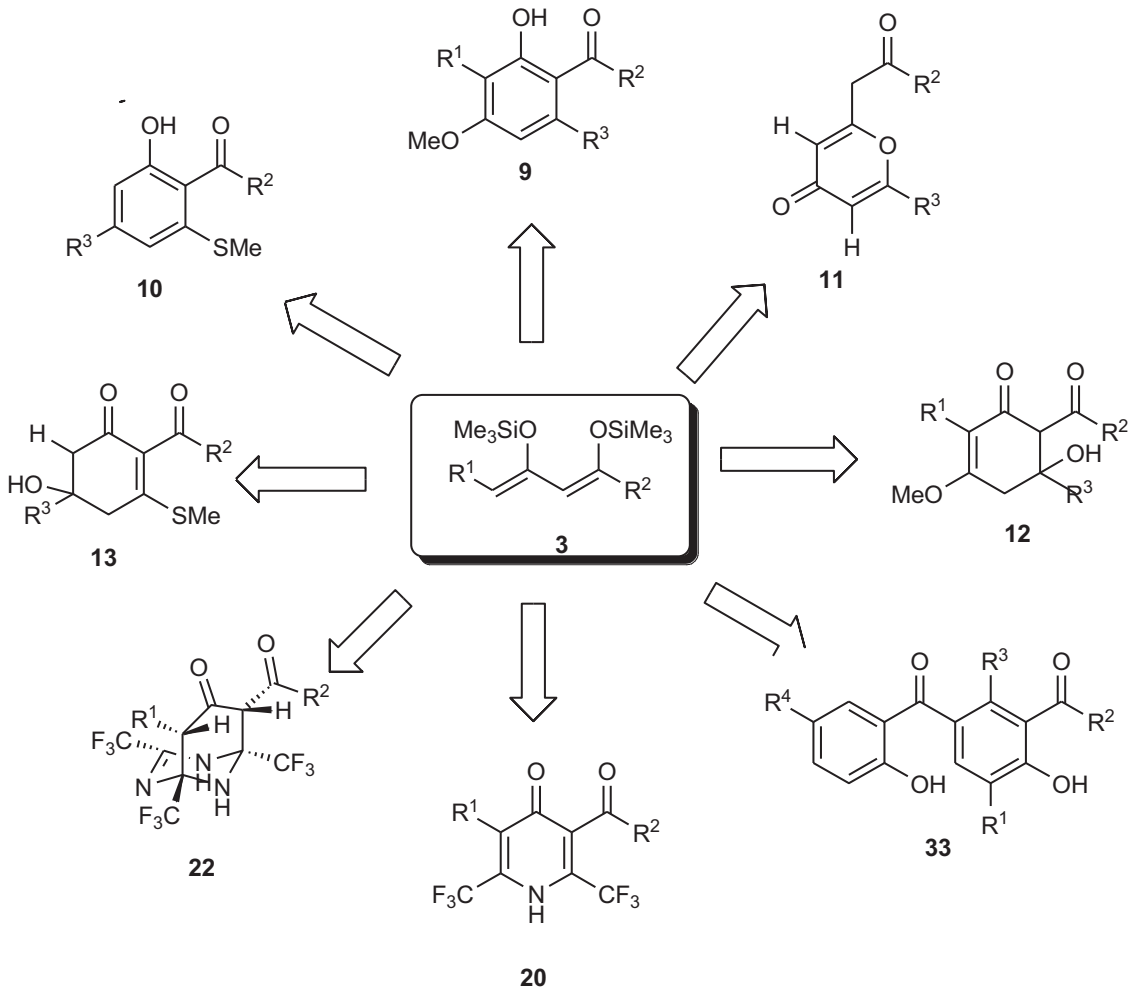
The scope of this thesis was to show the chemical potential of 1,3-bis-silyl-enol ethers **3** as building blocks for the synthesis of new interesting ring systems.

As described in Chapter 3, the $TiCl_4$-mediated cyclocondensation with 4,4-dimethoxy-butenones and 4,4-dimethylthio-butenones afforded a variety of functionalized halogen-substituted salicylates **9** and **10**, while the Me_3SiOTf-mediated cyclocondensation afforded halogen-substituted *γ*-pyrones **11** and cyclohexenones **12** and **13**. The influence of the Lewis acids on the formal [3+3]-cyclization of 1,3-bis-silyl-enol ethers **3** was studied.

According to Chapter 4, a new type of formal [3+3]-cyclization reaction with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine has been discovered. The reaction provided a convenient approach to functionalized 2,6-bis(trifluoromethyl)pyridones **20** starting from the same 1,3-bis-silyl-enol ethers **3**. An unusual bicyclic intermediate **22** was isolated.

Another objective of this work was the synthesis of functionalized benzophenones starting from 1,3-bis-silyl-enol ethers **3**. Chapter 5 describeed a novel two-step reaction with 3-methoxalylchromones and their derivatives to give a great variety of functionalized 2,4-dihydroxybenzophenones. The isolation of a uncommon tricyclic intermediate unlocked new concepts over the mechanistic progress of this type of reactions. The benzophenones were successfully functionalized by Suzuki C-C-coupling reaction. These methods afforded a wide range of novel UV absorbers with good UV absorbing properties.

Scheme 6.1 gives once more an overview of the [3+3]-reactions of 1,3-bis-silyl-enol ethers **3** and the obtained products.



Scheme 6.1: The chemical potential of 1,3-bis-silyl-enol ethers **3**.

Supplement 1

Experimental part

1.1. Analytics

^{1}H-NMR-Spectroscopy: Bruker AV 300 (300 MHz) and Bruker AV 400 (400 MHz). References: 0.00 for TMS, 7.26 for $CDCl_3$. Peak characterization: s = singlet, d = doublet, t = triplet, dd =double dublet, dt = double triplet, q = quartet, m = multiplet. The spectra were measured with standard number of scans. In case of unclear assignment all possible hydrogen atoms were stated.

^{13}C-NMR-Spectroscopy: Bruker AV 300 (75 MHz) and Bruker AV 400 (100 MHz). References: 0.00 for TMS, 77.00 for $CDCl_3$. Peak characterization: t = triplet, q = quartet. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms. All spectra were measured with standard number of scans and when necessary with 4000 scans. In case of unclear assignment all possible carbon atoms were stated.

^{19}F-NMR-Spectroscopy: Bruker AV 300 (282 MHz). The spectra were measured with standard number of scans.

Mass spectrometry (MS): Finnigan MAT 95 XP (electron ionisation EI, 70 eV).

High resolution MS (HRMS): Finnigan MAT 95 XP. Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct.

Infrared spectroscopy (IR): Nicolet 550 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. Signal characterization: w = weak, m = medium, s = strong.

X-ray crystallography: STOE imaging plate diffraction systems with monochromatic Mo-Kα radiation.

Elemental analysis (EA): Leco 932 C, H, N, S.

UV/Vis spectroscopy: Lambda 2 (Perkin Elmer)

Melting point determination (mp): Micro-Hot-Stage Galen^{TM} III Cambridge Instruments. The melting points are not corrected.

Thin layer chromatography (TLC): Merck Silica 60 F254 on aluminium tin foil from Macherey-Nagel. Detection with UV light at 254 nm and afterwards development with vanillin-sulfuric acid solution (6 g vanillin, 2.5 mL conc. sulfuric acid, 250 mL ethanol).

Column chromatography: Separation on Fluka silica gel 60 (0.063-0.200 mm, 70-320 mesh). Eluents were distilled before use.

1.2 Chemicals and techniques

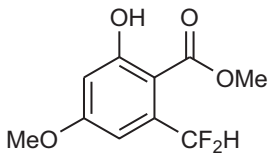
The 1,3-bis-silyl-enol ethers were obtained according to the literature method [17], [18] and used without further purification. Commercially available chemicals were used without further purification. All reactions took place in dry Schlenk flasks and inert gas atmosphere. Dry THF, CH_2Cl_2, pyridine and benzene were acquired from Acros.

1.3 General procedures and product characterisations

GP 1: General procedure for the synthesis of 4-methoxy-6-(diifluoromethyl)salicylates and the 4-methoxy-6-(trichloromethyl)salicylates **9r-ai**:

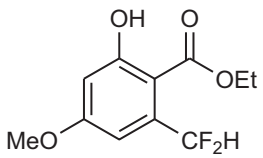
To a CH_2Cl_2 solution (2 mL/1.0 mmol of **8**) of **8** (1.0 mmol) was added **3** (2.0 mmol) and, subsequently, $TiCl_4$ (0.1 mL, 1.0 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12−14 h with stirring. To the solution was added hydrochloric acid (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography to obtain **9r-ai**. The purification of **9ab,ae,ag,ah** afforded a regioisomer mixture with **10ab,ae,ag,ah**.

Methyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9r).



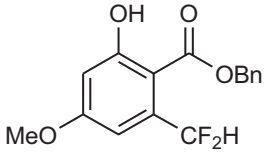
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **(3a)** (0.521 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (5 mL), the product **9r** was isolated as a white solid (0.081 g, 35%); mp = 72-73°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.55 (d, ^4J = 2.4 Hz, 1H, CH), 6.88 (d, ^4J = 2.4 Hz, 1H, CH), 7.24 (t, ^2J = 55.6 Hz, 1H, CF_2H), 11.60 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.5, 55.7 (OCH_3), 102.7 (t, $J_{C\text{-}F}$ = 1.6 Hz, C-3), 102.8 (bs, C-1), 106.7 (t, $J_{C\text{-}F}$ = 10.5 Hz, C-5), 111.9 (t, $J_{C\text{-}F}$ = 237.7 Hz, CF_2H), 136.9 (t, $J_{C\text{-}F}$ = 21.4 Hz, C-6), 164.5, 165.4, 170.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.3 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097 (w), 2950 (w), 2923 (w), 2848 (w), 1652 (s), 1620 (s), 1583 (s), 1519 (w), 1436 (s) 1259 (s), 999,6 (s), 752 (s). MS (EI, 70 eV): m/Z (%): 232 (M^+, 41), 201 (21), 200 (100), 172 (34), 157 (21). HRMS (EI, 70 eV): calcd. for $C_{10}H_{10}F_2O_4$ (M^+) 232.05417, found 232.05483.

Ethyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9s).



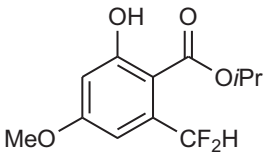
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)- 1,3-butadiene (**3b**) (0.549 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **9s** was isolated as a white solid (0.082 g, 33%); mp = 71−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.44 (q, ^3J = 7.2 Hz, 2H, CH_2), 6.55 (d, ^4J = 2.7 Hz, 1H, CH), 6.88 (d, ^4J = 2.7 Hz, 1H, CH), 7.28 (t, ^2J = 55.5 Hz, 1H, CF_2H), 11.71 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 55.6 (OCH_3), 62.0 (CH_2), 102.7 (t, $J_{C\text{-}F}$ = 1.5 Hz, C-3), 103.1 (t, $J_{C\text{-}F}$ = 4.4 Hz, C-1), 106.6 (t, $J_{C\text{-}F}$ = 10.5 Hz, C-5), 111.9 (t, $J_{C\text{-}F}$ = 237.7 Hz, CF_2H), 136.9 (t, $J_{C\text{-}F}$ = 21.3 Hz, C-6), 164.4, 165.5, 169.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.2 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3094 (w), 2983 (w), 2925 (w), 2854 (w), 1649 (m), 1617 (m), 1589 (m), 1527 (w), 1445 (m), 1370 (s), 1255 (s), 996 (s), 862 (s), 624 (s), 411 (s). GC-MS (EI, 70 eV): *m/z* (%): 246 (M^+, 31), 201 (22), 200 (100), 172 (31), 157 (15). HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}F_2O_4$ (M^+) 246.06982, found 246.07028.

Benzyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9t).



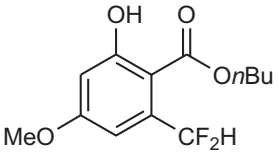
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **9t** was isolated as a yellow oil (0.091 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.55 (d, ^4J = 2.7 Hz, 1H, CH), 6.84 (d, ^4J = 2.7 Hz, 1H, CH), 7.20 (t, ^2J = 57.0 Hz, 1H, CF_2H), 7.37–7.47 (m, 5H, Ph), 11.65 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 67.9 (CH_2), 102.7 (bs, C-3), 102.8 (t, $J_{C\text{-}F}$ = 4.0 Hz, C-1), 106.8 (t, $J_{C\text{-}F}$ = 11.0 Hz, C-5), 111.7 (t, $J_{C\text{-}F}$ = 237.5 Hz, CF_2H), 128.6, 128.8, 134.5 (Ph), 137.0 (t, $J_{C\text{-}F}$ = 21.5 Hz, C-6), 164.5, 165.6, 169.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.0 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066 (w), 3033 (w), 2959 (w), 2852 (w), 1655 (s), 1618 (s), 1581 (m), 1498 (w), 1441 (w), 1373 (s), 1248 (s), 1161 (s), 1030 (s), 951 (s), 749 (s), 695 (s). GC-MS (EI, 70 eV): *m/z* (%): 308 (M^+, 18), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{16}H_{14}F_2O_4$ (M^+) 308.08547, found 308.08601.

Isopropyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9u).



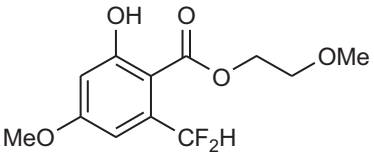
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.577 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **9u** was isolated as a yellow oil (0.151 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 3.84 (s, 3H, OCH_3), 5.26−5.38 (m, 1H, CH), 6.54 (d, ^4J = 2.7 Hz, 1H, CH), 6.84 (d, ^4J = 2.7 Hz, 1H, CH), 7.28 (t, ^2J = 55.5 Hz, 1H, CF_2H), 11.79 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 55.6 (OCH_3), 70.4 (CH), 102.7 (bs, C-3), 103.5 (t, $J_{C\text{-}F}$ = 4.1 Hz, C-1), 106.5 (t, $J_{C\text{-}F}$ = 10.5 Hz, C-5), 111.8 (t, $J_{C\text{-}F}$ = 237.7 Hz, CF_2H), 137.0 (t, $J_{C\text{-}F}$ = 21.3 Hz, C-6), 164.3, 165.5, 169.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.1 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2983 (w), 2935 (w), 2853 (w), 1654 (s), 1617 (s), 1583 (m), 1444 (w), 1360 (s), 1254 (s), 1098 (s), 1032 (s), 954 (s), 757 (s). GC-MS (EI, 70 eV): *m/z* (%): 260 (M^+, 17), 218 (17), 201 (20), 200 (100), 172 (22). Anal. calcd. for $C_{12}H_{14}F_2O_4$ (260.23): C, 55.38; H, 5.42. Found: C, 55.77; H, 5.74.

Butyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9v).



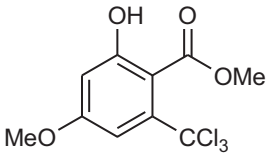
Starting with ,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3e**) (0.605 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **9w** was isolated as a white solid (0.101 g, 37%); mp = 43 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.40-1.54 (m, 2H, CH_2), 1.73-1.84 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.39 (t, ^3J = 6.7 Hz, 2H, OCH_2), 6.55 (d, ^4J = 2.7 Hz, 1H, CH), 6.88 (d, ^4J = 2.7 Hz, 1H, CH), 7.26 (t, ^2J = 55.6 Hz, 1H, CF_2H) 11.74 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.6 (CH_3), 19.2, 30.4 (CH_2), 55.6 (OCH_3), 66.0 (OCH_2), 102.8 (C-3), 103.1 (t, $J_{C\text{-}F}$ = 4.3 Hz, C-1), 106.6 (t, $J_{C\text{-}F}$ = 10.8 Hz, C-5), 111.9 (t, $J_{C\text{-}F}$ = 239.2 Hz, CF_2H), 136.9 (t, $J_{C\text{-}F}$ = 21.5 Hz, C-6), 164.4, 165.5, 169.9 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.4 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2937 (w), 2875 (w), 1724 (w), 1658 (s), 1618 (s), 1582 (m), 1504 (w), 1463 (m), 1444 (m), 1433 (m), 1396 (m), 1372 (s), 1330 (s), 1249 (s), 1205 (s), 1162 (s), 1108 (s), 1051 (m), 1032 (s), 1002 (s), 954 (s), 843 (m), 757 (s). GC-MS (EI, 70 eV): m/z (%): 274 (M^+, 21), 201 (20), 200 (100), 172 (18), 157 (8), 153 (8). Anal. calcd. for $C_{13}H_{16}F_2O_4$ (274.26): C, 56.93; H, 5.88. Found: C, 57.19; H, 5.95.

2-Methoxyethyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (9x).



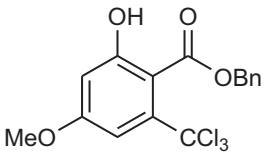
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3i**) (0.609 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **9v** was isolated as a white solid (0.082 g, 30%); mp = 63−64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 3H, OCH_3), 3.72 (t, ^3J = 4.8 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.50 (t, ^3J = 4.8 Hz, 2H, CH_2), 6.54 (d, ^4J = 2.7 Hz, 1H, CH), 6.89 (d, ^4J = 2.7 Hz, 1H, CH), 7.31 (t, ^2J = 55.3 Hz, 1H, CF_2H), 11.47 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6, 58.9 (OCH_3), 64.5, 69.8 (CH_2), 102.6 (bs, C-3), 103.0 (t, $J_{C\text{-}F}$ = 4.5 Hz, C-1), 106.7 (t, $J_{C\text{-}F}$ = 10.5 Hz, C-5), 112.0 (t, $J_{C\text{-}F}$ = 237.5 Hz, CF_2H), 137.3 (t, $J_{C\text{-}F}$ = 21.5 Hz, C-6), 164.5, 165.3, 169.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.1 (d, ^2J = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3339 (w), 3095 (w), 2995 (w), 2922 (w), 2852 (w), 2820 (w), 1649 (s), 1613 (s), 1590 (s), 1488 (w), 1436 (s), 1372 (s), 1258 (s), 1205 (s), 1107 (s), 1024 (s), 995 (s), 755 (s), 543 (s). GC-MS (EI, 70 eV): *m/z* (%): 276 (M^+, 27), 218 (12), 201 (41), 200 (100), 172 (18). HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}F_2O_5$ (M^+) 276.08038, found 276.08054.

Methyl 2-(trichloromethyl)-6-hydroxy-4-methoxybenzoate (9z).



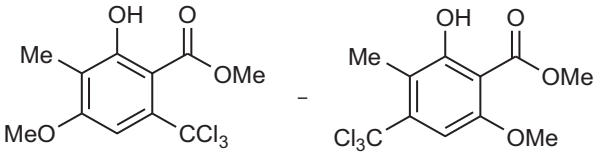
Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), the product **9z** was isolated as a slight yellow solid (0.086 g, 30%); mp = 93-95°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.54 (d, ^4J = 3 Hz, 1H, CH), 7.34 (d, ^4J = 2.4 Hz, 1H, CH), 9.61 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 55.8 (OCH_3), 96.4 (CCl_3), 102.3 (Ar), 105.9 (C), 110.0 (CH), 144.3, 161.5, 162.1, 170.0 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3214 (w), 3120 (w), 3025 (w), 3011 (w), 2973 (w), 2954 (w), 2844 (w), 2616 (w), 1737 (w), 1672 (s), 1612 (s), 1570 (m), 1481 (w), 1442 (m), 1425 (s), 1326 (s), 1250 (s), 1193 (s), 1152 (s), 956 (s), 766 (s). GC-MS (EI, 70 eV): m/Z (%): 300 (M^+, 31), 299 (M^+, 3), 298 (M^+, 34), 270 (34), 268 (100), 267 (31), 266 (97), 233 (30), 231 (38), 227 (41), 212 (58), 210 (27), 205 (29), 203 (40), 149 (33). HRMS (EI, 70 eV): calcd. for $C_{10}H_9Cl_2{}^{37}ClO_4$ (M^+) 299.95314, found 299.95339. Anal. calcd for $C_{10}H_9Cl_3O_4$ (299.54): C, 40.10; H, 3.03. Found: C, 40.27; H, 3.49.

Benzyl 2-(trichloromethyl)-6-hydroxy-4-methoxybenzoate (9aa).



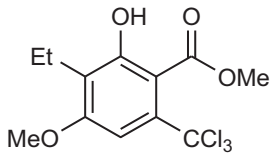
Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), the product **9aa** was isolated as a dark yellow solid (0.110 g, 30%); mp = 88-89°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OCH_3), 6.37 (s, 2H, CH_2), 6.53 (d, ^4J = 2.4 Hz, 1H, CH), 7.30-7.46 (m, 6H, CH+Ph), 9.49 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 68.2 (CH_2), 96.3 (CCl_3), 102.3 (Ar), 105.2 (C), 109.9, 128.5, 128.7, 129.4 (CH), 134.1, 144.2, 161.2, 162.0, 169.4 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3235 (w), 3087 (w), 3063 (w), 3027 (w), 2961 (w), 2936 (w), 2685 (w), 1703 (s), 1606 (s), 1589 (m), 1497 (m), 1452 (m), 1257 (s), 1158 (s), 957 (s), 768 (s), 708 (s), 579 (s). HRMS (ESI): calcd. for $C_{16}H_{13}Cl_3NaO_4$ ([M+Na]$^+$) 396.9771, found 396.9764.

Methyl 6-(trichloromethyl)-2-hydroxy-4-methoxy-3-methylbenzoate (9ab) and methyl 4-(trichloromethyl)-2-hydroxy-6-methoxy-3-methylbenzoate (10ab).



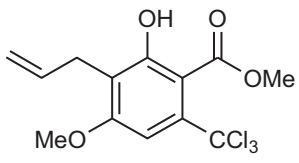
Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), a mixture of regioisomers **9ab** and **10ab** (1 : 0.1) was isolated as a white solid (0.130 g, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): for **9ab** δ = 2.13 (s, 3H, CH_3), 3.92 (bs, 6H, $(OCH_3)_2$), 7.31 (s, 1H, CH), 9.28 (s, 1H, OH); for **10ab** δ = 2.12 (s, 0.3H, CH_3), 3.96 (s, 0.3H, OCH_3), 4.02 (s, 0.3H, OCH_3), 7.22 (s, 0.1H, CH), 11.54 (s, 0.08H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): for **9ab** δ = 8.42 (CH_3), 52.3, 55.7 (OCH_3), 97.0 (CCl_3), 103.6 (Ar), 106.9, 116.4, 141.2, 157.4, 159.3, 170.5 (C).

Methyl 6-(trichloromethyl)-3-ethyl-2-hydroxy-4-methoxybenzoate (9ac).



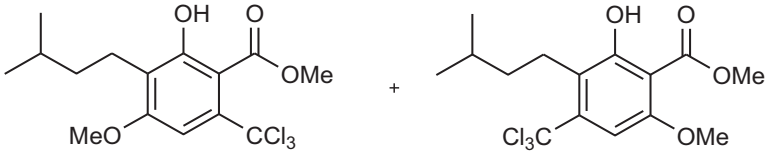
Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3k**) (0.576 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), the product **9ac** was isolated as a white crystalline solid (0.152 g, 46%); mp = 120-122°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.68 (q, ^3J = 7.5 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.31 (s, 1H, CH), 9.23 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 16.5 (CH_2), 52.3, 55.7 (OCH_3), 97.0 (CCl_3), 103.9 (Ar), 107.1, 122.3, 141.3, 157.2, 159.0, 170.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3254 (w), 3130 (w), 3007 (w), 2968 (w), 2953 (w), 2923 (w), 2874 (w), 2851 (w), 1664 (s), 1602 (m), 1569 (m), 1496 (m), 1435 (m), 1285 (s), 1127 (s), 822 (s), 761 (s), 693 (s), 613 (s). GC-MS (EI, 70 eV): m/Z (%): 328 (M^+, 16), 327 (M^+, 2), 326 (M^+, 17), 260 (68), 258 (100). HRMS (EI, 70 eV): calcd. for $C_{12}H_{13}Cl_3O_4$ (M^+) 325.9873, found 325.9867; calcd. for $C_{12}H_{13}Cl_2{}^{37}ClO_4$ (M^+) 327.9844, found 327.9839; calcd. for $C_{12}H_{13}Cl^{37}Cl_2O_4$ (M^+) 329.9814, found 329.9811. Anal. calcd for $C_{12}H_{13}Cl_3O_4$ (327.59): C, 44.00; H, 4.00. Found: C, 44.04; H, 4.34.

Methyl 3-allyl-6-(trichloromethyl)-2-hydroxy-4-methoxybenzoate (9ad).



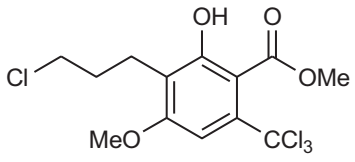
Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3,6-heptatriene (**3o**) (0.601 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), the product **9ad** was isolated as a colourless oil (0.109 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42-3.45 (m, 2H, CH_2), 4.97 (s, 3H, OCH_3), 4.97-5.09 (m, 2H, CH_2), 5.83-5.89 (m, 2H, CH), 7.33 (s, 1H, CH), 9.22 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_2), 52.3, 55.8 (OCH_3), 96.9 (CCl_3), 103.9 (Ar), 107.3 (C), 115.3 (CH_2), 118.0 (C), 134.9, 141.9, 157.3, 159.1, 170.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3409 (w), 3079 (w), 3005 (w), 2950 (w), 2847 (w), 1673 (m), 1638 (w), 1600 (m), 1573 (w), 1497 (w), 1276 (s), 1186 (s), 1155 (s), 1113 (s), 1034 (s), 758 (s), 603 (s), 370 (s). GC-MS (EI, 70 eV): m/Z (%): 340 (M^+, 26), 339 (M^+, 4), 338 (M^+, 28), 303 (30), 273 (50), 272 (76), 271 (78), 270 (100), 237 (26), 207 (49). HRMS (EI, 70 eV): calcd. for $C_{13}H_{13}Cl_3O_4$ (M^+) 337.9873, found 337.9871. Anal. calcd for $C_{13}H_{13}Cl_3O_4$ (339.60): C, 45.98; H, 3.86. Found: C, 48.22; H, 4.34.

Methyl 6-(trichloromethyl)-2-hydroxy-3-isopentyl-4-methoxybenzoate (9ae) and methyl 4-(trichloromethyl)-2-hydroxy-3-isopentyl-6-methoxybenzoate (10ae).



Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**8c**) (0.233 g, 1.0 mmol), 1-methoxy-7-methyl-1,3-bis(trimethylsilyloxy)-1,3-octadiene (**3u**) (0.689 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), a mixture of regioisomers **9ae** and **10ae** (1 : 0.3) was isolated as a colourless oil (0.153 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): for **9ae** δ = 0.94 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 1.32-1.43 (m, 2H, CH_2), 1.52-1.63 (m, 2H, CH_2), 2.62-2.68 (m, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.30 (s, 1H, CH), 9.21 (s, 1H, OH); for **10ae** δ = 0.87 (s, ^3J = 9.0 Hz, 6H, CH_3) 1.32-1.43 (m, 0.6H, CH_2), 1.52-1.63 (m, 0.6H, CH_2), 2.62-2.68 (m, 0.6H, CH_2), 3.94 (s, 1H, OCH_3), 4.01 (s, 1H, OCH_3), 7.20 (s, 1H, CH), 11.48 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): for **9ae** δ = 21.2 (CH_2), 22.5 (CH_3), 28.3 (CH), 37.5 (CH_2), 52.3, 55.7 (OCH_3), 97.1 (CCl_3), 103.9 (Ar), 107.0, 121.4, 141.2, 157.3, 159.2, 170.5 (C).

Methyl 6-(trichloromethyl)-3-(3-chloropropyl)-2-hydroxy-4-methoxybenzoate (9af).

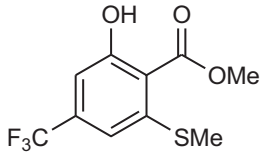


Starting with 4,4-dimethoxy-1,1,1-trichlorobut-3-en-2-one (**9c**) (0.233 g, 1.0 mmol), 1-methoxy-7-cloro-1,3-bis(trimethylsilyloxy)-1,3-heptadiene (**3ag**) (0.674 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), the product **9af** was isolated as a slight yellow solid (0.171 g, 45%); mp = 69-70°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95-2.05 (m, 2H, CH_2), 2.80 (t, ^3J = 7.3 Hz, 2H, CH_2), 3.54 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 7.32 (s, 1H, CH), 9.32 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 31.4, 44.9 (CH_2), 52.4, 55.8 (OCH_3), 96.9 (CCl_3), 103.8 (Ar), 107.1 (C), 119.0, 141.9, 157.5, 159.3, 170.4 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 3002 (w), 2950 (w), 2848 (w), 1674 (m), 1600 (m), 1573 (w), 1497 (w), 1435 (m), 1280 (s), 1153 (s), 1109 (s), 761 (s), 697 (s). MS (EI, 70 eV): m/Z (%): 376 (M^+, 10), 309 (93), 307 (100), 246 (34), 244 (53). HRMS (EI, 70 eV): calcd. for $C_{13}H_{14}Cl_4O_4$ (M^+) 373.9640, found 373.9646; calcd. for $C_{13}H_{14}Cl_3{}^{37}ClO_4$ (M^+) 375.9611, found 375.9615; calcd. for $C_{13}H_{14}Cl_2{}^{37}Cl_2O_4$ (M^+) 377.9581, found 377.9588. Anal. calcd for $C_{13}H_{14}Cl_4O_4$ (376.06): C, 41.52; H, 3.75. Found: C, 42.32; H, 4.14.

GP 2: General procedure for the synthesis of 6-methylthio-4-(trifluoromethyl)salicylates **10** and 4-methylthio-6-(trifluoromethyl)salicylates **9**.

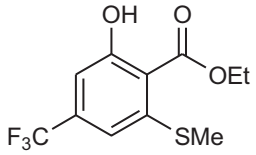
To a CH_2Cl_2 solution (1 mL/1.0 mmol of **8d**) of **8d** (1.0 mmol) was added **3** (2.0 mmol) and, subsequently, $TiCl_4$ (0.1 mL, 1.0 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 12−14 h with stirring. To the solution was added hydrochloric acid (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography to obtain **10ai-aq**. The purification of **10ar-bb** afforded a regioisomer mixture with **9ar-bb.**

Methyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10aj).



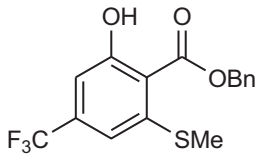
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.521 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10aj** was isolated as a colourless solid (0.138 g, 52%); mp = 91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H, SCH_3), 4.04 (s, 3H, OCH_3), 6.86 (brs, 1H, CH), 6.99 (d, ^4J = 1.1 Hz, 1H, CH), 11.46 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.4 (SCH_3), 52.4 (OCH_3), 110.7 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-3), 111.3 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-5), 112.5 (C-1), 123.1 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 135.4 (q, $J_{C\text{-}F}$ = 32.8 Hz, C-4), 146.0, 163.4, 170.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041 (w), 2960 (w), 2922 (w), 1667 (w), 1610 (w), 1575 (w), 1557 (w), 1441 (w), 1416 (w), 1351 (w), 1338 (w), 1292 (w), 1107 (m), 929 (m), 799 (m), 744 (m), 699 (m). GC-MS (EI, 70 eV): *m/z* (%): 266 (M^+, 52), 236 (11), 235 (18), 234 (100), 206 (47), 191 (39), 163 (7). HRMS (EI, 70 eV): calcd. for $C_{10}H_9F_3O_3S$ (M^+) 266.02190, found 266.021597. Anal. calcd. for $C_{10}H_9F_3O_3S$ (266.24): C, 45.11; H, 3.41. Found: C, 45.30; H, 3.09.

Ethyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10ak).



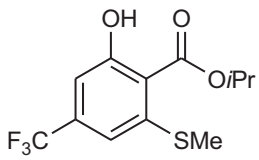
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10ak** was isolated as a colourless solid (0.143 g, 51%); mp = 65-66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.46 (s, 3H, SCH_3), 4.52 (q, ^3J = 7.2 Hz, 2H, CH_2), 6.85 (brs, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.57 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.1 (CH_3), 16.4 (SCH_3), 62.8 (CH_2), 110.7 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-3), 111.2 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C\text{-}F}$ = 273.3 Hz, CF_3), 135.3 (q, $J_{C\text{-}F}$ = 32.7 Hz, C-4), 146.2, 163.4, 169.8 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3000 (w), 2925 (w), 1661 (w), 1607 (w), 1576 (w), 1466 (w), 1450 (w), 1412 (w), 1374 (w), 1349 (m), 1289 (m), 1221 (m), 1014 (w), 956 (m), 801 (m), 773 (w), 698 (m). GC-MS (EI, 70 eV): *m/z* (%): 280 (M^+, 40), 235 (21), 234 (100), 206 (42), 191 (29). HRMS (EI, 70 eV): calcd. for $C_{11}H_{11}F_3O_3S$ (M^+) 280.03755, found 280.038326. Anal. calcd. for $C_{11}H_{11}F_3O_3S$ (280.26): C, 47.14; H, 3.96. Found: C, 47.08; H, 3.33.

Benzyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10al).



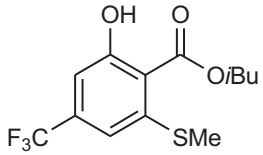
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10al** was isolated as slight yellow solid (0.175 g, 51%); mp = 82-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H, SCH_3), 5.50 (s, 2H, CH_2), 6.85 (brs, 1H, CH), 6.98 (d, ^4J = 0.9 Hz, 1H, CH), 7.36-7.53 (m, 5H, Ph), 11.48 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (SCH_3), 68.0 (OCH_2), 110.7 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-5), 112.5 (C-1), 123.1 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 128.5, 128.7, 128.7 (CH), 134.4 (C), 135.4 (q, $J_{C\text{-}F}$ = 32.8 Hz, C-4), 146.3, 163.5, 169.6 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3031 (w), 2988 (w), 2956 (w), 2925 (w), 1731 (w), 1698 (w), 1663 (m), 1611 (w), 1600 (w), 1577 (m), 1496 (m), 1455 (w), 1428 (m), 1412 (m), 1387 (m), 1342 (m), 1289 (s), 1218 (s), 1182 (s), 1116 (s), 964 (s), 909 (s), 860 (s), 846 (s), 799 (s), 762 (m), 746 (s), 695 (s). GC-MS (EI, 70 eV): *m/z* (%): 342 (M^+, 33), 92 (9), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{16}H_{13}F_3O_3S$ (M^+) 342.05320, found 342.053391.

Isopropyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10am).



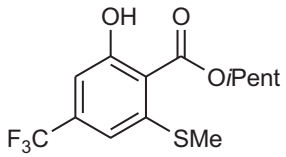
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadien (**3d**) (0.577 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10am** was isolated as a colourless oil (0.164 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, ^3J = 6.2 Hz, 6H, $(CH_3)_2$), 2.45 (s, 3H, SCH_3), 5.31-5.44 (m, 1H, OCH), 6.85 (bs, 1H, CH), 6.97 (d, ^3J = 1.1 Hz, 1H, CH), 11.65 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (SCH_3), 22.1 (CH_3), 71.8 (CH), 110.6 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-5), 113.0 (C-1), 123.2 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 135.1 (q, $J_{C\text{-}F}$ = 32.6 Hz, C-4), 146.2, 163.4, 169.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985 (w), 2925 (w), 1724 (w), 1660 (m), 1609 (m), 1575 (m), 1468 (w), 1455 (w), 1412 (s), 1373 (m), 1342 (s), 1289 (s), 1276 (m), 1221 (s), 1190 (s), 1123 (s), 1097 (s), 959 (s), 907 (m), 805 (m), 758 (m), 699 (s). GC-MS (EI, 70 eV): *m/z* (%): 294 (M^+, 24), 252 (17), 235 (22), 234 (100), 206 (27), 191 (16). HRMS (EI, 70 eV): calcd. for $C_{12}H_{13}F_3O_3S$ (M^+) 294.05320, found 294.053170. Anal. calcd. for $C_{12}H_{13}F_3O_3S$ (294.29): C, 48.97; H, 4.45. Found: C, 48.99; H, 4.32.

Isobutyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10an).



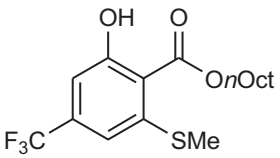
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10an** was isolated as a colourless solid (0.150 g, 49%); mp = 49-50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, ^3J = 6.8 Hz, 6H, $(CH_3)_2$), 2.12-2.25 (m, 1H, CH), 2.47 (s, 3H, SCH_3), 4.25 (d, ^3J = 6.4 Hz, 2H, CH_2), 6.86 (brs, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.69 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (SCH_3), 19.3 (CH_3), 27.6 (CH), 73.1 (CH_2), 110.7 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-3), 111.1 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 135.3 (q, $J_{C\text{-}F}$ = 32.6 Hz, C-4), 146.1, 163.3, 170.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 2967 (w), 2924 (w), 2873 (w), 1666 (s), 1610 (w), 1571 (m), 1465 (w), 1414 (m), 1381 (m), 1369 (m), 1342 (s), 1222 (m), 1184 (s), 1114 (s), 956 (m), 938 (s), 776 (m), 697 (s). GC-MS (EI, 70 eV): *m/z* (%): 308 (M^+, 27), 252 (11), 235 (25), 234 (100), 206 (20), 191 (12). HRMS (EI, 70 eV): calcd. for $C_{13}H_{15}F_3O_3S$ (M^+) 308.06885, found 308.068642. Anal. calcd. for $C_{13}H_{15}F_3O_3S$ (308.07): C, 50.64; H, 4.90. Found: C, 49.96; H, 4.77.

Isopentyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10ao).



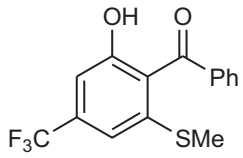
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3g**) (0.633 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10ao** was isolated as a colourless solid (0.180 g, 56%); mp = 32-33 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, ^3J = 6.4 Hz, 6H, $(CH_3)_2$), 1.71-1.93 (m, 3H, CH_2+CH), 2.46 (s, 3H, SCH_3), 4.49 (t, ^3J = 6.8 Hz, 2H, CH_2), 6.85 (brs, 1H, CH), 6.98 (brs, 1H, CH), 11.63 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (SCH_3), 22.4 (CH_3), 25.0 (CH), 37.1 (CH_2), 65.5 (OCH_2), 110.7 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-3), 111.2 (q, $J_{C\text{-}F}$ = 3.9 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 135.3 (q, $J_{C\text{-}F}$ = 32.6 Hz, C-4), 146.1, 163.5, 170.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2929 (w), 2872 (w), 1726 (w), 1665 (m), 1608 (w), 1575 (m), 1464 (w), 1412 (s), 1349 (s), 1289 (s), 1220 (s), 1189 (s), 1118 (s), 963 (m), 934 (m), 803 (m), 758 (m), 699 (s). GC-MS (EI, 70 eV): *m/z* (%): 322 (M^+, 28), 252 (11), 235 (32), 234 (100), 206 (18), 191 (11). HRMS (EI, 70 eV): calcd. for $C_{14}H_{17}F_3O_3S$ (M^+) 322.08450, found 322.084625. Anal. calcd. for $C_{14}H_{17}F_3O_3S$ (323.09): C, 52.16; H, 5.32. Found: C, 52.25; H, 5.30.

Octyl 2-hydroxy-6-(methylthio)-4-(trifluoromethyl)benzoate (10ap).



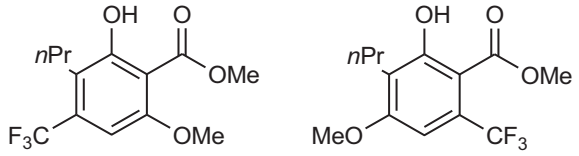
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3h**) (0.717 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10ap** was isolated as a colourless solid (0.200 g, 55%); mp = 49-50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.26-1.54 (m, 12H, $(CH_2)_6$), 2.46 (s, 3H, SCH_3), 4.45 (t, ^3J = 6.6 Hz, 2H, OCH_2), 6.86 (brs, 1H, CH), 6.98 (d, ^4J = 1.1 Hz, 1H, CH), 11.63 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.1 (CH_3), 16.5 (SCH_3), 22.6, 26.0, 28.4, 29.1, 29.1, 31.7 (CH_2), 67.0 (OCH_2), 110.7 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-3), 111.2 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-5), 112.7 (C-1), 123.2 (q, $J_{C\text{-}F}$ = 273.4 Hz, CF_3), 135.2 (q, $J_{C\text{-}F}$ = 32.7 Hz, C-4), 146.1, 163.5, 170.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2924 (m), 2855 (w), 2158 (w), 1976 (w), 1665 (m), 1636 (w), 1608 (w), 1575 (m), 1457 (w), 1412 (m), 1346 (s), 1289 (s), 1220 (s), 1189 (s), 1118 (s), 961 (m), 938 (m), 804 (m), 756 (m), 699 (s). GC-MS (EI, 70 eV): *m/z* (%): 364 (M^+, 17), 252 (11), 235 (28), 234 (100), 206 (11). HRMS (EI, 70 eV): calcd. for $C_{17}H_{23}F_3O_3S$ (M^+) 364.13145, found 364.130709. Anal. calcd. for $C_{17}H_{23}F_3O_3S$ (364.42): C, 56.03; H, 6.36. Found: C, 56.20; H, 6.39.

4-Trifluoromethyl-2-hydroxy-6-(methylthio)benzophenone (10aq).



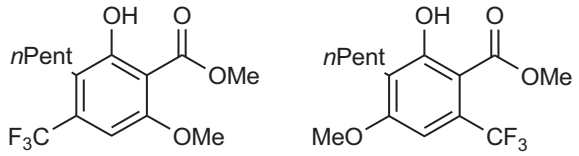
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-phenyl-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3ak**) (0.613 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the product **10aq** was isolated as a brown solid (0.120 g, 39%); mp = 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, SCH_3), 7.07 (s, 1H, CH), 7.08 (s, 1H, CH), 7.45-7.50 (m, 2H, Ph), 7.59-7.65 (m, 1H, Ph), 7.75-7.79 (m, 2H, Ph), 8.13 (brs, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.5 (SCH_3), 111.6 (q, $J_{C\text{-}F}$ = 3.8 Hz, C-3), 115.5 (q, $J_{C\text{-}F}$ = 4.0 Hz, C-5), 123.2 (q, $J_{C\text{-}F}$ = 273.1 Hz, CF_3), 126.3 (C-1) 128.8, 129.5, 133.9 (CH), 134.1 (q, $J_{C\text{-}F}$ = 33.0 Hz, C-4), 137.6, 141.5, 157.0, 197.9 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -63.5 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3331 (w), 3081 (w), 3064 (w), 2928 (w), 1679 (w), 1653 (m), 1594 (w), 1579 (w), 1484 (m), 1448 (m), 1416 (w), 1345 (w), 1324 (w), 1309 (w), 1284 (w), 1265 (w), 1244 (w), 1128 (m), 1087 (m), 954 (m), 924 (m), 856 (m), 713 (m), 683 (m), 626 (w). GC-MS (EI, 70 eV): *m/z* (%): 312 (M^+, 14), 311 (10), 297 (21), 295 (18), 294 (72), 293 (100), 235 (14), 105 (22), 77 (39), 51 (10), 32 (20), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{15}H_{11}F_3O_2S$ (M^+) 312.04264, found 312.042315. Anal. calcd. for $C_{15}H_{11}F_3O_2S$ (312.31): C, 57.69; H, 3.55. Found: C, 57.51; H, 3.57.

Methyl 4-(trifluoromethyl)-2-hydroxy-6-methoxy-3-propylbenzoate (9at) and **methyl 6-(trifluoromethyl)-2-hydroxy-4-methoxy-3-propylbenzoate (10at).**



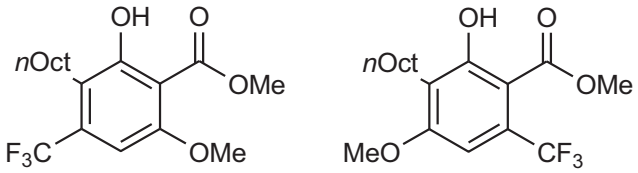
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-heptadiene (**3p**) (0.605 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the isomer mixture of **9at** and **10at** was isolated as a colourless oil (0.119 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00, **1.01** (t, ^3J = 7.4 Hz, 3H, CH_3), 1.51 – 1.65 (m, 2H, CH_2), **2.45**, 2.51 (s, 3H, SCH_3), **2.70 (t, ^3J = 8.0 Hz, 2H, CH_2)**, 2.76 (t, ^3J = 7.9 Hz, 2H, CH_2), 3.96, **4.03** (s, 3H, OCH_3), **6.90**, 7.07 (brs, 1H, Ph), 11.18, **11.78** (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.3 **14.5** (CH_3), 14.8, **16.2** (SCH_3), 20.9, **22.7**, **28.6**, 29.1 (CH_2), **52.4**, 52.7 (OCH_3), 106.5, **112.1** (C-3), **111.5 (q, $J_{C\text{-}F}$ = 6.4 Hz, C-5)**, 113.9 (q, $J_{C\text{-}F}$ = 7.2 Hz, C-5), 123.5 (q, $J_{C\text{-}F}$ = 273.3 Hz, CF_3), **123.8 (q, $J_{C\text{-}F}$ = 275.1 Hz, CF_3)**, **126.3**, 131.9 (C-1), 127.8 (q, $J_{C\text{-}F}$ = 31.9 Hz, CCF_3), **133.1 (q, $J_{C\text{-}F}$ = 29.3 Hz, CCF_3)**, **141.4**, 145.6, 159.3, **162.3**, 170.2, **170.8** (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = **-60.5**, -58.7 (CF_3).

Methyl 4-(trifluoromethyl)-2-hydroxy-6-methoxy-3-pentylbenzoate (9aw) and **methyl 6-(trifluoromethyl)-2-hydroxy-4-methoxy-3-pentylbenzoate (10aw).**



Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-nonadiene (**3t**) (0.689 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the isomer mixture of **9aw** and **10aw** was isolated as a colourless oil (0.127 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91, **0.91** (t, ^3J = 7.1 Hz, 3H, CH_3), 1.36 – 1.59 (m, 9H, $CH_3(CH_2)_3$), **2.44**, 2.51 (s, 3H, SCH_3), **2.71**, 2.77 (t, ^3J = 7.8 Hz, 2H, CH_2), 4.42, **4.52** (q, ^3J = 7.2 Hz, 2H, OCH_2), **6.90**, 7.07 (brs, 1H, Ph), 11.31, **11.86** (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.5, 14.0, **14.0, 14.2** ($2CH_3$) 14.8, **16.3** (SCH_3), **22.4**, 22.5, **26.6,** 27.1**,** 27.2, **29.1**, 32.0, **32.3** (CH_2), 62.3, **62.7** (OCH_2), 106.7, **112.3** (C-3), 113.9 (q, $J_{C\text{-}F}$ = 7.3 Hz, C-5), **111.4 (q, $J_{C\text{-}F}$ = 6.3 Hz, C-5)**, 123.5 (q, $J_{C\text{-}F}$ = 273.3 Hz, CF_3), **123.9 (q, $J_{C\text{-}F}$ = 275.1 Hz, CF_3)**, **126.5**, 132.1, (C-1), 127.7 (q, $J_{C\text{-}F}$ = 31.6 Hz, CCF_3), **132.9 (q, $J_{C\text{-}F}$ = 29.3 Hz, CCF_3)**, 145.2, **141.5**, 159.4, **162.3**, 169.8, **170.4** (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = **-60.4**, -57.9 (CF_3).

Methyl 4-(trifluoromethyl)-2-hydroxy-6-methoxy-3-octylbenzoate (9ay) and **methyl 6-(trifluoromethyl)-2-hydroxy-4-methoxy-3-octylbenzoate (10ay).**

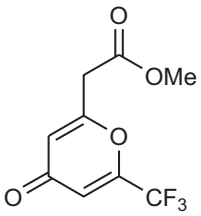


Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-dodecadiene (**3x**) (0.745 g, 2.0 mmol) and $TiCl_4$ (0.11 mL, 1.0 mmol) in CH_2Cl_2 (1.0 mL), the isomer mixture of **9ay** and **10ay** was isolated as a coulourless oil (0.190 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88, **0.89** (t, ^3J = 6.7 Hz, 3H, CH_3), 1.28 – 1.58 (m, 12H, $(CH_2)_6$), **2.44**, 2.51 (s, 3H, SCH_3), 2.71 (t, ^3J = 8.0 Hz, 2H, CH_2), **2.77 (t, ^3J = 7.8 Hz, 2H, CH_2)**, 3.96, **4.03** (s, 3H, OCH_3), **6.90**, 7.07 (brs, 1H, Ph), 11.17, **11.77** (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.1, **14.1** (CH_3), 14.8, **16.2** (SCH_3), 22.7, **22.7**, **26.5** 27.2, 27.5, 29.2, **29.2, 29.3,** 29.4, **29.4**, 29.9, **30.1**, 31.9, **31.9** (CH_2), **52.4,** 52.7 (OCH_3), 106.5, **112.1** (C-3) 113.9 (q, $J_{C\text{-}F}$ = 7.2 Hz, C-5), **111.5 (q, $J_{C\text{-}F}$ = 6.4 Hz, C-5),** 123.5 (q, $J_{C\text{-}F}$ = 273.3 Hz, CF_3), **123.8 (q, $J_{C\text{-}F}$ = 275.1 Hz, CF_3)**, **126.5**, 131.9 (C-1), 127.8 (q, $J_{C\text{-}F}$ = 31.7 Hz, (CCF$_3$), **132.0 (q, $J_{C\text{-}F}$ = 29.6 Hz, CCF$_3$)**, **141.3**, 145.6, 159.4, **162.3**, 170.2, **170.8** (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = **-60.5**, -58.7 (CF_3).

GP 3: General procedure for the synthesis of 6-(trifluoromethyl)-4*H*-pyran-4-ones **11a-f**, 6-(difluoromethyl)-4*H*-pyran-4-ones **11g,h**, 4-methoxy-6-(diifluoromethyl)cyclohexenones **12i-q** and 6-methylthio-4-(trifluoromethyl)salicylates **13r-u**:

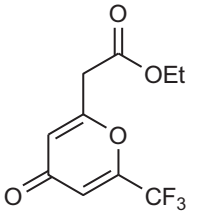
To a CH_2Cl_2 solution (10 mL/1.0 mmol of **8**) of **8** (1.0 mmol) was added **3** (2.0 mmol) and, subsequently, Me_3SiOTf (0.18 mL, 1.0 mmol) at -78 °C. The temperature of the solution was allowed to warm to 20 °C during 12-14 h with stirring. To the solution was added hydrochloric acid (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography.

Methyl 2-(6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-yl)acetate (11a).



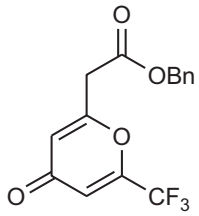
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11a** was isolated as a yellow solid (0.148 g, 63%); mp = 83−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 6.38 (d, ^4J = 2.2 Hz, 1H, CH), 6.69 (d, ^4J = 2.2 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.8 (CH_2), 52.87 (OCH_3), 114.6 (q, J_{C-F} = 2.5 Hz, C-5), 117.5 (C-3), 118.2 (q, J_{C-F} = 271.9 Hz, CF_3), 152.8 (q, J_{C-F} = 39.5 Hz, C-6), 161.3, 166.9, 177.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2969 (w), 2940 (w), 1726 (s), 1672 (s), 1626 (s), 1440 (m), 1415 (m), 1342 (m), 1201 (s), 1139 (s), 1090 (s), 979 (s), 917 (s), 719 (m). GC-MS (EI, 70 eV): *m/z* (%): 236 (M^+, 100), 205 (10), 192 (65), 189 (13), 149 (68), 123 (17), 99 (29), 95 (19), 69 (55), 59 (98), 39 (13). Anal. calcd. for $C_9H_7F_3O_4$ (236.14): C, 45.78; H, 2.9. Found: C, 45.83; H, 3.03.

Ethyl 2-(6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-yl)acetate (11b).



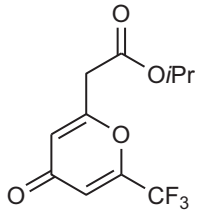
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one **(8a)** (0.184 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **(3b)** (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product (**11b**) was isolated as a yellow solid (0.172 g, 69%); mp = 73-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 7.2 Hz, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.24 (q, ^3J = 7.3 Hz, 2H, CH_2), 6.38 (d, ^4J = 2.3 Hz, 1H, CH), 6.69 (d, ^4J = 2.2 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 39.2 (CH_2), 62.1 (OCH_2), 114.6 (q, J_{C-F} = 2.6 Hz, C-5), 117.5 (C-3), 120.0 (q, J_{C-F} = 272.3 Hz, CF_3), 152.6 (q, J_{C-F} = 39.7 Hz, C-6), 161.6, 166.4, 177.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2990 (w), 2974 (w), 2936 (w), 1722 (s), 1673 (s), 1627 (s), 1414 (m), 1367 (s), 1334 (s), 1282 (s), 1143 (s), 916 (s), 719 (s). GC-MS (EI, 70 eV): m/Z (%): 250 (M^+, 56), 205 (25), 203 (10), 178 (100), 177 (13), 149 (52), 139 (22), 99 (22), 69 (50), 39 (10). Anal. calcd for $C_{10}H_9F_3O_4$ (250.17): C, 48.01; H, 3.63. Found: C, 48.16; H, 3.79.

Benzyl 2-(6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-yl)acetate (11c).



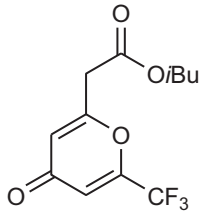
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11c** was isolated as a yellow oil (0.099 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 2H, CH_2), 5.20 (s, 2H, CH_2Ph), 6.36, (d, ^4J = 2.2 Hz, 1H, CH), 6.67 (d, ^4J = 2.2 Hz, 1H, CH), 7.31−7.40 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.0, 67.7 (CH_2), 114.6 (q, $J_{C\text{-}F}$ = 2.5 Hz, C-5), 117.6 (C-3), 118.1 (q, $J_{C\text{-}F}$ = 272.2 Hz, CF_3), 128.3, 128.6, 128.7, 134.6 (Ph), 153.0 (q, $J_{C\text{-}F}$ = 39.5 Hz, C-6), 161.2, 166.2, 177.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3070 (w), 2938 (w), 1740 (m), 1674 (s), 1641 (m), 1619 (m), 1498 (w), 1362 (w), 1274 (s), 1147 (s), 1083 (s), 968 (m), 877 (m), 696 (s). GC-MS (EI, 70 eV): *m/z* (%): 312 (M^+, 0.71), 178 (59), 91 (100), 65 (10). HRMS (EI, 70 eV): calcd. for $C_{15}H_{11}F_3O_4$ (M^+) 312.06039, found 312.06008.

Isopropyl 2-(6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-yl)acetate (11d).



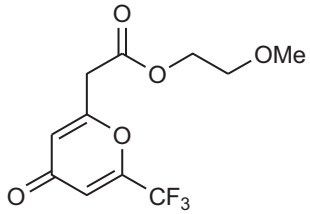
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.577 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11d** was isolated as a yellow oil (0.170 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, ^3J = 9.0 Hz, 6H, $(CH_3)_2$), 3.60 (s, 2H, CH_2), 5.04−5.13 (m, 1H, CH), 6.37 (d, ^4J = 2.1 Hz, 1H, CH), 6.69 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 39.6 (CH_2), 70.0 (CH), 114.7 (q, $J_{C\text{-}F}$ = 2.7 Hz, C-5), 117.5 (C-3), 118.2 (q, $J_{C\text{-}F}$ = 272.0 Hz, CF_3), 153.1 (q, $J_{C\text{-}F}$ = 39.5 Hz, C-6), 161.9, 166.0, 177.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.3 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076 (w), 2985 (w), 2940 (w), 1735 (m), 1674 (s), 1643 (m), 1410 (w), 1361 (m), 1274 (s), 1201 (s), 1148 (s), 1083 (s), 961 (m), 876 (m), 721 (w). GC-MS (EI, 70 eV): *m/z* (%): 264 (M^+, 9), 205 (38), 178 (36), 177 (11), 149 (38), 99 (11), 69 (19), 43 (100), 41 (19). Anal. calcd. for $C_{11}H_{11}F_3O_4$ (264.20): C, 50.01; H, 4.20. Found: C, 50.16; H, 4.55.

Isobutyl 2-(6-(trifluoromethyl)-4-oxo-4H-pyran-2-yl)acetate (11e).



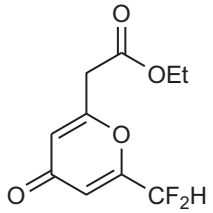
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11e** was isolated as a brown oil (0.178 g, 64%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 1.88−2.01 (m, 1H, CH), 3.63 (s, 2H, CH_2), 3.96 (d, ^3J = 6.6 Hz, 2H, CH_2), 6.38 (d, ^4J = 2.4 Hz, 1H, CH), 6.69 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8 (CH_3), 27.5 (CH), 39.2, 72.0 (CH_2), 114.6 (q, $J_{C\text{-}F}$ = 1.9 Hz, C-5), 117.5 (C-3), 118.2 (q, $J_{C\text{-}F}$ = 272.1 Hz, CF_3), 152.8 (q, $J_{C\text{-}F}$ = 39.6 Hz, C-6), 161.6, 166.4, 177.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076 (w), 2965 (w), 2878 (w), 1740 (m), 1675 (s), 1644 (m), 1620 (w), 1471 (w), 1361 (m), 1274 (s), 1201 (s), 1150 (s), 1084 (s), 973 (m), 876 (m), 721 (m). GC-MS (EI, 70 eV): *m/z* (%): 278 (M^+, 2), 223 (100), 205 (24), 178 (60), 177 (12), 149 (64), 99 (17), 69 (24), 57 (51), 56 (15), 41 (39), 39 (12), 29 (15). Anal. calcd. for $C_{12}H_{13}F_3O_4$ (278.22): C, 51.80; H, 4.71. Found: C, 51.84; H, 4.82

2-Methoxyethyl 2-(6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-yl)acetate (11f).



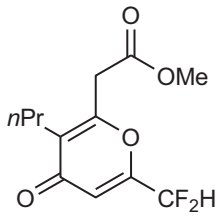
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one **(8a)** (0.183 g, 1.0 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3i**) (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11f** was isolated as a yellow oil (0.112 g, 40%). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 3.61 (t, ^3J = 4.5 Hz, 2H, CH_2), 3.67 (s, 2H, CH_2), 4.34 (t, ^3J = 4.5 Hz, 2H, CH_2), 6.39 (d, ^4J = 2.1 Hz, 1H, CH), 6.69 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.0 (CH_2), 59.0 (OCH_3), 64.1, 70.2 (CH_2), 114.7 (q, $J_{C\text{-}F}$ = 2.3 Hz, C-5), 117.7 (C-3), 118.2 (q, $J_{C\text{-}F}$ = 271.5 Hz, CF_3), 152.9 (q, $J_{C\text{-}F}$ = 39.0 Hz, C-6), 161.4, 166.6, 177.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -71.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2928 (w), 2897 (w), 2849 (w), 2825 (w), 1741 (s), 1675 (s), 1642 (m), 1620 (w), 1362 (m), 1275 (s), 1199 (m), 1150 (s), 1084 (s), 1032 (m), 974 (m), 877 (s), 722 (s). GC-MS (EI, 70 eV): m/Z (%): 280 (M^+, 2), 250 (15), 222 (20), 178 (87), 161 (11), 149 (56), 99 (19), 69 (29), 58 (33), 45 (100), 43 (11), 29 (16). Anal. calcd for $C_{11}H_{11}F_3O_5$ (280.02): C, 47.15; H, 3.96. Found: C, 47.14; H, 4.31.

Ethyl 2-(6-(difluoromethyl)-4-oxo-4H-pyran-2-yl)acetate (11g).



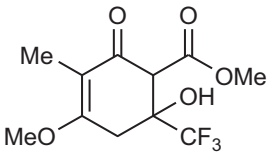
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11g** was isolated as an orange solid (0.140 g, 60%); mp = 49-51 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 6.0 Hz, 3H, CH_3), 3.59 (s, 2H, CH_2), 4.23 (q, ^3J = 7.1 Hz, 2H, CH_2), 6.32 (d, ^4J = 3.0 Hz, 1H, CH), 6.36 (t, ^2J = 52.5 Hz, 1H, CF_2H), 6.56 (d, ^4J = 3.0 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 39.3 (CH_2), 62.0 (CH_2), 108.7 (t, J_{C-F} = 241.1 Hz, CF_2H), 114.1 (t, J_{C-F} = 3.7 Hz, C-5),117.3 (C-3), 157.5 (t, J_{C-F} = 27.3 Hz, C-6), 161.4, 166.7, 178.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -123.4, -123.2 (CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3233 (w), 3055 (w), 2987 (w), 2973 (w), 2934 (w), 2855 (w), 1724 (s), 1668 (s), 1622 (s), 1416 (m), 1371 (s), 1337 (s), 1223 (s), 1114 (s), 1026 (s), 905 (s). GC-MS (EI, 70 eV): m/Z (%): 232 (M^+, 63), 187 (24), 160 (100), 131 (42), 121 (17), 109 (28), 69 (45), 29 (62). Anal. calcd for $C_{10}H_{10}F_2O_4$ (232.18): C, 51.73; H, 4.34. Found: C, 51.14; H, 4.58.

Methyl 2-(6-(difluoromethyl)-4-oxo-3-propyl-4H-pyran-2-yl)acetate (11h).



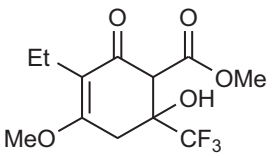
Starting with 4,4-dimethoxy-1,1-difluorobut-3-en-2-one (**8b**) (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-heptadiene (**3p**) (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **11h** was isolated as an orange oil (0.082 g, 32%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.41-1.53 (m, 2H, CH_2), 2.38 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.67 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.31 (t, ^2J = 53.7 Hz, 1H, CF_2H), 6.54 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.5, 26.5, 37.0 (CH_2), 52.7 (OCH_3), 108.8 (t, J_{C-F} = 242.4 Hz, CF_2H), 112.8 (t, J_{C-F} = 3.9 Hz, C-5), 129.1 (C-3), 156.6 (t, J_{C-F} = 27.8Hz, C-6), 157.3, 167.8, 178.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -123.7, -123.5 (CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3083 (w), 2961 (w), 2936 (w), 2874 (w), 1741 (s), 1668 (s), 1631 (m), 1609 (s), 1456 (w), 1434 (m), 1420 (m), 1380 (m), 1338 (m), 1309 (m), 1262 (m), 1195 (m), 1177 (m), 1158 (m), 1136 (s), 1092 (s), 1051 (s), 1011 (m), 873 (m), 801 (m), 649 (w). GC-MS (EI, 70 eV): m/z (%): 260 (M^+, 24), 259 (10), 246 (11), 245 (100), 232 (50), 229 (17), 228 (24), 213 (14), 201 (41), 200 (12), 199 (25), 187 (63), 185 (31), 174 (44), 173 (22), 121 (13), 79 (16), 77 (11), 69 (18), 59 (18), 53 (14), 51 (14). Anal. calcd for $C_{12}H_{14}F_2O_4$ (260.23): C, 55.38; H, 5.42. Found: C, 55.16; H, 5.44.

Methyl 6-(trifluoromethyl)-6-hydroxy-4-methoxy-3-methyl-2-oxocyclohex-3-enecarboxylate (12i).



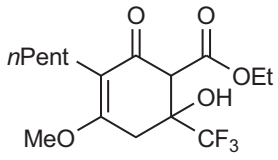
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12i** was isolated as a light yellow solid (0.107 g, 38%); mp = 123-126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72-1.74 (m, 3H, CH_3), 2.78 (brd, ^2J = 17.6 Hz, 1H, H-5a), 2.95 (d, ^2J = 17.5 Hz, 1H, H-5b), 3.69 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.49 (s, 0.5H, OH-a), 5.50 (s, 0.5H, OH-b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.3 (CH_3), 30.4 (C-5), 52.9 (C-1), 53.1, 55.7 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 29.1 Hz, C-6), 113,4 (C-3), 124.5 (q, $J_{C\text{-}F}$ = 286.4 Hz, CF_3), 166.4, 171.3, 188.4 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3428 (w), 3013 (w), 2965 (w), 2926 (w), 2867 (w), 1739 (s), 1648 (m), 1613 (s), 1461 (w), 1440 (w), 1164 (s), 1117 (s), 1063 (s), 972 (s), 688 (m). GC-MS (EI, 70 eV): *m/z* (%): 282 (M^+, 4), 264 (100), 233 (16), 232 (41), 220 (32), 212 (18), 207 (27), 205 (40), 204 (22), 189 (16), 181 (31), 175 (14), 83 (20), 69 (36) 59 (20), 43 (15). Anal. calcd. for $C_{11}H_{13}F_3O_5$ (282.21): C, 46.81; H, 4.64. Found: C, 46.88; H, 4.63.

Methyl 6-(trifluoromethyl)-3-ethyl-6-hydroxy-4-methoxy-2-oxocyclohex-3-enecarboxylate (12j).



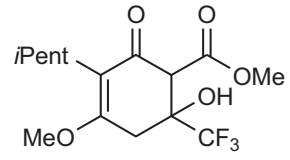
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one **(8a)** (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3k**) (0.577 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12j** was isolated as a white solid (0.146 g, 50%); mp = 106-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.21−2.48 (m, 2H, CH_2Ar), 2.78 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.68 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.89 (s, 3H, OCH_3), 5.50 (s, 0.5H, OH-a), 5.51 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 15.6 (CH_2), 30.3 (C-5), 52.9 (C-1), 53.1, 55.7 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 28.7 Hz, C-6), 119,6 (C-3), 124.5 (q, $J_{C\text{-}F}$ = 279.0 Hz, CF_3), 166.3, 171.4, 188.0 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3437 (w), 3021 (w), 2963 (w), 2942 (w), 2879 (w), 1741 (s), 1649 (m), 1611 (s), 1441 (w), 1413 (w), 1250 (s), 1165 (s), 1132 (s), 1120 (s), 986 (s), 659 (m). GC-MS (EI, 70 eV): *m/z* (%): 296 (M^+, 2), 278 (30), 246 (14), 220 (11), 219 (100), 195 (13), 83 (13), 69 (19). Anal. calcd. for $C_{12}H_{15}F_3O_5$ (296.24): C, 48.65; H, 5.10. Found: C, 48.70; H, 5.12.

Ethyl 6-(trifluoromethyl)-6-hydroxy-4-methoxy-2-oxo-3-pentylcyclohex-3-enecarboxylate (12k).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-nonadiene (**3t**) (0.689 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12k** was isolated as a yellow solid (0.138 g, 39%); mp = 73-75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.25−1.38 (m, 9H, $(CH_2)_3CH_3$), 2.19-2.34 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.4 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.4 Hz, 1H, H-5b), 3.64 (s, 1H, H-1), 3.87 (s, 3H, OCH_3), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 5.59 (s, 0.5H, OH-a), 5.60 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0 (CH_3), 22.1, 22.4, 27.9 (CH_2), 30.3 (C-5), 31.7 (CH_2), 52.9 (C-1), 55.6 (OCH_3), 62.5 (CH_2), 74.1 (q, $J_{C\text{-}F}$ = 28.5 Hz, C-6), 118,4 (C-3), 124.6 (q, $J_{C\text{-}F}$ = 285.0 Hz, CF_3), 166.3, 171.0, 188.3 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3439 (w), 2959 (w), 2932 (w), 2873 (w), 2849 (w), 1735 (s), 1648 (m), 1612 (s), 1463 (w), 1414 (w), 1336 (m), 1250 (m), 1171 (s), 1122 (s), 1024 (s), 946 (m), 657 (m). GC-MS (EI, 70 eV): *m/z* (%): 352 (M^+, 1), 334 (13), 314 (12), 257 (20), 233 (15), 232 (24), 231 (22), 206 (15), 205 (100), 69 (11). Anal. calcd. for $C_{16}H_{23}F_3O_5$ (352.35): C, 54.54; H, 6.58. Found: C, 54.64; H, 6.64.

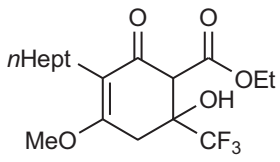
Methyl 6-(trifluoromethyl)-6-hydroxy-3-isopentyl-4-methoxy-2-oxocyclohex-3-enecarboxylate (12l).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1 mmol), 1-methoxy-7-mthyl-1,3-bis(trimethylsilyloxy)-1,3-octadiene **(3u)** (0.661 g, 2 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12l** was isolated as a yellow solid (0.193 g, 55%); mp = 90-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, ^3J = 6.0 Hz 6H, $(CH_3)_2$), 1.14−1.28 (m, 2H, CH_2), 1.45-1.54 (m, 1H, CH), 2.22-2.32 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.68 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.50 (s, 0.5H, OH-a), 5.51 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (CH_2), 22.4, 22.5 (CH_3), 28.1 (CH), 30.3 (C-5), 37.3 (CH_2), 53.0 (C-1), 53.1, 55.6 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 28.7 Hz, C-6), 118,6 (C-3), 124.5 (q, $J_{C\text{-}F}$ = 284.7 Hz, CF_3), 166.3, 171.4, 188.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = −81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3435 (w), 2959 (w), 2933 (w), 2876 (w), 2853 (w), 1740 (s), 1650 (m), 1612 (s), 1452 (w), 1439 (w), 1342 (m), 1249 (s), 1168 (s), 1140 (s), 1124 (s), 1041 (m), 978 (m), 658 (m). GC-MS (EI, 70 eV): *m/z* (%): 338 (M^+, 2), 320 (32), 300 (17), 288 (11), 273 (10), 263 (16), 261 (18), 260 (11), 251 (13), 245 (16), 244 (18), 237 (14), 233 (14), 232 (73), 231 (35),

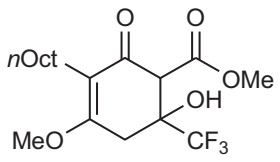
219 (17), 206 (12), 205 (100), 181 (10), 159 (15), 153 (10), 69 (23), 59 (15), 43 (12), 41 (11). Anal. calcd. for $C_{15}H_{21}F_3O_5$ (338.32): C, 53.25; H, 6.26. Found: C, 54.37; H, 6.61.

Ethyl 6-(trifluoromethyl)-3-heptyl-6-hydroxy-4-methoxy-2-oxocyclohex-3-enecarboxylate (12m).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-undecadiene (**3w**) (0.754 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12m** was isolated as a slight yellow solid (0.133 g, 35%); mp = 20-25 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.25-1.38 (m, 13H, $(CH_2)_5CH_3$), 2.19-2.31 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.4 Hz, 1H, H-5b), 3.64 (s, 1H, H-1), 3.87 (s, 3H, OCH_3), 4.35 (d, ^3J = 7.2 Hz, 2H, CH_2), 5.59 (s, 0.5H, OH-a), 5.60 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0 (CH_3), 22.1, 22.6, 28.3, 29.1, 29.5 (CH_2), 30.3 (C-5), 31.8 (CH_2), 52.9 (C-1), 55.6 (OCH_3), 62.5 (CH_2), 74.1 (q, $J_{C\text{-}F}$ = 28.7 Hz, C-6), 118,4 (C-3), 124.6 (q, $J_{C\text{-}F}$ = 285.0 Hz, CF_3), 166.3, 171.0, 188.3 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3427 (w), 2960 (w), 2927 (w), 2856 (w), 1722 (m), 1638 (w), 1605 (s), 1446 (w), 1426 (w), 1375 (m), 1245 (s), 1171 (s), 1122 (s), 1016 (m), 656 (m). GC-MS (EI, 70 eV): *m/z* (%): 380 (M^+, 1), 362 (21), 342 (15), 285 (31), 233 (17), 232 (50), 231 (37), 206 (16), 205 (100), 204 (12), 29 (10). HRMS (ESI): calcd for $C_{18}H_{28}F_3O_5$ [$(M+H)^+$] 381.1883, found 381.1884; calcd for $C_{18}H_{27}F_3NaO_5$ [$(M+Na)^+$] 403.1702, found 403.1705. Anal. calcd. for $C_{18}H_{27}F_3O_5$ (380.40): C, 56.83; H, 7.15. Found: C, 56.89; H, 7.19.

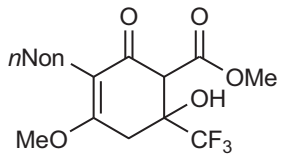
Methyl 6-(trifluoromethyl)-6-hydroxy-4-methoxy-3-octyl-2-oxocyclohex-3-enecarboxylate (12n).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-dodecadiene (**3x**) (0.745 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12n** was isolated as a yellow solid (0.236 g, 62%); mp = 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.24−1.31 (m, 12H, $(CH_2)_6CH_3$), 2.21-2.31 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.6 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.6 Hz, 1H, H-5b), 3.68 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.50 (s, 0.5H, OH-a), 5.51 (s, 0.5H, OH-b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.2, 22.6, 28.2, 29.2, 29.4, 29.5 (CH_2), 30.3 (C-5), 31.8 (CH_2), 53.0 (C-1), 53.1, 55.6 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 29.0 Hz, C-6), 118.4 (C-3),

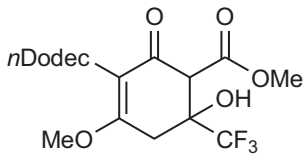
124.5 (q, $J_{C\text{-}F}$ = 285.0 Hz, CF_3), 166.3, 171.4, 188.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3438 (m), 3025 (w), 2958 (w), 2928 (m), 2854 (w), 1739 (s), 1650 (m), 1612 (s), 1461 (w), 1438 (m), 1341 (m), 1258 (s), 1166 (s), 1123 (s), 1069 (m), 974 (m), 659 (m). GC-MS (EI, 70 eV): *m/z* (%): 380 (M^+, 1), 362 (28), 342 (17), 232 (27), 219 (18), 205 (100), 69 (17). HRMS (ESI): calcd for $C_{18}H_{28}F_3O_5$ [$(M+H)^+$] 381.1883, found 381.1880; calcd for $C_{18}H_{27}F_3NaO_5$ [$(M+Na)^+$] 403.1702, found 403.1704. Anal. calcd. for $C_{18}H_{27}F_3O_5$ (380.40): C, 56.83; H, 7.15. Found: C, 56.84; H, 7.12.

Methyl 6-(trifluoromethyl)-6-hydroxy-4-methoxy-3-nonyl-2-oxocyclohex-3-enecarboxylate (12o).



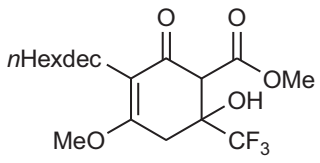
Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3y**) (0.745 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12o** was isolated as a yellow solid (0.225 g, 57%); mp = 63-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.24−1.31 (m, 14H, $(CH_2)_7CH_3$), 2.25-2.27 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.6 Hz, 1H, H-5b), 3.68 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.50 (s, 0.5H, OH-a), 5.51 (s, 0.5H, OH-b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.2, 22.6, 28.2, 29.3, 29.4, 29.5, 29.6 (CH_2), 30.3 (C-5), 31.8 (CH_2), 53.0 (C-1), 53.1, 55.6 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 28.9 Hz, C-6), 118.4 (C-3), 124.5 (q, $J_{C\text{-}F}$ = 286.9 Hz, CF_3), 166.3, 171.4, 188.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3439 (m), 3025 (w), 2958 (w), 2925 (m), 2855 (w), 1739 (s), 1651 (m), 1613 (s), 1461 (w), 1438 (w), 1248 (s), 1167 (s), 1123 (s), 975 (m), 659 (m). GC-MS (EI, 70 eV): *m/z* (%): 394 (M^+, 1), 376 (41), 356 (23), 345 (15), 313 (70), 263 (16), 259 (15), 245 (18), 233 (17), 232 (100), 231 (84), 219 (21), 212 (15), 205 (99), 204 (19), 181 (19), 69 (16). HRMS (ESI): calcd for $C_{19}H_{30}F_3O_5$ [$(M+H)^+$] 395.2039, found 395.2042; calcd for $C_{19}H_{29}F_3NaO_5$ [$(M+Na)^+$] 417.1859, found 417.1860. Anal. calcd. for $C_{19}H_{29}F_3O_5$ (394.20): C, 57.86; H, 7.41. Found: C, 57.78; H, 7.30.

Methyl 6-(trifluoromethyl)-3-dodecyl-6-hydroxy-4-methoxy-2-oxocyclohex-3-enecarboxylate (12p).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadecadiene (**3aa**) (0.857 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12p** was isolated as a yellow solid (0.252 g, 58%); mp = 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.24−1.29 (m, 20H, $(CH_2)_{10}CH_3$), 2.20-2.32 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 17.6 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.6 Hz, 1H, H-5b), 3.68 (s, 0.5H, H-1a), 3.70 (s, 0.5H, H-1b), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.49 (s, 0.5H, OH-a), 5.50 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.2, 22.6, 28.2, 29.3, 29.4 (CH_2), 29.6 (m, $(CH_2)_6$), 30.3 (C-5), 31.9 (CH_2), 52.9 (C-1), 53.1, 55.6 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 28.7 Hz, C-6), 118,4 (C-3), 124.7 (q, $J_{C\text{-}F}$ = 284.9 Hz, CF_3), 166.3, 171.4, 188.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3413 (w), 2953 (w), 2916 (m), 2848 (m), 1734 (m), 1656 (m), 1614 (s), 1463 (w), 1439 (w), 1245 (s), 1160 (s), 1140 (s), 1119 (s), 664 (m). HRMS (ESI): calcd for $C_{22}H_{36}F_3O_5$ [$(M+H)^+$] 437.2509, found 437.2510; calcd for $C_{22}H_{35}F_3NaO_5$ [$(M+Na)^+$] 459.2328, found 459.2327. Anal. calcd. for $C_{22}H_{35}F_3O_5$ (436.51): C, 60.53; H, 8.08. Found: C, 60.74; H, 8.08.

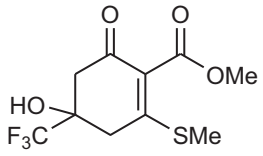
Methyl 6-(trifluoromethyl)-3-hexadecyl-6-hydroxy-4-methoxy-2-oxocyclohex-3-enecarboxylate (12q).



Starting with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**8a**) (0.184 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-icosadiene (**3ab**) (0.969 g, 2 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **12q** was isolated as a yellow solid (0.264 g, 54%); mp = 82-84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.24−1.31 (m, 28H, $(CH_2)_{14}CH_3$), 2.20-2.32 (m, 2H, CH_2Ar), 2.77 (brd, ^2J = 18.0 Hz, 1H, H-5a), 2.94 (d, ^2J = 17.6 Hz, 1H, H-5b), 3.68 (s, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.49 (s, 0.5H, OH-a), 5.50 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.2, 22.6, 28.2, 29.3, 29.4 (CH_2), 29.6 (m, $(CH_2)_{10}$), 30.3 (C-5), 31.9 (CH_2), 52.9 (C-1), 53.1, 55.6 (OCH_3), 74.1 (q, $J_{C\text{-}F}$ = 28.7 Hz, C-6), 118,4 (C-3), 124.5 (q, $J_{C\text{-}F}$ = 285.0 Hz, CF_3), 166.3, 171.4, 188.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3413 (w), 2952 (w), 2916 (s), 2847 (s), 1735 (m), 1655 (m), 1613 (s), 1462 (m), 1439 (m), 1245 (s), 1161 (s), 1140 (s), 1120 (s), 664 (m). GC-MS (EI, 70 eV): *m/z* (%): 492 (M^+, 1), 475 (11), 474 (48), 454 (15), 423 (15), 411 (55), 474 (48), 442 (22), 411 (55),

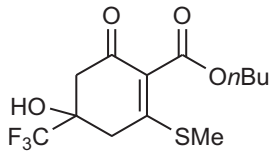
263 (16), 233 (25), 232 (100), 231 (83), 205 (83). HRMS (ESI): calcd for $C_{26}H_{44}F_3O_5$ [$(M+H)^+$] 493.3135, found 493.3134; calcd for $C_{26}H_{43}F_3NaO_5$ [$(M+Na)^+$] 515.2954, found 515.2955. Anal. calcd. for $C_{26}H_{43}F_3O_5$ (492.61): C, 63.39; H, 8.80. Found: C, 63.71; H, 8.87.

Methyl 4-hydroxy-2-(methylthio)-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (13r).



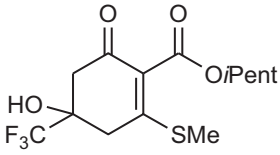
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-metoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a** (0.520 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **13r** was isolated as a colourless solid (0.110 g, 39%); mp = 142-143 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 2.53 (s, 3H, SCH_3), 2.60-2.88 (m, 2H, CH_2), 3.07-3.23 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 5.69 (s, 1H, OH). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 14.1 (SCH_3), 34.6, 42.0 (CH_2), 52.1 (OCH_3), 73.7 (q, J_{C-F} = 29.5 Hz, C-4), 126.2 (q, J_{C-F} = 283.0 Hz, CF_3), 129.1 (C-6), 159.7, 166.3, 187.5 (C). ^{19}F-NMR (282 MHz, $(CD_3)_2CO$): δ = -83.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3429 (m), 3252 (w), 3011 (w), 2957 (w), 2930 (w), 2850 (w), 1721 (s), 1640 (s), 1549 (s), 1431 (m), 1403 (m), 1164 (s), 1044 (s), 813 (m), 552 (m). HRMS (ESI): calcd for $C_{10}H_{12}F_3O_4S$ [$(M+H)^+$] 285.0402, found 285.0400; calcd for $C_{10}H_{11}F_3NaO_4S$ [$(M+Na)^+$] 307.0222, found 307.0221. Anal. calcd. for $C_{10}H_{11}F_3O_4S$ (284.25): C, 42.25; H, 3.90; S, 11.28. Found: C, 42.45; H, 4.26; S, 11.16.

Butyl 4-hydroxy-2-(methylthio)-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (13b).



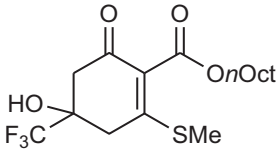
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3e** (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **13b** was isolated as a colourless solid (0.170 g, 52%); mp = 137-138 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 0.93 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.36−1.49 (m, 2H, CH_2), 1.60-1.70 (m, 2H, CH_2), 2.53 (s, 3H, SCH_3), 2.59-2.88 (m, 2H, CH_2), 3.05-3.24 (m, 2H, CH_2), 4.41 (t, ^3J = 6.6 Hz, 2H, CH_2), 5.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 13.9 (CH_3), 14.1 (SCH_3), 19.7, 31.3, 34.5, 42.0, 65.3 (CH_2), 73.7 (q, J_{C-F} = 29.2 Hz, C-4), 126.2 (q, J_{C-F} = 283.1 Hz, CF_3), 129.4 (C-6), 159.1, 165.8, 187.5 (C). ^{19}F-NMR (282 MHz, $(CD_3)_2CO$): δ = -83.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3294 (m), 2963 (w), 2934 (w), 2874 (w), 1707 (s), 1648 (s), 1558 (m), 1470 (w), 1405 (m), 1180 (s), 1043 (s), 946 (m), 540 (m). HRMS (ESI): calcd for $C_{13}H_{18}F_3O_4S$ [$(M+H)^+$] 327.0872, found 327.0869; calcd for $C_{13}H_{17}F_3NaO_4S$ [$(M+Na)^+$] 349.0692, found 325.0694.

Isopentyl 4-hydroxy-2-(methylthio)-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (13t).



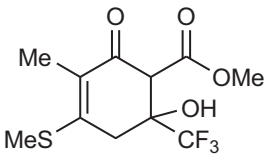
Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3g** (0.633 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **13t** was isolated as a colourless solid (0.110 g, 36%); mp = 130-132 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ = 0.93 (d, ^3J = 9.0 Hz, 6H, $(CH_3)_2$), 1.53-1.59 (m, 2H, CH_2), 1.72-1.81 (m, 1H, CH), 2.53 (s, 3H, SCH_3), 2.58-2.88 (m, 2H, CH_2), 3.05-3.24 (m, 2H, CH_2), 4.21 (t, ^3J = 6.7 Hz, 2H, OCH_2), 5.69 (s, 1H, OH). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 14.1 (SCH_3), 22.6 (CH_3), 25.5 (CH), 34.4, 38.0, 42.0, 64.1 (CH_2), 73.7 (q, $J_{C\text{-}F}$ = 29.0 Hz, C-4), 126.2 (q, $J_{C\text{-}F}$ = 282.9 Hz, CF_3), 129.3 (C-6), 159.3, 165.9, 187.6 (C). ^{19}F-NMR (282 MHz, $(CD_3)_2CO$): δ = -83.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3312 (m), 2946 (w), 2811 (w), 1720 (s), 1643 (s), 1547 (s), 1430 (m), 1403 (m), 1267 (s), 1043 (s), 786 (m), 533 (m). HRMS (ESI): calcd for $C_{14}H_{20}F_3O_4S$ [$(M+H)^+$] 341.1029, found 341.1029; calcd for $C_{14}H_{19}F_3NaO_4S$ [$(M+Na)^+$] 363.0848, found 363.0857. Anal. calcd. for $C_{14}H_{19}F_3O_4S$ (340.36): C, 49.40; H, 5.63; S, 9.42. Found: C, 50.05; H, 5.88; S, 9.45.

Octyl 4-hydroxy-2-(methylthio)-6-oxo-4-(trifluoromethyl)cyclohex-1-enecarboxylate (13u).



Starting with 4,4-dimethylthio-1,1,1-trifluorobut-3-en-2-one (**8d**) (0.216 g, 1.0 mmol), 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3h** (0.717 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (10 mL), the product **13u** was isolated as a colourless solid (0.130 g, 34%); mp = 98-99 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 0.88 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.28-1.45 (m, 10H, $(CH_2)_5CH_3$), 1.64-1.71 (m, 2H, CH_2), 2.53 (s, 3H, SCH_3), 2.60-2.87 (m, 2H, CH_2), 3.07-3.23 (m, 2H, CH_2), 4.18 (t, ^3J = 6.4 Hz, 2H, OCH_2), 5.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ = 14.1 (SCH_3), 14.3 (CH_3), 23.2, 26.6, 29.8, 29.9, 32.5, 34.4, 42.0, 65.6 (CH_2), 73.7 (q, $J_{C\text{-}F}$ = 29.2 Hz, C-4), 126.2 (q, $J_{C\text{-}F}$ = 282.9 Hz, CF_3), 129.3 (C-6), 159.1, 165.8, 187.5 (C). ^{19}F-NMR (282 MHz, $(CD_3)_2CO$): δ = -83.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3348 (m), 2935 (m), 2855 (w), 1712 (s), 1653 (s), 1564 (s), 1464 (w), 1437 (w), 1318 (s), 1159 (s), 1045 (s), 938 (m), 544 (m), 488 (m). HRMS (ESI): calcd for $C_{17}H_{26}F_3O_4S$ [$(M+H)^+$] 383.1498, found 383.1503; calcd for $C_{17}H_{25}F_3NaO_4S$ [$(M+Na)^+$] 405.1318, found 405.1324. Anal. calcd. for $C_{17}H_{25}F_3O_4S$ (382.44): C, 53.39; H, 6.59; S, 8.38. Found: C, 54.26; H, 6.53; S, 9.20.

Methyl 6-hydroxy-3-methyl-4-methylthio-2-oxo-6-(trifluoromethyl)cyclohex-3-enecarboxylate (12v).

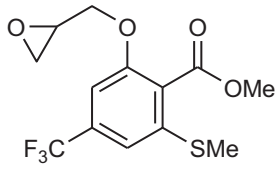


To a solution of **8d** (0.216 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene **3j** (0.549 g, 2.0 mmol) and, subsequently, $AlCl_3$ (0.134 g, 1.0 mmol) at -78°C. The temperature of the solution was allowed to warm to 20°C during 12-14 h with stirring. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography to give **12v** as a colorless solid (0.154 g, 52%); mp = 93°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (s, 3 H, CH_3), 2.44 (s, 3 H, SCH_3), 2.80 (d, ^2J = 17.8 Hz, $^4J_{H,F}$ = 2.1 Hz, 1 H, H-5a), 2.97 (br d, ^2J = 17.8 Hz, 1 H, H-5b), 3.72 (s, 1 H, CH), 3.87 (s, 3 H, OCH_3), 5.35 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6 (CH_3), 14.0 (SCH_3), 33.1 (CH_2), 53.1 (CH), 53.3 (OCH_3), 74.7 (q, $J_{C,F}$ = 28.8 Hz, C-6), 124.4 (q, $J_{C,F}$ = 287.0 Hz, CF_3), 127.0, 154.0, 171.0 (C), 184.8 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -81.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3431 (w), 3285 (w), 3024 (w), 2962 (w), 2935 (w), 2919 (w), 2858 (w), 2635 (w), 1737 (m), 1651 (m), 1574 (m), 1441 (w), 1414 (w), 1372 (w), 1356 (w), 1333 (m), 1301 (m), 1267 (m) 1222 (w), 1200 (m), 1162 (m), 1129 (m), 1068 (m), 1003 (m), 630 (m), 569 (m). GC-MS (EI, 70 eV): *m/z* (%) = 298 (M^+, 13), 281 (13), 280 (100), 265 (30), 248 (16), 223 (27), 221 (49), 197 (24), 193 (22), 175 (16), 85 (16), 81 (22), 69 (33), 59 (19), 53 (18). HRMS (EI, 70 eV): calcd for $C_{11}H_{13}F_3O_4S$ (M^+) 298.04812, found 298.048772. Anal. Calcd for $C_{11}H_{13}F_3O_4S$ (298.28): C, 44.29; H, 4.39. Found: C, 44.34; H, 4.67.

GP 4: General Procedure for the Synthesis of Compounds 14, 15, 16 and 17.

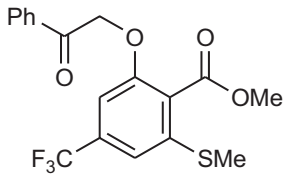
To a solution of salicylate **7a** in acetone (2.0 mL/1.0 mmol) was added K_2CO_3 (1.2 mmol) and the respective alkyl bromide (1.2 mmol). The mixture was then heated at 55°C for 8 h and the resulting suspension was filtered and washed with diethyl ether. The ether solution was washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography.

Methyl 2-methylthio-6-(oxiran-2-ylmethoxy)-4-(trifluoromethyl)benzoate (14).



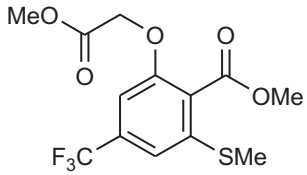
Starting with **10aj** (0.275 g, 1.1 mmol) and 2-(bromomethyl)oxirane (0.170 g, 1.3 mmol) and K_2CO_3 (0.172 g, 1.3 mmol) in acetone (2.1 mL), the product **14** was isolated as a colorless solid (0.330 g, 99%); mp = 45°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, SCH_3), 2.73 (dd, ^2J = 4.9 Hz, ^3J = 2.6 Hz, 1 H, OC*H*H), 2.87 (dd, ^2J = 4.9 Hz, ^3J = 4.2 Hz, 1 H, OCH*H*), 3.28–3.33 (m, 1 H, CH), 3.94 (s, 3 H, OCH_3), 4.02 (dd, ^2J = 11.1 Hz, ^3J = 5.5 Hz, OC*H*H), 4.33 (dd, ^2J = 11.3 Hz, ^3J = 2.6 Hz, OCH*H*), 6.99 (br s, 1 H, CH), 7.16 (br s, 1 H, CH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.7 (SCH_3), 44.2 (OCH_2), 49.7 (CH), 52.6 (OCH_3), 69.8 (OCH_2), 106.9 (q, $J_{C,F}$ = 3.7 Hz, C-5), 116.6 (q, $J_{C,F}$ = 4.0 Hz, C-3), 123.3 (q, $J_{C,F}$ = 273.0 Hz, CF_3), 127.1 (C), 132.9 (q, $J_{C,F}$ = 32.7 Hz, C-4), 139.3, 155.7, 166.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -63.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 3003 (w), 2960 (w), 2930 (w), 2854 (w), 1714 (m), 1605 (w), 1573 (w), 1464 (w), 1432 (w), 1425 (w), 1387 (m), 1322 (m), 1283 (m), 1250 (m), 1201 (m), 1169 (m), 1120 (s), 1086 (m), 1074 (m), 1024 (m), 993 (m), 842 (s), 704 (m). GC-MS (EI, 70 eV): m/z (%) = 322 (M^+, 100), 303 (21), 291 (60), 235 (42), 234 (85), 206 (38), 191 (44), 163 (12), 57 (49) 45 (54), 31 (23), 29 (45). HRMS (EI, 70 eV): calcd for $C_{13}H_{13}F_3O_4S$ (M^+) 322.04812, found 322.048212. Anal. Calcd for $C_{13}H_{13}F_3O_4S$ (322.05): C, 48.45; H, 4.07. Found: C, 48.70; H, 4.06.

Methyl 2-methylthio-6-phenacyloxy-4-(trifluoromethyl)benzoate (15).



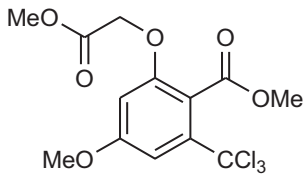
Starting with **10aj** (0.275 g, 1.1 mmol) and 2-bromoacetophenone (0.247 g, 1.3 mmol) and K_2CO_3 (0.172 g, 1.3 mmol) in acetone (2.1 mL), the product **11** was isolated as a colorless solid (0.121 g, 32%); mp = 82°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, SCH_3), 3.89 (s, 3 H, OCH_3), 5.31 (s, 2 H, CH_2), 6.87 (br s, 1 H, CH), 7.18 (br s, 1 H, CH), 7.47–7.52 (m, 2 H, Ph), 7.60–7.65 (m, 1 H, Ph), 7.94–7.97 (m, 2 H, Ph). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.7 (SCH_3), 52.6 (OCH_3), 71.7 (CH_2), 106.6 (q, $J_{C,F}$ = 3.7 Hz, C-5), 117.0 (q, $J_{C,F}$ = 3.8 Hz, C-3), 123.2 (q, $J_{C,F}$ = 273.1 Hz, CF_3), 128.2, 128.8, 128.9, 132.8 (q, $J_{C,F}$ = 32.8 Hz, C-4), 134.1 (CH), 134.1, 139.7, 155.3, 165.9, 192.9 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -63.0 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084 (w), 3009 (w), 2959 (w), 2925 (w), 2908 (w), 2841 (w), 1710 (m), 1597 (w), 1579 (w), 1468 (w), 1448 (w), 1421 (m), 1325 (m), 1278 (w), 1255 (m), 1224 (m), 1180 (w), 1159 (m), 1122 (m), 1093 (m), 1074 (m), 984 (m), 760 (m), 670 (m). GC-MS (EI, 70 eV): *m/z* (%) = 384 (M^+, 22), 353 (13), 106 (8), 105 (100), 91 (11), 77 (24), 45 (9). HRMS (EI, 70 eV): calcd for $C_{18}H_{15}F_3O_4S$ (M^+) 384.06377, found 384.063943.

Methyl 2-(2-methoxy-2-oxoethoxy)-6-methylthio-4-(trifluoromethyl)benzoate (16).



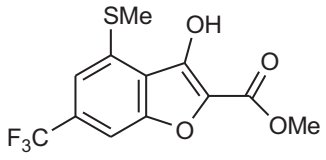
Starting with **10aj** (0.400 g, 1.5 mmol), methyl bromoacetate (0.549 g, 2.0 mmol) and K_2CO_3 (0.249 g, 1.8 mmol) in acetone (3.0 mL), the product **16** was isolated as a yellow solid (0.362 g, 71%); mp = 64°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, SCH_3), 3.79, 3.96 (s, 3 H, OCH_3), 4.68 (s, 2 H, CH_2), 6.83 (br s, 1 H, CH), 7.19 (br s, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7 (SCH_3), 52.4, 52.7 (OCH_3), 66.2 (OCH_2), 106.6 (q, $J_{C,F}$ = 3.7 Hz, C-3), 117.2 (q, $J_{C,F}$ = 3.9 Hz, C-5), 123.2 (q, $J_{C,F}$ = 273.1 Hz, CF_3), 127.3 (C), 135.9 (q, $J_{C,F}$ = 32.8 Hz, C-4), 139.8, 155.1, 165.8, 168.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -63.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3457 (w), 3188 (w), 3098 (w), 3010 (w), 2961 (w), 2915 (w), 2860 (w), 1733 (m), 1698 (w), 1605 (w), 1580 (w), 1557 (w), 1471 (w), 1449 (w), 1417 (m), 1389 (w), 1330 (w), 1303 (m), 1249 (m), 1206 (w), 1161 (m), 1120 (m), 1078 (m), 1066 (m), 1018 (m), 935 (m), 864 (m), 705 (m). GC-MS (EI, 70 eV): *m/z* (%) = 338 (M^+, 47), 319 (17), 307 (51), 279 (27), 249 (19), 248 (16), 247 (100), 246 (31), 219 (14), 218 (37), 191 (22), 189 (12), 45 (92). HRMS (ESI): calcd for $C_{13}H_{14}F_3O_5S$ [$(M+H)^+$] 339.0509, found 339.0508; calcd for $C_{13}H_{13}F_3NaO_5S$ [$(M+Na)^+$] 361.0328, found 361.0329. Anal. Calcd for $C_{13}H_{13}F_3O_5S$ (338.04): C, 46.15; H, 3.87. Found: C, 46.27; H, 3.77.

Methyl 2-(2-methoxy-2-oxoethoxy)-4-methoxy-6-(trichloromethyl)benzoate (17).



Starting with **9z** (0.320 g, 1.1 mmol), methyl bromoacetate (0.196 g, 1.3 mmol) and K_2CO_3 (0.177 g, 1.3 mmol) in acetone (2.2 mL), the product **17** was isolated as a braun solid (0.390 g, 98%); mp = 169°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 6.48 (d, ^4J = 2.3 Hz, 1H, Ar), 7.29 (d, ^4J = 2.3 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 52.7, 55.7 (OCH_3), 66.7 (CH_2), 95.3 (C), 101.8, 105.6 (CH), 115.5, 142.1, 157.0, 160.3, 166.7, 168.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3102 (w), 2993 (w), 2953 (w), 2917 (w), 2849 (w), 1763 (m), 1727 (s), 1604 (m), 1575 (m), 1485 (w), 1461 (w), 1440 (m), 1428 (m), 1399 (w), 1323 (m), 1271 (s), 1232 (m), 1215 (m), 1201 (s), 1162 (s), 1115 (m), 1102 (m), 1051 (s), 1012 (m), 966 (s), 808 (s), 778 (s). GC-MS (EI, 70 eV): m/z (%): 372 (M^+, 28) 370 (M^+, 29), 343 (14), 341 (41), 339 (53), 338 (15), 337 (65), 336 (16), 335 (100), 306 (13), 305 (20), 304 (20), 303 (26), 285 (17), 227 (15), 205 (14), 203 (13), 45 (47). HRMS (EI, 70 eV): calcd. for $C_{13}H_{13}{}^{35}Cl_3O_6$ (M^+) 369.97722, found 369.977530; calcd. for $C_{13}H_{13}{}^{35}Cl_2{}^{37}ClO_6$ (M^+) 371.97427, found 371.975175.

Methyl 3-hydroxy-4-methylthio-6-(trifluoromethyl)benzofuran-2-carboxylate (18).

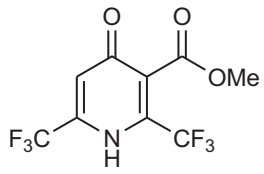


To a solution of **16** (0.160 g, 0.5 mmol) in MeOH/CH_2Cl_2 (1:1, 3.0 mL) was added MeONa (0.065 g, 0.6 mmol). The reaction mixture was then heated at 50°C for 6 h. To the solution was added HCl (10%, 15 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography to give **18** as an yellow solid (0.045 g, 31%); mp = 179°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, SCH_3), 4.02 (s, 3 H, OCH_3), 7.16 (br s, 1 H, CH), 7.44 (s, 1 H, CH), 8.26 (br s, 1 H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.9 (SCH_3), 52.3 (OCH_3), 106.4 (q, $J_{C,F}$ = 4.4 Hz, C-7), 114.6 (q, $J_{C,F}$ = 3.7 Hz, C-5), 137.1, 150.9, 152.5, 162.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3331 (w), 3087 (w), 3003 (w), 2959 (w), 2930 (w), 2864 (w), 1688 (w), 1604 (w), 1575 (w), 1499 (w), 1455 (w), 1377 (w), 1335 (m), 1258 (w), 1216 (m), 1198 (m), 1148 (m), 1115 (m), 1074 (m), 966 (m), 849 (m), 658 (m). GC-MS (EI, 70 eV): *m/z* (%) = 306 (M^+, 100), 275 (15), 274 (49), 273 (15), 247 (17), 246 (65), 217 (21), 190 (17), 189 (33), 143 (15), 121 (15). HRMS (EI, 70 eV): calcd for $C_{12}H_9F_3O_4S$ (M^+) 306.01682, found 306.015912.

GP 5: General Procedure for the Synthesis of **20**.

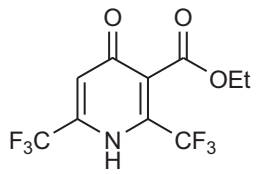
To a CH_2Cl_2 solution (2 mL/1 mmol of **19**) of **19** (1.0 mmol) was added **3** (2.0 mmol) and, subsequently, Me_3SiOTf (0.18 mL, 1.0 mmol) at -78 °C. The temperature of the solution was allowed to warm to 20 °C during 12-14 h with stirring. To the solution was added HCl (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was heated at 50-60 °C in EtOH (20 mL/1 mmol of **2**) during 10-25 h. The solvent was removed *in vacuo* and the product was washed with CH_2Cl_2.

Methyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20a).



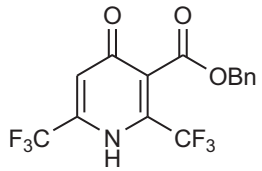
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 10 h, the product **20a** was isolated as a white solid (0.110 g, 78%); mp = 154-156 °C. ^{1}H NMR (300 MHz, DMSO): δ = 3.70 (s, 3H, OCH_3), 6.58 (s, 1H, CH), 7.22 (bs, 4H, NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 51.9 (OCH_3), 114.5 (CH), 121.7 (q, J_{C-F} = 274.0 Hz, CF_3), 121.9 (q, J_{C-F} = 273.0 Hz, CF_3), 122.6 (C), 142.8 (q, J_{C-F} = 32.0 Hz, C), 146.7 (q, J_{C-F} = 32.7 Hz, C), 167.7, 173.3 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.0, -64.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3273 (m), 2954 (m), 2917 (m), 2847 (m), 2711 (m), 2116 (w), 1906 (w), 1714 (s), 1590 (m), 1486 (s), 1435 (w), 1399 (m), 1274 (s), 1126 (s), 992 (s), 873 (s), 734 (m). GC-MS (EI, 70 eV): *m/z* (%): 289 (M^+, 70), 270 (13), 258 (100), 257 (82), 229 (68), 210 (55). HRMS (EI, 70 eV): calcd for $C_9H_5F_6NO_3$ (M^+) 289.0168, found 289.0162.

Ethyl 2,6-bis(trifluoromethyl)-1,4-dihydro-4-oxopyridine-3-carboxylate (20b).



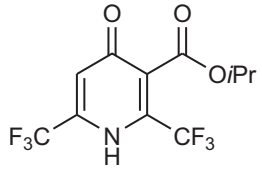
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 15 h, the product **20b** was isolated as a white solid (0.288 g, 95%); mp = 145-147 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.21 (t, ^3J = 7.5 Hz, 3H, CH_3), 4.16 (q, ^3J = 7.0 Hz, 2H, CH_2), 6.55 (s, 1H, CH), 7.22 (bs, 5H, NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 13.9 (CH_3), 60.4 (CH_2), 114.6 (CH), 121.8 (q, J_{C-F} = 283.0 Hz, CF_3), 122.0 (q, J_{C-F} = 272.7 Hz, CF_3), 122.9 (C), 142.7, 146.6 (q, J_{C-F} = 32.2 Hz, C), 167.1, 173.4 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.0, -63.8 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3257 (w), 3049 (w), 2847 (w), 1696 (m), 1662 (w), 1592 (w), 1520 (w), 1479 (s), 1404 (m), 1273 (s), 1183 (s), 1129 (s), 987 (s), 871 (m), 734 (m), 532 (w). GC-MS (EI, 70 eV): *m/z* (%): 303 (M^+, 14), 275 (23), 258 (66), 257 (100), 234 (13), 229 (57), 210 (29). HRMS (ESI): calcd for $C_{10}H_8F_6NO_3$ [$(M+H)^+$] 304.0403, found 304.0406.

Benzyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20c).



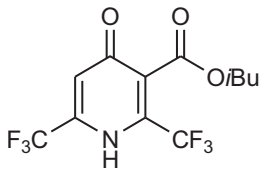
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 14 h, the product **20c** was isolated as a slight yellow solid (0.209 g, 57%); mp = 92-94 °C. ^{1}H NMR (300 MHz, MeOD): δ = 5.32 (s, 2H, CH_2), 7.00 (s, 1H, CH), 7.31 -7.44 (m, 5H, Ph). ^{13}C NMR (75 MHz, DMSO): δ = 66.9 (CH_2), 113.2 (CH), 121.1 (q, $J_{C\text{-}F}$ = 273.7 Hz, CF_3), 121.2 (q, $J_{C\text{-}F}$ = 272.6 Hz, CF_3), 121.3 (C), 143.5 (q, $J_{C\text{-}F}$ = 33.7 Hz, C), 147.4 (q, $J_{C\text{-}F}$ = 33.5 Hz, C), 165.1, 169.7 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.1, -63.9 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3181 (w), 3037 (w), 2894 (w), 1725 (m), 1591 (m), 1467 (s), 1406 (s), 1303 (m), 1269 (s), 1187 (s), 1117 (s), 988 (s), 750 (m), 695 (s). GC-MS (EI, 70 eV): *m/z* (%): 365 (M^+, 6), 210 (13), 108 (16), 91 (100). HRMS (ESI): calcd for $C_{15}H_{10}F_6NO_3$ [$(M+H)^+$] 366.0559, found 366.0563.

Isopropyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20d).



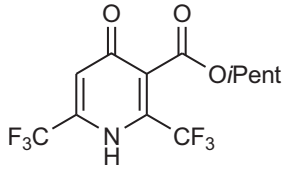
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.577 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 22 h, the product **20d** was isolated as a white solid (0.204 g, 64%); mp = 112-114 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.22 (s, ^3J = 6.0 Hz, 6H, CH_3), 1.23 (s, 3H, CH_3), 4.95-5.08 (m, 1H, CH), 6.57 (s, 1H, CH), 7.23 (bs, 5H, NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 21.4 (CH_3), 67.8 (CH), 114.5 (CH), 121.8 (q, $J_{C\text{-}F}$ = 273.7 Hz, CF_3), 121.9 (q, $J_{C\text{-}F}$ = 272.7 Hz, CF_3), 123.2 (C), 142.6, 146.6 (q, $J_{C\text{-}F}$ = 32.2 Hz, C), 166.5, 173.3 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.0, -63.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3341 (w), 3189 (w), 3086 (w), 3005 (w), 2918 (w), 1721 (m), 1675 (w), 1588 (w), 1455 (m), 1409 (m), 1270 (s), 1187 (s), 1140 (s), 1099 (s), 987 (s), 873 (m), 634 (m). GC-MS (EI, 70 eV): *m/z* (%): 317 (M^+, 2), 276 (62), 258 (100), 257 (64), 229 (24), 210 (27), 43 (31). HRMS (ESI): calcd for $C_{11}H_{10}F_6NO_3$ [$(M+H)^+$] 318.0559, found 318.0562.

Isobutyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20e).



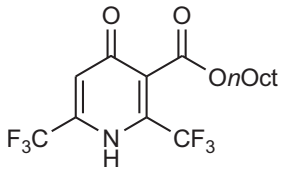
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 22 h, the product **20e** was isolated as a white solid (0.229 g, 69%); mp = 105-107 °C. ^{1}H NMR (300 MHz, DMSO): δ = 0.90 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 1.84-198 (m, 1H, CH), 3.95 (d, ^3J = 6.6 Hz, 2H, CH_2), 6.80 (s, 1H, CH), 7.20 (bs, 4H, NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 18.8 (CH_3), 27.1 (CH), 70.9 (CH_2), 113.8 (CH), 121.5 (q, $J_{C\text{-}F}$ = 274.0 Hz, CF_3), 121.6 (q, $J_{C\text{-}F}$ = 272.7 Hz, CF_3), 122.4 (C), 142.9, 146.9 (q, $J_{C\text{-}F}$ = 33.0 Hz, C), 166.2, 171.6 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.1, -63.9 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3182 (w), 2963 (w), 2881 (w), 1727 (m), 1697 (m), 1669 (m), 1591 (m), 1457 (s), 1409 (s), 1270 (s), 1179 (s), 1112 (s), 992 (s), 878 (m), 736 (m). GC-MS (EI, 70 eV): *m/z* (%): 331 (M^+, 1), 276 (27), 258 (100), 210 (37), 57 (50), 56 (28), 41 (18). HRMS (ESI): calcd for $C_{12}H_{12}F_6NO_3$ [$(M+H)^+$] 332.0716, found 332.0720; calcd for $C_{12}H_{11}F_6NNaO_3$ [$(M+Na)^+$] 354.0535, found 354.0539.

Isopentyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20f).



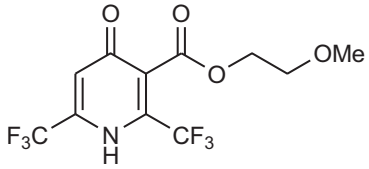
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**2g**) (0.633 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 25 h, the product **20f** was isolated as a white solid (0.138 g, 40%); mp = 142-145 °C. ^{1}H NMR (300 MHz, DMSO): δ = 0.87 (d, ^3J = 9.0 Hz, 6H, $(CH_3)_2$), 1.84-155 (m, 2H, CH_2), 1.64-1.75 (m, 1H, CH), 4.24 (t, ^3J = 6.6 Hz, 2H, CH_2), 7.07 (bs, 5H, CH+NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 22.1 (CH_3), 24.3 (CH), 36.5, 63.8 (CH_2), 113.0 (CH), 121.1 (q, $J_{C\text{-}F}$ = 273.7 Hz, CF_3), 121.2 (q, $J_{C\text{-}F}$ = 273.0 Hz, CF_3), 121.6 (C), 143.4 (q, $J_{C\text{-}F}$ = 33.0 Hz, C), 147.3 (q, $J_{C\text{-}F}$ = 33.7 Hz, C), 165.0, 169.1 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.1, -63.9 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3192 (w), 3087 (w), 2962 (m), 2874 (w), 1715 (m), 1594 (m), 1527 (w), 1457 (m), 1431 (m), 1403 (m), 1183 (s), 1144 (s), 975 (s), 878 (m), 736 (m), 635 (m). GC-MS (EI, 70 eV): *m/z* (%): 345 (M^+, 1), 326 (6), 258 (46), 210 (18), 71 (79), 70 (75), 55 (32), 43 (100). HRMS (ESI): calcd for $C_{13}H_{14}F_6NO_3$ [$(M+H)^+$] 346.0872, found 346.0872; calcd for $C_{13}H_{13}F_6NNaO_3$ [$(M+Na)^+$] 368.0692, found 368.0691.

Octyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20g).



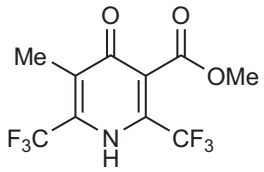
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3h**) (0.717 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 22 h, the product **20g** was isolated as a slight yellow oil (0.209 g, 54%).[1]H NMR (300 MHz, DMSO): δ = 0.81 (bs, 3H, CH_3), 1.21 (bs, 10H, $(CH_2)_5$), 4.19 (t, ^3J = 7.5 Hz, 2H, CH_2), 7.03 (s, 1H, CH), 7.07 (bs, 3H, NH+H_2O). ^{13}C NMR (100 MHz, DMSO): δ = 13.8 (CH_3), 21.9, 25.1, 27.8, 28.4, 28.5, 31.1, 65.2 (CH_2), 113.0 (CH), 121.1 (q, $J_{C\text{-}F}$ = 274.0 Hz, CF_3), 121.2 (q, $J_{C\text{-}F}$ = 273.0 Hz, CF_3), 121.7 (C), 143.3 (q, $J_{C\text{-}F}$ = 33.0 Hz, C), 147.2 (q, $J_{C\text{-}F}$ = 33.6 Hz, C), 165.2, 169.7 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.1, -64.0 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3201 (w), 2958 (w), 2927 (m), 2857 (w), 1719 (m), 1587 (w), 1455 (m), 1399 (m), 1307 (m), 1264 (s), 1188 (s), 1143 (s), 975 (s), 881 (m), 736 (s). HRMS (ESI): calcd for $C_{16}H_{20}F_6NO_3$ [$(M+H)^+$] 388.1432, found 388.1345.

2-Methoxyethyl 4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20h).



Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3i**) (0.609 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 13 h, the product **20h** was isolated as a slight yellow solid (0.257 g, 77%); mp = 137-139 °C. ^{1}H NMR (300 MHz, DMSO): δ = 3.25 (s, 3H, OCH_3), 3.54, 4.22 (t, ^2J = 4.8 Hz, 2H, CH_2), 6.55 (s, 1H, CH), 7.20 (bs, 3H, NH+H_2O). ^{13}C NMR (75 MHz, DMSO): δ = 58.0 (OCH_3), 63.7, 69.6 (CH_2), 115.6 (CH), 121.8 (q, $J_{C\text{-}F}$ = 274.0 Hz, CF_3), 122.0 (q, $J_{C\text{-}F}$ = 273.0 Hz, CF_3), 122.7 (C), 142.7 (q, $J_{C\text{-}F}$ = 33.2 Hz, C), 146.7 (q, $J_{C\text{-}F}$ = 32.5 Hz, C), 167.2, 173.4 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -67.0, -63.9 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3186 (w), 3022 (w), 2963 (w), 2906 (w), 2793 (m), 1746 (s), 1593 (m), 1523 (w), 1472 (s), 1412 (s), 1266 (s), 1186 (s), 1124 (s), 988 (s), 871 (s), 735 (m), 701 (m). GC-MS (EI, 70 eV): *m/z* (%): 333 (M^+, 1), 314 (18), 258 (100), 210 (47), 58 (62), 45 (77). HRMS (ESI): calcd for $C_{11}H_{10}F_6NO_4$ [$(M+H)^+$] 334.0509, found 334.0514.

Methyl 5-methyl-4-oxo-2,6-bis(trifluoromethyl)-1,4-dihydropyridine-3-carboxylate (20i).

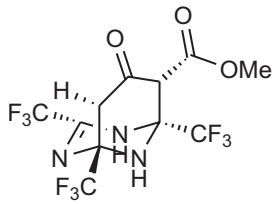


Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.18 mL, 1.0 mmol) in CH_2Cl_2 (2 mL) and then heating in EtOH (20 mL) for 12 h, the product **20i** was isolated as a white solid (0.105 g, 35%). ^1H NMR (300 MHz, MeOD): δ = 2.20 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, MeOD): δ = 11.1 (CH_3), 52.8 (OCH_3), 122.2 (C), 123.0 (q, J_{C-F} = 272.6 Hz, CF_3), 124.0 (q, J_{C-F} = 273.5 Hz, CF_3), 128.4 (C), 142.1 (q, J_{C-F} = 33.0 Hz, C), 145.5 (q, J_{C-F} = 31.5 Hz, C), 170.0, 174.5 (C). ^{19}F-NMR (282 MHz, DMSO): δ = -66.1, -65.1 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3223 (w), 3046 (w), 2960 (w), 2924 (w), 2853 (w), 1734 (m), 1661 (w), 1561 (w), 1437 (m), 1405 (m), 1240 (s), 1127 (s), 1028 (s), 957 (s), 641 (s). GC-MS (EI, 70 eV): *m/z* (%): 303 (M^+, 33), 271 (23), 251 (100). HRMS (EI, 70 eV): calcd for $C_{10}H_7F_6NO_3$ (M^+) 303.03246, found 303.032939.

GP 6: General Procedure for the Synthesis of **22**.

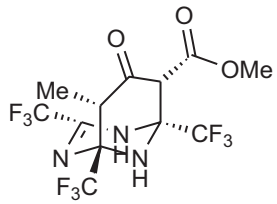
To a CH_2Cl_2 solution (2 mL/1.0 mmol of **19**) of **19** (1.0 mmol) was added **3** (2.0 mmol) at -78 °C. The temperature of the solution was allowed to warm to 20 °C during 12-14 h with stirring. To the solution was added HCl (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography.

Methyl 7-oxo-1,3,5-tris(trifluoromethyl)-2,4,9-triazabicyclo[3.3.1]non-2-ene-6-carboxylate (22a).



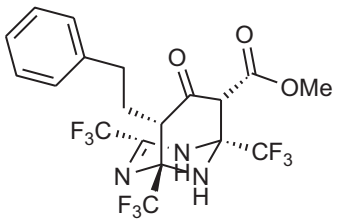
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol) in CH_2Cl_2 (2 mL), the product **22a** was isolated as a white solid (0.173 g, 43%); mp = 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.86 (bs, 1H, NH), 3.00-3.03 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.01 (s, 1H, CH), 6.93 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6 (CH_2), 53.3 (CH), 59.2 (OCH_3), 70.4 (q, J_{C-F} = 31.7 Hz, C), 74.2 (q, J_{C-F} = 31.2 Hz, C), 116.6 (q, J_{C-F} = 276.3 Hz, CF_3), 121.6 (q, J_{C-F} = 282.7 Hz, CF_3), 122.6 (q, J_{C-F} = 279.7 Hz, CF_3), 147.5 (q, J_{C-F} = 38.5 Hz, C), 166.3, 194.6 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -83.5, -81.4, -73.7 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3341 (w), 3329 (w), 3279 (m), 3016 (w), 2964 (w), 2898 (w), 2857 (w), 1751 (m), 1754 (s), 1729 (s), 1663 (m), 1523 (w), 1458 (w), 1339 (m), 1141 (s), 1086 (s), 806 (s), 710 (s), 511 (s). GC-MS (EI, 70 eV): *m/z* (%): 401 (M^+, 42), 300 (31), 286 (71), 266 (52), 258 (100), 232 (28), 116 (55), 96 (35), 69 (52). Anal. calcd. for $C_{11}H_8F_9N_3O_3$ (401.19): C, 32.93; H, 2.01; N, 10.47. Found: C, 32.98; H, 2.14; N, 10.57.

Methyl 8-methyl-7-oxo-1,3,5-tris(trifluoromethyl)-2,4,9-triazabicyclo[3.3.1]non-2-ene-6-carboxylate (22b).



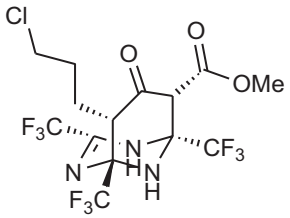
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol) in CH_2Cl_2 (2 mL), the product **22b** was isolated as a white solid (0.226 g, 54%); mp = 99-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23-1.26 (dd, 3H, CH_3), 2.98 (bs, 1H, NH), 3.24 (q, ^3J = 7.0 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 4.07 (s, 1H, CH), 6.96 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.9 (CH_3), 51.6, 53.6 (CH), 59.1 (OCH_3), 70.1 (q, J_{C-F} = 31.7 Hz, C), 71.7 (q, J_{C-F} = 28.2 Hz, C), 116.5 (q, J_{C-F} = 276.2 Hz, CF_3), 121.6 (q, J_{C-F} = 282.7 Hz, CF_3), 122.9 (q, J_{C-F} = 282.2 Hz, CF_3), 147.2 (q, J_{C-F} = 38.5 Hz, C), 166.5, 197.4 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.6, -79.1, -73.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3365 (w), 3341 (w), 3019 (w), 2964 (w), 2947 (w), 2855 (w), 1743 (m), 1729 (s), 1668 (m), 1497 (w), 1460 (w), 1439 (w), 1147 (s), 1092 (s), 995 (s), 721 (s). GC-MS (EI, 70 eV): *m/z* (%): 415 (M^+, 6), 300 (31), 286 (42), 266 (42), 258 (51), 130 (100), 101 (93), 69 (46). HRMS (ESI): calcd for $C_{12}H_{11}N_3O_3F_9$ [$(M+H)^+$] 416.0651, found 416.0656; calcd for $C_{12}H_{10}F_9N_3NaO_3$ [$(M+Na)^+$] 438.0470, found 438.048. Anal. calcd. for $C_{12}H_{10}F_9N_3O_3$ (415.21): C, 34.71; H, 2.43; N, 10.12. Found: C, 34.77; H, 2.53; N, 9.87.

Methyl 7-oxo-8-phenethyl-1,3,5-tris(trifluoromethyl)-2,4,9-triazabicyclo[3.3.1]non-2-ene-6-carboxylate (22c).



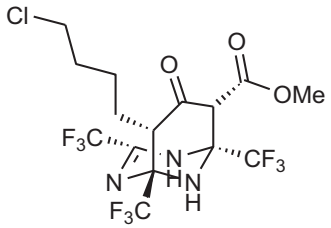
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 6-phenyl-1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3ad**) (0.729 g, 2.0 mmol) in CH_2Cl_2 (2 mL), the product **22c** was isolated as a white solid (0.241 g, 42%); mp = 84-85 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ = 2.04-2.21, 2.49-2.66 (m, 2H, CH_2), 2.96 (bs, 1H, NH), 3.08-3.12 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 4.08 (bs, 1H, CH), 6.96 (bs, 1H, NH), 7.16-7.32 (m, 7H, Ph + $CHCl_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 33.7 (CH_2), 53.2, 55.8 (CH), 59.7 (OCH_3), 70.1 (q, J_{C-F} = 31.6 Hz, C), 74.6 (q, J_{C-F} = 29.0 Hz, C), 116.5 (q, J_{C-F} = 276.3 Hz, CF_3), 121.6, 122.9 (q, J_{C-F} = 282.6 Hz, CF_3), 126.2 128.4, 128.5, 140.8 (Ph), 147.2 (q, J_{C-F} = 38.0 Hz, C), 166.4, 197.3 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.4, -78.3, -73.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3329 (w), 3288 (m), 3031 (w), 2960 (w), 2936 (w), 2864 (w), 1751 (s), 1725 (s), 1662 (m), 1525 (w), 1496 (w), 1211 (s), 1146 (s), 1091 (s), 698 (s), 492 (s). HRMS (ESI): calcd for $C_{19}H_{17}N_3O_3F_9$ [(M+H)$^+$] 506.1121, found 506.1129; calcd for $C_{19}H_{16}ClF_9N_3NaO_3$ [(M+Na)$^+$] 528.094, found 528.0947.

Methyl 8-(3-chloropropyl)-7-oxo-1,3,5-tris(trifluoromethyl)-2,4-9-triazabicyclo[3.3.1]non-2-ene-6-carboxylate (20d).



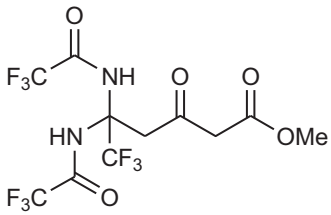
Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 7-chloro-1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-heptadiene (**3ag**) (0.674 g, 2.0 mmol) in CH_2Cl_2 (2 mL), the product **20d** was isolated as a slight yellow solid (0.341 g, 71%); mp = 86-88 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.66-2.07 (m, 4H, $(CH_2)_2$), 2.99 (bs, 1H, NH), 3.15-3.19 (m, 1H, CH), 3.49-3.54 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.11 (bs, 1H, CH), 6.97 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 30.6, 44.5 (CH_2), 53.3, 56.3 (CH), 59.7 (OCH_3), 70.0 (q, J_{C-F} = 31.7 Hz, C), 74.6 (q, J_{C-F} = 39.7 Hz, C), 116.5 (q, J_{C-F} = 276.3 Hz, CF_3), 121.5 (q, J_{C-F} = 282.7 Hz, CF_3), 124.6 (q, J_{C-F} = 283.5 Hz, CF_3), 147.1 (q, J_{C-F} = 37.5 Hz, C), 166.3, 197.1 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.5, -78.4, -73.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3374 (w), 3305 (w), 3050 (w), 3018 (w), 2965 (w), 2942 (w), 2886 (w), 1751 (m), 1724 (m), 1663 (m), 1510 (w), 1439 (w), 1237 (s), 1199 (s), 1155 (s), 1089 (s), 714 (s). HRMS (ESI): calcd for $C_{14}H_{14}N_3O_3F_9Cl$ [(M+H)$^+$] 478.0574, found 478.0578; calcd for $C_{14}H_{13}ClF_9N_3NaO_3$ [(M+Na)$^+$] 500.0393, found 500.0401. Anal. calcd. for $C_{14}H_{13}ClF_9N_3O_3$ (477.05): C, 35.20; H, 2.74; N, 8.80. Found: C, 35.28; H, 2.83; N, 8.76.

Methyl 8-(4-chlorobutyl)-7-oxo-1,3,5-tris(trifluoromethyl)-2,4,9-triazabicyclo[3.3.1]non-2-ene-6-carboxylate (22e).



Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 8-chloro-1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-octadiene (**3ah**) (0.702 g, 2 mmol) in CH_2Cl_2 (2 mL), the product **22e** was isolated as a colorless oil (0.238 g, 48%).^{1}H NMR (300MHz, $CDCl_3$): δ = 1.31-1.93 (m, 6H, $(CH_2)_3$), 2.98 (bs, 1H, NH), 3.07-3.10 (m, 1H, CH), 3.49-3.55 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.10 (bs, 1H, CH), 6.96 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 25.5, 32.4, 44.5 (CH_2), 53.2, 56.8 (CH), 59.7 (OCH_3), 70.1 (q, $J_{C\text{-}F}$ = 31.7 Hz, C), 74.6 (q, $J_{C\text{-}F}$ = 28.0 Hz, C), 116.5 (q, $J_{C\text{-}F}$ = 276.3 Hz, CF_3), 121.5, 122.9 (q, $J_{C\text{-}F}$ = 282.7 Hz, CF_3), 147.3 (q, $J_{C\text{-}F}$ = 38.2 Hz, C), 166.3, 197.2 (C). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -81.4, -78.3, -73.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3338 (w), 2960 (w), 2873 (w), 1748 (m), 1728 (m), 1672 (m), 1491 (w), 1439 (w), 1151 (s), 1091 (s), 727 (m). HRMS (ESI): calcd for $C_{15}H_{16}ClN_3O_3F_9$ [$(M+H)^+$] 492.0731, found 492.0733; calcd for $C_{15}H_{15}ClF_9N_3NaO_3$ [$(M+Na)^+$] 514.0550, found 514.0553. Anal. calcd. for $C_{14}H_{13}ClF_9N_3O_3$ (491.07): C, 35.20; H, 2.74; N, 8.80. Found: C, 35.28; H, 2.83; N, 8.76.

(Z)-Methyl 6,6,6-trifluoro-3-hydroxy-5,5-bis(2,2,2-trifluoroacetamido)hex-2-enoate (23a).

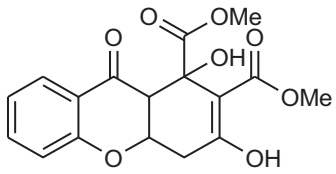


Starting with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**19**) (0.18 mL, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2 mmol) in CH_2Cl_2 (2 mL) and then reflux in EtOH (20 mL) for 30 h at 90°C, the product **23a** was isolated as a white solid (0.200 g, 47%); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): *δ* = 3.37-3.58 (m, 2H; CH_2), 3.77 (s, 3H; OCH_3), 5.33 (bs, 1H; CH), 6.63 (bs, 1H; NH), 11.27 (bs, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): *δ* = 28.4 (CH_2), 51.9 (OCH_3), 71.0 (q, ^1J (C,F) = 32.3 Hz; C), 98.9 (CH), 115.1 (q, ^1J (C,F) = 288.3 Hz; CF_3), 117.0 (q, ^1J (C,F) = 278.0 Hz; CF_3), 123.2 (q, ^1J (C,F) = 287.5 Hz; CF_3), 143.1 (C), 146.8 (q, ^2J (C,F) = 38.0 Hz; C), 155.6 (q, ^2J (C,F) = 38.4 Hz; C), 168.7 (C); ^{19}F-NMR (282 MHz, $CDCl_3$, 25°C): *δ* = -80.9, -75.5, -72.7 (CF_3).

GP 7: General procedure for the synthesis of **31** and **32**.

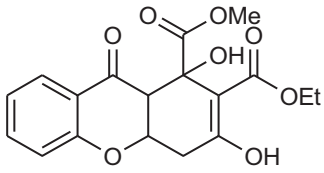
Me_3SiOTf (2.0 mmol) was added to chromone **28** (1.0 mmol) at 20 °C. After stirring for 1 h, CH_2Cl_2 (4 mL / mmol **28**) and the 1,3-bis-silyl-enol ether **3** (2.0 mmol) were added at 0 °C. The mixture was stirred for 12 h at 0-20 °C and was then poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography.

Dimethyl 1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31a).



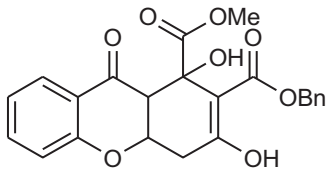
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31a** was isolated as a white solid (0.183 g, 52%); mp = 170-171 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.90-3.16 (m, 2H, CH_2), 3.24 (d, ^3J = 13.5 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.12 (bs, 1H, OH), 4.90-5.00 (m, 1H, CH), 6.96-7.06 (m, 2H, Ar), 7.46-7.52 (m, 1H, Ar), 7.84-7.87 (m, 1H, Ar), 13.00 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (CH_2), 52.0, 53.4, 54.9 (CH/OCH_3), 71.8 (CH), 73.0 (C), 101.9 (C), 117.7 (Ar), 121.2 (C), 122.0, 127.3, 136.5 (Ar), 160.4, 171.0, 172.7, 174.0, 189.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3459 (m), 2950 (w), 2903 (w), 1746 (s), 1726 (s), 1683 (s), 1655 (m), 1607 (s), 1466 (s), 1219 (s), 1083 (s), 854 (s), 764 (s), 466 (s). HRMS (ESI): calcd. for $C_{17}H_{17}O_8$ [$(M+H)^+$] 349.0918, found 349.0921; calcd. for $C_{17}H_{16}NaO_8$ [$(M+Na)^+$] 371.0737, found 371.0743. Anal. calcd. for $C_{17}H_{16}O_8$ (348.30): C, 58.62; H, 4.63. Found: C, 58.64; H, 4.69.

2-Ethyl 1-methyl 1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31b).



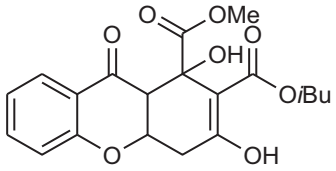
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31b** was isolated as a white solid (0.173 g, 47%); mp = 159-160 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 7.1 Hz, 3H, CH_3CH$_2$), 2.89-3.15 (m, 2H, CH_2), 3.24 (d, ^3J = 13.5 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 4.13 (bs, 1H, OH), 4.15-4.35 (m, 2H, CH_3CH_2), 4.90-5.00 (m, 1H, CH), 6.95-7.06 (m, 2H, Ar), 7.46-7.52 (m, 1H, Ar), 7.84-7.87 (m, 1H, Ar), 13.11 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 35.9 (CH_2), 53.4, 55.1 (CH/OCH_3), 61.3 (CH_2), 71.8 (CH), 73.0 (C), 101.9 (C), 117.7 (Ar), 121.2 (C), 122.0, 127.3, 136.4 (Ar), 160.4, 170.6, 172.5, 174.0, 189.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3463 (m), 2975 (w), 1743 (s), 1693 (m), 1637 (m), 1605 (s), 1578 (m), 1230 (s), 1095 (s), 760 (s), 577 (s). MS (EI, 70 eV): *m/z* (%): 362 (M^+, 3), 303 (35), 257 (100), 160 (16), 121 (66). HRMS (ESI): calcd. for $C_{18}H_{18}NaO_8$ [$(M+Na)^+$] 385.0894, found 385.0901. Anal. calcd. for $C_{18}H_{18}O_8$ (362.33): C, 59.64; H, 5.01. Found: C, 59.70; H, 5.01.

2-Benzyl 1-methyl 1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31c).



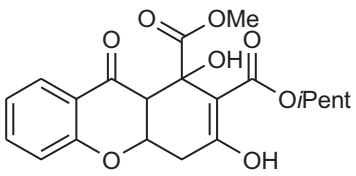
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.673 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31c** was isolated as a slight yellow solid (0.174 g, 41%); mp = 166-168 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.90-3.16 (m, 2H, CH_2), 3.23 (d, ^3J = 13.5 Hz, 1H, CH), 3.45 (s, 3H, OCH_3), 4.11 (bs, 1H, OH), 4.89-4.99 (m, 1H, CH), 5.22 (dd, ^2J = 12.0 Hz, 2H, CH_2Ph), 6.95-7.05 (m, 2H, Ar), 7.33-7.39 (m, 5H, Ph), 7.46-7.51 (m, 1H, Ar), 7.82-7.86 (m, 1H, Ar), 13.07 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (CH_2), 52.9, 55.1 (CH/OCH_3), 66.9 (CH_2), 71.8 (CH), 73.1 (C), 101.8 (C), 117.7 (Ar), 121.2 (C), 121.9, 127.3 (Ar), 128.5, 128.6, 128.7, 134.7 (Ph), 136.4 (Ar), 160.3, 170.5, 172.9, 173.7, 189.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3462 (m), 2953 (w), 1751 (s), 1688 (m), 1637 (m), 1603 (s), 1577 (m), 1285 (s), 1229 (s), 757 (s), 697 (s), 586 (s). MS (EI, 70 eV): *m/z* (%): 424 (M^+, 3), 365 (43), 257 (38), 121 (23), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{23}H_{20}O_8$ (M^+) 424.11527, found 424.11508. Anal. calcd. for $C_{23}H_{20}O_8$ (424.40): C, 65.09; H, 4.75. Found: C, 65.13; H, 4.66.

2-Isobutyl 1-methyl 1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31d).



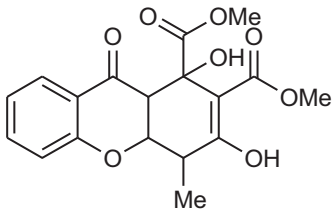
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31d** was isolated as a slight yellow solid (0.167 g, 43%); mp = 152-153 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92-0.97 (m, 6H, $(CH_3)_2$), 1.88-2.00 (m, 1H, C*H*$(CH_3)_2$), 2.89-3.15 (m, 2H, CH_2), 3.24 (d, ^3J = 13.2 Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 3.92-4.01 (m, 2H, C*H*$_2$CH$(CH_3)_2$), 4.15 (bs, 1H, OH), 4.89-4.99 (m, 1H, CH), 6.95-7.05 (m, 2H, Ar), 7.46-7.52 (m, 1H, Ar), 7.84-7.87 (m, 1H, Ar), 13.18 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 19.1 (CH_3), 27.5 (CH), 36.0 (CH_2), 53.4, 55.1 (CH/OCH_3), 71.7 (CH_2), 71.8 (CH), 73.0 (C), 101.8 (C), 117.7 (Ar), 121.3 (C), 122.0, 127.3, 136.4 (Ar), 160.4, 170.9, 172.6, 173.8, 189.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3476 (m), 2961 (w), 1749 (s), 1690 (m), 1633 (m), 1605 (s), 1460 (m), 1294 (s), 1230 (s), 1076 (s), 764 (s). MS (EI, 70 eV): *m/z* (%): 390 (M^+, 2), 331 (35), 257 (100), 121 (32). HRMS (EI, 70 eV): calcd. for $C_{20}H_{22}O_8$ (M^+) 390.13092, found 390.13090. Anal. calcd. for $C_{20}H_{22}O_8$ (390.38): C, 61.53; H, 5.68. Found: C, 61.44; H, 5.62.

2-Isopentyl 1-methyl 1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31e).



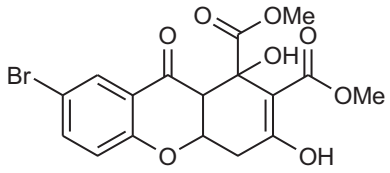
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-isopentyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3g**) (0.633 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31e** was isolated as a white solid (0.210 g, 52%); mp = 137-138 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, ^3J = 6.5 Hz, 6H, $(CH_3)_2$), 1.46-1.59 (m, 2H, CH_2*CH*$_2$CH), 1.61-1.76 (m, 1H, C*H*$(CH_3)_2$), 2.89-3.14 (m, 2H, (CH_2)), 3.22 (d, ^3J = 13.4 Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 4.12 (bs, 1H, OH), 4.20 (t, ^3J = 6.9 Hz, 2H, OC*H*$_2$), 4.89-4.99 (m, 1H, CH), 6.95-7.05 (m, 2H, Ar), 7.46-7.52 (m, 1H, Ar), 7.84-7.87 (m, 1H, Ar), 13.13 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 22.4 (CH_3), 24.7 (CH), 35.9, 36.9 (CH_2), 53.3, 55.0 (CH/OCH_3), 64.1 (CH_2), 71.8 (CH), 73.0 (C), 101.9 (C), 117.7 (Ar), 121.3 (C), 122.0, 127.3, 136.4 (Ar), 160.4, 170.8, 172.5, 173.9, 189.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3476 (m), 2958 (m), 1741 (s), 1687 (s), 1639 (m), 1603 (s), 1463 (m), 1241 (s), 1077 (s), 859 (s), 762 (s). MS (EI, 70 eV): *m/z* (%): 404 (M^+, 2), 345 (43), 257 (100), 121 (33). HRMS (EI, 70 eV): calcd. for $C_{21}H_{24}O_8$ (M^+) 404.14657, found 404.14628. Anal. calcd. for $C_{21}H_{24}O_8$ (404.41): C, 62.37; H, 5.98. Found: C, 62.27; H, 5.80.

Dimethyl 1,3-dihydroxy-4-methyl-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31f).



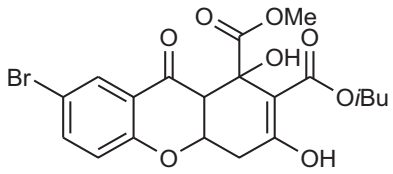
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31f** was isolated as a white solid (0.152 g, 42%); mp = 156-157 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, ^3J = 7.2 Hz, 3H, CH_3), 3.12-3.18 (m, 1H, CH), 3.41 (d, ^3J = 14.0 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.13 (bs, 1H, OH), 5.00-5.05 (m, 1H, CH), 6.96-7.03 (m, 2H, Ar), 7.46-7.50 (m, 1H, Ar), 7.83-7.86 (m, 1H, Ar), 13.06 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (CH_3), 38.2, 49.8 (CH), 52.0, 53.4 (OCH_3), 73.0 (C), 73.5 (CH), 100.6 (C), 117.8 (Ar), 121.0 (C), 121.8, 127.2, 136.4 (Ar), 160.5, 171.4, 174.1, 177.1, 190.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3475 (m), 2947 (w), 1746 (s), 1680 (s), 1657 (m), 1607 (s), 1467 (s), 1218 (s), 1101 (s), 1044 (s), 780 (s). MS (EI, 70 eV): *m/z* (%): 362 (M^+, 1), 303 (34), 271 (97), 174 (32), 151 (22), 121 (100). HRMS (EI, 70 eV): calcd. for $C_{18}H_{18}O_8$ (M^+) 362.09962, found 362.09931. Anal. calcd. for $C_{18}H_{18}O_8$ (362.33): C, 59.67; H, 5.01. Found: C, 59.50; H, 4.97.

Dimethyl 7-bromo-1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31g).



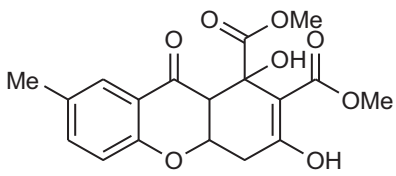
Starting with 6-bromo-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31g** was isolated as a slight orange solid (0.220 g, 51%); mp = 160-162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.89-3.15 (m, 2H, CH_2), 3.22 (d, ^3J = 13.4 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.11 (bs, 1H, OH), 4.88-4.98 (m, 1H, CH), 6.88 (d, ^3J = 8.7 Hz, 1H, Ar), 7.54-7.58 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz 1H, Ar), 7.95 (d, ^4J = 2.5 Hz, 1H, Ar), 12.99 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.7 (CH_2), 52.0, 53.5, 54.7 (CH/OCH_3), 72.0 (CH), 72.9 (C), 101.9, 114.7 (C), 119.8 (Ar), 122.4 (C), 129.8, 139.0 (Ar), 159.4, 170.0, 172.4, 173.8, 188.6 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3461 (m), 2954 (w), 1749 (s), 1695 (m), 1659 (m), 1618 (m), 1597 (m), 1471 (m), 1285 (s), 1218 (s), 1110 (s), 839 (s), 639 (s), 584 (s). HRMS (ESI): calcd. for $C_{17}H_{15}Br^{79}NaO_8$ [$(M+Na)^+$] 448.9842, found 448.9840; calcd. for $C_{17}H_{15}Br^{81}NaO_8$ [$(M+Na)^+$] 450.9824, found 450.9822. Anal. calcd. for $C_{17}H_{15}BrO_8$ (427.20): C, 47.80; H, 3.54. Found: C, 48.05; H, 3.56.

2-Isobutyl 1-methyl 7-bromo-1,3-dihydroxy-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31h).



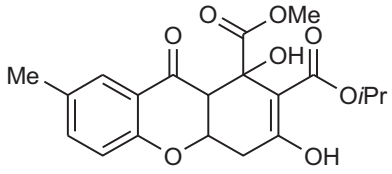
Starting with 6-bromo-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-isobuoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31h** was isolated as a white solid (0.375 g, 80%); mp = 129-131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92-0.97 (m, 6H, $(CH_3)_2$), 1.88-1.04 (m, 1H, CH), 2.89-3.14 (m, 2H, CH_2), 3.22 (d, ^3J = 13.4 Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 3.88-4.01 (m, 2H, CH_2), 4.14 (bs, 1H, OH), 4.87-4.97 (m, 1H, CH), 6.88 (d, ^3J = 8.8 Hz, 1H, Ar), 7.54-7.58 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz 1H, Ar), 7.95 (d, ^4J = 2.5 Hz, 1H, Ar), 13.18 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 19.1 (CH_3), 27.5 (CH), 35.8 (CH_2), 53.5, 54.8 (CH/OCH_3), 71.8 (CH_2), 72.1 (CH), 72.9 (C), 101.8, 114.7 (C), 119.8 (Ar), 122.5 (C), 129.8, 139.0 (Ar), 159.2, 170.8, 172.3, 173.6, 188.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3430 (w), 2952 (w), 2894 (w), 2731 (w), 1755 (m), 1692 (s), 1639 (m), 1598 (s), 1467 (m), 1409 (s), 1231 (s), 1100 (s), 820 (s), 638 (s), 386 (s). MS (EI, 70 eV): *m/z* (%): 470 (M^+, 5), 468 (M^+, 5), 411 (34), 409 (34), 364 (26), 362 (26), 337 (99), 335 (100), 201 (32), 199 (33). HRMS (ESI): calcd. for $C_{20}H_{21}Br^{79}NaO_8$ [(M+Na)$^+$] 491.0312, found 491.0322; calcd. for $C_{20}H_{21}Br^{81}NaO_8$ [(M+Na)$^+$] 493.0294, found 493.0307. Anal. calcd. for $C_{20}H_{21}BrO_8$ (468.28): C, 51.19; H, 4.51. Found: C, 51.18; H, 4.67.

Dimethyl 1,3-dihydroxy-7-methyl-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31i).



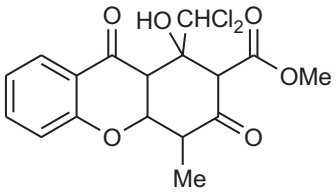
Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31i** was isolated as a slight orange solid (0.260 g, 71%); mp = 165-167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s. 3H, CH_3), 2.87-3.24 (m, 2H, CH_2), 3.49-3.54 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.92 (bs, 1H, OH), 4.54 (bs, 1H, OH), 4.85-4.95 (m, 1H, CH), 6.88 (d, ^3J = 8.4 Hz, 1H, Ar), 7.29-7.33 (m, 1H, Ar), 7.66-7.67 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 46.1 (CH_2), 52.7. 53.5, 54.5 (CH/OCH_3), 62.9, 74.6 (CH), 75.5 (C), 117.5 (Ar), 120.5 (C), 127.1 (Ar), 131.8 (C), 137.6 (Ar), 158.8, 167.9, 172.0, 188.3, 197.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3454 (m), 2956 (w), 2923 (w), 1768 (s), 1726 (s), 1682 (s), 1617 (m), 1579 (w), 1488 (s), 1220 (s), 1126 (s), 823 (s), 761 (s), 602 (s), 503 (s). HRMS (ESI): calcd. for $C_{18}H_{19}O_8$ [(M+H)$^+$] 363.1074, found 360.1082; calcd. for $C_{18}H_{18}NaO_8$ [(M+Na)$^+$] 385.0893, found 363.1082. Anal. calcd. for $C_{18}H_{18}O_8$ (362.33): C, 59.67; H, 5.01. Found: C, 59.87; H, 5.12.

2-Isopropyl 1-methyl 1,3-dihydroxy-7-methyl-9-oxo-4,4a,9,9a-tetrahydro-1H-xanthene-1,2-dicarboxylate (31j).



Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-isopropoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.577 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the product **31j** was isolated as a slight orange solid (0.176 g, 45%); mp = 128-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24-1.29 (m, 6H, $(CH_3)_2$), 2.28 (s. 3H, CH_3), 2.86-3.12 (m, 2H, CH_2), 3.20 (d, ^3J = 13.4 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 4.11 (bs, 1H, OH), 4.84-4.94 (m, 1H, CH), 5.06-5.15 (m, 1H, CH), 6.87 (d, ^3J = 8.4 Hz, 1H, Ar), 7.28-7.31 (m, 1H, Ar), 7.64 (d, ^4J = 2.2 Hz, 1H, Ar), 13.18 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.4, 21.6 (CH_3), 35.9 (CH_2), 53.2, 55.1 (CH/OCH_3), 69.3, 71.8 (CH), 73.0 102.7 (C), 117.4 (Ar), 120.9 (C), 126.8 (Ar), 131.4 (C), 137.4 (Ar), 158.5, 170.2, 172.4, 174.0, 189.9 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3493 (w), 2980 (w), 2957 (w), 1734 (m), 1684 (s), 1612 (s), 1487 (m), 1441 (w), 1421 (w), 1217 (s), 1095 (s), 832 (s), 796 (s), 586 (s). MS (EI, 70 eV): *m/z* (%): 390 (M^+, 4), 331 (37), 271 (100), 135 (71). HRMS (EI): calcd. for $C_{20}H_{22}O_8$ (M^+) 390.1309, found 390.1306. Anal. calcd. for $C_{20}H_{22}O_8$ (390.38): C, 61.53; H, 5.68. Found: C, 61.50; H, 5.56.

Methyl 1-(dichloromethyl)-1-hydroxy-4-methyl-3,9-dioxo-2,3,4,4a,9,9a-hexahydro-1H-xanthene-2-carboxylate (32).

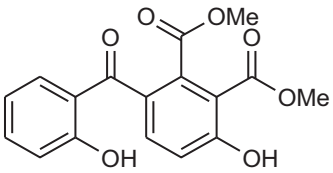


Starting with 3-dichloroacetylchromone (**8d**) (0.257 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), a mixture of isomers of **32** was isolated as a white solid (0.210 g, 54%); mp = 186-188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, ^3J = 6.3 Hz, 0.3H, CH_3), 1.39 (d, ^3J = 6.3 Hz, 3H, CH_3), 2.96-3.06 (m, 1H, CH), 3.53-3.58 (m, 1H, CH), 3.75 (s, 0.8H, OCH_3), 3.87 (s, 3H, OCH_3), 4.18 (bs, 0.3H, OH), 4.19 (bs, 1H, OH), 4.26-4.40 (m, 0.4H, CH), 4.42-4.50 (m, 0.4H, CH), 5.8 (d, ^4J = 2.0 Hz, 1H, CH), 6.99-7.03 (m, 0.6H, Ar), 7.03-7.11 (m, 2H, Ar), 7.48 (bs, 0.3H, Ar), 7.49-7.56 (m, 1H, Ar), 7.78 (s, 1H, *CH*Cl_2), 7.86-7.89 (m, 0.3H, Ar), 7.92-7.95 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.2, 10.8 (CH_3), 46.6, 48.3, 50.2, 51.9, 53.1, 53.3 (OCH_3), 56.7, 62.1, 75.9 (CH), 79.8 (C), 79.9 (CH), 81.2 (C), 81.7 (CH), 117.4, 117.6 (Ar), 121.5 (C), 121.9, 122.4, 127.6, 128.0, 136.6 (Ar), 160.0, 170.7, 189.0, 200.4 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3850 (w), 3732 (w), 3667 (w), 3646 (w), 3626 (w), 3328 (w), 3042 (w), 2942 (w), 2874 (w), 1731 (s), 1704 (m), 1667 (s), 1603 (s), 1581 (m), 1308 (s), 1201 (s), 767 (s), 611 (s). MS (ESI, 70 eV): *m/z* (%): 409.0214 [$(M+Na)^+$]. Anal. calcd. for $C_{16}H_{14}Cl_2O_6$ (373.18): C, 51.49; H, 3.78. Found: C, 51.81; H, 4.24.

GP 8: General procedure for the synthesis of **33**.

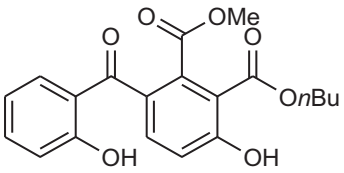
Me_3SiOTf (2.0 mmol) was added to chromone **8** (1.0 mmol) at 20 °C. After stirring for 1 h, CH_2Cl_2 (4 mL) and the 1,3-bis-silyl-enol ether **3** (2.0 mmol) were added at 0 °C. The mixture was stirred for 12 h at 0-20 °C and was then poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. To the mixture was added p-TsOH (3 mol%) and was heated at 80-90 °C in EtOH (4-8 mL/1 mmol of **8**) during 5-10 h. The solvent was removed *in vacuo* and the product was purified by chromatography.

Dimethyl 3-hydroxy-6-(2-hydroxybenzoyl)phthalate (33a).



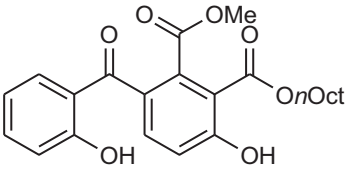
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33a** was isolated as a yellow solid (0.208 mg, 63%); mp = 153-154 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 6.82-6.88 (m, 1H, Ar), 7.02-7.06 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz 1H, Ar), 7.11 (d, ^3J = 8.7 Hz, 1H, Ar), 7.37-7.40 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, Ar), 7.47-7.53 (m, 1H, Ar), 7.56 (d, ^3J = 8.6 Hz, 1H, Ar), 11.08 (s, 1H, OH), 11.62 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7, 53.3 (OCH_3), 111.0 (C), 118.4, 118.8 (Ar), 119.0, 128.3 (C), 133.1, 135.3 (Ar), 136.4 (C), 136.8 (Ar), 163.0, 163.1, 167.5, 168.9, 199.6 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3291 (w), 2961 (w), 1731 (m), 1683 (s), 1626 (s), 1609 (m), 1590 (m), 1442 (s), 1320 (s), 1184(s), 1119 (s), 1012 (s), 759 (s), 719 (s), 638 (s), 530 (s), 388 (s). GC-MS (EI, 70 eV): *m/z* (%) = 330 (M^+, 7), 298 (37), 239 (100). HRMS (EI, 70 eV): calcd. for $C_{17}H_{14}O_7$ (M^+) 330.07340, found 330.07361. Anal. calcd. for $C_{17}H_{14}O_7$ (330.29): C, 61.82; H, 4.27. Found: C, 61.54; H, 4.28.

1-Butyl 2-methyl 6-hydroxy-3-(2-hydroxybenzoyl)phthalate (33b).



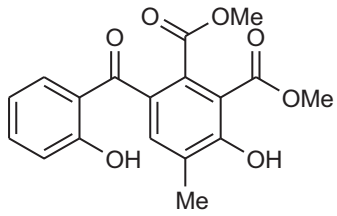
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3e**) (0.605 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33b** was isolated as a yellow oil (0.311 mg, 84%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.33-1.50 (m, 2H, CH_2), 1.61-1.74 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 4.34 (t, ^3J = 6.7 Hz, 2H, CH_2), 6.82-6.87 (m, 1H, Ar), 7.02-7.05 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.11 (d, ^3J = 8.7 Hz, 1H, Ar), 7.37-7.40 (dd, ^3J = 8.1 Hz, ^4J = 1.6 Hz, 1H, Ar), 7.46-7.52 (m, 1H, Ar), 7.54 (d, ^3J = 8.6 Hz, 1H, Ar), 11.27 (s, 1H, OH), 11.64 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.8, 30.1 (CH_2), 52.6 (OCH_3), 66.7 (CH_2), 111.0 (C), 118.3, 118.4, 118.8 (Ar), 119.0, 128.2 (C), 133.1, 135.1 (Ar), 136.3 (C), 136.7 (Ar), 163.0, 163.1, 167.4, 168.7, 199.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 2874 (w), 1736 (s), 1673 (s), 1625 (s), 1608 (m), 1581 (s), 1442 (s), 1325 (s), 1211(s), 1146 (s), 1018 (s), 756 (s) , 641 (s). GC-MS (EI, 70 eV): *m/z* (%) = 372 (M^+, 7), 340 (47), 284 (21), 283 (34), 239 (100), 212 (22). HRMS (EI, 70 eV): calcd. for $C_{20}H_{20}O_7$ (M^+) 372.12035, found 372.12116. Anal. calcd. for $C_{20}H_{20}O_7$ (372.37): C, 64.51; H, 5.41. Found: C, 64.28; H, 5.54.

1-Methyl 2-octyl 3-hydroxy-6-(2-hydroxybenzoyl)phthalate (33c).



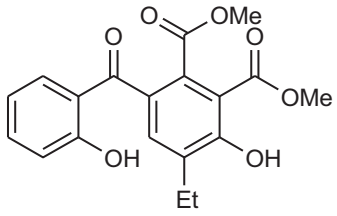
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-octyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3h**) (0.717 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33c** was isolated as a yellow oil (0.342 mg, 80%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.26-1.42 (m, 10H, $(CH_2)_5$), 1.66-1.76 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.34 (t, ^3J = 6.8 Hz, 2H, CH_2), 6.83-6.88 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.11 (d, ^3J = 8.7 Hz, 1H, Ar), 7.37-7.41 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ar), 7.47-7.53 (m, 1H, Ar), 7.55 (d, ^3J = 8.6 Hz, 1H, Ar), 11.28 (s, 1H, OH), 11.65 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5, 25.7, 28.2, 29.1, 29.2, 31.7 (CH_2), 52.6 (OCH_3), 67.1 (CH_2), 111.1 (C), 118.4, 118.8 (Ar), 119.1, 128.3 (C), 133.1, 135.2 (Ar), 136.4 (C), 136.8 (Ar), 163.0, 163.3, 167.4, 168.7, 199.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (m), 2855 (m), 1738 (s), 1674 (s), 1627 (s), 1609 (m), 1583 (s), 1443 (s), 1329 (s), 1214(s), 1147 (s), 1018 (s), 757 (s), 642 (s). GC-MS (EI, 70 eV): *m/z* (%) = 428 (M^+, 4), 396 (47), 284 (44), 283 (42), 239 (100), 212 (22). HRMS (ESI): calcd. for $C_{24}H_{29}O_7$ [$(M+H)^+$] 429.1902, found 429.1902; calcd. for $C_{24}H_{28}NaO_7$ [$(M+Na)^+$] 451.1727, found 451.1730. Anal. calcd. for $C_{24}H_{28}O_7$ (428.47): C, 67.28; H, 6.59. Found: C, 67.23; H, 7.42.

Dimethyl 3-hydroxy-6-(2-hydroxybenzoyl)-4-methylphthalate (33d).



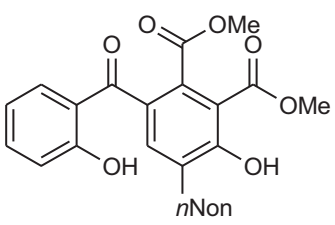
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33d** was isolated as a slight yellow solid (0.230 mg, 67%); mp = 98-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.82-6.88 (m, 1H, Ar), 7.02-7.05 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.38-7.42 (m, 2H, Ar), 7.47-7.53 (m, 1H, Ar), 11.30 (s, 1H, OH), 11.66 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (CH_3), 52.6, 53.2 (OCH_3), 111.0 (C), 118.3, 118.8 (Ar), 119.2, 127.8, 128.23 (C), 133.1 (Ar), 133.8 (C), 135.4, 136.6 (Ar), 161.5, 162.9, 167.7, 169.4, 200.0 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3004 (w), 2951 (w), 2850 (w), 1728 (s), 1676 (s), 1622 (s), 1601 (s), 1577 (s), 1438 (s), 1349 (s), 1253 (s), 1151 (s), 1048 (s), 980 (s), 762 (s), 662 (s). GC-MS (EI, 70 eV): *m/z* (%) = 344 (M^+, 5), 312 (35), 280 (32), 253 (100). HRMS (EI, 70 eV): calcd. for $C_{18}H_{16}O_7$ (M^+) 344.08905, found 344.09011. Anal. calcd. for $C_{18}H_{16}O_7$ (344.32): C, 62.79; H, 4.64. Found: C, 62.70; H, 4.69.

Dimethyl 5-ethyl-3-(2-hydroxybenzoyl)phthalate (33e).



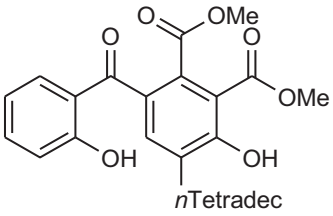
Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3k**) (0.577 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33e** was isolated as a slight yellow solid (0.237 mg, 66%); mp = 126-128 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, ^3J = 7.4 Hz , 3H, CH_3), 2.73 (q, ^3J = 7.4 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.83-6.88 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.37-7.42 (m, 2H, Ar), 7.47-7.53 (m, 1H, Ar), 11.31 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_3), 22.9 (CH_2), 52.6, 53.2 (OCH_3), 111.3 (C), 118.3, 118.7 (Ar), 119.2, 127.9 (C), 133.1 (Ar), 133.7 (C), 133.9 (Ar), 134.0 (C), 136.6 (Ar), 161.2, 163.0, 167.8, 169.5, 200.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973 (w), 2954 (w), 1725 (s), 1675 (s), 1624 (s), 1599 (s), 1575 (m), 1446 (s), 1359 (s), 1248 (s), 1154 (s), 755 (s), 716 (s), 657 (s), 384 (s). GC-MS (EI, 70 eV): *m/z* (%) = 358 (M^+, 5), 326 (37), 294 (24), 267 (100). HRMS (ESI): calcd. for $C_{19}H_{19}O_7$ [$(M+H)^+$] 359.1125, found 359.1122; calcd. for $C_{19}H_{18}NaO_7$ [$(M+Na)^+$] 381.0945, found 381.0943. Anal. calcd. for $C_{19}H_{18}O_7$ (358.34): C, 63.68; H, 5.06. Found: C, 63.71; H, 5.22.

Dimethyl 3-(2-hydroxybenzoyl)-5-nonylphthalate (33f).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3y**) (0.773 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33f** was isolated as a slight yellow oil (0.318 mg, 70%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.8 Hz , 3H, CH_3), 1.21-1.29 (m, 12H, $(CH_2)_6$), 1.54-1.61 (m, 2H, CH_2), 2.68 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.82-6.88 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.4 Hz, ^4J = 1.0 Hz, 1H, Ar), 7.38-7.41 (m, 2H, Ar), 7.48-7.53 (m, 1H, Ar), 11.31 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 28.9, 29.2, 29.3, 29.4, 29.5, 29.7, 31.8 (CH_2), 52.7, 53.2 (OCH_3), 110.4 (C), 118.3, 118.7 (Ar), 119.2, 127.7, 132.7 (C), 133.1 (Ar), 133.8 (C), 134.8, 136.6 (Ar), 161.3, 163.0, 167.8, 169.5, 200.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3074 (w), 2948 (m), 2925 (s), 2853 (m), 1739 (s), 1685 (s), 1625 (s), 1610 (m), 1577 (m), 1439 (s), 1359 (s), 1241 (s), 1152 (s), 1057 (s), 770 (s). MS (EI, 70 eV): *m/z* (%) = 456 (M^+, 10), 425 (41), 424 (90), 397 (46), 393 (39), 392 (98), 366 (34), 365 (100), 281 (32), 280 (89), 252 (25), 121 (32), 84 (28), 83 (23), 71 (27), 69 (30), 57 (48), 55 (39), 44 (38), 43 (65), 41 (43). HRMS (EI, 70 eV): calcd. for $C_{26}H_{32}O_7$ (M^+) 456.21425, found 456.21447. Anal. calcd. for $C_{29}H_{32}O_7$ (456.53): C, 68.40; H, 7.07. Found: C, 68.88; H, 7.08.

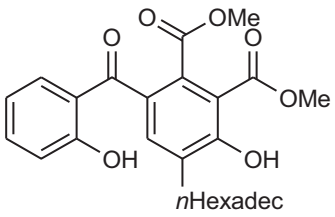
Dimethyl 3-(2-hydroxybenzoyl)-5-tetradecylphthalate (33g).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-octadecadiene (**3ab**) (0.913 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33g** was isolated as a yellow solid (0.390 mg, 74%); mp = 82-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.7 Hz , 3H, CH_3), 1.24-1.29 (m, 22H, $(CH_2)_{11}$), 1.54-1.64 (m, 2H, CH_2), 2.68 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.82-6.88 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.3 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.38-7.41 (m, 2H, Ar), 7.47-7.53 (m, 1H, Ar), 11.31 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.9, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (CH_2), 52.6, 53.2 (OCH_3), 110.4 (C), 118.3, 118.7 (Ar), 119.2, 127.7, 132.7 (C), 133.1 (Ar), 133.8 (C), 134.8, 136.6 (Ar), 161.3, 163.0, 167.8, 169.5, 200.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 2916 (s), 2848 (m), 1729 (s), 1674 (s), 1627 (s), 1602 (m), 1576 (m), 1446 (s), 1359 (s),

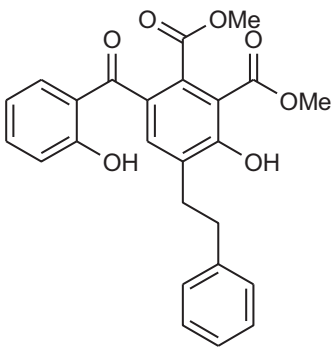
1269 (s), 1211 (s), 1155 (s), 766 (s), 723 (s), 664 (s). MS (EI, 70 eV): *m/z* (%) = 526 (M^+, 3), 495 (34), 494 (100), 467 (30), 463 (24), 462 (76), 453 (55), 282 (22), 280 (62), 121 (21), 44 (40), 43 (26), 41 (20). HRMS (EI, 70 eV): calcd. for $C_{31}H_{42}O_7$ (M^+) 526.29251, found 526.29356. Anal. calcd. for $C_{31}H_{42}O_7$ (526.66): C, 70.70; H, 8.04. Found: C, 70.86; H, 8.06.

Dimethyl 5-hexadecyl-3-(2-hydroxybenzoyl)phthalate (33h).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-icosadiene (**3ac**) (0.969 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (3 mL) with 3 mol% of p-TsOH, the product **33h** was isolated as a slight yellow solid (0.399 mg, 72%); mp = 78-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.6 Hz , 3H, CH_3), 1.24-1.29 (m, 26H, $(CH_2)_{13}$), 1.54-1.61 (m, 2H, CH_2), 2.68 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.82-6.88 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1H, Ar), 7.38-7.41 (m, 2H, Ar), 7.47-7.53 (m, 1H, Ar), 11.31 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.9, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (CH_2), 52.7, 53.2 (OCH_3), 110.4 (C), 118.3, 118.7 (Ar), 119.2, 127.7, 132.7 (C), 133.1 (Ar), 133.8 (C), 134.8, 136.6 (Ar), 161.3, 163.0, 167.8, 169.5, 200.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916 (s), 2848 (s), 1741 (s), 1686 (s), 1624 (s), 1608 (m), 1577 (m), 1439 (s), 1359 (s), 1254 (s), 1221 (s), 1198 (s), 1154 (s), 1057 (s), 759 (s), 600 (s). MS (EI, 70 eV): *m/z* (%) = 554 (M^+, 4), 523 (41), 522 (100), 495 (33), 490 (62), 463 (36), 280 (34), 69 (27), 55 (28), 44 (92), 43 (51), 41 (27). HRMS (EI, 70 eV): calcd. for $C_{33}H_{46}O_7$ (M^+) 554.32381, found 554.32305. Anal. calcd. for $C_{33}H_{46}O_7$ (554.71): C, 71.45; H, 8.36. Found: C, 71.58; H, 8.65.

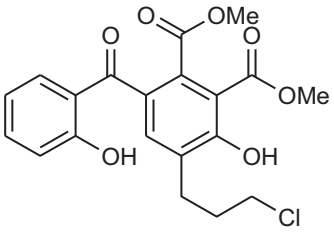
Dimethyl 3-(2-hydroxybenzoyl)-5-phenethylphthalate (33i).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-6-phenyl-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3ad**) (0.729 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL) and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33i** was isolated as a yellow solid (0.161 mg, 37%); mp = 129-131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98-3.10 (m, 24H, $(CH_2)_2$), 3.82 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.79-6.84 (m, 1H, Ar), 7.06-7.36 (m, 8H, Ar), 7.50-7.56 (m, 1H, Ar), 11.48 (s, 1H, OH), 11.73 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.2, 34.6 (CH_2), 52.7, 53.3 (OCH_3), 110.5 (C), 118.2, 118.9 (Ar), 119.0 (C), 126.0 (Ar), 127.6 (C),

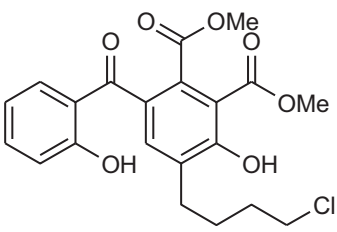
128.4, 128.5 (Ar), 131.0 (C), 133.1 (Ar), 134.3 (C), 135.4, 136.6 (Ar), 161.4, 163.0, 167.8, 169.5, 199.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3032 (w), 2952 (w), 1723 (s), 1669 (s), 1622 (s), 1594 (s), 1574 (s), 1434 (s), 1344 (s), 1267 (s), 1220 (s), 1148 (s), 1052 (s), 975 (s), 815 (s), 763 (s), 698 (s). MS (EI, 70 eV): *m/z* (%) = 434 (M^+, 13), 403 (24), 402 (66), 375 (28), 371 (25), 370 (100), 343 (78), 279 (38), 251 (48), 91 (55). HRMS (EI, 70 eV): calcd. for $C_{25}H_{22}O_7$ (M^+) 434.13600, found 434.13619. Anal. calcd. for $C_{25}H_{22}O_7$ (434.44): C, 69.12; H, 5.10. Found: C, 69.15; H, 4.99.

Dimethyl 4-(3-chloropropyl)-3-hydroxy-6-(2-hydroxybenzoyl)phthalate (33j).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-7-chlor-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3ag**) (0.674 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), the precipitated product **33j** was isolated as a slight yellow solid (0.216 mg, 53%); mp = 160-161 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06-2.15 (m, 2H, CH_2), 2.88 (t, ^3J = 7.4 Hz , 2H, CH_2), 3.54 (t, ^3J = 6.3 Hz , 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.83-6.89 (m, 1H, Ar), 7.03-7.06 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz, 1H, Ar), 7.37-7.40 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, Ar), 7.46 (s, 1H, Ar), 7.48-7.54 (m, 1H, Ar), 11.38 (s, 1H, OH), 11.65 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 31.2, 44.2 (CH_2), 52.7, 53.3 (OCH_3), 110.6 (C), 118.4, 118.8 (Ar), 119.1 (C), 127.9, 130.5 (C), 133.1 (Ar), 134.6 (C), 135.3, 136.8 (Ar), 161.3, 163.0, 167.6, 169.4, 199.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3168 (w), 3002 (w), 2954 (w), 2849 (w), 1723 (s), 1677 (s), 1622 (s), 1595 (s), 1576 (s), 1436 (s), 1255 (s), 1154 (s), 1053 (s), 979 (s), 816 (s), 770 (s), 633 (s). MS (EI, 70 eV): *m/z* (%) = 406 (M^+, 7), 374 (53), 317 (34), 315 (100), 307 (56), 280 (49), 279 (90), 69 (31), 57 (33), 43 (29). HRMS (ESI): calcd. for $C_{20}H_{20}Cl^{35}O_7$ [$(M+H)^+$] 407.0892, found 407.0888; calcd. for $C_{20}H_{19}Cl^{35}NaO_7$ [$(M+Na)^+$] 429.0712, found 429.0712; calcd. for $C_{20}H_{19}Cl^{37}NaO_7$ ([$M+Na]^+$) 431.0691, found 431.0690. Anal. calcd. for $C_{20}H_{19}ClO_7$ (406.08): C, 59.05; H, 4.71. Found: C, 59.18; H, 4.65.

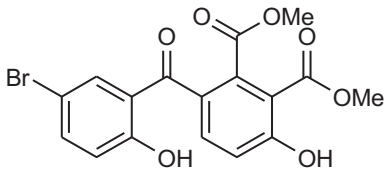
Dimethyl 4-(3-chloropropyl)-3-hydroxy-6-(2-hydroxybenzoyl)phthalate (33k).



Starting with 3-methoxalylchromone (**8a**) (0.232 g, 1.0 mmol) and 1-methoxy-8-chlor-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3ah**) (0.702 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 10 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33k** was isolated as a yellow solid (0.237 mg, 56%); mp = 87-88 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71-1.87 (m, 4H, $(CH_2)_2$),

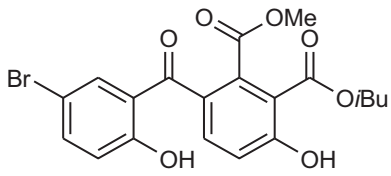
2.73 (t, ^{3}J = 7.0 Hz , 2H, CH_2), 3.55 (t, ^{3}J = 6.3 Hz , 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.83-6.89 (m, 1H, Ar), 7.03-7.06 (dd, ^{3}J = 8.4 Hz, ^{4}J = 0.9 Hz, 1H, Ar), 7.36-7.41 (dd, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, 1H, Ar), 7.41 (s, 1H, Ar), 7.48-7.54 (m, 1H, Ar), 11.34 (s, 1H, OH), 11.65 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 28.9, 32.1, 44.6 (CH_2), 52.7, 53.3 (OCH_3), 110.5 (C), 118.4, 118.8 (Ar), 119.2 (C), 127.9, 131.8 (C), 133.1 (Ar), 134.1 (C), 134.8, 136.7 (Ar), 161.2, 163.0, 167.7, 169.4, 199.9 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2994 (w), 2949 (m), 2927 (m), 2898 (m), 1723 (s), 1675 (s), 1623 (s), 1597 (s), 1547 (s), 1437 (s), 1348 (s), 1223 (s), 1151 (s), 1054 (s), 762 (s), 742 (s), 648 (s), 634 (s). MS (EI, 70 eV): *m/z* (%) = 420 (M^+, 10), 390 (38), 389 (33), 388 (85), 361 (26), 331 (66), 330 (36), 329 (100), 321 (34), 293 (73), 121 (26). HRMS (EI, 70 eV): calcd. for $C_{21}H_{21}O_7Cl$ (M^+) 420.09703, found 420.09622. Anal. calcd. for $C_{21}H_{21}ClO_7$ (420.84): C, 59.93; H, 5.03. Found: C, 60.87; H, 5.10.

Dimethyl 3-(5-bromo-2-hydroxybenzoyl)-6-hydroxyphthalate (33l).



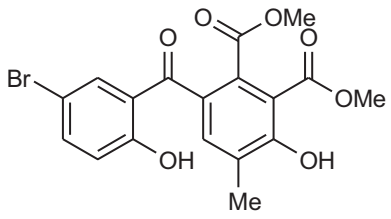
Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (8 mL), and then 5 h heating in EtOH (4 mL) with 3 mol% of p-TsOH, the product **33l** was isolated as a yellow solid (0.200 mg, 49%); mp = 112-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.01 (d, ^{3}J = 8.8 Hz, 1H, Ar), 7.21 (d, ^{3}J = 8.7 Hz, 1H, Ar), 7.53 (d, ^{4}J = 2.4 Hz, 1H, Ar), 7.59-7.64 (m, 2H, Ar), 11.18 (s, 1H, OH), 11.58 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.8, 53.4 (OCH_3), 110.4, 111.1 (C), 118.7 (Ar), 120.3 (C), 120.4 (Ar), 127.6 (C), 134.9, 135.1 (Ar), 136.6 (C), 139.4 (Ar), 161.9, 163.4, 167.4, 168.8, 198.6 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305 (w), 2950 (w), 2927 (m), 1738 (m), 1686 (m), 1628 (m), 1590 (m), 1464 (m), 1434 (m), 1184 (s), 1144 (s), 1120 (s), 1019 (s), 942 (s), 648 (s), 525 (s). MS (EI, 70 eV): *m/z* (%) = 409 (M^+, 2), 378 (46), 376 (46), 319 (99), 318 (33), 317 (100). HRMS (ESI): calcd. for $C_{17}H_{13}Br^{79}NaO_7$ [$(M+Na)^+$] 430.9736, found 430.9728; calcd. for $C_{17}H_{13}Br^{81}NaO_7$ [$(M+Na)^+$] 432.9718, found 432.97135. Anal. calcd. for $C_{17}H_{13}BrO_7$ (409.18): C, 49.90; H, 3.20. Found: C, 49.66; H, 3.44.

1-Isobutyl 2-methyl 3-(5-bromo-2-hydroxybenzoyl)-6-hydroxyphthalate (33m).



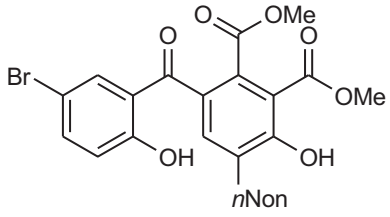
Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-isobutoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.605 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33m** was isolated as a yellow solid (0.325 mg, 72%); mp = 106-108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 1.95-2.08 (m, 1H, CH), 3.74 (s, 3H, OCH_3), 4.14 (d, ^3J = 6.9 Hz, 2H, CH_2), 6.96 (d, ^3J = 8.8 Hz, 1H, Ar), 7.15 (d, ^3J = 8.7 Hz, 1H, Ar), 7.49-7.59 (m, 3H, Ar), 11.32 (s, 1H, OH), 11.56 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 ($(CH_3)_2$), 27.6 (CH), 52.7 (OCH_3), 73.0 (CH_2), 110.4, 111.2 (C), 118.7 (Ar), 120.3 (C), 120.4 (Ar), 127.6 (C), 134.9 (Ar), 136.4 (C), 139.4 (Ar), 161.9, 163.6, 167.2, 168.6, 198.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 1724 (s), 1669 (m), 1625 (m), 1602 (m), 1581 (m), 1464 (s), 1321 (s), 1221 (s), 1147 (s), 1018 (s), 624 (s). MS (EI, 70 eV): *m/z* (%) = 451 (M^+, 2), 420 (46), 418 (45), 364 (100), 363 (29), 362 (96), 319 (70), 318 (21), 317 (69) 57 (29). Anal. calcd. for $C_{20}H_{19}BrO_7$ (451.26): C, 53.23; H, 4.24. Found: C, 53.37; H, 4.42.

Dimethyl 6-(5-bromo-2-hydroxybenzoyl)-3-hydroxy-4-methylphthalate (33n).



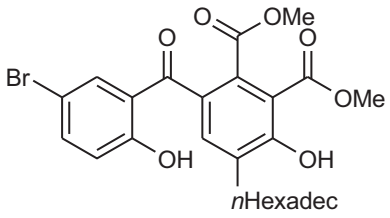
Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33n** was isolated as a yellow solid (0.318 mg, 75%); mp = 150-153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.95 (d, ^3J = 8.8 Hz, 1H, Ar), 7.39 (bs, 1H, Ar), 7.48 (d, ^4J = 2.4 Hz, 1H, Ar), 7.57 (dd, ^3J = 8.8 Hz, ^4J = 2.4 Hz, 1H, Ar), 11.33 (s, 1H, OH), 11.56 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (CH_3), 52.7, 53.3 (OCH_3), 110.3, 110.4 (C), 120.4 (Ar), 120.5, 127.2, 128.5 (C), 134.9, 135.0, 139.3 (Ar), 161.8, 161.9, 167.7, 169.4, 199.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 1734 (s), 1673 (m), 1630 (m), 1595 (m), 1464 (m), 1357 (s), 1255 (s), 1158 (s), 1053 (s), 990 (s), 803 (s), 683 (s), 625 (s), 416 (s). MS (EI, 70 eV): *m/z* (%) = 423 (M^+, 2), 392 (52), 390 (50), 360 (36), 358 (34), 333 (96), 332 (33), 331 (100). HRMS (EI, 70 eV): calcd. for $C_{18}H_{15}O_7Br^{79}$ (M^+) 421.99957, found 421.99850; calcd. for $C_{18}H_{15}O_7Br^{81}$ (M^+) 423.9975, found 423.99705. Anal. calcd. for $C_{18}H_{15}BrO_7$ (423.21): C, 51.08; H, 3.57. Found: C, 51.17; H, 3.66.

Dimethyl 6-(5-bromo-2-hydroxybenzoyl)-3-hydroxy-4-nonylphthalate (33o).



Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3y**) (0.773 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33o** was isolated as a yellow oil (0.414 mg, 77%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.6 Hz, 3H, CH_3), 1.25-1.36 (m, 12H, $(CH_2)_6$), 1.56-1.66 (m, 2H, CH_2), 2.70 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.96 (d, ^3J = 8.8 Hz, 1H, Ar), 7.38 (bs, 1H, Ar), 7.50 (d, ^4J = 2.4 Hz, 1H, Ar), 7.57 (dd, ^3J = 8.8 Hz, ^4J = 2.4 Hz, 1H, Ar), 11.36 (s, 1H, OH), 11.59 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.9, 29.3, 29.4, 29.7, 31.8 (CH_2), 52.7, 53.3 (OCH_3), 110.3, 110.5 (C), 120.4 (Ar), 120.5, 127.0, 133.1, 133.9 (C), 134.6, 135.1, 139.2 (Ar), 161.6, 161.9, 167.7, 169.4, 199.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 2953 (w), 2920 (s), 2853 (m), 1729 (s), 1688 (m), 1634 (s), 1610 (m), 1438 (s), 1264 (s), 1227 (s), 1192 (s), 1167 (s), 975 (s), 811 (s), 713 (s), 695 (s). MS (EI, 70 eV): *m/z* (%) = 535 (M^+, 2), 505 (28), 504 (100), 503 (29), 502 (94), 445 (78), 444 (17), 443 (76), 360 (46), 359 (13), 358 (45). HRMS (ESI): calcd. for $C_{26}H_{31}Br^{79}NaO_7$ [(M+Na)$^+$] 557.1145, found 557.1140; calcd. for $C_{26}H_{31}Br^{81}NaO_7$ [(M+Na)$^+$] 559.1129, found 559.1144. Anal. calcd. for $C_{26}H_{31}BrO_7$ (535.42): C, 58.32; H, 5.84. Found: C, 57.06; H, 6.33.

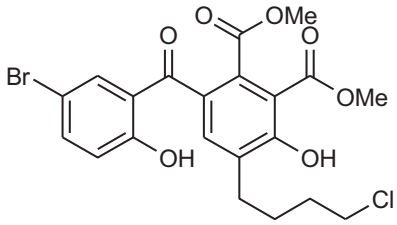
Dimethyl 6-(5-bromo-2-hydroxybenzoyl)-4-hexadecyl-3-hydroxyphthalate (33p).



Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-icosadiene (**3ac**) (0.969 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33p** was isolated as a yellow solid (0.340 mg, 54%); mp = 82-83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.17-1.24 (m, 26H, $(CH_2)_{13}$), 1.49-1.59 (m, 2H, CH_2), 2.63 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.89 (d, ^3J = 8.8 Hz, 1H, Ar), 7.31 (bs, 1H, Ar), 7.43 (d, ^4J = 2.4 Hz, 1H, Ar), 7.50 (dd, ^3J = 8.8 Hz, ^4J = 2.4 Hz, 1H, Ar), 11.29 (s, 1H, OH), 11.52 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 28.9, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9 (CH_2), 52.7, 53.3 (OCH_3), 110.3, 110.5 (C), 120.4 (Ar), 120.5, 127.0, 133.1, 133.9 (C), 134.6, 135.0, 139.2 (Ar), 161.6, 161.9, 167.7, 169.4, 199.1 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2919 (s), 2852 (s), 1731 (s), 1673 (s), 1634 (s), 1608 (w), 1583 (w), 1435 (s), 1264 (s), 1226 (s), 1208 (s), 1191 (s), 1170 (s), 979 (s), 701 (s), 692 (s). MS (EI, 70 eV): *m/z* (%) = 633 (M^+, 1), 603 (32), 602 (100), 601 (32), 600 (93), 570 (11),

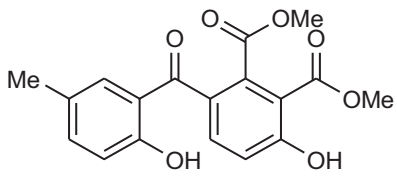
568 (10), 543 (19), 541 (18), 360 (17), 358 (16). HRMS (ESI): calcd. for $C_{33}H_{45}Br^{79}NaO_7$ [(M+Na)$^+$] 655.2240, found 655.2238; calcd. for $C_{33}H_{45}Br^{81}NaO_7$ [(M+Na)$^+$] 657.2226, found 657.2229. Anal. calcd. for $C_{33}H_{43}BrO_7$ (633.61): C, 62.55; H, 7.16. Found: C, 62.56; H, 7.47.

Dimethyl 6-(5-bromo-2-hydroxybenzoyl)-4-(4-chlorobutyl)-3-hydroxyphthalate (33q).



Starting with 6-brom-3-methoxalylchromone (**8b**) (0.309 g, 1.0 mmol) and 1-methoxy-8-chlor-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3ah**) (0.702 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33q** was isolated as a yellow oil (0.412 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72-1.88 (m, 4H, $(CH_2)_2$), 2.75 (t, ^3J = 7.0 Hz, 2H, CH_2), 3.57 (t, ^3J = 6.1 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.96 (d, ^3J = 8.7 Hz, 1H, Ar), 7.39 (bs, 1H, Ar), 7.48 (d, ^4J = 2.3 Hz, 1H, Ar), 7.58 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz, 1H, Ar), 11.40 (s, 1H, OH), 11.55 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 28.9, 31.9, 44.6 (CH_2), 52.7, 53.4 (OCH_3), 110.3, 110.6 (C), 120.4 (Ar), 120.5, 127.1, 132.1, 134.2 (C), 134.7, 135.0, 139.3 (Ar), 161.6, 161.9, 167.5, 169.3, 198.9 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 1735 (s), 1675 (s), 1628 (s), 1602 (w), 1573 (w), 1462 (m), 1251 (s), 1189 (s), 1162 (s), 1052 (s), 808 (s), 692 (s). HRMS (ESI): calcd. for $C_{21}H_{20}BrClNaO_7$ [(M+Na)$^+$] 520.9973, found 520.9972; calcd. for $C_{21}H_{20}BrClNaO_7$ [(M+Na)$^+$] 522.9952, found 522.9955; calcd. for $C_{21}H_{20}BrClNaO_7$ [(M+Na)$^+$] 524.9935, found 524.9933. Anal. calcd. for $C_{21}H_{20}BrClO_7$ (499.74): C, 50.47; H, 4.03. Found: C, 50.48; H, 4.26.

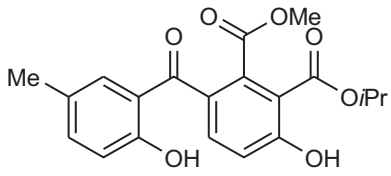
Dimethyl 3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)phthalate (33r).



Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33r** was isolated as a yellow solid (0.207 mg, 60%); mp = 116-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.94 (d, ^3J = 8.4 Hz, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.31 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 1H, Ar), 7.56 (d, ^3J = 8.6 Hz, 1H, Ar), 11.09 (s, 1H, OH), 11.44 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH_3), 52.7, 53.3 (OCH_3), 110.9 (C), 118.1, 118.4 (Ar), 118.7, 128.0, 128.6 (C), 132.6, 135.3 (Ar), 136.3 (C), 137.8 (Ar), 160.9, 163.0, 167.6, 168.9, 199.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3031 (w), 2953 (w), 1726 (s), 1674 (m), 1630 (m), 1612 (m), 1585 (m), 1440 (s), 1324 (s), 1210 (s), 1144 (s), 713 (s), 650 (s), 652 (s). GC-MS (EI, 70 eV): *m/z* (%) = 344 (M$^+$, 11), 312 (34), 253 (100), 252 (20). HRMS (EI, 70 eV):

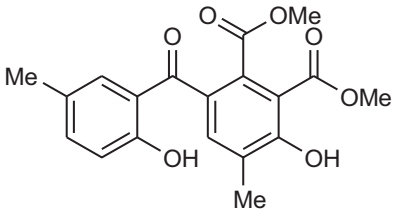
calcd. for $C_{18}H_{16}O_7$ (M^+) 344.08905, found 344.08950. Anal. calcd. for $C_{18}H_{16}O_7$ (344.32): C, 62.79; H, 4.68. Found: C, 62.77; H, 4.97.

2-Isopropyl 1-methyl 3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)phthalate (33s).



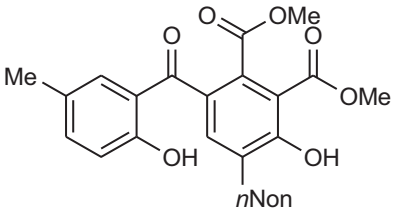
Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-isopropoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.577 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33s** was isolated as a yellow oil (0.236 mg, 63%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, ^3J = 6.0 Hz, 6H, $(CH_3)_2$), 2.22 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.25-5.34 (m, 1H, CH), 6.94 (d, ^3J = 8.4 Hz, 1H, Ar), 7.11 (d, ^3J = 8.6 Hz, 1H, Ar), 7.15 (d, ^4J = 2.1 Hz, 1H, Ar), 7.31 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 1H, Ar), 7.54 (d, ^3J = 8.7 Hz, 1H, Ar), 11.34 (s, 1H, OH), 11.47 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.4 (CH_3), 52.5 (OCH_3), 71.2 (CH), 111.2 (C), 118.1, 118.3 (Ar), 118.8, 128.0, 128.4 (C), 132.7, 135.0 (Ar), 136.2 (C), 137.8 (Ar), 160.9, 163.3, 167.4, 168.2, 199.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 1736 (m), 1671 (m), 1631 (m), 1608 (m), 1582 (m), 1320 (s), 1215 (s), 1096 (s), 802 (s), 647 (s). GC-MS (EI, 70 eV): *m/z* (%) = 372 (M^+, 14), 340 (39), 298 (74), 253 (100). HRMS (ESI): calcd. for $C_{20}H_{20}NaO_7$ [$(M+Na)^+$] 395.1101, found 395.1100.

Dimethyl 3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)-4-methylphthalate (33t).



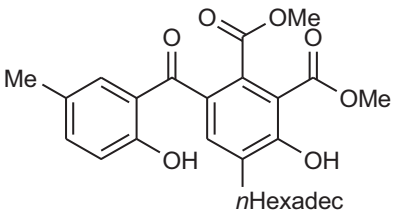
Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3j**) (0.549 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33t** was isolated as a yellow solid (0.264 mg, 74%); mp = 110-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.94 (d, ^3J = 8.4 Hz, 1H, Ar), 7.14 (d, ^4J = 2.1 Hz, 1H, Ar), 7.31 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H, Ar), 7.40 (bs, 1H, Ar), 11.28 (s, 1H, OH), 11.47 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 20.3 (CH_3), 52.6, 53.2 (OCH_3), 110.1 (C), 118.0 (Ar), 118.9, 127.9, 128.1, 128.4, (C), 132.7 (Ar), 133.6 (C), 135.2, 137.7 (Ar), 160.8, 161.4, 167.7, 169.5, 200.0 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3030 (w), 2995 (w), 2950 (w), 2923 (w), 1736 (s), 1686 (s), 1630 (s), 1598 (s), 1484 (s), 1438 (s), 1351 (s), 1242 (s), 1206 (s), 1155 (s), 1049 (s), 986 (s), 815 (s), 671 (s). GC-MS (EI, 70 eV): *m/z* (%) = 358 (M^+, 10), 326 (36), 294 (35), 267 (100). HRMS (EI, 70 eV): calcd. for $C_{19}H_{18}O_7$ (M^+) 358.10470, found 358.10607. Anal. calcd. for $C_{19}H_{18}O_7$ (358.34): C, 63.68; H, 5.06. Found: C, 63.66; H, 5.20.

Dimethyl 3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)-4-nonylphthalate (33v).



Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3y**) (0.773 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33v** was isolated as a yellow oil (0.298 mg, 63%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.20-1.36 (m, 12H, $(CH_2)_6$), 1.55-1.65 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.69 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.95 (d, ^3J = 8.4 Hz, 1H, Ar), 7.16 (d, ^4J = 2.0 Hz, 1H, Ar), 7.32 (dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz, 1H, Ar), 7.40 (bs, 1H, Ar), 11.31 (s, 1H, OH), 11.50 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.3 (CH_3), 22.6, 28.9, 29.2, 29.3, 29.4, 29.5, 29.7, 31.8 (CH_2), 52.6, 53.2 (OCH_3), 110.3 (C), 118.1 (Ar), 118.9, 127.9, 128.0, 132.7 (C), 132.8 (Ar), 133.7 (C), 134.9, 137.7 (Ar), 160.9, 161.2, 167.9, 169.5, 200.0 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (s), 2853 (m), 1737 (s), 1675 (s), 1632 (s), 1607 (m), 1482 (m), 1436 (s), 1354 (s), 1251 (s), 1206 (s), 1153 (s), 1052 (s), 719 (s), 675 (s). MS (EI, 70 eV): *m/z* (%) = 470 (M^+, 8), 438 (70), 406 (29), 379 (100), 294 (42). HRMS (ESI): calcd. for $C_{27}H_{35}O_7$ [$(M+H)^+$] 471.2383, found 471.2383; calcd. for $C_{27}H_{34}NaO_7$ [$(M+Na)^+$] 493.2196, found 493.2203. Anal. calcd. for $C_{27}H_{34}O_7$ (470.55): C, 68.92; H, 7.28. Found: C, 69.06; H, 7.22.

Dimethyl 4-hexadecyl-3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)phthalate (33w).



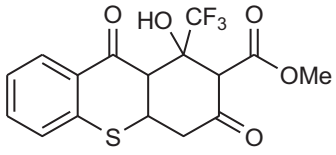
Starting with 6-methyl-3-methoxalylchromone (**8c**) (0.246 g, 1.0 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-icosadiene (**3ac**) (0.969 g, 2.0 mmol), Me_3SiOTf (0.36 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), and then 5 h heating in EtOH (8 mL) with 3 mol% of p-TsOH, the product **33w** was isolated as an orange solid (0.409 mg, 72%); mp = 65-68 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.6 Hz, 3H, CH_3), 1.24-1.30 (m, 26H, $(CH_2)_{13}$), 1.55-1.62 (m, 2H, CH_2), 2.22 (s, 2H, CH_3), 2.69 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.95 (d, ^3J = 8.4 Hz, 1H, Ar), 7.16 (d, ^4J = 1.8 Hz, 1H, Ar), 7.31 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H, Ar), 7.39 (bs, 1H, Ar), 11.31 (s, 1H, OH), 11.50 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.3 (CH_3), 22.6, 28.9, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9 (CH_2), 52.6, 53.2 (OCH_3), 110.3 (C), 118.1 (Ar), 118.9, 127.9, 128.0, 132.7 (C), 132.9 (Ar), 133.7 (C), 134.9, 137.7 (Ar), 160.9, 161.2, 167.8, 169.5, 200.0 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 2919 (s), 2852 (s), 1733 (s), 1672 (s), 1632 (s), 1583 (w), 1488 (w), 1437 (s), 1207 (s), 1154 (s), 981 (s), 708 (s). MS (EI, 70 eV): *m/z* (%) = 568 (M^+, 5), 537 (41), 536 (100), 504 (25), 477 (44), 294 (28). HRMS (ESI): calcd. for $C_{34}H_{49}O_7$ [$(M+H)^+$] 569.3472, found 569.3471; calcd. for $C_{34}H_{48}NaO_7$

[$(M+Na)^+$] 591.3292, found 591.3301. Anal. calcd. for $C_{34}H_{48}O_7$ (568.74): C, 71.80; H, 8.51. Found: C, 71.78; H, 8.82.

GP 9: General Procedure for the synthesis of **34a,b**.

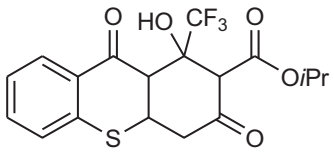
To a CH_2Cl_2 solution (1.5 mL / mmol **30**) of **30** (1.0 mmol) was added Me_3SiOTf (2.0 mmol). After stirring for 1 h, CH_2Cl_2 (8.5 mL / mmol **30**) was added, the solution was cooled to 0 °C and **2** (3.0 mmol) was added. The temperature of the solution was allowed to warm to 20 °C during 12-14 h with stirring. To the solution was added HCl (10%, 15 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography.

Methyl 1-hydroxy-3,9-dioxo-1-(trifluoromethyl)-2,3,4,4a,9,9a-hexahydro-1H-thioxanthene-2-carboxylate (34a).



Starting with 3-trifluoroacetylthiochromone (**30**) (0.258 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.781 g, 3.0 mmol) and Me_3SiOTf (0.444 g, 2.0 mmol) in CH_2Cl_2 (10 mL), the product **34a** was isolated as a colourless solid (0.151 g, 40%); mp = 145-147 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.86-3.18 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.89-4.01 (m, 2H, CH+OH), 4.28-4.33 (m, 1H, CH), 7.14 (s, 1H, CH), 7.28-7.34 (m, 2H, Ph), 7.48-7.53 (m, 1H, Ph), 8.03-8.06 (m, 1H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.3 (CH), 42.3 (CH_2), 50.9 (CH), 53.3 (OCH_3), 61.8 (CH), 78.3 (q, $J_{C\text{-}F}$ = 28.0 Hz, C-1), 125.3 (q, $J_{C\text{-}F}$ = 288.4 Hz, CF_3), 126.7, 127.2, 128.1 (CH), 131.7 (C), 134.7 (CH), 139.4, 166.3, 195.5, 198.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): -72.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3435 (w), 3311 (w), 3041 (w), 3001 (w), 2976 (w), 2950 (w), 2914 (w), 2883 (w), 2854 (w), 1733 (m), 1716 (s), 1686 (m), 1644 (m), 1585 (m), 1459 (w), 1207 (s), 1176 (s), 767 (s), 592 (s). EI (70 eV): *m/z* (%): 374 (M^+, 17), 297 (21), 259 (100), 189 (42), 163 (17), 137 (20), 136 (87), 108 (22), 43 (15). HRMS (EI, 70 eV): calcd. for $C_{16}H_{13}F_3O_5S$ (M^+) 374.04303, found 374.04312. Anal. calcd. for $C_{16}H_{13}F_3O_5S$ (374.33): C, 51.34; H, 3.50; S, 8.57. Found: C, 51.45; H, 3.61; S, 8.63.

Isopropyl 1-hydroxy-3,9-dioxo-1-(trifluoromethyl)-2,3,4,4a,9,9a-hexahydro-1H-thioxanthene-2-carboxylate (34b).

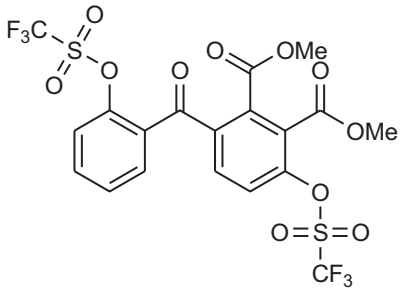


Starting with methyl 3-trifluoroacetylthiochromone (**30**) (0.258 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3d** (0.865 g, 3.0 mmol) and Me_3SiOTf (0.444 g, 2.0 mmol) in CH_2Cl_2 (10 mL), the product **34b** was isolated as a colourless solid (0.128 g, 32 %); mp = 137-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27-1.33 (m, 6H, $(CH_3)_2$), 2.84-3.18 (m, 2H, CH_2), 3.89-4.00 (m, 2H, CH+OH), 4.33-4.38 (m, 1H, CH), 5.03-5.11 (m, 1H, CH), 7.06 (s, 1H, CH), 7.27-7.33 (m, 2H, Ph), 7.47-7.52 (m, 1H, Ph), 8.02-8.05 (m, 1H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.53 (CH_3), 37.4 (CH), 42.3 (CH_2), 50.9, 62.2, 70.9 (CH), 78.4 (q, J_{C-F} = 27.9 Hz, C-1), 125.3 (q, J_{C-F} = 288.4 Hz, CF_3), 126.7, 128.1, 130.1 (CH), 131.8 (C), 134.7 (CH), 139.5, 165.3, 195.9, 198.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): -72.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3386 (w), 3348 (w), 3080 (w), 3063 (w), 2980 (w), 2966 (w), 2940 (w), 2903 (w), 2887 (w), 1717 (s), 1701 (s), 1688 (s), 1655 (m), 1584 (m), 1461 (w), 1181 (s), 1157 (s), 1096 (s), 761 (s), 598 (m). EI (70 eV): *m/z* (%): 402 (M^+, 6), 297 (20), 259 (36), 189 (21), 177 (12), 176 (100), 163 (17), 137 (21), 136 (67), 108 (19), 69 (28), 45 (18), 44 (15), 43 (30). HRMS (EI, 70 eV): calcd. for $C_{18}H_{17}F_3O_5S$ (M^+) 402.07433, found 402.07488. Anal. calcd. for $C_{18}H_{17}F_3O_5S$ (402.38): C, 53.73; H, 4.26; S, 7.97. Found: C, 54.06; H, 4.26; S, 7.96.

GP 10: General procedure for the synthesis of **35a,b**.

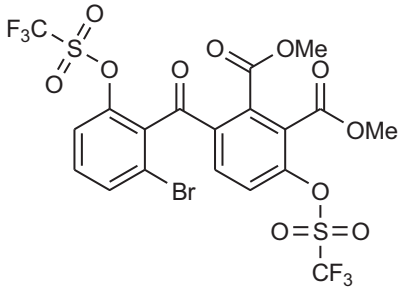
To a CH_2Cl_2 solution (10 mL / mmol **33**) of **33** (1.0 equiv) was added pyridine (4.0 equiv) at -78 °C under argon atmosphere. After stirring for 10 min, Tf_2O (2.4 equiv) was added at -78°C. The mixture was allowed to warm to 0 °C and stirred for 4 h. The reaction mixture was extracted with water. The organic layer was separated, dried (Na_2SO_4), filtered and the filtrate and was concentrated *in vacuo*. Products were isolated by column chromatography.

Dimethyl 3-(trifluoromethylsulfonyloxy)-6-(2-(trifluoromethylsulfonyloxy)benzoyl) phthalate (35a).



Starting with dimethyl 3-hydroxy-6-(2-hydroxybenzoyl)phthalate (**33a**) (0.642 g, 1.9 mmol), pyridine (0.6 mL, 7.6 mmol) and Tf_2O (0.7 mL, 4.6 mmol) in CH_2Cl_2 (19 mL), the product **35a** was isolated as a yellow oil (0.738 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.64-7.77 (m, 6H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.3, 53.4 (OCH_3), 118.5, 118.6 (q, $J_{C\text{-}F}$ = 319.6 Hz, CF_3), 122.9, 123.9 (Ar), 127.6 (C), 128.4 (Ar), 130.2 (C), 132.6, 134.6 (Ar), 138.5, 147.3, 147.9, 163.2, 165.1, 190.5 (C). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -72.9, -72.8 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 1733 (s), 1672 (s), 1630 (s), 1594 (m), 1464 (m), 1447 (m), 1255 (s), 1157 (s), 1053 (s), 802 (s), 683 (s). HRMS (ESI): calcd. for $C_{19}H_{13}F_6O_{11}S_2$ [$(M+H)^+$] 594.9798, found 594.9802; calcd. for $C_{19}H_{12}F_6NaO_{11}S_2$ [$(M+Na)^+$] 616.9617, found 616.9616. Anal. calcd. for $C_{19}H_{12}F_6O_{11}S_2$ (594.41): C, 38.39; H, 2.03; S, 10.79. Found: C, 39.09; H, 2.21; S, 11.01.

Dimethyl 3-(2-bromo-5-(trifluoromethylsulfonyloxy)benzoyl)-6-(trifluoromethylsulfonyloxy)phthalate (35b).

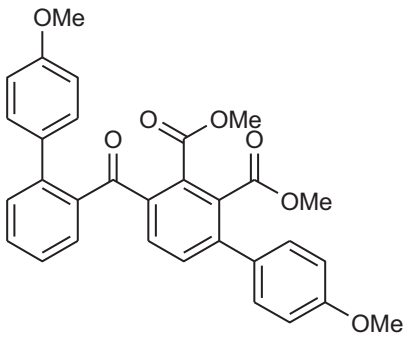


Starting with dimethyl 3-(5-bromo-2-hydroxybenzoyl)-6-hydroxyphthalate (**33l**) (1.0 g, 2.4 mmol), pyridine (0.7 mL, 9.7 mmol) and Tf_2O (0.9 mL, 5.8 mmol) in CH_2Cl_2 (25 mL), the product **35b** was isolated as a yellow solid (1.2 g, 73%); mp = 86-87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.29 (d, ^3J = 8.7 Hz, 1H, Ar), 7.54 (d, ^3J = 8.6 Hz, 1H, Ar), 7.65-7.69 (m, 2H, Ar), 7.80 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.3, 53.4 (OCH_3), 118.4, 118.5 (q, $J_{C\text{-}F}$ = 320.6 Hz, CF_3), 122.0 (C), 124.0, 124.4 (Ar), 127.7, 131.8 (C), 132.6, 134.8, 137.3 (Ar), 137.6, 146.0, 148.2, 163.0, 165.0, 189.2 (C). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -72.8, -72.6 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3096 (w), 2952 (w), 1736 (s), 1696 (m), 1584 (w), 1422 (s), 1385 (w), 1207 (s), 1135 (s), 1000 (s), 824 (s), 605 (s). HRMS (ESI): calcd. for $C_{19}H_{12}Br^{79}F_6O_{11}S_2$ [$(M+H)^+$] 672.8903, found 672.8891; calcd. for $C_{19}H_{12}Br^{81}F_6O_{11}S_2$ [$(M+H)^+$] 674.8884, found 674.8877; calcd. for $C_{19}H_{11}Br^{79}F_6NaO_{11}S_2$ [$(M+Na)^+$] 694.8722, found 694.8727; calcd. for $C_{19}H_{11}Br^{81}F_6NaO_{11}S_2$ [$(M+Na)^+$] 696.8703, found 696.8709. Anal. calcd. for $C_{19}H_{11}BrF_6O_{11}S_2$ (673.31): C, 33.89; H, 1.65; S, 9.52. Found: C, 34.38; H, 1.77; S, 10.37.

GP 11: General Procedure for double Suzuki reactions – synthesis of **36a-d**.

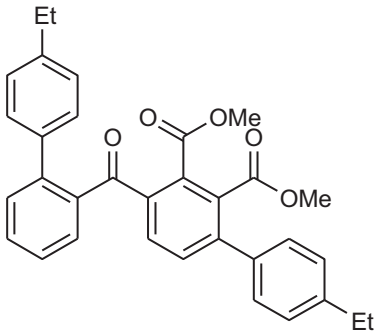
A 1,4-dioxane (5 mL/mmol **35a**) solution of the arylboronic acid (2.0 equiv), K_3PO_4 (3.0 equiv), 6mol% $Pd(PPh_3)_4$, and **35a** (1.0 equiv) was stirred at 90°C for 4 h under argon atmosphere. After cooling to 20 °C, the reaction mixture was poured into water. The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography.

Dimethyl 4'-methoxy-4-(4'-methoxybiphenylcarbonyl)biphenyl-2,3-dicarboxylate (36a).



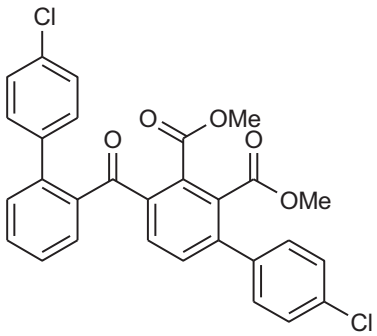
Starting with dimethyl 3-(trifluoromethylsulfonyloxy)-6-(2-(trifluoromethylsulfonyloxy) benzoyl) phthalate (**35a**) (0.382 g, 0.7 mmol), K_3PO_4 (0.408 g, 1.9 mmol), $Pd(PPh_3)_4$ (6mol%) and 4-methoxyphenylboronic acid (0.244 g, 1.6 mmol) in 1,4-dioxane (3 mL), the product **36a** was isolated as a yellow solid (0.195 g, 60%); mp = 59-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.74-7.68 (m, 14H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 52.7, 55.2, 55.3 (OCH_3), 113.7, 113.9, 126.8, 129.2, 130.3, 130.4, 130.5, 130.8 (Ar), 131.3 (C), 131.5 (Ar), 132.0, 132.2, 136.4, 137.3, 142.0, 143.2, 159.0, 159.6, 167.9, 168.1, 196.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948 (w), 2836 (w), 1726 (s), 1659 (m), 1607 (m), 1579 (m), 1514 (s), 1240 (s), 1177 (s), 829 (s), 762 (s). GC-MS (EI, 70 eV): *m/z* (%) = 510 (M^+, 100), 419 (43), 211 (31). HRMS (ESI): calcd. for $C_{31}H_{27}O_7$ [$(M+H)^+$] 511.1751, found 511.1757; calcd. for $C_{31}H_{26}NaO_7$ [$(M+Na)^+$] 533.1570, found 533.1582. Anal. calcd. for $C_{31}H_{26}O_7$ (510.53): C, 72.93; H, 5.13. Found: C, 72.78; H, 5.56.

Dimethyl 4'-ethyl-4-(4'-ethylbiphenylcarbonyl)biphenyl-2,3-dicarboxylate (10b).



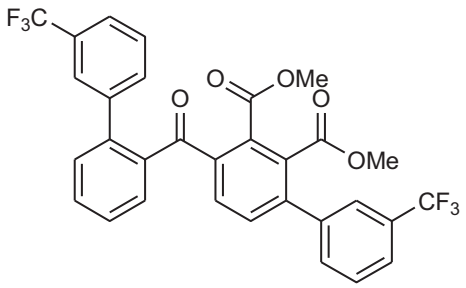
Starting with dimethyl 3-(trifluoromethylsulfonyloxy)-6-(2-(trifluoromethylsulfonyloxy) benzoyl) phthalate (**35a**) (0.356 g, 0.6 mmol), K_3PO_4 (0.382 g, 1.8 mmol), $Pd(PPh_3)_4$ (6mol%) and 4-ethylphenylboronic acid (0.224 g, 1.5 mmol) in 1,4-dioxane (3 mL), the product **36b** was isolated as a white solid (0.183 g, 60%); mp = 48-50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.30 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.61 (q, ^3J = 7.5 Hz, 2H, CH_2), 2.73 (q, ^3J = 7.5 Hz, 2H, CH_2), 3.64 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 7.09-7.74 (m, 15H, Ar + $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 15.5 (CH_3), 28.4, 28.5 (CH_2), 52.3, 52.7 (OCH_3), 126.9, 127.7, 127.9, 128.0, 129.2, 130.3, 130.4, 130.7, 131.4, 131.5 (Ar), 132.0, 132.6, 136.3, 136.5, 137.1, 137.4, 142.4, 143.5, 144.3, 167.9, 168.0, 196.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2871 (w), 1728 (s), 1661 (m), 1612 (w), 1585 (m), 1515 (w), 1232 (s), 1150 (s), 940 (s), 828 (s), 761 (s). GC-MS (EI, 70 eV): *m/z* (%) = 506 (M^+, 5), 474 (43), 443 (42), 442 (100), 424 (52), 414 (45), 413 (67), 207 (41). HRMS (ESI): calcd. for $C_{33}H_{31}O_5$ [$(M+H)^+$] 507.2166, found 507.2178; calcd. for $C_{31}H_{30}NaO_5$ [$(M+Na)^+$] 529.1985, found 529.1998. Anal. calcd. for $C_{33}H_{30}O_5$ (506.59): C, 78.24; H, 5.97. Found: C, 78.24; H, 6.16.

Dimethyl 4'-chloro-4-(4'-chlorobiphenylcarbonyl)biphenyl-2,3-dicarboxylate (36c).



Starting with dimethyl 3-(trifluoromethylsulfonyloxy)-6-(2-(trifluoromethylsulfonyloxy) benzoyl) phthalate (**35a**) (0.356 g, 0.6 mmol), K_3PO_4 (0.382 g, 1.8 mmol), $Pd(PPh_3)_4$ (6mol%) and 4-chlorophenylboronic acid (0.234 g, 1.5 mmol) in 1,4-dioxane (3 mL), the product **36c** was isolated as a yellow solid (0.218 g, 70%); mp = 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 7.10-7.65 (m, 15H, Ar + $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.6, 52.9 (OCH_3), 127.5, 128.2, 128.7, 129.3, 130.5, 130.6, 131.0, 131.3, 131.8 (Ar), 132.2, 132.3, 133.5, 134.5, 137.1, 137.3, 137.4, 138.3, 141.2, 142.4, 167.3, 167.5, 196.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 1938 (w), 1747 (s), 1722 (s), 1663 (m), 1583 (w), 1494 (w), 1253 (s), 1151 (s), 1086 (s), 828 (s), 785 (s), 674 (s). GC-MS (EI, 70 eV): *m/z* (%) = 520 (M^+, 39), 519 (M^+, 24), 518 (M^+, 59), 429 (65), 428 (26), 427 (100), 333 (24), 332 (11), 331 (73), 215 (62), 152 (51). HRMS (ESI): calcd. for $C_{29}H_{20}Cl_2NaO_5$ [$(M+Na)^+$] 541.0580, found 541.0578; calcd. for $C_{29}H_{20}Cl_2NaO_5$ [$(M+Na)^+$] 543.0558, found 543.0569. Anal. calcd. for $C_{29}H_{20}Cl_2O_5$ (519.37): C, 67.06; H, 3.88. Found: C, 66.96; H, 3.88.

Dimethyl 3'-(trifluoromethyl)-4-(3'-(trifluoromethyl)biphenylcarbonyl)biphenyl-2,3-dicarboxylate (36d).

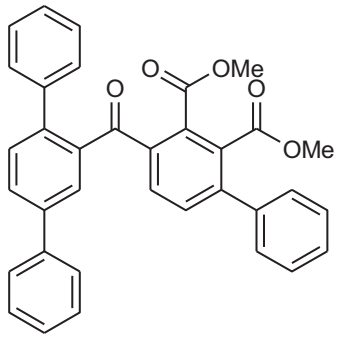


Starting with dimethyl 3-(trifluoromethylsulfonyloxy)-6-(2-(trifluoromethylsulfonyloxy) benzoyl) phthalate (**35a**) (0.356 g, 0.6 mmol), K_3PO_4 (0.382 g, 1.8 mmol), $Pd(PPh_3)_4$ (6mol%) and 3-**(**trifluoromethyl)phenylboronic acid (0.284 g, 1.5 mmol) in 1,4-dioxane (3 mL), the product **36d** was isolated as a yellow oil (0.137 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 7.29-7.82 (m, 16H, Ar + $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 52.8 (OCH_3), 124.1, 124.8, 125.0, 125.7 (q, J_{C-F} = 3.9 Hz, CH), 127.9, 128.7, 129.0 (Ar), 129.5, 130.1, 130.6, 137 (C), 130.8, 131.1, 131.2, 131.4, 132.0 (Ar), 132.3, 132.5 (C), 132.8 (Ar), 137.0, 137.8, 139.5, 140.7, 141.0, 141.9, 167.1, 167.3, 196.0 (C). ^{19}F NMR (235 MHz, $CDCl_3$): δ = -62.3, -62.2 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3011 (w), 2957 (w), 1726 (s), 1661 (m), 1592 (w), 1428 (w), 1406 (w), 1333 (s), 1239 (s), 1116 (s), 1067 (s), 808 (s), 767 (s), 695 (s). GC-MS (EI, 70 eV): *m/z* (%) = 586 (M^+, 27), 495 (61), 365 (100), 249 (71), 201 (35). HRMS (ESI): calcd. for $C_{31}H_{20}F_6NaO_5$ [$(M+Na)^+$] 609.1107, found 609.1100. Anal. calcd. for $C_{31}H_{20}F_6O_5$ (586.48): C, 63.40; H, 3.44. Found: C, 63.46; H, 3.57.

GP 12: General Procedure for triple Suzuki reactions – synthesis of **37**

A 1,4-dioxane (5 mL/mmol **35b**) solution of the arylboronic acid (4.0 equiv), KF (4.5 equiv), 6mol% $Pd(PPh_3)_4$, and **35b** (1.0 equiv) was stirred at 90°C for 4 h under argon atmosphere. After cooling to 20 °C, the reaction mixture was poured into water. The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography.

Dimethyl 4-(4-phenylbiphenylcarbonyl)biphenyl-2,3-dicarboxylate (37).



Starting with **35b** (0.336 g, 0.5 mmol), KF (0.130 g, 2.2 mmol), $Pd(PPh_3)_4$ (6mol%) and phenylboronic acid (0.243 g, 2.0 mmol) in 1,4-dioxane (2.5 mL), the product **37** was isolated as a yellow solid (0.130 g, 50%); mp = 155-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 7.10-7.83 (m, 23H, Ar + $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 52.8 (OCH_3), 127.0, 124.4, 127.9, 128.2, 128.3, 128.4, 128.8, 129.0, 129.2 (Ar), 130.0, 130.9, 131.1, 131.6, 132.8, 136.6, 137.8, 139.0, 139.4, 140.1, 141.2, 143.7, 167.8, 196.6 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050 (w), 3028 (w), 2996 (w), 2948 (w), 2855 (w), 1739 (s), 1723 (s), 1588 (w), 1473 (w), 1232 (s), 1150 (s), 754 (s), 692 (s). GC-MS (EI, 70 eV): *m/z* (%) = 526 (M^+, 88), 525 (39), 436 (42), 435 (100), 297 (45), 257 (44), 228 (33). HRMS (ESI): calcd. for $C_{35}H_{26}NaO_5$ [$(M+Na)^+$] 549.1672, found 549.1670. Anal. calcd. for $C_{35}H_{26}O_5$ (526.58): C, 79.83; H, 4.98. Found: C, 79.90; H, 4.91.

Supplement 2

Crystallographic data

Crystal data and structure refinement for **9z**

Identification code	ks1007t	
Empirical formula	$C_{12}H_{13}Cl_3O_4$	
Formula weight	327.57	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 8.5809(5) Å	α = 115.336(5)°
	b = 9.3838(6) Å	β = 105.449(5)°
	c = 10.1271(6) Å	γ = 94.711(5)°
Volume	692.15(7) $Å^3$	
Z	2	
Calculated density	1.572 mg/m^3	
Absorption coefficient	0.668 mm^{-1}	
F(000)	336	
Crystal size	0.38 x 0.38 x 0.30 mm	
Θ range for data collection	2.36 to 27.91°	
Limiting indices	-11<=h<=11, -12<=k<=12, -13<=l<=13	
Reflections collected / unique	11891 / 3306 [R(int) = 0.0248]	
Completeness to Θ = 27.91°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3306 / 0 / 179	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0240, wR2 = 0.0624	
R indices (all data)	R1 = 0.0322, wR2 = 0.0639	
Largest diff. peak and hole	0.326 and -0.247 e. A^{-3}	

Crystal data and structure refinement for **9ac**

Identification code	ks1009	
Empirical formula	$C_{10}H_9Cl_3O_4$	
Formula weight	299.52	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 7.6005(3) Å	α = 90°
	b = 19.7289(6) Å	β = 97.652(3)°
	c = 7.9532(3) Å	γ = 90°
Volume	1181.96(7) $Å^3$	
Z	4	
Calculated density	1.683 mg/m^3	
Absorption coefficient	0.773 mm^{-1}	
F(000)	608	
Crystal size	0.45 x 0.40 x 0.03 mm	
Θ range for data collection	2.06 to 27.93°	
Limiting indices	-9<=h<=9, -26<=k<=25, -10<=l<=10	
Reflections collected / unique	19990 / 2821 [R(int) = 0.0336]	
Completeness to Θ = 27.93°	99.8 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9888 and 0.6905	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2821 / 0 / 160	
Goodness-of-fit on F^2	0.923	
Final R indices [I>2sigma(I)]	R1 = 0.0236, wR2 = 0.0550	
R indices (all data)	R1 = 0.0331, wR2 = 0.0567	
Largest diff. peak and hole	0.341 and -0.190 e. $Å^{-3}$	

Crystal data and structure refinement for **10aj**

Identification code	is_ld105	
Empirical formula	$C_{10}H_9F_3O_3S$	
Formula weight	266.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P21/n	
Unit cell dimensions	a = 7.1074(2) Å	α = 90°
	b = 11.7647(4) Å	β = 97.112(2)°
	c = 26.2080(7) Å	γ = 90°
Volume	2174.56(11) $Å^3$	
Z	8	
Calculated density	1.626 mg/m^3	
Absorption coefficient	0.333 mm^{-1}	
F(000)	1088	
Crystal size	0.76 x 0.17 x 0.11 mm	
Θ range for data collection	2.33 to 29.99°	
Limiting indices	-9≤h≤9, -16≤k≤14, -36≤l≤35	
Reflections collected / unique	24815 / 6293 [R(Int) = 0.0366]	
Completeness to Θ = 29.99°	99.3 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9643 and 0.7860	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6293 / 0 / 375	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2σ(I)]	R1 = 0.0443, wR2 = 0.1103	
R indices (all data)	R1 = 0.0712, wR2 = 0.1201	
Largest diff. peak and hole	0.324 and -0.368 e. $Å^{-3}$	

Crystal data and structure refinement for **10aq**

Identification code	is_ld76b	
Empirical formula	$C_{15}H_{11}F_3O_2S$	
Formula weight	312.30	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P21	
Unit cell dimensions	a = 8.9606(3) Å	α = 90°
	b = 8.1807(2) Å	β = 114.197(2)°
	c = 10.6159(3) Å	γ = 90°
Volume	709.82(4) $Å^3$	
Z	2	
Calculated density	1.461 mg/m^3	
Absorption coefficient	0.262 mm^{-1}	
F(000)	320	
Crystal size	0.66 x 0.30 x 0.26 mm	
Θ range for data collection	2.49 to 31.06°	
Limiting indices	-12≤h≤9, -11≤k≤11, -11≤l≤15	
Reflections collected / unique	8690 / 4329 [R(Int) = 0.0145]	
Completeness to Θ = 31.06°	99.6 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9349 and 0.8459	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4329 / 1 / 195	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2σ(I)]	R1 = 0.0401, wR2 = 0.1111	
R indices (all data)	R1 = 0.0418, wR2 = 0.1126	
Largest diff. peak and hole	0.564 and -0.326 e. $Å^{-3}$	

Crystal data and structure refinement for **11a**

Identification code	ks837	
Empirical formula	$C_9H_7F_3O_4$	
Formula weight	236.15	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 12.5362(7) Å	α = 90°
	b = 4.65657(16) Å	β = 94.503(4)°
	c = 16.8665(9) Å	γ = 90°
Volume	981.55(8) $Å^3$	
Z	4	
Calculated density	1.598 mg/m^3	
Absorption coefficient	0.160 mm^{-1}	
F(000)	480	
Crystal size	0.50 x 0.25 x 0.17 mm	
θ range for data collection	2.42 to 27.50°.	
Limiting indices	$-16\leq h\leq 16$, $-5\leq k\leq 6$, $-21\leq l\leq 21$	
Reflections collected / unique	14702 / 2245 [R(int) = 0.0311]	
Completeness to θ = 27.50	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9239 and 0.7999	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2245 / 0 / 145	
Goodness-of-fit on F^2	0.989	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0294, wR2 = 0.0717	
R indices (all data)	R1 = 0.0448, wR2 = 0.0745	
Largest diff. peak and hole	0.208 and -0.183 e. $Å^{-3}$	

Crystal data and structure refinement for **12i**

Identification code	ks902m	
Empirical formula	$C_{11}H_{13}F_3O_5$	
Formula weight	282.21	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, C2/c	
Unit cell dimensions	a = 16.8907(13) Å	α = 90°
	b = 9.8633(6) Å	β = 98.844(6)°
	c = 14.5585(11) Å	γ = 90°.
Volume	2396.6(3) $Å^3$	
Z	8	
Calculated density	1.564 mg/m^3	
Absorption coefficient	0.151 mm^{-1}	
F(000)	1168	
Crystal size	0.45 x 0.45 x 0.20 mm	
Θ range for data collection	2.40 to 28.00°	
Limiting indices	-22<=h<=22, -13<=k<=13, -19<=l<=19	
Reflections collected / unique	20174 / 2899 [R(int) = 0.0369]	
Completeness to Θ = 28.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2899 / 0 / 180	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0875	
R indices (all data)	R1 = 0.0462, wR2 = 0.0912	
Extinction coefficient	0.0047(6)	
Largest diff. peak and hole	0.235 and -0.208 e. $Å^{-3}$	

Crystal data and structure refinement for **13r**

Identification code	ks1027	
Empirical formula	$C_{10}H_{11}F_3O_4S$	
Formula weight	284.25	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 7.7539(3) Å	α = 90°
	b = 17.4533(7) Å	β = 102.291(3)°
	c = 8.6744(3) Å	γ= 90°
Volume	1147.01(8) $Å^3$	
Z	4	
Calculated density	1.646 mg/m^3	
Absorption coefficient	0.327 mm^{-1}	
F(000)	584	
Crystal size	0.45 x 0.40 x 0.15 mm	
Θ range for data collection	2.33 to 28.00°	
Limiting indices	-10<=h<=10, -22<=k<=22, -11<=l<=10	
Reflections collected / unique	19752 / 2769 [R(int) = 0.0250]	
Completeness to Θ = 28.00°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9611 and 0.8544	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2769 / 0 / 169	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0722	
R indices (all data)	R1 = 0.0355, wR2 = 0.0742	
Largest diff. peak and hole	0.411 and -0.260 e. $Å^{-3}$	

Crystal data and structure refinement for **12v**

Identification code	is_ld117	
Empirical formula	$C_{11}H_{13}F_3O_4S$	
Formula weight	298.27	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, C2/c	
Unit cell dimensions	a = 17.1795(6) Å	α = 90°.
	b = 10.0815(3) Å	β = 98.235(2)°.
	c = 14.9817(5) Å	γ = 90°.
Volume	2568.00(15) $Å^3$	
Z	8	
Calculated density)	1.543 mg/m^3	
Absorption coefficient	0.296 mm^{-1}	
F(000)	1232	
Crystal size	0.40 x 0.33 x 0.32 mm	
Θ range for data collection	2.35 to 30.00°	
Limiting indices	-24≤h≤19, -14≤k≤14, -21≤l≤21	
Reflections collected / unique	14469 / 3736 [R(int) = 0.0184]	
Completeness to Θ = 30.00°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9111 and 0.8907	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3736 / 0 / 179	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2σ(I)]	R1 = 0.0306, wR2 = 0.0885	
R indices (all data)	R1 = 0.0361, wR2 = 0.0916	
Largest diff. peak and hole	0.466 and -0.226 e. $Å^{-3}$	

Crystal data and structure refinement for **20b**

Identification code	ks1097t	
Empirical formula	$C_{10}H_9F_6NO_4$	
Formula weight	321.18	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Tetragonal, P4(2)/n	
Unit cell dimensions	a = 18.858(3) Å	α = 90°
	b = 18.858(3) Å	β = 90°
	c = 7.5275(15) Å	γ = 90°
Volume	2677.0(8) $Å^3$	
Z	8	
Calculated density	1.594 mg/m^3	
Absorption coefficient	0.173 mm^{-1}	
F(000)	1296	
Crystal size	0.50 x 0.40 x 0.34 mm	
Θ range for data collection	2.16 to 27.50°.	
Limiting indices	-24<=h<=24, -24<=k<=24, -9<=l<=9	
Reflections collected / unique	42937 / 3077 [R(int) = 0.0308]	
Completeness to Θ = 27.50°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3077 / 33 / 227	
Goodness-of-fit on F^2	1.112	
Final R indices [I>2sigma(I)]	R1 = 0.0632, wR2 = 0.1913	
R indices (all data)	R1 = 0.0783, wR2 = 0.1993	
Largest diff. peak and hole	0.554 and -0.513 e. $Å^{-3}$	

Crystal data and structure refinement for **22a**

Identification code	ks1048	
Empirical formula	$C_{11}H_8F_9N_3O_3$	
Formula weight	401.20	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/c	
Unit cell dimensions	a = 20.5341(7) Å	α = 90°
	b = 8.39476(18) Å	β = 103.639(3)°
	c = 17.3957(6) Å	γ = 90°
Volume	2914.09(15) $Å^3$	
Z	8	
Calculated density	1.829 mg/m^3	
Absorption coefficient	0.206 $mm^{-}1$	
F(000)	1600	
Crystal size	0.40 x 0.40 x 0.15 mm	
Θ range for data collection	2.04 to 26.00°	
Limiting indices	-25<=h<=25, -10<=k<=10, -20<=l<=21	
Reflections collected / unique	39943 / 5728 [R(int) = 0.0310]	
Completeness to Θ = 26.00°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9751 and 0.8955	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5728 / 66 / 543	
Goodness-of-fit on F^2	0.881	
Final R indices [I>2sigma(I)]	R1 = 0.0266, wR2 = 0.0585	
R indices (all data)	R1 = 0.0440, wR2 = 0.0613	
Largest diff. peak and hole	0.269 and -0.178 e. $Å^{-3}$	

Crystal data and structure refinement for **22d**

Identification code	ks1072	
Empirical formula	$C_{14}H_{13}ClF_9N_3O_3$	
Formula weight	477.72	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/n	
Unit cell dimensions	a = 10.2723(3) Å	α = 90°
	b = 10.5001(4) Å	β = 101.059(2)°
	c = 17.7270(5) Å	γ = 90°
Volume	1876.53(10) $Å^3$	
Z	4	
Calculated density	1.691 Mg/m^3	
Absorption coefficient	0.313 mm^{-1}	
F(000)	960	
Crystal size	0.45 x 0.40 x 0.35 mm	
Θ range for data collection	2.13 to 29.24°	
Limiting indices	-14<=h<=14, -14<=k<=14, -24<=l<=23	
Reflections collected / unique	35131 / 5072 [R(int) = 0.0279]	
Completeness to Θ = 29.24°	99.3 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9497 and 0.8651	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5072 / 124 / 337	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.1189	
R indices (all data)	R1 = 0.0614, wR2 = 0.1254	
Largest diff. peak and hole	0.454 and -0.494 e. $Å^{-3}$	

Crystal data and structure refinement for **23a**

Identification code	ks1080	
Empirical formula	$C_{11}H_9F_9N_2O_5$	
Formula weight	420.20	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, Fdd2	
Unit cell dimensions	a = 14.206(3) Å	α = 90°
	b = 33.868(7) Å	β = 90°
	c = 13.014(3) Å	γ = 90°
Volume	6261(2) $Å^3$	
Z	16	
Calculated density	1.783 mg/m^3	
Absorption coefficient	0.204 mm^{-1}	
F(000)	3360	
Crystal size	0.50 x 0.47 x 0.33 mm	
Θ range for data collection	2.21 to 27.94°	
Limiting indices	-18<=h<=18, -44<=k<=44, -17<=l<=17	
Reflections collected / unique	26143 / 3749 [R(int) = 0.0307]	
Completeness to Θ = 27.94°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3749 / 1 / 253	
Goodness-of-fit on F^2	0.892	
Final R indices [I>2sigma(I)]	R1 = 0.0285, wR2 = 0.0652	
R indices (all data)	R1 = 0.0396, wR2 = 0.0674	
Absolute structure parameter	0.2(5)	
Largest diff. peak and hole	0.225 and -0.198 e. $Å^{-3}$	

Crystal data and structure refinement for **31b**

Identification code	ks1145t	
Empirical formula	$C_{18}H_{18}O_8$	
Formula weight	362.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 8.2989(6) Å	α = 86.560(5)°
	b = 10.1312(7) Å	β = 83.809(5)°
	c = 10.4773(7) Å	γ = 70.127(5)°
Volume	823.36(10) A^3	
Z	2	
Calculated density	1.461 mg/m^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	380	
Crystal size	0.50 x 0.30 x 0.25 mm	
Θ range for data collection	1.96 to 27.91°	
Limiting indices	-10<=h<=10, -13<=k<=13, -13<=l<=13	
Reflections collected / unique	13589 / 3926 [R(int) = 0.0249]	
Completeness to Θ = 27.91°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3926 / 0 / 245	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0938	
R indices (all data)	R1 = 0.0497, wR2 = 0.0971	
Largest diff. peak and hole	0.335 and -0.249 e. A^{-3}	

Crystal data and structure refinement for **31c**

Identification code	ks1189	
Empirical formula	$C_{23}H_{20}O_8$	
Formula weight	424.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 7.9176(4) Å	α = 89.052(5)°
	b = 11.1261(6) Å	β = 80.895(4)°
	c = 11.5814(7) Å	γ = 77.206(4)°
Volume	982.18(9) $Å^3$	
Z	2	
Calculated density	1.435 mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	444	
Crystal size	0.45 x 0.35 x 0.16 mm	
Θ range for data collection	1.78 to 27.50°	
Limiting indices	-10<=h<=10, -14<=k<=14, -15<=l<=15	
Reflections collected / unique	16353 / 4524 [R(int) = 0.0296]	
Completeness to Θ = 27.50°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9731 and 0.8339	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4524 / 0 / 289	
Goodness-of-fit on F^2	0.850	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0741	
R indices (all data)	R1 = 0.0527, wR2 = 0.0773	
Largest diff. peak and hole	0.295 and -0.180 e. $Å^{-3}$	

Crystal data and structure refinement for **32**

Identification code	ks1140	
Empirical formula	$C_{17}H_{16}Cl_2O_6$	
Formula weight	387.20	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, C 2/c	
Unit cell dimensions	a = 27.4384(10) Å	α = 90°
	b = 5.6289(2) Å	β = 112.241(3)°
	c = 22.7063(8) Å	γ = 90°
Volume	3246.0(2) A^3	
Z	8	
Calculated density	1.585 mg/m^3	
Absorption coefficient	0.433 mm^{-1}	
F(000)	1600	
Crystal size	0.50 x 0.45 x 0.30 mm	
Θ range for data collection	1.60 to 27.93°	
Limiting indices	-36<=h<=36, -7<=k<=7, -29<=l<=29	
Reflections collected / unique	25744 / 3889 [R(int) = 0.0245]	
Completeness to Θ = 27.93°	99.5 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9389 and 0.7898	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3889 / 0 / 232	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2sigma(I)]	R1 = 0.0264, wR2 = 0.0702	
R indices (all data)	R1 = 0.0339, wR2 = 0.0719	
Largest diff. peak and hole	0.395 and -0.176 e. $Å^{-3}$	

Crystal data and structure refinement for **33i**

Identification code	ks1189	
Empirical formula	$C_{23}H_{20}O_8$	
Formula weight	424.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 7.9176(4) Å	α = 89.052(5)°
	b = 11.1261(6) Å	β = 80.895(4)°
	c = 11.5814(7) Å	γ = 77.206(4)°
Volume	982.18(9) $Å^3$	
Z	2	
Calculated density	1.435 mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	444	
Crystal size	0.45 x 0.35 x 0.16 mm	
Θ range for data collection	1.78 to 27.50°	
Limiting indices	-10<=h<=10, -14<=k<=14, -15<=l<=15	
Reflections collected / unique	16353 / 4524 [R(int) = 0.0296]	
Completeness to Θ = 27.50°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9731 and 0.8339	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4524 / 0 / 289	
Goodness-of-fit on F^2	0.850	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0741	
R indices (all data)	R1 = 0.0527, wR2 = 0.0773	
Largest diff. peak and hole	0.295 and -0.180 e. $Å^{-3}$	

Crystal data and structure refinement for **33j**

Identification code	ks1245	
Empirical formula	$C_{20}H_{19}ClO_7$	
Formula weight	406.80	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/n	
Unit cell dimensions	a = 9.7224(3) Å	α = 90°
	b = 8.1879(2) Å	β = 95.519(3)°
	c = 23.1457(8) Å	γ = 90°
Volume	1834.00(10) A^3	
Z	4	
Calculated density	1.473 mg/m^3	
Absorption coefficient	0.250 mm^{-1}	
F(000)	848	
Crystal size	0.30 x 0.25 x 0.22 mm	
Θ range for data collection	1.77 to 27.91°	
Limiting indices	-12<=h<=12, -10<=k<=10, -30<=l<=30	
Reflections collected / unique	30879 / 4380 [R(int) = 0.0336]	
Completeness to Θ = 27.91°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9655 and 0.8322	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4380 / 0 / 263	
Goodness-of-fit on F^2	0.968	
Final R indices [I>2sigma(I)]	R1 = 0.0303, wR2 = 0.0720	
R indices (all data)	R1 = 0.0446, wR2 = 0.0743	
Largest diff. peak and hole	0.272 and -0.373 e. $Å^{-3}$	

Crystal data and structure refinement for **33p**

Identification code	ks1279	
Empirical formula	$C_{33}H_{45}BrO_7$	
Formula weight	633.60	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 9.0595(4) Å	α = 73.732(3)°
	b = 11.5721(5) Å	β = 84.917(3)°
	c = 15.5179(6) Å	γ = 87.568(3)°
Volume	1555.32(11) $Å^3$	
Z	2	
Calculated density	1.353 mg/m^3	
Absorption coefficient	1.368 mm^{-1}	
F(000)	668	
Crystal size	0.50 x 0.35 x 0.15 mm	
Θ range for data collection	1.96 to 29.22°	
Limiting indices	-12<=h<=12, -15<=k<=15, -21<=l<=21	
Reflections collected / unique	29997 / 8406 [R(int) = 0.0537]	
Completeness to Θ = 29.22°	99.5 %	
Absorption correction	Numerical	
Max. and min. transmission	0.8415 and 0.5578	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8406 / 0 / 381	
Goodness-of-fit on F^2	0.874	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0633	
R indices (all data)	R1 = 0.0580, wR2 = 0.0669	
Largest diff. peak and hole	0.568 and -0.437 e. A^{-3}	

Crystal data and structure refinement for **34a**

Identification code	ks971	
Empirical formula	$C_{16}H_{13}F_3O_5S$	
Formula weight	374.32	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P2/n	
Unit cell dimensions	a = 11.8379(4) Å	α = 90°
	b = 12.0659(3) Å	β = 114.905(3)°
	c = 12.0697(4) Å	γ = 90°
Volume	1563.66(8) A^3	
Z	4	
Calculated density	1.590 mg/m^3	
Absorption coefficient	0.266 mm^{-1}	
F(000)	768	
Crystal size	0.5 x 0.5 x 0.2 mm	
Θ range for data collection	1.69 to 29.20°	
Limiting indices	-16<=h<=16, -16<=k<=16, -16<=l<=16	
Reflections collected / unique	29451 / 4224 [R(int) = 0.0226]	
Completeness to Θ = 29.20°	99.3 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9511 and 0.8689	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4224 / 0 / 231	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0292, wR2 = 0.0771	
R indices (all data)	R1 = 0.0375, wR2 = 0.0793	
Largest diff. peak and hole	0.374 and -0.216 e. $Å^{-3}$	

Supplement 3

List of abbreviations

Ar	Aromatic
Anal	Elemental Analysis
ATR	Attenuated Total Reflection
n-BuLi	*n*-Butyllithium
d	Day
DCM/CH_2Cl_2	Dichloromethane
DMF	Dimethylformamide
DEPT	Distortionless Enhancement by Polarisation Transfer
DiPA	Diisoproylamin
ε	Extinction coefficient
E	Extinction
EI	Electron Ionization
ESI	Electrospray Ionization
Et_2O	Diethyl ether
EU	European Union
GC	Gas Chromatography
h	Hour
HRMS	High Resolution Mass Spectroscopy
HOMO	Highest Occupied Molecule Orbital
Hz	Hertz
IR	Infrared Spectroscopy
J	Coupling constant
LDA	Lithium Diisopropylamide
LUMO	Lowes Unoccupied Molecule Orbital
λ	Wavelength
MS	Mass Spectrometry
Me_3SiOTf	Trimethylsilyl trifluoro methanesulfonate
Me_3SiCl	Trimethylsilyl chloride
mp	Melting Point
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
O-H···O	Hydrogen bond
PABA	*para*-Aminobenzoic Acid

Ph	Phenyl
p-TsOH / PTSA	*para*-Toluenesulfonic Acid
R	Alkyl rest
R^F	Perfuorinated
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic Acid
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
UV	Ultraviolet

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Curriculum vitae and list of publications

Angaben zur Person

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Adresse	Bei der Tweel 8, 18059 Rostock
Staatsangehörigkeit	Deutsch, Rumänisch
Geburtsdatum, Ort	06.07.1983, Bukarest, Rumänien
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Familienstand	ledig, keine Kinder

Schul- und Berufsbildung

Datum	seit Oktober 2008
Tätigkeit	**Promotion im Bereich der organischen Chemie**
Thema	“Bis-silyl-enol ethers as convenient building blocks for the design and synthesis of Salicylates, Pyrones, Cyclohexenones, Pyridones and Benzophenones.”
Bildungseinrichtung	Leibniz Institut für Katalyse e.V. an der Universität Rostock

Datum	von April 2003 bis September 2008
Tätigkeit	**Studentin**
Abschluss	Diplom-Chemikerin
Thema	“Synthesis of 6−trifluoromethyl−salicylates and 6−trifluoromethyl−4H−pyran−4−ones based on formal [3+3] cyclizations of 1,3−bis(trimethylsilyloxy)−1,3−butadienes.”
Bildungseinrichtung	Universität Rostock, Fachbereich Chemie

Datum	von Oktober 2002 bis März 2003
Tätigkeit	**Studentin**
Bildungseinrichtung	„Politehnica“ Universität Bukarest, Rumänien, Fachbereich Chemie

Datum	von September 1998 bis September 2002
Tätigkeit	**Schülerin**
Abschluss	Abitur / Bacalaureat
Bildungseinrichtung	“Sfantul Sava” Gymnasium Bukarest, Rumänien

Articles in journals

1. Viktor O. Iaroshenko,* Alina Bunescu, Anke Spannenberg, and Peter Langer*, *Chem. Eur. J.* **2011**, 17, 7188.

2. Viktor O. Iaroshenko,* Alina Bunescu, Lutz Domke, Anke Spannenberg, Dmitri V. Sevenard, Alexander Villinger, Vyacheslav Y. Sosnovskikh, Peter Langer*, *J. Fluor. Chem.* **2011**, 132, 7, 441.

3. Viktor O. Iaroshenko,* Alina Bunescu, Anke Spannenberg, Peter Langer*, *Org. Biomol. Chem.*, **2011**, 9 (21), 7554.

4. Viktor O. Iaroshenko,* Friedrich Erben, Satenik Mkrtchyan, Ani Hakobyan, Marcelo Vilches-Herrera, Sergii Dudkin, Alina Bunescu, Alexander Villinger, Vyacheslav Ya Sosnovskikh and Peter Langer*, *Tetrahedron*, **2011**, DOI:10.1016/j.tet.2011.08.030, in print.

5. Alina Bunescu, Sebastian Reimann, Mathias Lubbe, Anke Spannenberg, Peter Langer*, *J. Org. Chem.* **2009**, 74, 5002.

6. Mathias Lubbe, Alina Bunescu, Alexander Villinger, Peter Langer*, *Synlett* **2008**, 1862.

7. Sebastian Reimann, Alina Bunescu, Robert Ludwig, Silke Erfle, Lutz Domke, Franziska Bendrath, Alexander Villinger, Peter Langer*, *J. Fluor. Chem*, submitted.

8. Stefan Büttner, Alina Bunescu, T. H. Tam Dang, Thomas Pundt, Renske Klassen, Andreas Schmidt, Alexander Villinger, Peter Langer*, *Synthesis*, submitted.

Poster contributions to academic conferences

1. S. Reimann, L.R. Knopke, A. Bunescu, U. Bentrup, O. Kuhn, P.Langer, - “Influence of Lewis acids on the product diversity in [3+3] cyclocondensation reactions” - 2nd Interdisciplinary Scientific Seminar, 25th March 2010 Rostock-Warnemünde, Germany.

2. Mathias Lubbe, Alina Bunescu, Muhammad Sher, Peter Langer, - “First cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one” – Orchem, 30th August – 2th September 2008, Weimar, Germany.