Synthesis of Bridged and Non-Bridged *N*-Heterocycles, Dichloromethyl- and Formyl-Salicylates, Pyran-4-ones, Chromanes and Isochromanes based on Cyclocondensation Reactions of 1,3-Bis(silyloxy)-1,3-butadienes and Oxime Dianions

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Vahuni Karapetyan

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General introduction

Creation is wonderful. We admire Nature's work first – from simple things such as the hoar frost that settled overnight on the red maples, to the most intricate creation, repeated thousands of times each day, a human infant brought to term and born. We admire human creation second – The Beatles and Bob Dylan, heroes from the sixties whose music and lyrics changed a whole generation. In the twenties Pablo Picasso and Paul Klee were among the artists who changed our conception of art. Chemists make molecules, and synthesis is a remarkable activity at the heart of chemistry, this puts chemistry close to art. We create molecules, study their properties, form theories about why they are stable, and try to discover how they react. But at our heart is the molecule that is made, either by a natural process or by a human being.

Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. It is the science of molecules. But organic chemistry is something more. It literally creates itself as it grows. Of course we need to study the molecules of nature both because they are interesting in their own right and because their functions are important to our lives. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. This creation of new molecules has given us new materials such as plastics, new dyes to colour our clothes, new perfumes to wear, new drugs to cure diseases.

Organic synthesis continues to play an important role in the design and development of new pharmaceuticals and advanced materials.[1] For example, since the discovery of penicillin, a large number of new bioactive compounds have been isolated from natural products and characterized.[2] For instance, astemisinin, a sesquiterpene with endoperoxide moiety, was isolated from *Astemisia annua*, a Chinese medicinal plant, which has been used in China for centuries for treatment of malaria. Natural products also provide a great help in drugs research and development. They are an integral part of important drugs, such as anidulafungin, galanthamine, erythromycin, bleomycin, paclitaxel (Taxol^{TM}), vancomycin, etc.[2,3] All these pharmacologically and biologically important compounds were not available in bulk quantities in nature. Nowadays many of them are synthetically available.[2,4]

More than 20 million chemical compounds are currently registered, about one half contain heterocyclic systems. Heterocycles are important, not only because of their abundance, but above all because of their chemical, biological and technical significance. Heterocycles are present in many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well

as pharmaceuticals, herbicides, dyes, and other products of technical importance (advanced materials, drugs, corrosion inhibitors, sensitizers, stabilizing agents, etc.).[4,5]

The synthesis of new antimicrobial agents represents an important field in medicinal chemistry, due to the increasing problem of the formation of resistant strains of bacterial pathogens. Thus, the development of new synthetic methodologies is especially important in modern organic chemistry.[5] Therefore, our studies are focused on the development of new and reliable synthetic strategies and their application to the preparation of functionalized carba- and heterocycles.[6]

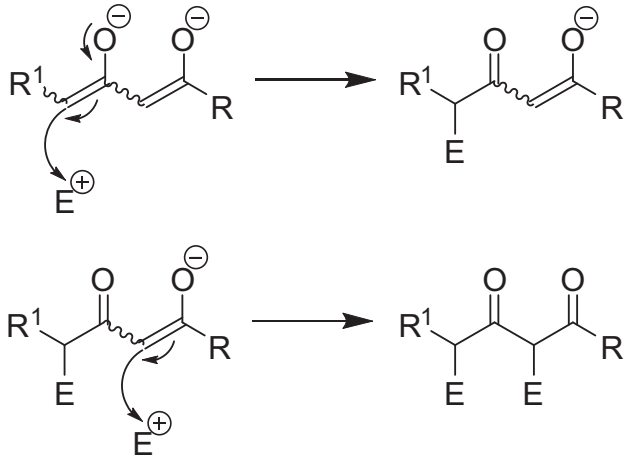
In the present thesis, the synthesis of natural product analogues is studied. These structures include various bridged and non-bridged *N*-heterocycles, 1-aminopyrroles, 1-aminoindoles, functionalized salicylates, pyran-4-ones, dihydrobenzopyranes and halomethyloxazines.

1. 1,3-Bis(silyloxy)-1,3-butadienes as powerful building blocks

1.1 Regioselectivity for reactions of 1,3-bis(silyloxy)-1,3-butadienes

One-pot cyclizations and domino reactions provide a versatile tool for the assembly of complex molecules from simple starting materials.[7,8] Dicarbonyl dianions represent important building blocks for the regioselective formation of carbon-carbon bonds.[9,10] 1,3-Dicarbonyl dianions are organic substrates containing two delocalized negative charges. They can be generated for example by the reaction of 1,3-dicarbonyl compounds in the presence of a strong base, such as LDA or *n*BuLi.[10]

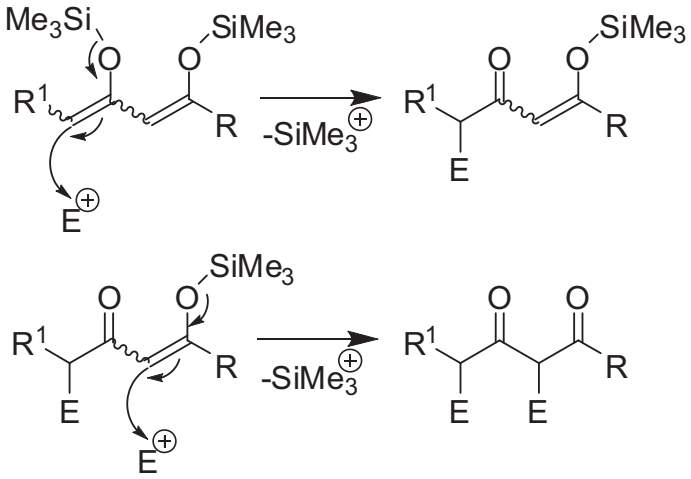
The regioselectivities observed for reactions of dicarbonyl monoanions and dicarbonyl dianions generally differ greatly. For example, the use of 1,3-dicarbonyl dianions allows the functionalization of the terminal rather than the central carbon atom of the substrate.[11] The terminal carbon atom of the dianion can be regioselectively coupled with one equivalent of an electrophile E^+ to give a dicarbonyl monoanion which can be subsequently trapped by addition of a second electrophile (**Scheme 1-1**).



Scheme 1-1. Regioselectivity of 1,3-dikarbonyl di- and mono-anions.

Due to their high basicity and reactivity, reactions of dianions can suffer from many side-reactions such as polymerisation, decomposition, deprotonation, formation of open-chained products, elimination, or SET-processes (SET = single electron transfer). To overcome these limitations, Lewis acid mediated reactions of electroneutral dianion equivalents (masked dianions) have been developed.[11] Many studies proved that 1,3-bis(silyloxy)-1,3-butadienes

can be considered as electroneutral equivalents of the corresponding 1,3-dicarbonyl dianions.[12] The regioselectivity observed for reactions of free and masked dianions is the same in many cases (**Scheme 1-2**).



Scheme 1-2. Regioselectivity of 1,3-bis(silyloxy)-1,3-butadienes as a masked dianions

The chemistry of bis-silyl enol ethers has been developed during the last three decades.[12] During the last years the Lewis acid mediated addition and cyclization reactions of 1,3-bis(silyl enol ethers) have been widely investigated by Prof. Dr. Peter Langer's research group.[11] It is, for example, known that silyl enol ethers can react with various electrophiles in the presence of Lewis acids.[8] These Lewis acid mediated reactions [13] (e. g. alkylation and aldol condensation) provide useful alternatives to classical enolate chemistry. In cyclization reactions, 1,3-bis(silyl enol ethers) (Chan's diene **A**) can react as 1,3-dinucleophiles or, similar to the well-known Danishefsky's diene (**B**) [14], as functionalized butadienes (**Figure 1-1**). 1,3-Bis(silyloxy)-1,3-butadienes undergo reactions with electrophiles at the terminal carbon atom followed by reaction of the central carbon or the oxygen atom.

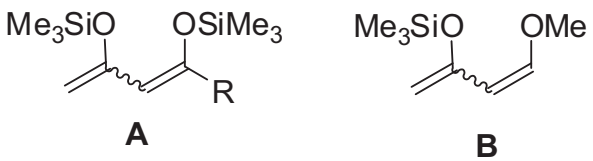
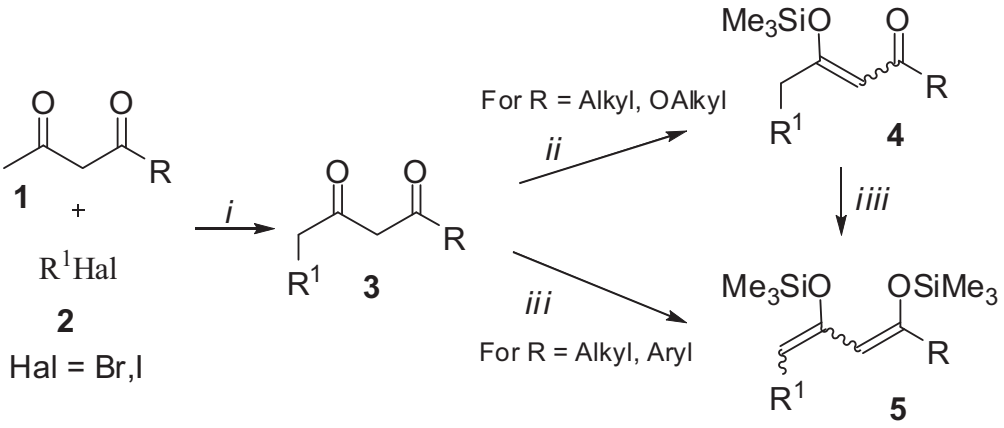


Figure 1-1. Chan's diene **A** and Danishefsky's diene **B**

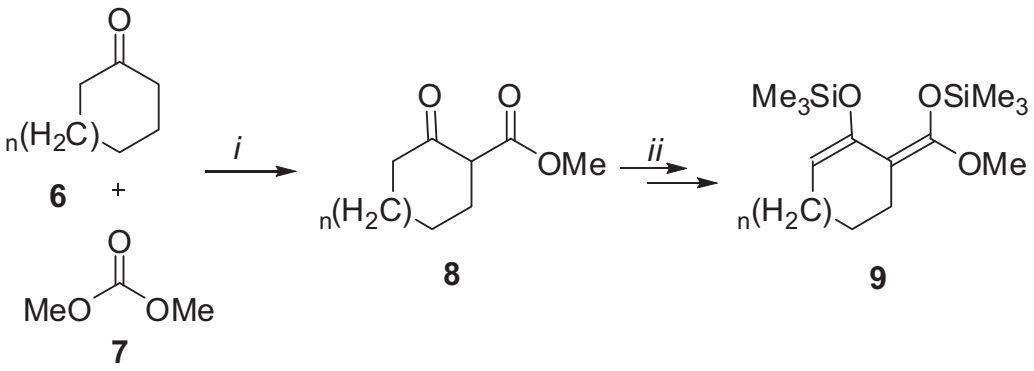
1.2 Synthesis of 1,3-bis(silyloxy)-1,3-butadienes

The preparation of 1,3-bis(silyloxy)-1,3-butadienes mainly follows the procedures reported by Chan and Molander. These syntheses rely on the preparation of mono-silyl enol ethers which are subsequently transformed into 1,3-bis(silyloxy)-1,3-butadiene by deprotonation with LDA and subsequent silylation.[15] The synthesis of alkyl substituted 1,3-bis(silyloxy)-1,3-butadiene derivatives require the synthesis of the respective β-ketoesters. It is known that the regioselectivities of the reactions of monoanions and dianions generally differ greatly. 1,3-Dicarbonyl monoanions are generally alkylated at the central carbon or at the oxygen atom, whereas the formation of dianions allows the functionalization of the terminal carbon atom. Based on this, the 4-alkyl-3-oxobutanoates **3** were prepared by reactions of the dianion of alkyl acetoacetate **1** with the respective alkylhalides **2** (R^1Hal).
Following the procedures of Chan and Molander, 1,3-bis(silyloxy)-1,3-butadienes **5** can be prepared from the respective 1,3-dicarbonyl compounds **3** in two steps.[12] Treatment of the *β*-ketoester **3** with NEt_3, Me_3SiCl afforded mono silyl enol ether **4.** Deprotonation of the latter with LDA and subsequent addition of Me_3SiCl afforded the diene **5** (**Scheme 1-3**).



Scheme 1-3. Synthesis of alkyl-substituted 1,3-bis(silyloxy)-1,3-butadienes **5**. Conditions *i*: 1) 2.5 LDA, THF, 0 ºC, 1 h; 2) R^1Hal, –78 → 20 ºC; *ii*: Me_3SiCl (1.5 equiv.), NEt_3 (1.5 equiv.), C_6H_6, 20 ºC, 48 h; *iii*: NEt_3 (2.0 equiv.), Me_3SiOTf (2.0 equiv.), Et_2O, 20 ºC, 24 h; *iiii*: 1) LDA (1.5 equiv.), THF, –78 ºC, 1 h; 2) Me_3SiCl (1.5 equiv.), 20 ºC, –78 → 20 ºC.

Simchen *et al*. reported that 1,3-diketones can be transferred into 1,3-bis(silyloxy)-1,3-butadienes in one step by treatment of an ether solution of the diketone with 2.0 equivalent of NEt_3 and Me_3SiOTf (**Scheme 1-3**).[16] Cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadienes **9** could also be prepared in high yields from corresponding 1,3-dicarbonyl compounds **8** by procedures of Chan and Molander.[12] Cyclic 1,3-dicarbonyl compounds **8** are available by treatment of cyclic ketone **6** with dimethylcarbonate **7** in benzene (**Scheme 1-4**)[17].



Scheme 1-4. Synthesis of cyclic 1,3-bis(silyloxy)-1,3-butadienes **9**. *Conditions i*: 1) **6** (1.0 equiv.), NaH (3.0 equiv.), benzene, 90 ºC, 0.5 h; 2) **7** (2.0 equiv.), 90 ºC, 4 h; *ii*: 1) Me_3SiCl (1.5 equiv.), NEt_3 (1.5 equiv.), C_6H_6, 20 ºC, 48 h; 2) LDA (1.5 equiv.), THF, –78 ºC, 1 h; 3) Me_3SiCl (1.5 equiv.), 20 ºC, –78 → 20 ºC.

1,3-Bis(trimethylsilyloxy)-1,3-butadienes can be stored in most cases at suitable conditions (-20 ºC, dry, inert gas atmosphere) for several months without decomposition.

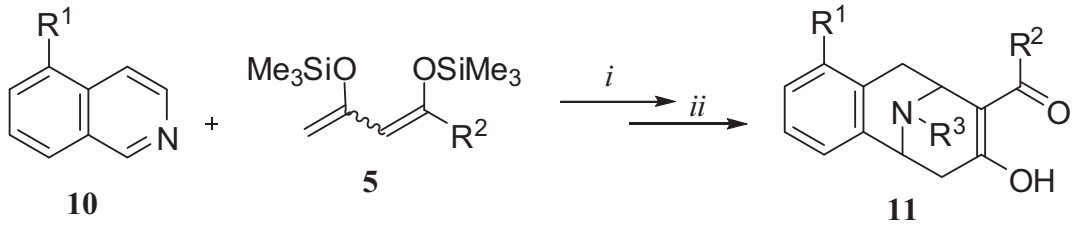
The masked dianions **5** and **9** are used in the cyclization reactions for synthesis of heterocycles and aromatic rings - important building blocks of natural product analogues.

2. Synthesis of Bridged and Non-Bridged *N*-Heterocycles based on Cyclocondensation Reactions of 1,3-Bis(silyloxy)-1,3-butadienes

2.1 *Synthesis of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes by cyclization of 1,3-bis(silyloxy)-1,3-butadiens with quinazolines*

2.1.1 Introduction

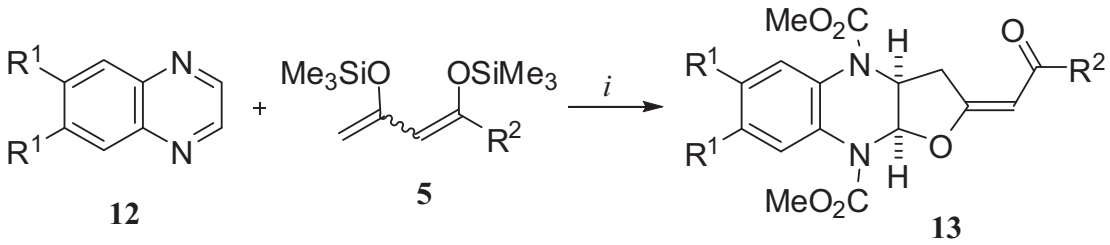
Iminium salts represent important synthetic building blocks.[18] In recent years, various bridged and non-bridged N-heterocycles have been synthesized, based on pioneering work of Peter Langer's research group, by cyclocondensation reactions of iminium salts with bis(silyl enol ethers) and 1,1-bis(trimethylsiloxy)ketene acetals.[19] Quinolinium-and isoquinolinium salts, generated by alkylation or acylation of quinoline and isoquinoline **10**,[20] represent important synthetic building blocks. Schmidt *et al.* have reported the synthesis of functionalized 7,8-benzo-3-hydroxy-9-azabicyclo[3.3.1]non-3-enes **11** by two-step cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes **5** with isoquinolines **10** (**Scheme 2-1**).[20] 3,4,7,8-Dibenzo-9-azabicyclo[3.3.1]nonanes contain an isoquinoline substructure and occur in a number of pavin alkaloids, such as argemonine, dinorargemonine, munitagine and pavine.[21]



Scheme 2-1. Cyclization of 1,3-bis(silyloxy)-1,3-butadiene **5** with isoquinolines **10**. *Conditions i*: $ClCO_2Me$, CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii*: TFA, CH_2Cl_2, 20 °C, 12 h

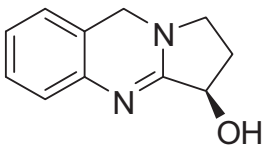
A convenient synthesis of 6-alkylidene-2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-enes **13** by cyclocondensation reactions of 1,3-bis(silyloxy)-1,3-butadienes **5** with quinoxaline **12**

has been reported (**Scheme 2-2**).[22] The products are of potential biological relevance as they represent analogues of riboflavin (vitamine B_2) and lumiflavin.[21]



Scheme 2-2. Cyclization of 1,3-bis(silyloxy)-1,3-butadiene **5** with quinoxalines **12.** *Conditions i*: 1) $ClCO_2Me$, CH_2Cl_2, 20 °C, 14 h; 2) TFA, CH_2Cl_2, reflux, 4 h

Quinazoline derivatives are of considerable pharmacological importance and occur in a number of natural products (e.g. tetrodotoxin, glomerine, or peganine) (**Figure 2-1**). For example, 1,2,4-triazolo[5,1-*b*]quinazolines show antihypertonic activity.[23] Antirheumatic and antianaphylactic activity has been recognized for 3-heteroaryl-1,2,4-triazolo[5,1-*b*]quinazolines.[24] 1,2,4-Triazolo[1,5-*c*]quinazolines possess antiasthmatic, tranquilizing and neuro-stimulating properties.[25] Aryl- and heteroaryl substituted derivatives have been shown to possess benzodiazepine binding behavior.[26] In addition, antiflammatory and antiviral activity has been reported.[27]



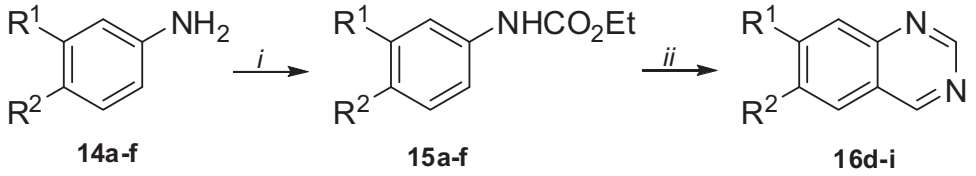
Peganine **I**

Figure 2-1. Peganine

In this chapter, I report the synthesis of functionalized 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes by one-pot cyclizations of 1,3-bis(silyloxy)-1,3-butadiene with quinazolines. General aspects of the mechanism of the cyclization were studied by B3LYP/6-31G(d) density functional theory computations. The products could be functionalized by Suzuki cross-coupling reactions.[28]

2.1.2 Synthesis of substituted quinazolines

Parent quinazoline (**16a**), 7-bromoquinazoline (**16b**) and 6-methylquinazoline (**16c**) are commercially available. These substrates were used in our preliminary studies. A number of novel quinazolines were prepared for the first time and successfully employed in our cyclization reaction. This includes, for example, derivatives containing an annulated ring or a lipophilic side-chain (hexyl group). The novel quinanzolines **16d-i** were prepared in two steps according to a procedure reported by Chilin and coworkers (**Scheme 2-3, Table 2-1**).[29] Anilines **14a-f** were transformed into the carbamates **15a-f**. Reflux of **15a-f** in the presence of hexamethylenetetramine (HMTA, urotropine) and trifluoroacetic acid (TFA) and subsequent reflux in the presence KOH ($EtOH/H_2O$ 1:1) and $K_3Fe(CN)_6$ afforded the novel quinazolines **16d-i** in 21-54% yields. The best yield was obtained for the tricyclic quinazoline **16i**.



Scheme 2-3. Synthesis of quinazolines **16d-i.** *Conditions i*: **14a-f** (1.0 equiv.), NEt_3 (2.0 equiv.), $ClCO_2Et$ (2.0 equiv.), THF, 20 °C, 1 h; *ii*, 1) **15a-f** (1.0 equiv.), HMTA (7.0 equiv.), TFA, reflux, 1 h; 2) 10% KOH ($EtOH/H_2O$ = 1:1), $K_3Fe(CN)_6$ (7.6 equiv.), reflux, 4 h

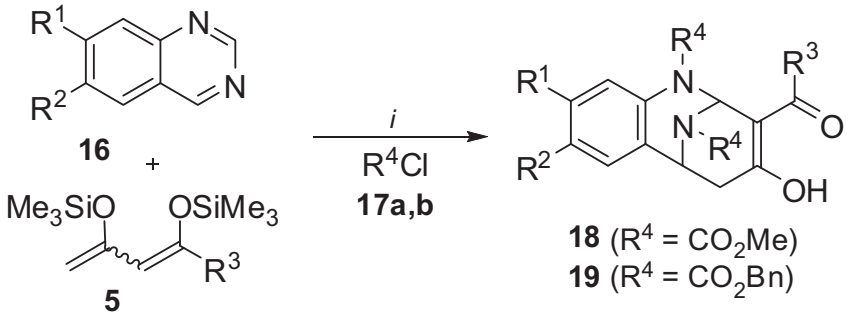
Table 2-1: Synthesis of quinazolines **16d-i**

14	16	R^1	R^2	% (16)[a]
a	**d**	H	Et	21
b	**e**	H	*i*-Pr	35
c	**f**	H	*t*-Bu	30
d	**g**	H	*n*-Hex	30
e	**h**	Me	Me	35
f	**i**	$-(CH_2)_3-$		54

[a] Isolated yields (based on **14**)

2.1.3 Synthesis of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes

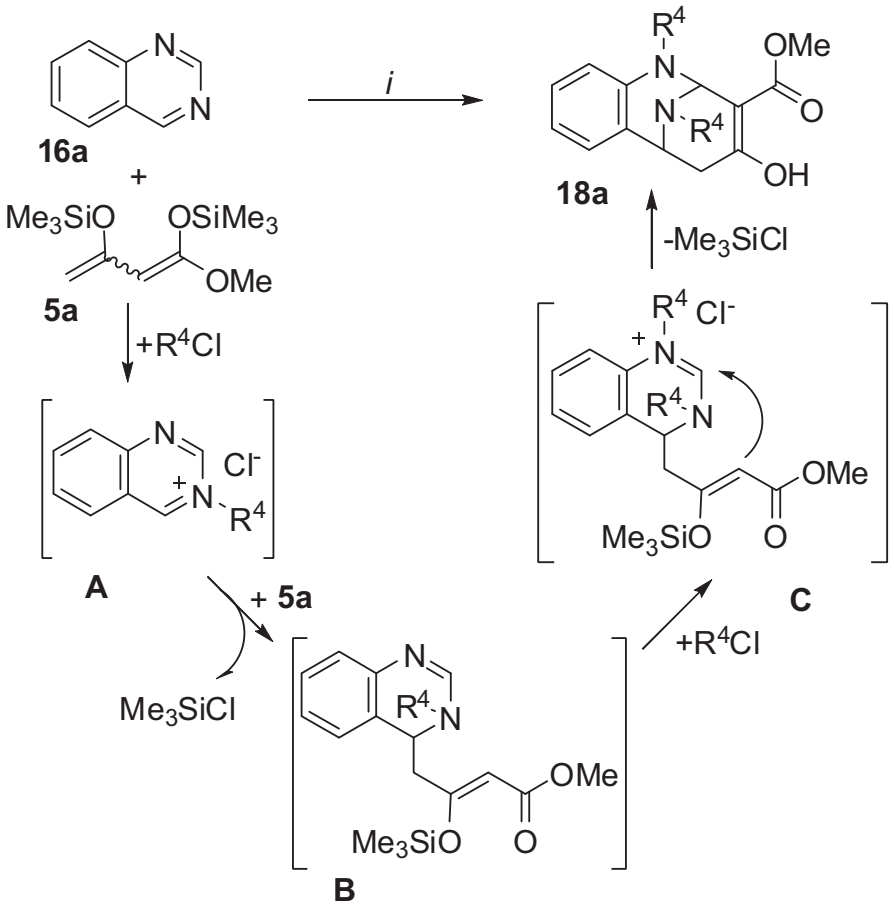
The cyclization of quinazolines **16a-i** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5**, in the presence of methyl chloroformate **17a** or benzyl chloroformate **17b** (4.0 equiv.), afforded the 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **18** and **19** (**Scheme 2-4**). The use of only 3.0 (rather than 4.0) equivalents of chloroformate **17** resulted in a decrease of the yield. Methyl or benzyl chloroformate was used as the activating agent. The employment of methyl iodide or TFA resulted in the formation of complex mixtures. Optimal yields were obtained when the reaction mixture was directly purified by chromatography (without aqueous work-up) and when the reaction was carried out at room temperature.



Scheme 2-4. Synthesis of **18** and **19**. *Conditions i*: **16a-i** (1.0 equiv.), **5** (1.4 equiv.), **17** (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h.

2.1.4 Mechanistic pathway of the synthesis of 3,4-Benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes

The formation of the products **18** and **19** can be explained (in a particular case for **18a**) by the generation of an iminium salt by reaction of **16a** with methyl chloroformate **17a** (intermediate **A**). Subsequent regioselective attack of the terminal carbon atom of the 1,3-bis(silyl enol ether) **5a** onto carbon atom C-4 of the quinazolinium salt afforded intermediate **B**. The reaction of the second nitrogen atom with methyl chloroformate **17a** again afforded an iminium ion (intermediate **C**). The attack of the central carbon atom of the 1,3-dicarbonyl unit onto second iminium iona and subsequent cyclization resulted in the formation of product **18a** (**Scheme 2-5**).



Scheme 2-5. Possible mechanism of the formation of bridged *N*-heterocycle **18a**. *Conditions i*: **16a** (1.0 equiv.), **5a** (1.4 equiv.), **17a** (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h.

2.1.5 Products and yields

The cyclization of quinazolines **16a-i** with 1,3-bis(silyloxy)-1,3-butadienes **5a-e**, in the presence of methyl chloroformate **17a** (4.0 equiv.), afforded the 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **18a-q** (**Table 2-2**).

Table 2-2. Synthesis of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **18a-q**

16	5	18	R^1	R^2	R^3	% (17) [a]
a	**a**	**a**	H	H	OMe	52
a	**b**	**b**	H	H	Me	63
a	**c**	**c**	H	H	*t*-Bu	12
b	**b**	**d**	Br	H	Me	37
c	**a**	**e**	H	Me	OMe	43
d	**a**	**f**	H	Et	OMe	43
d	**d**	**g**	H	Et	OEt	37
e	**a**	**h**	H	*i*-Pr	OMe	44
e	**d**	**i**	H	*i*-Pr	OEt	44
f	**a**	**j**	H	*t*-Bu	OMe	50
f	**e**	**k**	H	*t*-Bu	O*i*-Bu	54
g	**a**	**l**	H	*n*-Hex	OMe	37
g	**b**	**m**	H	*n*-Hex	Me	53
h	**a**	**n**	Me	Me	OMe	46
h	**b**	**o**	Me	Me	Me	48
i	**a**	**p**		$-(CH_2)_3-$	OMe	51
i	**b**	**q**		$-(CH_2)_3-$	Me	53

[a] Yields of isolated products; all products were isolated as racemates.

The one-pot cyclization of **16a** with **5b,** derived from acetylacetone, gave the acetyl-substituted diazabicyclo[3.3.1]nonene **18b**. The reaction of **16a** with 2,4-bis(trimethylsilyloxy)-5,5-dimethylhexane-1,3-diene **5c** afforded a separable mixture of diazabicyclo[3.3.1]nonene **18c** and an open-chained product. Due to the difficult separation, **18c** could be isolated in only low yield. The cyclization of 1,3-bis(silyloxy)-1,3-butadienes with the substituted quinazolines **16b-i** afforded the diazabicyclo[3.3.1]nonenes **18d-q**. The

deprotection (removal of the methoxycarbonyl groups from the nitrogens) of **18a** and **18b** failed under various conditions (decomposition).

The cyclization of quinazolines **16** with 1,3-bis(silyloxy)-1,3-butadienes **5** in the presence of benzyl chloroformate **17b** (4.0 equiv.), afforded the 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **19a-m** (**Scheme 2-4, Table 2-3**). The yields of the products **19** are generally equal when benzyl chloroformate **17b** was used as the activating agent instead of methyl chloroformate **17a** (**Tables 2-2, 2-3**).

Table 2-3. Synthesis of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **19a-m**

16	**5**	**19**	$\mathbf{R^1}$	$\mathbf{R^2}$	$\mathbf{R^3}$	%(**19**)[a,b]
a	**b**	**a**	H	H	Me	40
a	**a**	**b**	H	H	OMe	60
a	**d**	**c**	H	H	OEt	51
a	**f**	**d**	H	H	O*i*-Pr	57
a	**e**	**e**	H	H	O*i*-Bu	53
a	**g**	**f**	H	H	$O(CH_2)_2OMe$	49
d	**d**	**g**	H	Et	OEt	44
e	**d**	**h**	H	*i*-Pr	OEt	47
e	**f**	**i**	H	*i*-Pr	O*i*-Pr	45
h	**a**	**j**	Me	Me	OMe	43
h	**d**	**k**	Me	Me	OEt	42
i	**a**	**l**	$-(CH_2)_3-$		OMe	53
i	**d**	**m**	$-(CH_2)_3-$		OEt	52

[a] Yields of isolated products; all products were isolated as racemates.

The configurations of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **18** were elucidated by NMR-spectroscopy (HMBC, COSY, NOESY). For example, in the COSY spectrum of **18a,** correlations were observed between the hydrogen atoms of the $NCHCH_2$ moiety. In addition, NOE correlation signals between the hydrogen atoms of the ring $-CH_2-$ group and an aromatic hydrogen atom and the OH- proton were found. The HMBC- spectrum showed correlations between the ring $-C\mathit{H}_2$ group and the N*C*H, $NCHC_{Ar}$, *C*OH and COH*C*CO groups. Due to the hindered rotation of the carbamate moieties, a fine splitting of many of the signals of **18 and 19** was observed in their ^{1}H and ^{13}C NMR spectra. The

structures of **18h**, **18j**, **18n**, and **18p** were independently confirmed by X-ray crystal structure analyses (**Figures 2-2,3,4,5**).

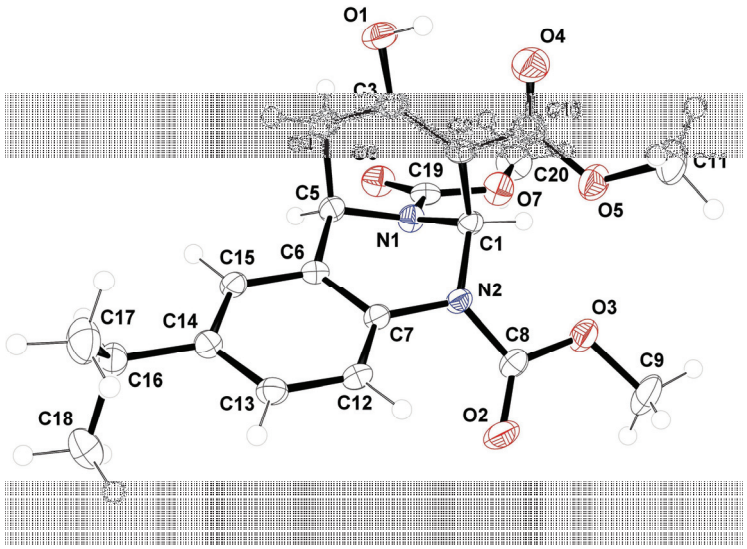


Figure 2-2: ORTEP plot of **18h** (50% probability level)

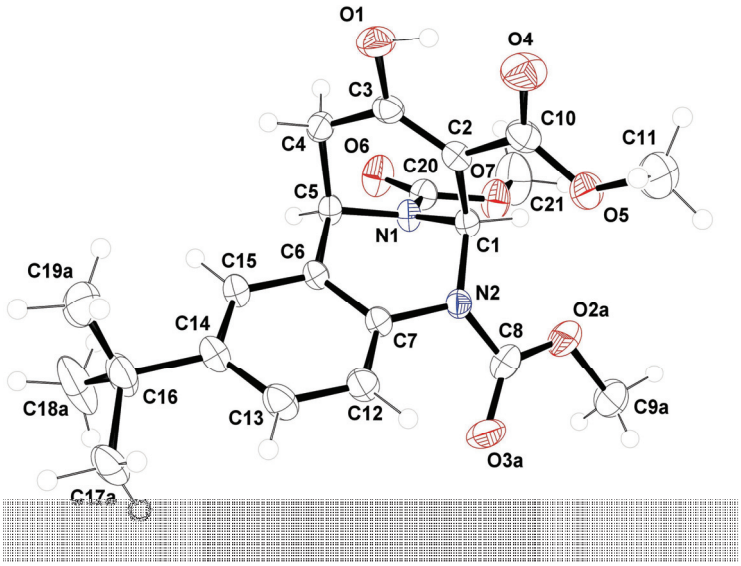


Figure 2-3: ORTEP plot of **18j** (50% probability level)

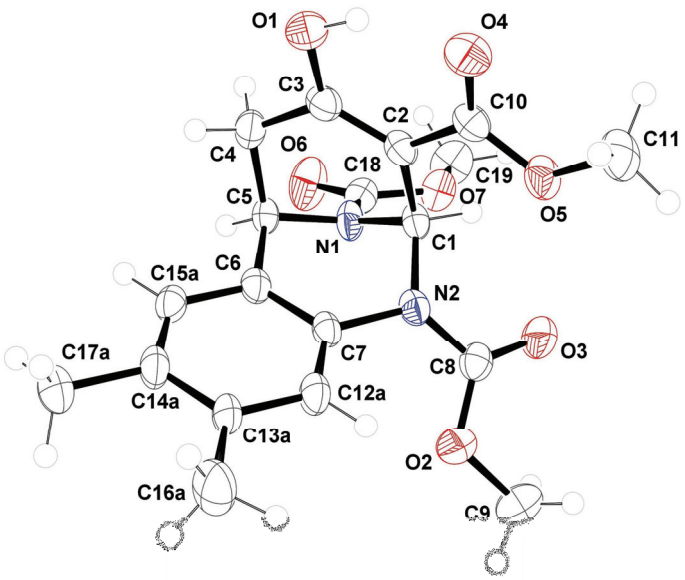


Figure 2-4. ORTEP plot of **18n** (50% probability level)

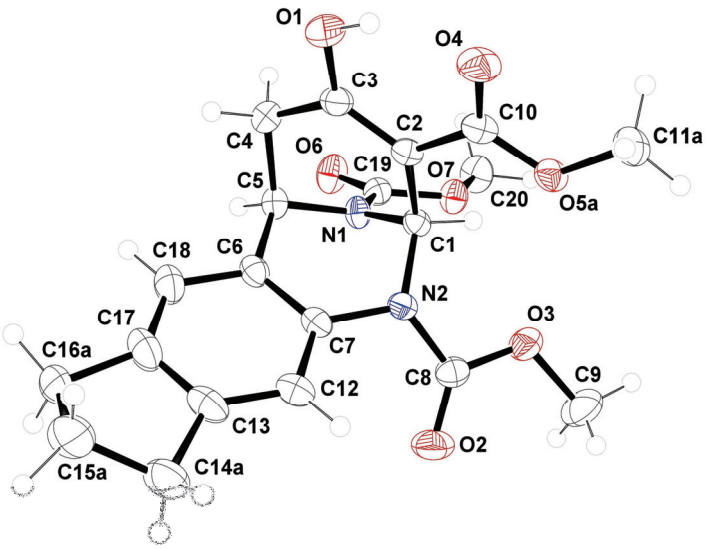


Figure 2-5: ORTEP plot of **18p** (50% probability level)

The structures of all products **19** were also confirmed by spectroscopic methods. The structure of **19e** was independently confirmed by X-ray crystal structure analysis (**Figure 2-6**).

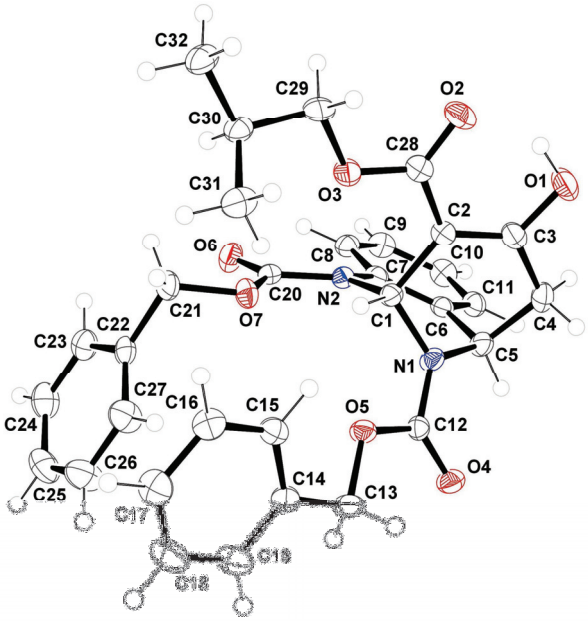
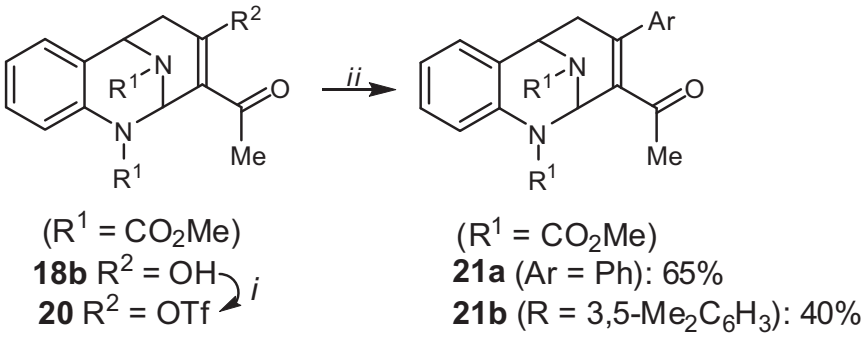


Figure 2-6. Ortep plot of **19e** (50% probability level)

2.1.6 Suzuki cross-coupling reactions of the products

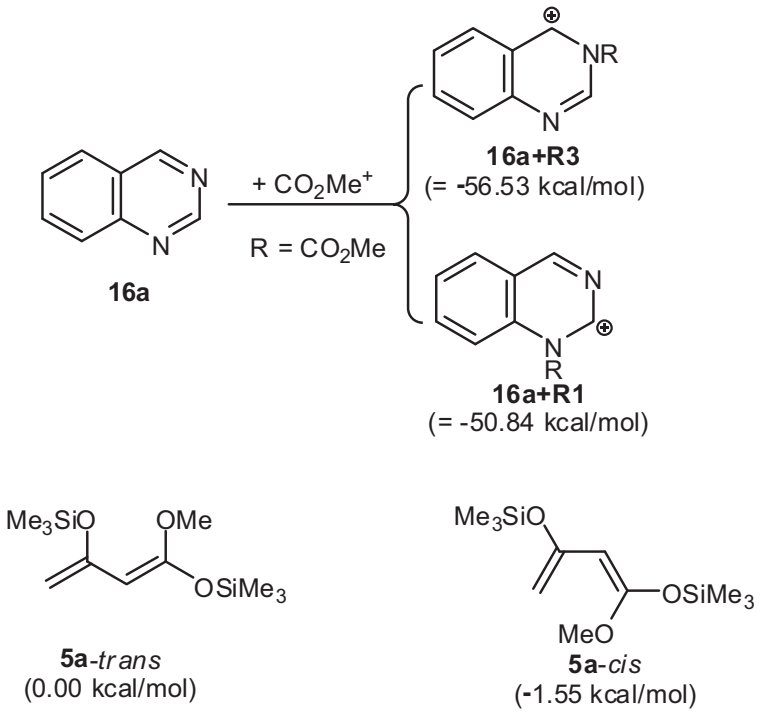
3,4-Benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-ene **18b** was transformed into its triflate **20** by conversion with Tf_2O in pyridine. The Suzuki cross-coupling reaction of **20** with phenyl- and 3,5-dimethylphenylboronic acid afforded products **21a** and **21b**, respectively (**Scheme 2-6**).[28] These reactions have been done by Andreas Schmidt.



Scheme 2-6. Synthesis of **21a,b**. *Conditions i*: Tf_2O, pyridine, −78 → 20 °C, 4 h; *ii*: **20** (1.0 equiv.), $ArB(OH)_2$ (1.3 equiv.), K_3PO_4 (1.6 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), 1,4-dioxane, reflux, 20 h

2.1.7 B3LYP/6-31G(d) density functional theory computation

Along with the synthetic efforts, it has been carried out **B3LYP/6-31G(d)** density functional theory computation [30,31,32] on the cyclization of 1,3-bis(silyloxy)-1,3-butadienes with quinazolines in order to get some mechanistic insight. The reaction of the unsubstituted reactants **16a** and **5a** was studied in detail. At **B3LYP/6-31(d)**, **16a** has a planar structure as energy minium (**Scheme 2-7**). Since the two nitrogen atoms in **16a** are non-equivalent, its reaction with methyl chloroformate can result in the formation of two different iminium ions, i. e. **16a+R1** and **16a+R3**. It is found that **16a+R3** is more stable than **16a+R1** by 5.69 kcal/mol in Gibbs free energy. Therefore, **16a+R3** should be the only product. It should also be noted that **16a+R3** has two rotameric forms (due to the carbamate group), from which one is higher in energy by less than 1.00 kcal mol^{-1}, and the computed rotation free energy barrier is 8.7 kcal mol^{-1}. In addition, we have found two conformers of **5a** which possess *s-trans* (**5a-*trans***) and *s-cis* (**5a-*cis***) butadiene moieties. The latter is more stable by 1.55 kcal mol^{-1} and the expected equilibrium ratio of **5a-*cis*** to **5a-*trans*** should be 93% to 7%. The computed rotation free energy barriers between **5a-*cis*** and **5a-*trans*** are in the range of 4.32 – 4.71 kcal mol^{-1}. On the basis of this equilibrium, we have considered for comparison the cyclization of **5a-*cis*** and **5a-*trans*** with **16a+R3**.

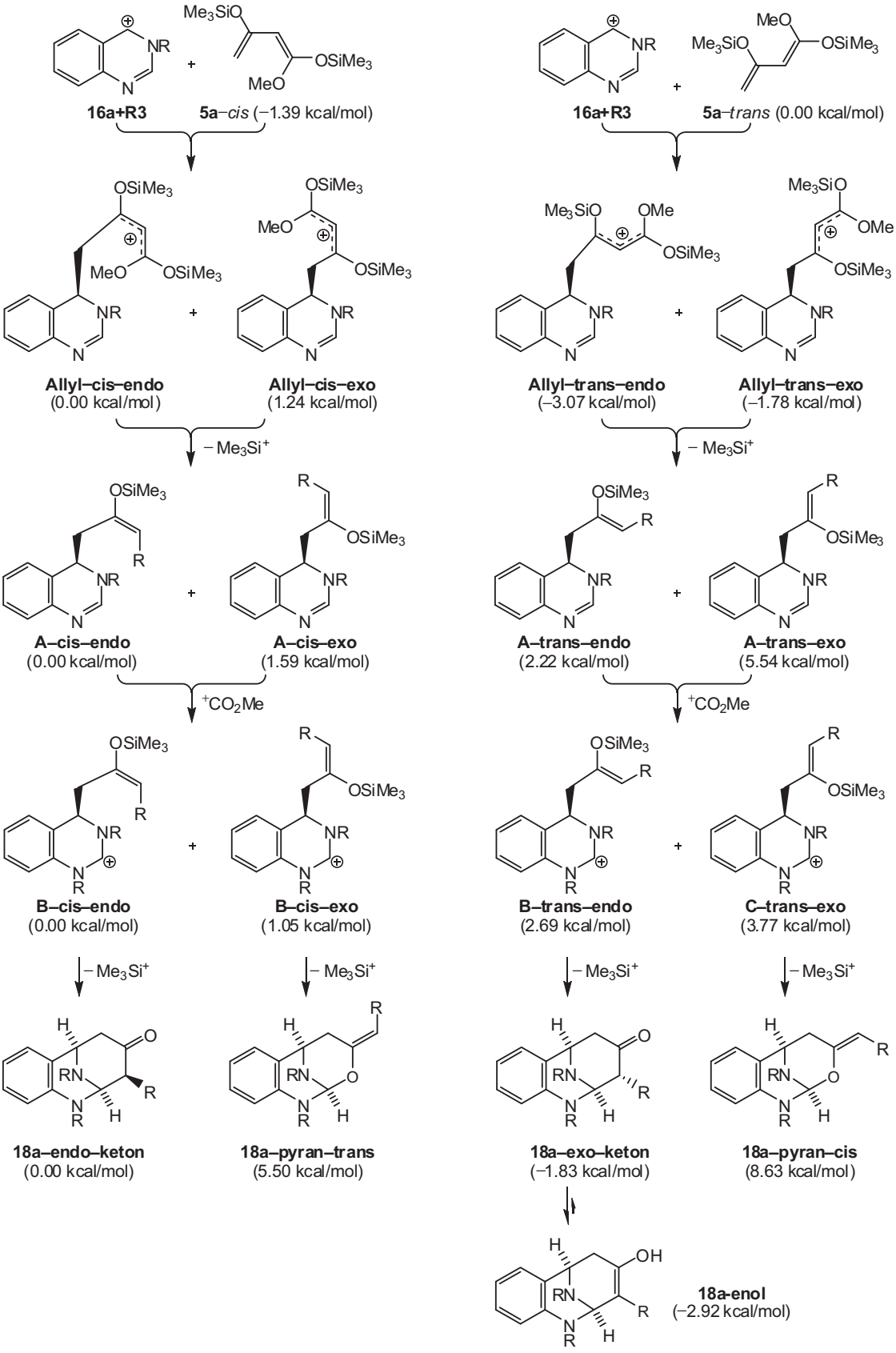


Scheme 2-7. Reaction free energies (ΔG_r) and relative free energies (B3LYP/6-31G(d) at 298K).

The reaction of **16a+R3** with **5a-*cis*** or **5a-*trans*** results in the formation of a racemic mixture. We have calculated the intermediates derived from the *R*-enantiomer. The reaction maps are shown in **Figure 2-8**. along with the reaction free energies (ΔG_r) and relative free energies. Upon the orientation of the butadiene moiety of **5a-*cis*** and **5a-*trans*** to the six-membered ring in **16a+R3**, there are two competitive allylic intermediates for each: **allyl-*cis-endo*/allyl-*cis-exo***, and **allyl-*trans-endo*/allyl-*trans-exo***. It is found that **allyl-*trans-endo*** is the most stable intermediate, while **allyl-*cis-endo*** and **allyl-*cis-exo*** are higher in free energy by 3.07 and 4.31 kcal mol^{-1}, respectively.

The large energy differences reveal that the addition of **5a-*cis*** to **16a+R3** is not competive, as compared to that of **5a-*trans*.** Thus, we have paid our attention to the addition of **5a-*trans*** to **16a+R3** (right side of **Scheme 2-8**). However, the data for the addition of **5a-*cis*** to **16a+R3** are shown for comparison (left side of **Scheme 2-8**). **Allyl-*trans-endo*** and **allyl-*trans-exo*** are close in free energy (1.29 kcal mol^{-1}), and the expected ratio should be 89% to 11%. For the neutral intermediates, formed by removing Me_3Si^+, **A-*trans-endo*** is more stable than **A-*trans-exo*** by 3.32 kcal mol^{-1}, and the expected ratio should be larger than 99% to 1%. Further addition of $^+CO_2Me$ results in **B-*trans-endo*** and **B-*trans-exo***, and the former is more stable than the latter by 1.08 kcal mol^{-1}. On the basis of all these energetic differences, one should expect that **B-*trans-endo*** should be the principal intermediate.

The next step is the intramolecular electrophilic substitution with the formation of the products. Due to the proper orientation of the C=C double bond, the expected product of **B-*trans-endo*** is **18a-*exo*-keton**, where the cation attacks the C=C double bond along with the extrusion of Me_3Si^+. Due to the orientation of the Me_3SiO group, the expected product of **B-*trans-exo*** is **18a-pyran-*cis***, formed when the cation attacks the oxygen atom along with the extrusion of Me_3Si^+. It has been found that **18a-*exo*-keton** is more stable than **18a-pyran-*cis*** by 10.46 kcal mol^{-1}. Therefore, **18a-*exo-keton*** is the only product. We have also calculated the transition state for the ring closure of **B-*trans-endo***; the activation barrier is 27.62 kcal mol^{-1}. In addition, we have calculated the enol form of the final product (**18a-enol**) which is more stable than **18a-*exo-keton*** by 0.96 kcal mol^{-1}. The expected ratio should be 86% to 14%. This result agrees reasonably with the experimental findings. Theoretical computations have been done by Prof. Haijun Jiao from Leibniz Institute for Catalysis at the University of Rostock.

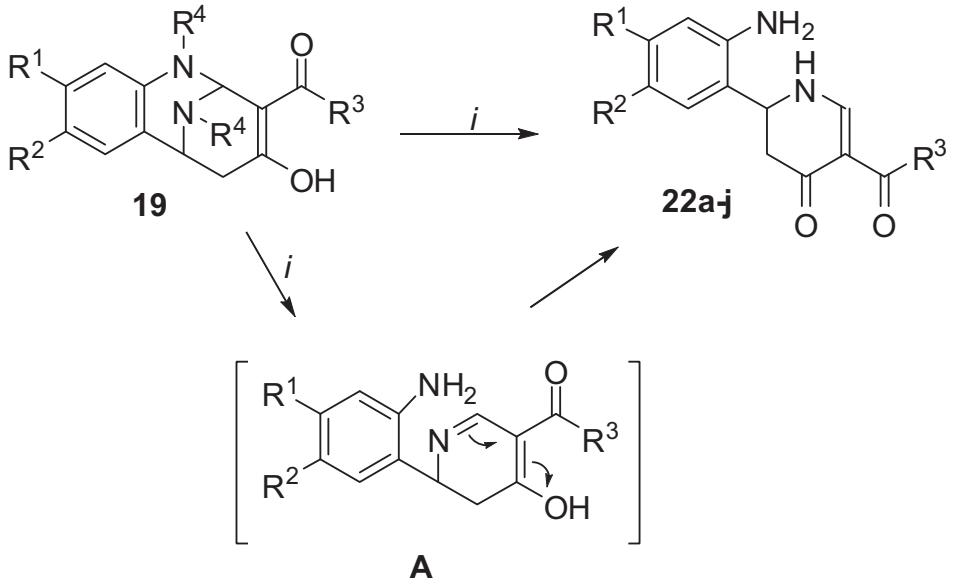


Scheme 2-8. Reaction free energies (ΔG_r) and relative free energies (B3LYP/6-31G(d) at 298K), R = CO_2Me.

It can be concluded that the addition reaction takes place via the **allyl-*trans-endo*** intermediate, formed by reaction of **16a-R3** with **5a-*trans***. The total reaction free energy from **16a** + **5a-*trans*** + $2ClCO_2Me$ to give **18a-enol** + 2 Me_3SiCl is highly exergonic by 50.50 kcal mol^{-1} at the B3LYP/6-31G(d) level, and this should be the driving force for the complete reaction.

2.1.8 Synthesis of 6-(2-aminophenyl)-4-oxo-1,4,5,6-tetrahydropyridines and 8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes by reductive cleavage of the benzyloxycarbonyl moiety as a protective group

While all attempts to deprotect the methoxycarbonyl-substituted products **18** proved to be unsuccessful, the deprotection (H_2, Pd/C) of benzyloxycarbonyl-substituted derivatives **19** was possible and gave 6-(2-aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridines **22a-j**. The products are formed by reductive cleavage of the N-R^4 and C_{Ar}N-CN bounds (**Scheme 2-9, Table 2-4**).



Scheme 2-9. Synthesis of 6-(2-aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridines **22**. *Conditions i*: Pd/C (10mmol%), H_2, MeOH, 20 °C, 12 h.

All reactions proceeded in moderate to excellent yields (**Table 2-4**).

Table 2-4. Synthesis of 6-(2-aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridines **22a-j**

19	22	R^1	R^2	R^3	%(22)[a]
a	**a**	H	H	Me	44
b	**b**	H	H	OMe	90
c	**c**	H	H	OEt	93
d	**d**	H	H	O*i*-Pr	83
e	**e**	H	H	O*i*-Bu	80
f	**f**	H	H	$O(CH_2)_2OMe$	81
j	**g**	Me	Me	OMe	66
k	**h**	Me	Me	OEt	60
l	**i**		$-(CH_2)_3-$	OMe	65
m	**j**		$-(CH_2)_3-$	OEt	68

[a] Yields of isolated products; all products were isolated as racemates.

The structures of all products were confirmed by spectroscopic methods. The structure of **22f** was independently confirmed by X-ray crystal structure analysis (**Figure 2-7**).

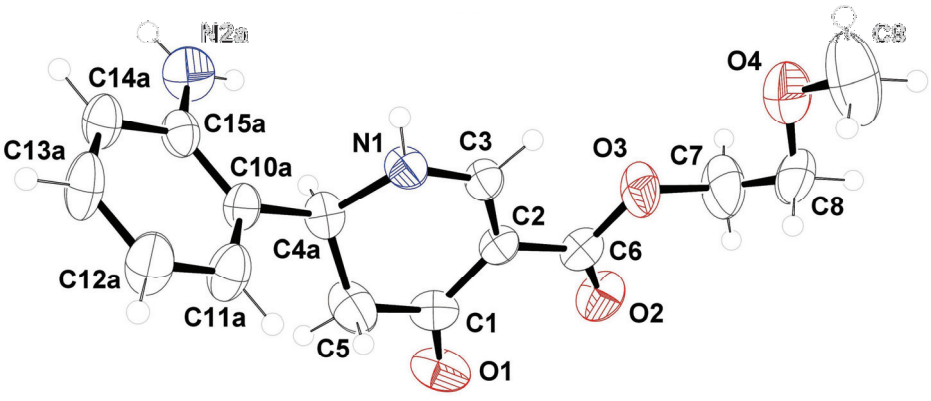
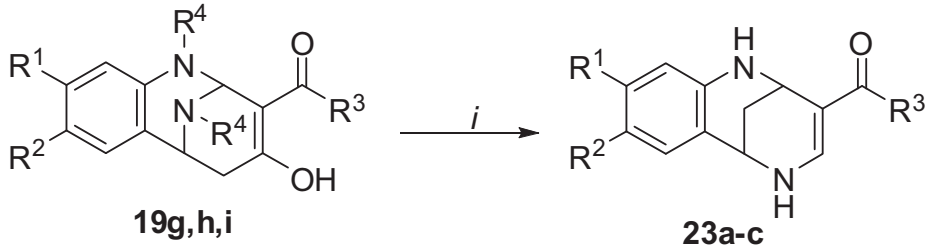


Figure 2-7. Ortep plot of **22f** (50% probability level)

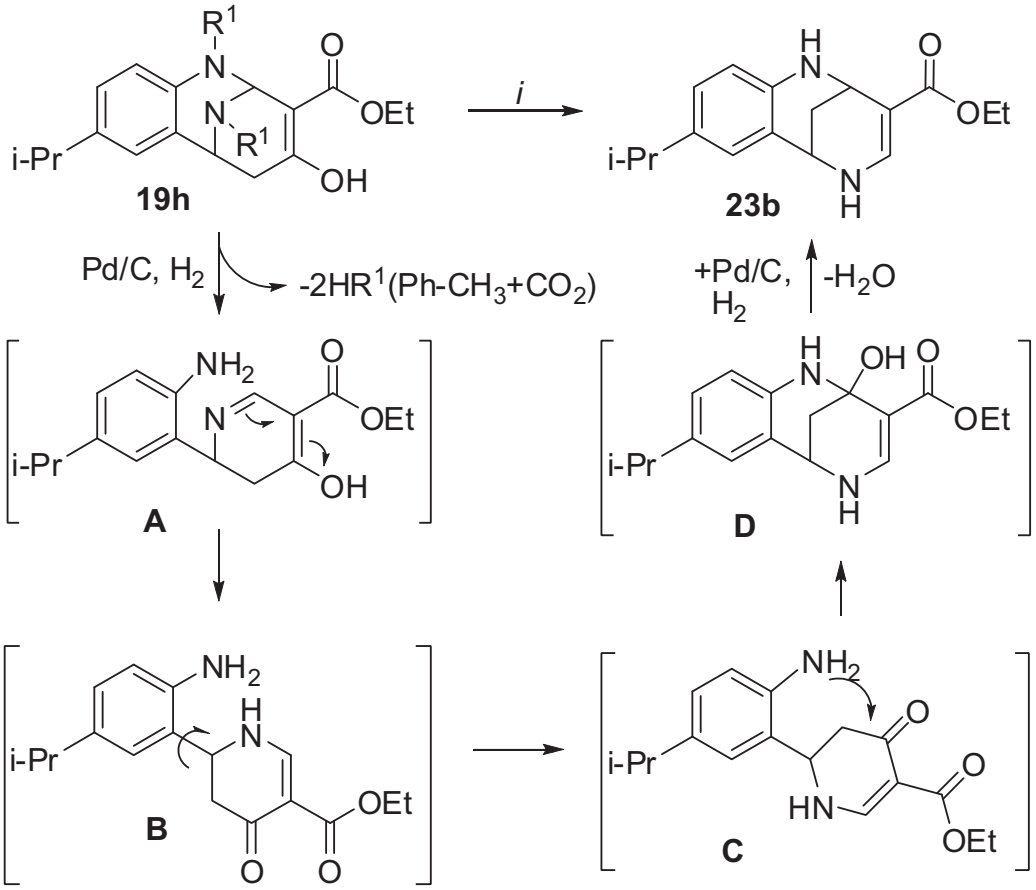
Interesting results were obtained by Pd/C-catalyzed hydrogenation of **19g,h,i.** These reactions directly resulted not only in cleavage of the protective benzyloxycarbonyl group, but also in intramolecular rearrangements to give bridged-*N*-heterocycles **23a-c** (**Scheme 2-10**).



Scheme 2-10. Synthesis of 4-alkyl-8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes **23a-c**. *Conditions i*: Pd/C (10mmol%), H_2, MeOH, 20 °C, 12 h.

2.1.9 Mechanistic pathway of the synthesis of 8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes

The Pd/C-catalyzed deprotection includes reductive cleavage of the N—R^4 and C_{Ar}N—CN bounds of **19h** to form intermediate **A** which undergoes en-one formation (intermediate **B**). The intramolecular attack of the NH_2 nitrogen atom onto carbonyl group afforded intermediate **D**. The reductive elimination of H_2O (intermediate **D**) resulted in the formation of product **23b** (**Scheme 2-11**).



Scheme 2-11. Possible mechanism of the formation of 4-alkyl-8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes **23**. Conditions: *i*: Pd/C (10mmol%), H_2, MeOH, 20 °C, 12 h.

The bridged heterocyclic 4-alkyl-8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes **23a-c** were isolated in moderate yields by Pd/C-catalyzed hydrogenation of **19g,h,i** (**Table 2-5**). The reactions were carried out in a methanol, at room temperature for 12 h.

Table 2-5. Synthesis of **23**

19	23	R^1	R^2	R^3	%(23)[a]
g	**a**	H	Et	OEt	55
h	**b**	H	*i*-Pr	OEt	45
i	**c**	H	*i*-Pr	O*i*-Pr	50

[a] Yields of isolated products; all products were isolated as racemates.

The structures of all products were confirmed by spectroscopic methods. The structure of **23b** was independently confirmed by X-ray crystal structure analysis (**Figure 2-8**).

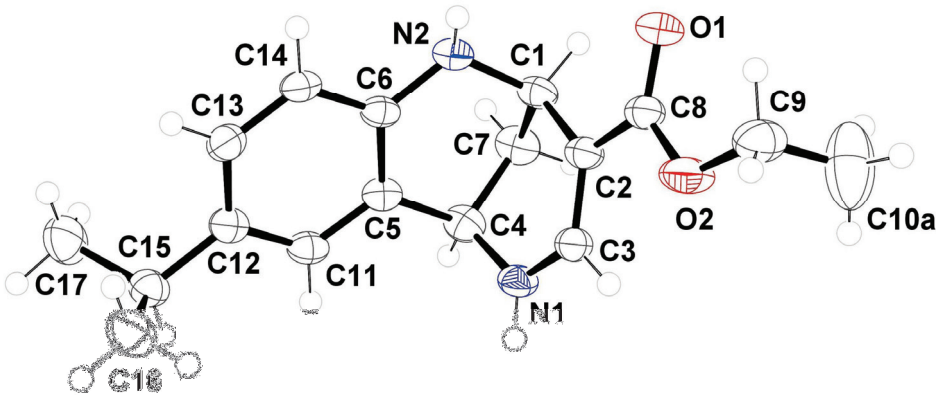


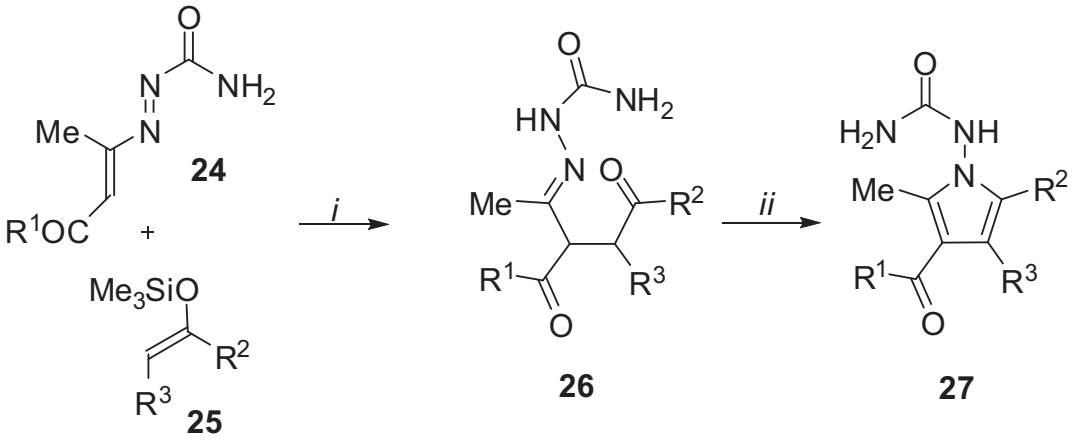
Figure 2-8. Ortep plot of **23b** (50% probability level)

2.2 *Regioselective Synthesis of New 1-Aminopyrroles and 1-Amino-4,5,6,7-tetrahydroindoles by One-Pot ′Conjugate Addition/Cyclization′ Reactions of 1,3-Bis(silyloxy)-1,3-butadienes with 1,2-Diaza-1,3-butadienes*

2.2.1 Introduction

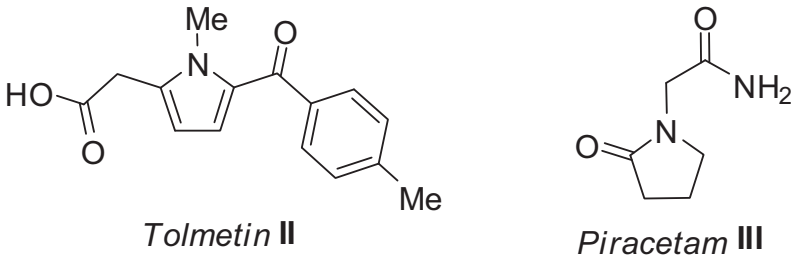
Michael addition to α,β-unsaturated systems is one of the most important carbon-carbon bond-forming processes in organic chemistry and offers an extremely powerful tool for the synthesis of highly functionalized organic molecules.[33] The use of silyl enol ethers in Lewis acid catalyzed conjugate additions, introduced by Mukaiyama and co-workers, offers a mild alternative to base-mediated variants.[34,35]

Recently, Attanasi *et al.* reported[36] the synthesis of 1-aminopyrrol-2-ones and 1-aminopyrroles **27** by Lewis acid catalyzed one-pot ′conjugate addition/cyclization′ reactions of simple silyl enol ethers **25** with 1,2-diaza-1,3-butadienes **24** (**Scheme 2-12**).[37,38]



Scheme 2-12. Mukaiyama-Michael-type addition/heterocyclization reaction of silyl enol ethers **25** on 1,2-diaza-1,3-butadienes **24**. *Conditions i:* $ZnCl_2$ (0.2 equiv.), CH_2Cl_2, 20 °C, 12 h; *ii*: TFA

Pyrroles and pyrrolidines are present in many natural products, such as the porphyrins, phthalocyanines, various alkaloids or vitamin B_{12}. Varieties of synthetic compounds are of pharmacological relevance and are used in the clinic. This includes, for example, triprolidine, piracetam, pyrrolnitrin, tolmetin, clemizole, dextromoramide, vinblastine, vincamine, reserpine and perfluoroalkylpyrroles (**Figure 2-9**).[39] Oligo- and polypyrroles also represent important electronic materials, due to their high electroconductivity.[40] 1-Aminopyrroles also represent pharmacologically important heterocycles. Recently, 1-aminopyrroles have been employed as intermediates during the synthesis of analgesic[41] and NMDA receptor antagonists.[42]



Tolmetin **II** *Piracetam* **III**

Figure 2-9. Tolmetin and Piracetam

Langer *et.al.* reported the Lewis acid catalyzed condensation of 1,3-bis(silyl enol ethers) with 1,1-dimethoxy-2-azidoethane and subsequent cyclization which allows a convenient synthesis of functionalized pyrroles.[43] Whereas a variety of pyrrole synthesis are known, methods for the direct preparation of functionalized 1-aminopyrroles are rare. Moreover, these approaches usually present significant limitations in terms of substitutents that can be introduced, the substitution pattern and/or regioselectivity. Therefore, the development of new methods for the synthesis of these compounds is of considerable ongoing interest.

2.2.2 Regioselective synthesis of new 1-aminopyrroles and 1-amino-4,5,6,7-tetrahydroindoles

The catalytic one-pot cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1,2-diaza-1,3-butadienes provides a convenient and direct approach to a variety of functionalized 1-aminopyrroles.[44] This synthetic strategy can be regarded as domino ′conjugate addition/cyclization′ reactions, allowing the construction of 1-aminopyrrole rings in an efficient manner from easily available intermediates (**Figure 2-10**).

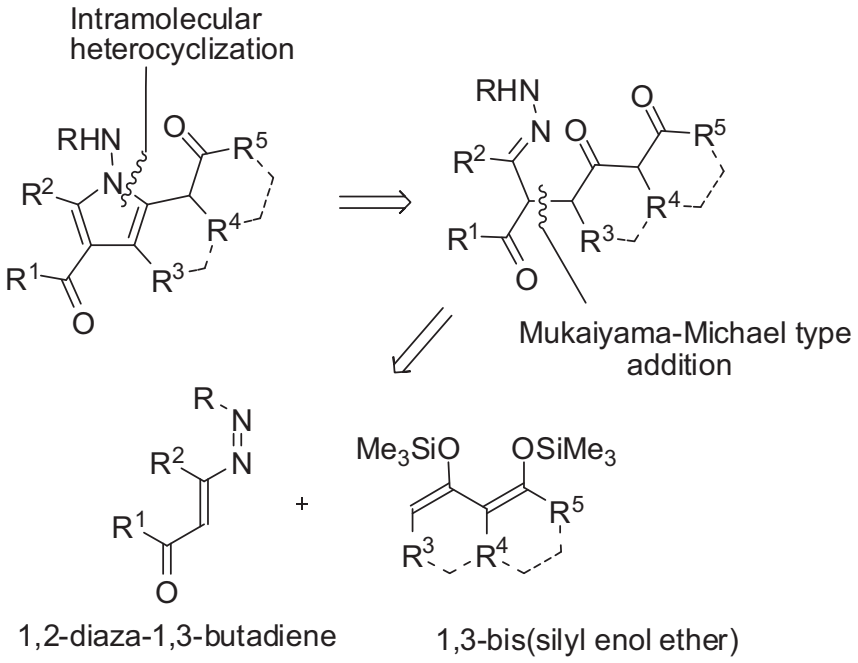
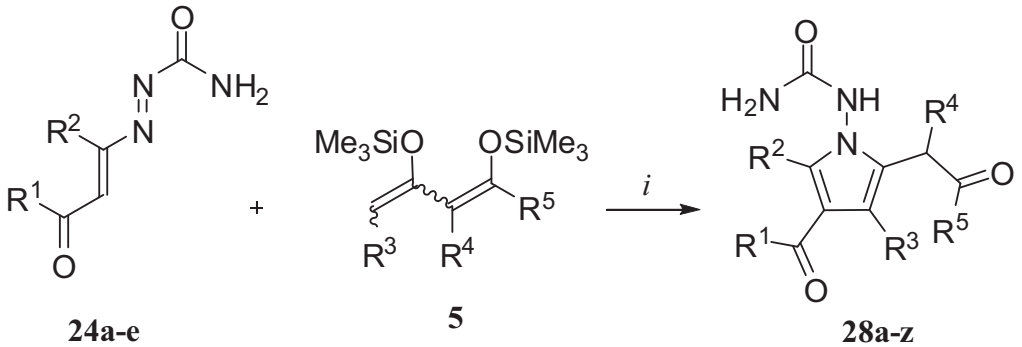


Figure 2-10. Retrosynthetic approach of pyrroles and tetrahydroindoles

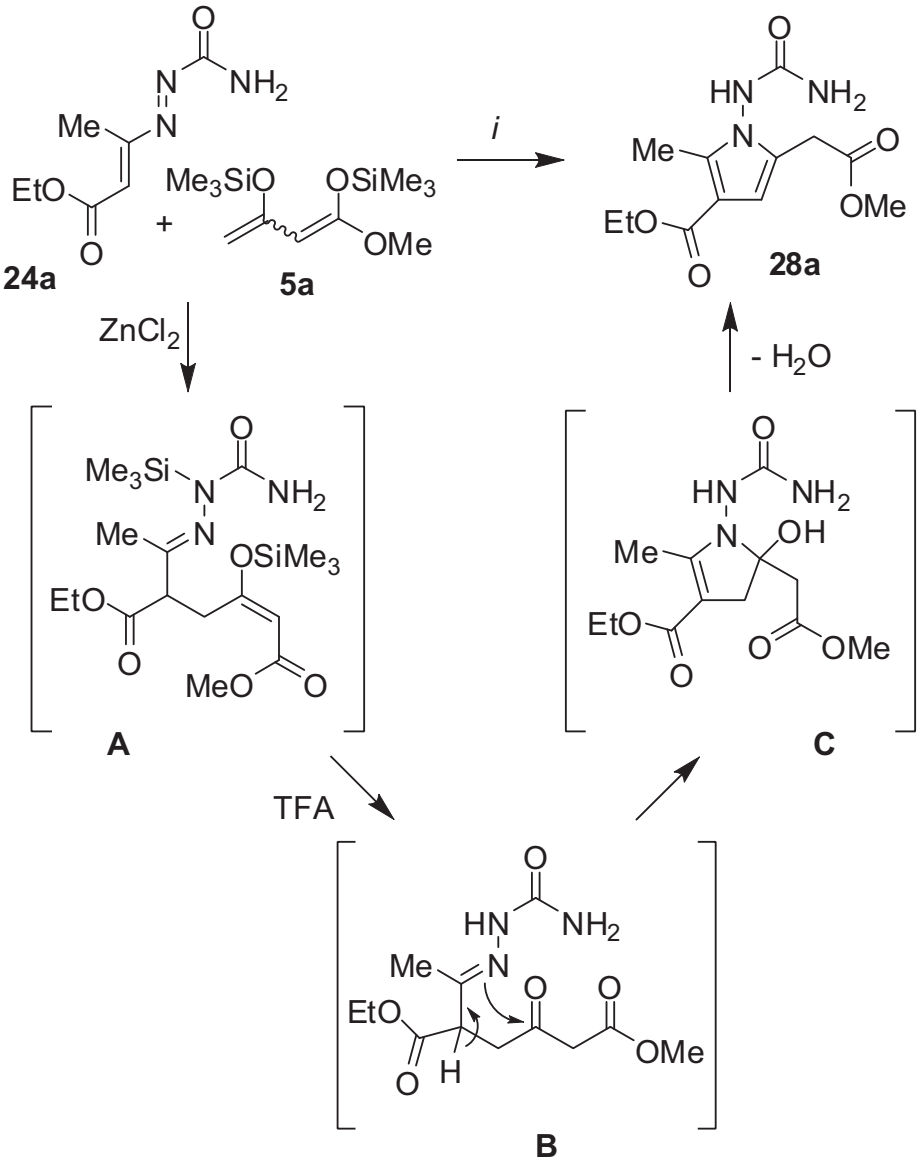
The Lewis acid catalyzed reaction of various 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5** with 1,2-diaza-1,3-butadienes **24** and subsequent addition of trifluoroacetic acid (TFA) afforded the highly functionalized 1-aminopyrroles **28** (**Scheme 2-13**). The best yields were obtained when $ZnCl_2$ and TFA were used as the Lewis acid catalyst and for protonation, respectively. The reaction was carried out following the protocol as previously reported for simple silyl enol ethers.[36] It is noteworthy that these products are not readily available by other methods. Moreover, the presence of different groups in these systems confers an interesting contribution to this work, making them suitable as intermediates for more complex compounds.



Scheme 2-13. Synthesis of 1-aminopyrroles **28a-z**. *Conditions i*: 1) $ZnCl_2$ (0.2 equiv.), CH_2Cl_2, 20 °C, 12 h; 2) TFA

2.2.3 Mechanistic pathway of the synthesis of 1-aminopyrroles

The generally accepted mechanism for a Lewis acid-catalyzed conjugate addition of silyl enol ethers to Michael acceptors involves an activation of the latter by the Lewis acid.[45] Attanasi *et al*. earlier reported mechanistic studies related to the reaction of simple silyl enol ethers (such as 1-methoxy-1-trimethylsilyloxyethene) with 1,2-diaza-1,3-butadienes.[36] The regioselective formation of **28** (in a particular case **28a**) can be explained by $ZnCl_2$-catalyzed attack of the terminal carbon atom of **5a** at the terminal carbon of the azo-ene system of **24a** (Mukaiyama-Michael addition) to give intermediate **A**. (**Scheme 2-14**).[46]



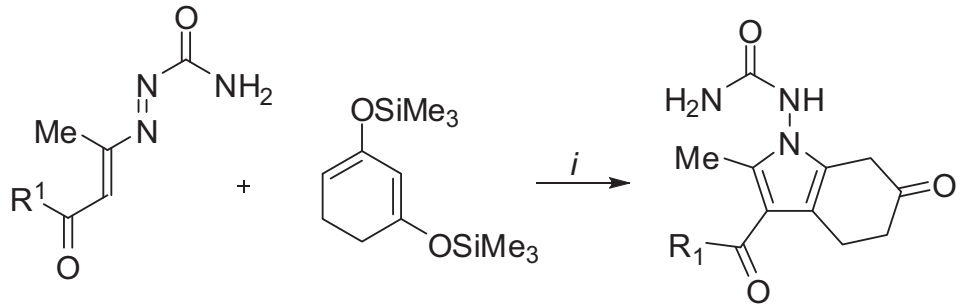
Scheme 2-14. Possible mechanism of the formation of 1-aminopyrrole **28a.** *Conditions i*: 1) $ZnCl_2$ (0.2 equiv.), CH_2Cl_2, 20 °C, 12 h; 2) TFA

The addition of TFA subsequently results in the cleavage of the silyl groups to give intermediate **B**. The latter undergoes an acid-catalyzed cyclization (by attack of the nitrogen atom to the carbonyl group) to give intermediate **C**. Subsequently, the acid catalyzed elimination of a water molecule affords the final product **28a** (**Scheme 2-14**).

2.2.4 Products and yields

The addition/cyclization of various 1,3-bis(silyloxy)-1,3-butadienes **5** with 1,2-diaza-1,3-butadienes **24a-d** afforded the novel 1-aminopyrroles **28a-v** (**Scheme 2-13, Table 2-6**) in different yields. 1-Aminopyrroles **28** were successfully prepared from 1,3-bis(trimethylsilyloxy)-1,3-butadienes derived from alkyl acetoacetate (products **28a-h**) or 1,3-diketone (**28i**), from open-chained (**28j-n,v**) or cyclic 1,3-dicarbonyl compounds (**28p-u**). The cyclizations generally proceeded in moderate up to very good yields (except for **28v**). The employment of the 7-membered cyclic 1,3-bis(silyl enol ether) **5x**, of 1,1,1-trifluoro-2,4-bis(trimethylsilyloxy)pentane-2,4-diene **5y**, and of methoxy-substituted diene **5z** proved to be unsuccessful. The failure of **5y** can be explained by its low reactivity. The failure of **5z** might be explained by competing chelation of the Lewis acid by the additional methoxy group. Noteworthy, the employment of the amide **24e** failed.

The cyclization of 1,2-diaza-1,3-butadienes **24a** and **24d** with cyclic 1,3-bis(silyloxy)-1,3-butadiene **5aa**, prepared from cyclohexane-1,3-dione, afforded the 1-amino-4,5,6,7-tetrahydroindol-6-ones **28aa** and **28ab**, respectively (**Scheme 2-15**).



24a,d **5aa** **28aa** (R^1 = Et), 50%
28ab (R^1 = Me), 32%

Scheme 2-15. Synthesis of 1-amino-4,5,6,7-tetrahydroindol-6-ones **28aa** and **28ab**. *Conditions i*: 1) $ZnCl_2$ (0.2 equiv.), CH_2Cl_2, 20 °C, 12 h; 2) TFA

Table 2-6. Synthesis of 1-aminopyrroles **28a-v**

24	5	28	R^1	R^2	R^3	R^4	R^5	% (**28**)[a]
a	**a**	**a**	OEt	Me	H	H	OMe	64
a	**d**	**b**	OEt	Me	H	H	OEt	92
a	**e**	**c**	OEt	Me	H	H	O*i*-Bu	80
a	**h**	**d**	OEt	Me	H	H	O*t*-Bu	81
b	**d**	**e**	OMe	Et	H	H	OEt	60
c	**d**	**f**	O*t*-Bu	Me	H	H	OEt	61
c	**g**	**g**	O*t*-Bu	Me	H	H	$O(CH_2)_2OMe$	60
a	**i**	**h**	OEt	Me	H	H	OBn	60
a	**j**	**i**	OEt	Me	H	H	Ph	60
a	**k**	**j**	OEt	Me	*n*-Pr	H	OMe	63
d	**l**	**k**	OMe	Me	*n*-Hex	H	OMe	65
d	**m**	**l**	OMe	Me	*n*-Hept	H	OEt	75
a	**n**	**m**	OEt	Me	*n*-Oct	H	OEt	47
a	**o**	**n**	OEt	Me	Allyl	H	OMe	44
a	**p**	**o**	OEt	Me	H	Me	OEt	45
a	**q**	**p**	OEt	Me	H		$-(CH_2)_2O-$	50
a	**r**	**q**	OEt	Me	$-(CH_2)_2-$		OMe	40
d	**s**	**r**	OMe	Me	$-(CH_2)_3-$		OEt	87
d	**t**	**s**	OMe	Me	$-CH_2CHMeCH_2-$		OMe	61
a	**u**	**t**	OEt	Me	$-CHMeCH_2CH_2-$		OEt	49
d	**v**	**u**	OMe	Me	$-(CH_2)_9-$		OMe	46
d	**w**	**v**	OMe	Me	CH_2CH_2Cl	H	OEt	20
a	**x**	**w**	OEt	Me	$-(CH_2)_4-$		OMe	0
a	**y**	**x**	OEt	Me	H	H	CF_3	0
a	**z**	**y**	OEt	Me	OMe	H	OMe	0
e	**a**	**z**	NMe_2	Me	H	H	OMe	0

[a] Isolated yields

The structures of all products were established by spectroscopic methods. The structure of **28u** was independently confirmed by X-ray crystal structure analysis (**Figure 2-11**).

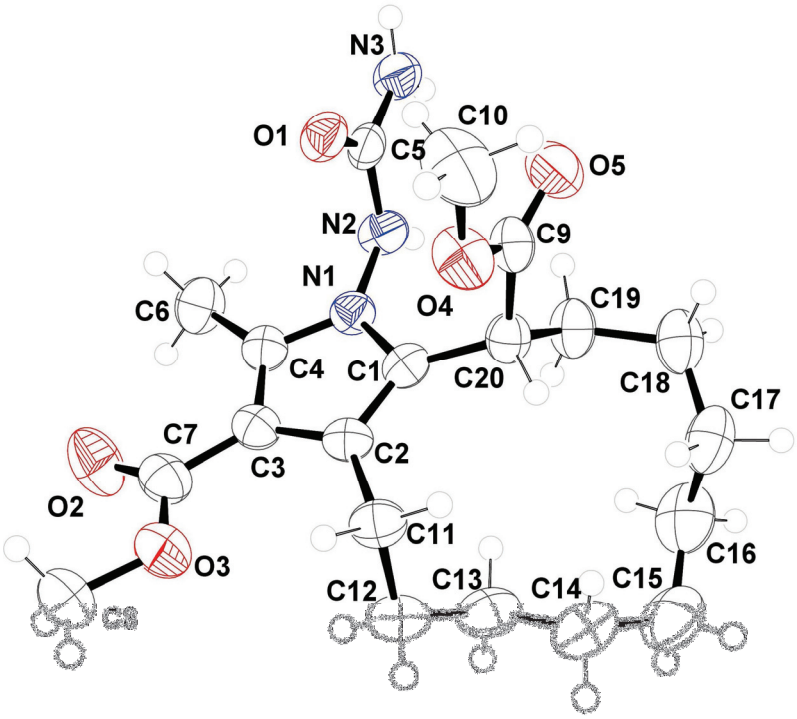
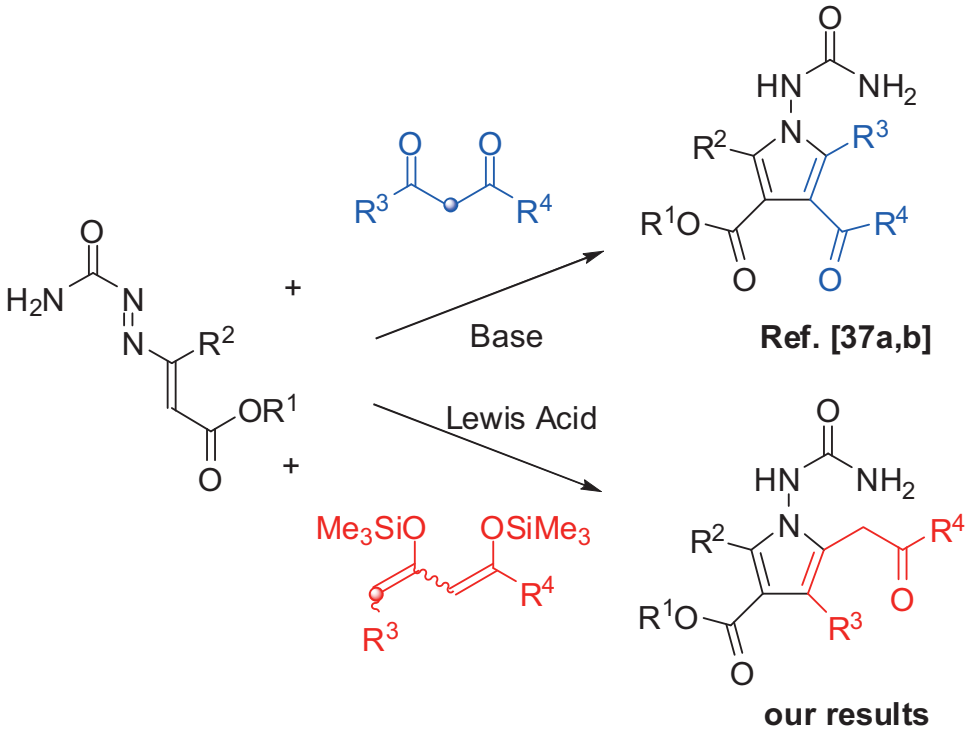


Figure 2-11. Ortep plot of **28u** (50% probability level)

It is noteworthy that the 1-aminopyrroles **28** cannot be obtained from 1,2-diaza-1,3-butadiene and β-dicarbonyl compounds related to 1,3-bis(silyloxy)-1,3-butadienes (**Scheme 2-16**). In fact, according to previous investigations,[37a,b] the reaction between 1,2-diaza-1,3-butadiene and β-ketoesters or β-diketones proceed by base-catalyzed nucleophilic attack of activated methylene group at the heterodiene system leading to 1-aminopyrroles which are regioisomers of 1-aminopyrroles **28** (**Scheme 2-16**).



Scheme 2-16. Regioselective reactions of 1,2-diaza-1,3-butadienes with β-dicarbonyl compounds or related 1,3-bis(silyloxy)-1,3-butadienes for the construction of different functionalized 1-aminopyrroles

The 1-aminopyrroles prepared represent useful synthetic building blocks. For example, it has been reported previously that 1-aminopyrroles, including derivatives containing a urea moiety (similar to products **28**), can be transformed into the corresponding pyrroles by reaction with $Cr_2(OAc)_4$,[47] KO-*t*-Bu/DMF,[48] or H_2/Reney Ni,[49] or by diazotation.[50]

2.3 *Conclusions*

In conclusion, I report the synthesis of a variety of functionalized 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes by one-pot cyclization of 1,3-bis(silyloxy)-1,3-butadienes with quinazolines. The Pd-catalyzed hydrogenation of the some products allow the cleavage of benzyloxycarbonyl group and the formation of new 6-(2-amino-phenyl)-4-oxo-1,4,5,6-tetrahydro-pyridines and 4-alkyl-8,12-diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5,10-tetraenes. In addition, **B3LYP/6-31G(d)** density functional theory computations have been performed to get some insight into the reaction mechanism.

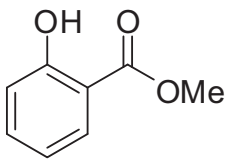
A variety of functionalized 1-aminopyrroles was synthesized by $ZnCl_2$-catalyzed one-pot ′conjugate addition/cyclization′ reactions of 1,2-diaza-1,3-butadienes with 1,3-bis(silyloxy)-1,3-butadienes. These reactions are easy to carry out, proceed under mild conditions and with high yields. It is noteworthy that the products are not directly available from the β-dicarbonyl compounds. In fact, previous investigations[37a,b] have shown that the reaction between 1,2-diaza-1,3-butadiene and β-ketoesters or 1,3-diketones proceed by base-catalyzed nucleophilic attack of the activated methylene group at the heterodiene system leading to regioisomeric 1-aminopyrroles.

3. Synthesis of Functionalized Salicylates and Pyran-4-ones Based on [3+3] Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes

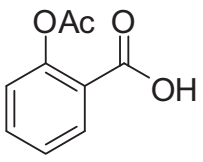
3.1 *Synthesis of Dichloromethyl- and Formylsalicylates based on Regioselective [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes*

3.1.1 Introduction

Polyfunctionalized benzene derivatives occur in many natural products and synthetic compounds which are of pharmacological relevance.[21] For example; salicylates possess anti-inflammatory, analgetic and antipyretic properties. The leaves and bark of the willow tree have been mentioned in ancient texts as a remedy for aches and fever.[51] This plant contains salicylic acid, which is the precursor of acetylsalicylic acid (**Figure 3-1)** known as the active component of aspirin®. *Aspirin* was the first discovered member of the class of non-steroidal anti-inflammatory drugs.



Methyl salicylate **IV**

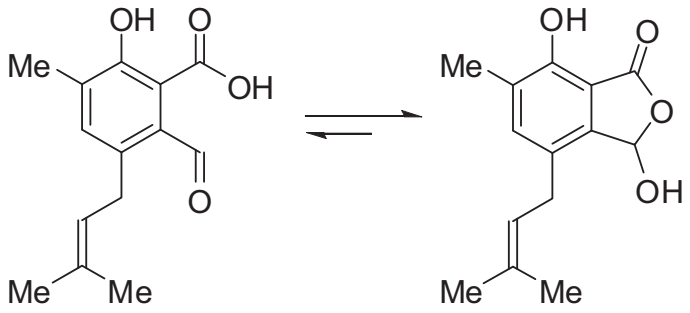


Acetylsalicylic acid **V**

Figure 3-1. Methyl salicylate and Acetylsalicylic acid

Dichloromethyl-substituted arenes and hetarenes are of considerable importance in the field of medicinal chemistry. They have been reported to show antiasthmatic activity,[52] irreversible inhibition of yeast α-glucosidase,[53] and antibiotic activity.[54] In addition, they are versatile synthetic building blocks.

A number of natural products combine hydroxyl, formyl and carboxylic acid groups in one molecule. Examples include *rubramin* and *hexyl rhizoglyphinate*.[55] 2-Formylbenzoic acid is known to exclusively exist in its lactol tautomeric form (i. e., 3-hydroxy-l-(3*H*)-isobenzofuranone).[56] This type of pseudo acid is also present in a number of pharmacologically important natural products, such as *salazinic acid*, *dihydrogladiolic acid*, *xylaral*, *asperdurin*, and *rubralide* C (**Figure 3-2**).[57]



Asperdurin **VI**

Figure 3-2. Asperdurin

Dichloromethyl-substituted arenes have been prepared by chlorination of the corresponding aldehydes using various chlorination agents (e. g., $SOCl_2$, PCl_5).[58] Despite its great utility, this approach suffers from the fact that the required starting materials, functionalized aromatic aldehyde, are not always readily available. An alternative approach is based on direct electrophilic substitution reactions of arenes with chloroform.[59] A drawback of this method is the formation of regioisomeric mixtures in some cases. Chan and Stoessel reported the synthesis of a 6-dichloromethyl-4-hydroxysalicylate by formal [5+1] cyclization of 1-methoxy-1,3,5-tris(silyloxy)-1,3,5-hexatriene with dichloroacetyl chloride.[60] Recently, Peter Langer's research group has reported a new approach to halogenated salicylates by formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 1-ethoxy-4,4,4-trifluorobut-1-en-3-ones and related compounds.[61,62]

Benzene derivatives containing hydroxyl, formyl and ester groups at specific positions are not readily available by electrophilic substitution reactions, due to problems associated with the regioselectivity. In addition, several side reactions are possible for functionalized substrates, due to the harsh reaction conditions. 6-Formylsalicylates have been previously prepared by cleavage of 6,7-dioxa-bicyclo[3.2.2]nona-3,8-dienes,[63a] electrophilic

substitutions,[63b-e] oxidative cleavage of 6-alkenylsalicylates,[63f] alkylation of l-(3*H*)-isobenzofuranones,[63g,h] and oxidation of 6-methylsalicylates.[63i] These strategies have several drawbacks with regard to the preparative scope. The synthesis of polyfunctionalized benzene derivatives by palladium(0)-catalyzed coupling reactions [64] suffers from the fact that the synthesis of the required starting materials, highly functionalized or sterically encumbered aryl halides or triflates, can be a difficult and tedious task.

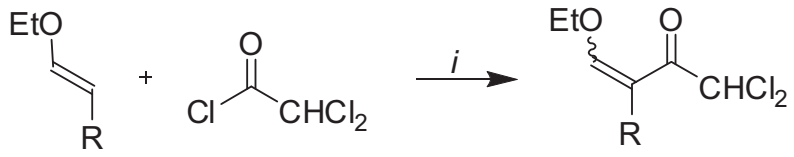
In recent years, Peter Langer's research group has developed this strategy and the novel methods have been applied to the synthesis of various functionalized arenes, and natural product analogues.[65,66]

In this chapter I report the synthesis of functionalized salicylates and pyran-4-ones based on regioselective cyclization of 1,3-bis(silyloxy)-1,3-butadienes.

3.1.2 Synthesis of starting materials

3.1.2.1 *Synthesis of 1,1-dichloro-4-ethoxy-3-buten-2-ones*

The reaction of ethylvinyl ether **29a** and ethyl(prop-1-enyl)ether **29b** (4.0 equivalent) with dichloroacetyl chloride **30** (1.0 equivalent) afforded, following a known procedure,[67] the 1,1-dichloro-4-ethoxy-3-buten-2-ones **31a,b** as mixture of *E/Z*-isomers (**Scheme 3-1**).

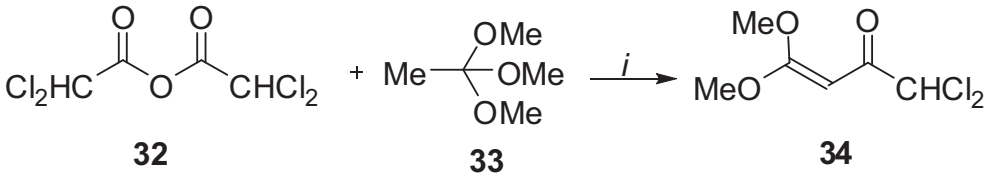


29a,b **30** **31a** (R = H)
31b (R = Me)

Scheme 3-1. Synthesis of 1,1-dichloro-4-ethoxy-3-buten-2-ones **31a,b**. *Conditions i*: 1) CH_2Cl_2, 0 °C, 16 h, 2) Et_3N, Et_2O

3.1.2.2 *Synthesis of 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one*

The synthesis of 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one **34** has not yet been reported.[68] It was prepared, in analogy to the procedure reported for the synthesis of 1,1-dimethoxy-4,4,4-triflurobut-1-en-3-one,[69] by reaction of 2.0 equivalent of dichloroacetic anhydride **32** with 1.0 equivalent of 1,1,1-trimethoxyethane **33** and 2.3 equivalent of pyridine. The product **34** was obtained in 67% yield (**Scheme 3-2**).



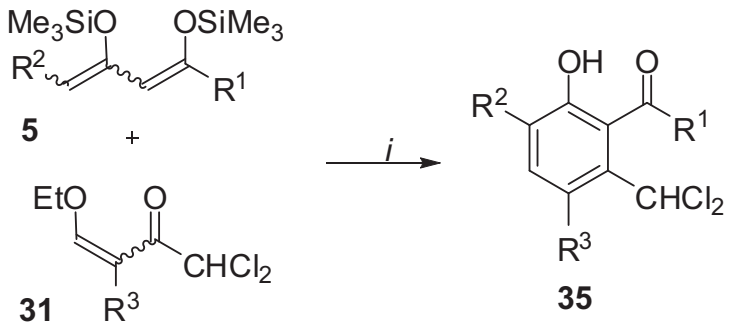
32 **33** **34**

Scheme 3-2. Synthesis of 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one **34**. *Conditions i*: 1) pyridine, CH_2Cl_2, 20 °C, 12 h; 2) ice-cold aqueous solution of Na_2CO_3 (10%)

1,3-Bis(trimethylsilyloxy)-1,3-butadienes **5** were prepared according to the literature from the corresponding β-diketones or β-ketoesters in one or two steps, respectively (see **Chapter 1**).[12,16]

3.1.3 Synthesis of 6-Dichloromethylsalicylates based on Regioselective [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dichloro-4-ethoxy-3-buten-2-ones

The $TiCl_4$-mediated formal [3+3] cyclization of 1,1-dichloro-4-ethoxy-3-buten-2-ones **31** with 1,3-bis(silyloxy)-1,3-butadienes **5**, afforded the 6-(dichloromethyl)salicylates **35** (**Scheme 3-3**).[70]

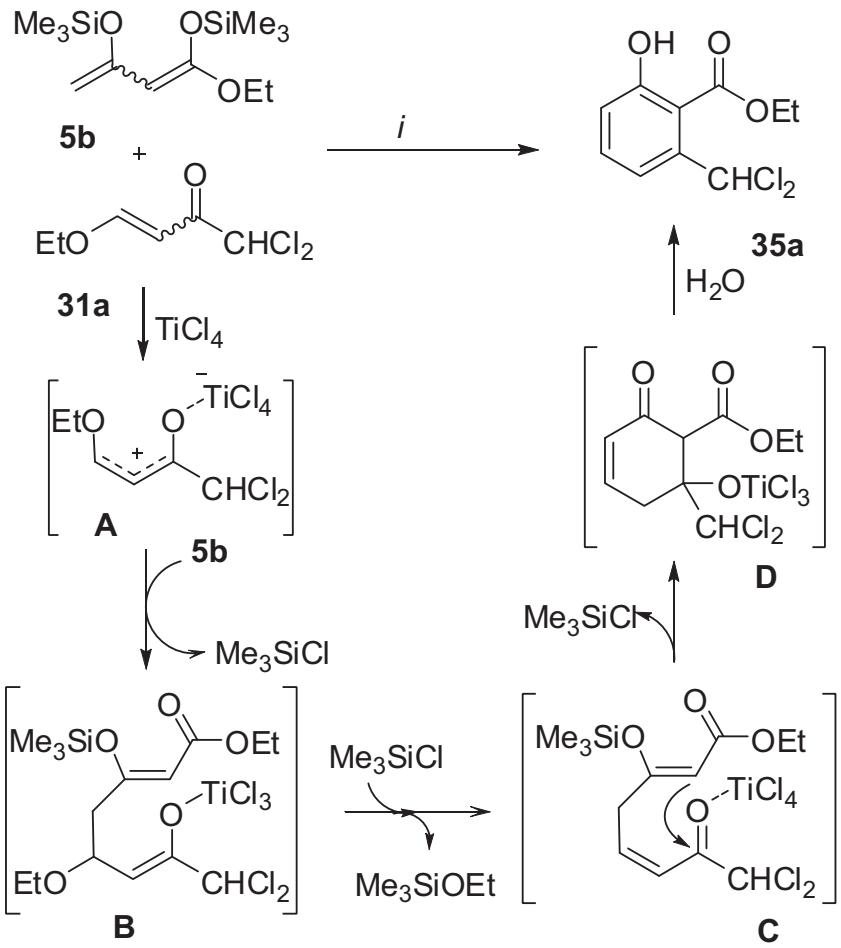


Scheme 3-3. Synthesis of 6-(dichloromethyl)salicylates **35.** *Conditions i*: 1) $TiCl_4$, CH_2Cl_2, -78 → 20 ºC, 18 h; 2) aqueous solution of HCl (10%)

The best yield was obtained when the solution was slowly warmed from -78 °C to 20 °C during 20 h, when the reaction was carried out in a highly concentrated solution (2 mL / 1.0 mmol of **31**), and when an excess (2.0 equiv.) of 1,3-bis(trimethylsilyloxy)-1,3-butadiene **5** and 1.0 equivalent of $TiCl_4$ was employed. For the work-up of the reaction mixture an aqueous solution of hydrochloric acid (10%) was employed.

3.1.4 Mechanistic pathway of the synthesis of 6-(dichloromethyl)-salicylates

The formation of **35** (in a particular case **35a**) can be explained by reaction of **31a** with $TiCl_4$ to give intermediate **A** (**Scheme 3-4**). The attack of the terminal carbon atom of **5b** onto **A** afforded intermediate **B**.



Scheme 3-4. Possible mechanism of the formation of 6-(dichloromethyl)salicylate **35a:** ***C**onditions i*: 1) $TiCl_4$, CH_2Cl_2, -78 → 20 ºC, 18 h; 2) aqueous solution of HCl (10%)

The elimination of ethoxytrimethylsilane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide (before or during the aqueous work-up) and aromatization resulted in the formation of product **35a**.

3.1.5 Products and yields

The $TiCl_4$ mediated formal [3+3] cyclization of **31a,b** with **5** afforded the 6-(dichloromethyl)salicylates **35a-p** in moderate yields (**Scheme 3-4, Table 3-1**). The yields of the products derived from **31a** are generally higher than those derived from **31b**.

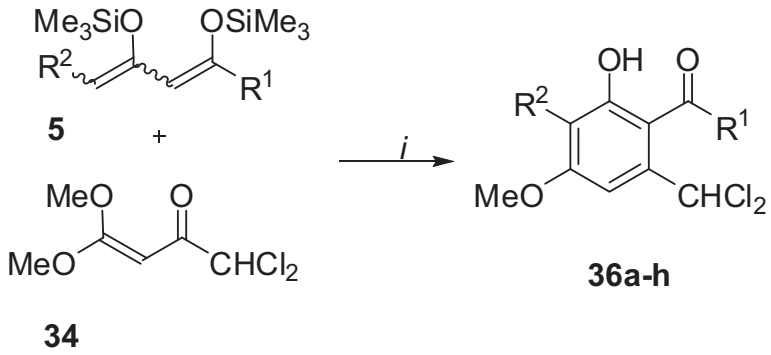
Table 3-1. Synthesis of 6-(dichloromethyl)salicylates **35a-p**

31	**5**	**35**	$\mathbf{R^1}$	$\mathbf{R^2}$	$\mathbf{R^3}$	% (**35**) [a]
a	**d**	**a**	OEt	H	H	52
a	**ab**	**b**	OMe	Me	H	56
a	**k**	**c**	OMe	*i*-Pr	H	40
a	**ac**	**d**	OMe	*n*-Bu	H	48
a	**ad**	**e**	OEt	*n*-Bu	H	25
a	**ae**	**f**	OMe	*n*-Pent	H	49
a	**l**	**g**	OMe	*n*-Hex	H	51
a	**af**	**h**	OMe	*n*-Oct	H	45
a	**n**	**i**	OEt	*n*-Oct	H	54
a	**o**	**j**	OMe	Allyl	H	46
b	**d**	**k**	OEt	H	Me	30
b	**ab**	**l**	OMe	Me	Me	27
b	**k**	**m**	OMe	*i*-Pr	Me	30
b	**ae**	**n**	OMe	*n*-Pent	Me	35
b	**o**	**o**	OMe	Allyl	Me	25
b	**ag**	**p**	OMe	$Ph(CH_2)_3$	Me	42

[a] Yields of isolated products

3.1.6 Synthesis of 6-Dichloromethylsalicylates based on Regioselective [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dimethoxy-4,4-dichlorobut-1-en-3-one

The $TiCl_4$-mediated reaction of 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one **34** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5** afforded 6-dichloromethyl-4-methoxysalicylates **36a-h** in 32-52 % yields (**Scheme 3-5**).[71]



Scheme 3-5. Synthesis of 6-dichloromethyl-4-methoxysalicylates **36a-h**. *Conditions i*: 1) $TiCl_4$, CH_2Cl_2, -78 → 20 °C, 20 h; 2) aqueous solution of HCl (10%)

The best yield was obtained when the solution was slowly warmed from -78 °C to 20 °C during 20 h, when the reaction was carried out in a highly concentrated solution (2 mL / 1.0 mmol of **34**), and when an excess (2.0 equiv.) of 1,3-bis(silyloxy)-1,3-butadiene **5** and 1.0 equivalent of $TiCl_4$ was employed. For the work-up of the reaction mixture an aqueous solution of hydrochloric acid (10%) was employed.

The proposed reaction mechanism of the formation of 6-dichloromethyl-4-methoxysalicylates **36** is similar to the reaction mechanism of the formation of 6-(dichloromethyl)salicylates **35** which is discussed abowe in **3.1.4**.

3.1.7 Products and yields

The $TiCl_4$-mediated reaction of **34** with 1,3-bis(silyloxy)-1,3-butadienes **5** afforded the 6-dichloromethyl-4-methoxysalicylates **36a-h** in moderate yields (**Scheme 3-6, Table 3-2**). The yields also depend on the type of diene employed. However, no clear trend was observed.

Table 3-2. Synthesis of 6-dichloromethyl-4-methoxysalicylates **36a-h**

5	36	R^1	R^2	% (36)[a]
d	**a**	OEt	H	45
g	**b**	$O(CH_2)_2OMe$	H	48
ab	**c**	OMe	Me	32
ah	**d**	OMe	Et	48
k	**e**	OMe	*n*-Pr	53
ac	**f**	OMe	*n*-Bu	46
o	**g**	OMe	Allyl	52
ag	**h**	OMe	$Ph(CH_2)_3$	43

[a] Yields of isolated products

The structures of all products were identified by NMR-Spectroscopy and in two particular cases by X-ray crystal structure analysis. In addition, all compounds gave correct analytical and high resolution mass data. Typical for this class of compounds is the sharp peak of the OH group in ^{1}H-NMR spectra. Its shift to low field area (10 to 12 ppm) shows a hydrogen bond to the ester group. The structures of **36e** and **36f** were independently confirmed by X-ray crystal structure analyses (**Figures 3-3 and 3-4**).

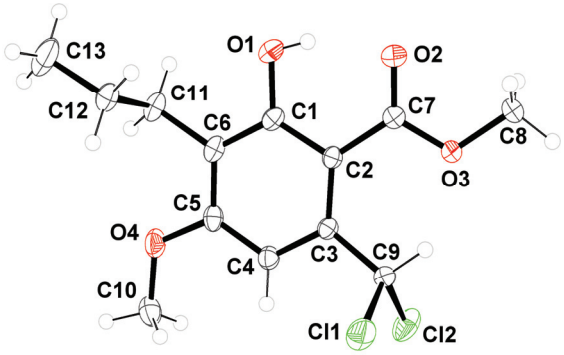


Figure 3-3. Ortep plot of **36e** (50% probability level)

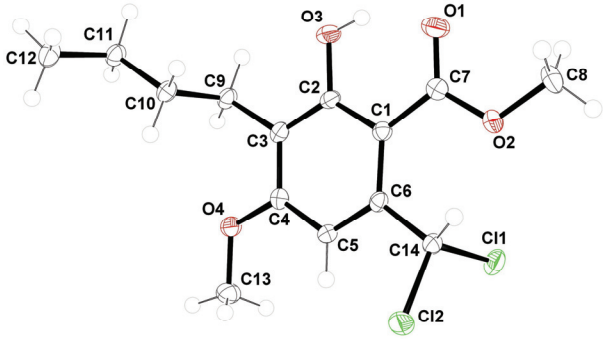
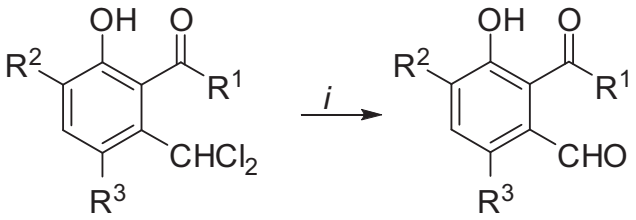


Figure 3-4. Ortep plot of **36f** (50% probability level)

3.1.8 Synthesis of 6-formylsalicylates

The reaction of **35a-d** and **35f-j** with NaOMe/MeOH or NaOEt/EtOH and subsequent addition of hydrochloric acid afforded the 6-formylsalicylates **37a-i** in good yields (**Scheme 3-6, Table 3-3**). [70]



35 **37a-i**

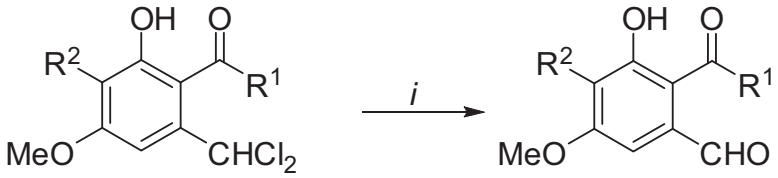
Scheme 3-6. Synthesis of **37.** *Conditions i*: 1) NaOMe, MeOH, 20 °C, 48 h, 2) HCl, H_2O

Table 3-3. Synthesis of 6-formylsalicylates **37**

35	**37**	**R^1**	**R^2**	**R^3**	% (**37**)[a]
a	**a**	OEt	H	H	70
b	**b**	OMe	Me	H	85
c	**c**	OMe	*i*-Pr	H	67
d	**d**	OMe	*n*-Bu	H	81
f	**e**	OMe	*n*-Pent	H	78
g	**f**	OMe	*n*-Hex	H	69
h	**g**	OMe	*n*-Oct	H	73
i	**h**	OEt	*n*-Oct	H	76
j	**i**	OMe	Allyl	H	81

[a] Yields of isolated products

The reaction of **36d,e,g,h** with NaOMe/MeOH and subsequent addition of hydrochloric acid afforded the 6-formyl-4-methoxysalicylates **38a-d** in good yields (**Scheme 3-7, Table 3-4**).[71]



36 **38a-d**

Scheme 3-7. Synthesis of 6-formyl-4-methoxysalicylates **38**. *Conditions i*: 1) NaOMe, MeOH, 20 °C, 24 h, 2) HCl, H_2O

Table 3-4. Synthesis of 6-formyl-4-methoxysalicylates **38a-d**

36	**38**	**R^1**	**R^2**	**% (38)[a]**
d	**a**	OMe	Et	70
e	**b**	OMe	*n*-Pr	77
g	**c**	OMe	Allyl	81
h	**d**	OMe	$Ph(CH_2)_3$	72

[a] Yields of isolated products

The structures of all products were confirmed by spectroscopic methods. In addition, all compounds gave correct analytical and high resolution mass data. Typical for this type of compounds is the sharp peak of the formyl group (CHO) in ^{1}H-NMR spectra. Its shift to low field area (10.3 to 10.6 ppm) compare to dichloromethyl group ($CHCl_2$) of educts **35, 36** which gives singlet at 7.0-8.0 ppm field area. Long-run ^{13}C-NMR analysis gave spectra with typical singlets of phormyl group at 191-193 ppm which is shifted to low field compare to signals of dichloromethyl group ($CHCl_2$) of educts **35, 36** which appears at 68-69 ppm.
The structures of **37a** and **38b** were independently confirmed by X-ray crystal structure analyses (**Figure 3-5** and **Figure 3-6**).

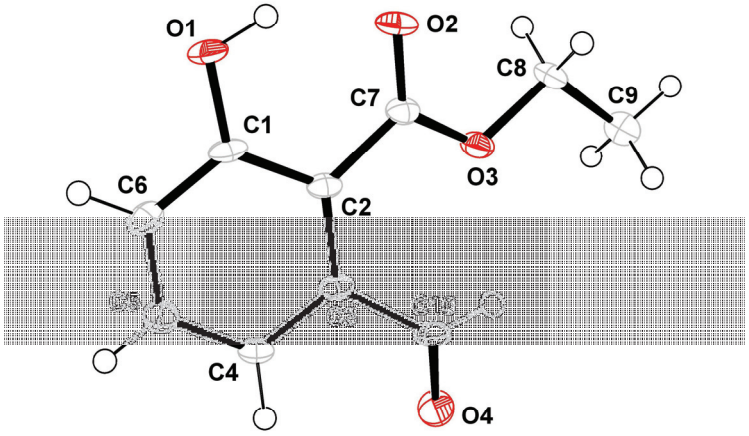


Figure 3-5. Crystal structure of **37a** (50% probability level)

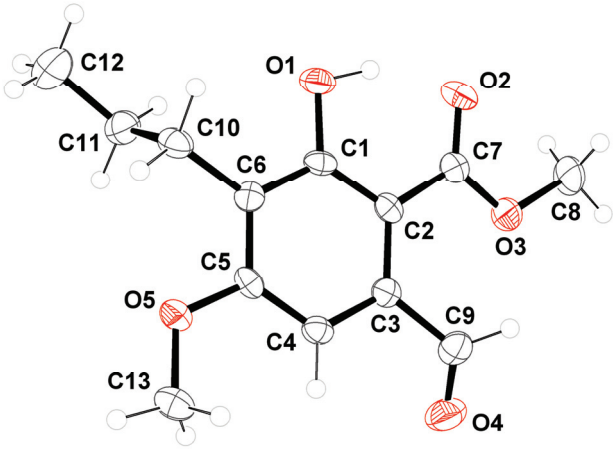
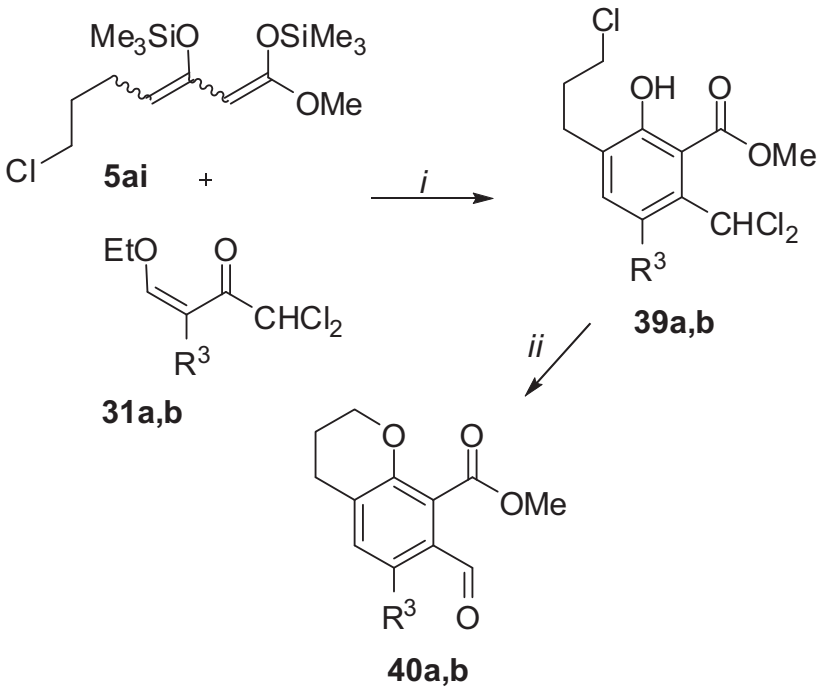


Figure 3-6. Ortep plot of **38b** (50% probability level)

3.1.9 Synthesis of formylchromanes

The cyclization of **31a** and **31b** with 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **5ai**, containing a chlorinated side-chain, afforded the 6-(dichloromethyl)salicylates **39a** and **39b**, respectively (**Scheme 3-8**).[70]



Scheme 3-8. Synthesis of **39a,b** and **40a,b.** *Conditions i*: 1) $TiCl_4$, CH_2Cl_2, -78 → 20 ºC, 18 h; 2) aqueous solution of HCl (10%), *ii*: 1) NaOMe, MeOH, 20 °C, 48 h, 2) HCl, H_2O

The reaction of the latter with NaOMe/MeOH and subsequent addition of hydrochloric acid afforded the 7-formyl-8-(methoxycarbonyl)chromanes **40a,b** (**Scheme 3-9, Table 3-5**). The formation of the latter can be explained by hydrolysis of the dichloromethyl group and base-mediated intramolecular Williamson reaction.

Table 3-5. Synthesis of 7-formyl-8-(methoxycarbonyl)chromanes **40a,b**

5	31	39	40	R^3	% (39) [a]	% (40) [a]
ag	**a**	**q**	**a**	H	57	83
ag	**b**	**r**	**b**	Me	53	81

[a] Yields of isolated products

The structures of all products were established by spectroscopic methods.

3.2 *Synthesis of Dichloromethyl-Substituted Pyran-4-ones by Me_3SiOTf-mediated Cyclocondensation of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dimethoxy-4,4-dichlorobut-1-en-3-one.*

3.2.1 Introduction

γ-Pyrone forms the central core of several natural compounds including maltol and kojic acid. Chelidonic acid is found in Chelidonium majus and meconic acid in opium. The more complex chromone (or 1,4-benzopyrone), flavone and flavonol derivatives are also found in various plants (**Figure 3-7**).[21]

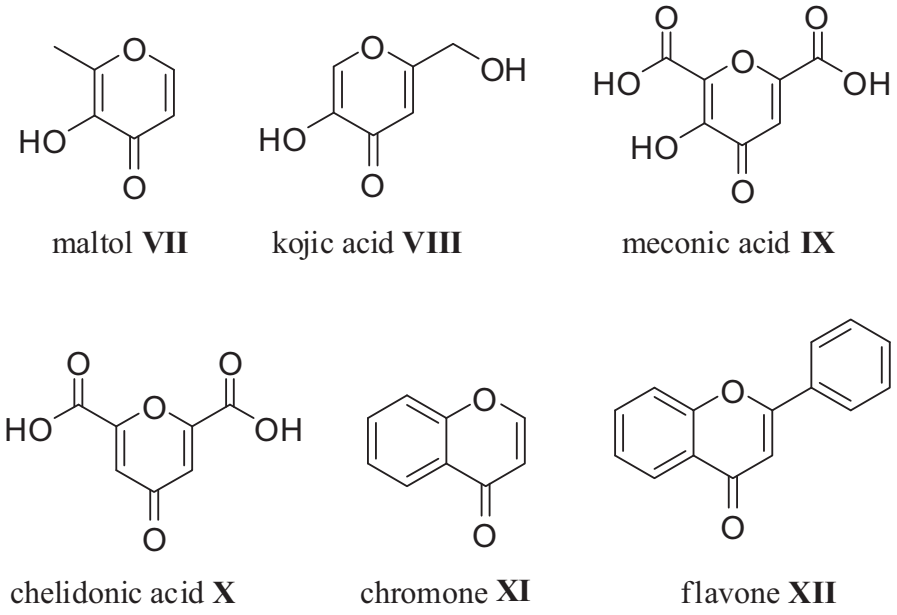
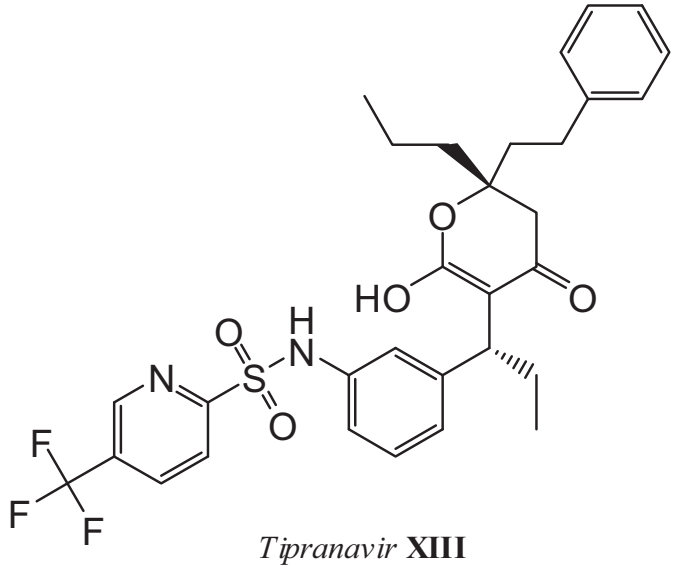


Figure 3-7. maltol, kojic acid, meconic acid, chelidonic acid, chromone, flavone backbones

Like all products found in nature that usually have a pharmacological or biological activity, pyrones and pyrone derivatives are important for pharmaceutical drug discovery and drug design.

Tipranavir (**Figure 3-8**) is a nonpeptidic protease inhibitor manufactured by Boehringer-Ingelheim under the trade name *Aptivus*. It is administered with Ritonavir in combination therapy to treat HIV infection. The structure of tipranavir includes a γ-pyrone core.[72]



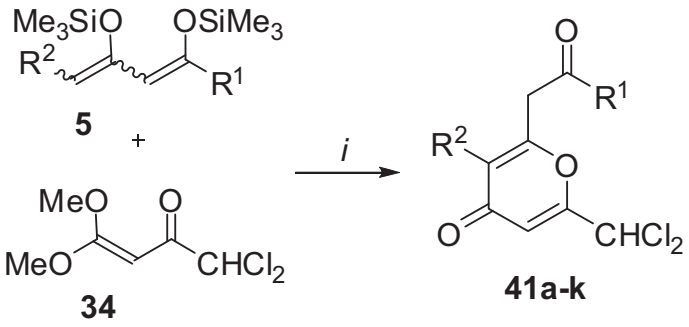
Tipranavir **XIII**

Figure 3-8. *Tipranavir*

Heterocyclic compounds containing halomethyl substituents have attracted much attention due to their remarkable biological activity, their specific chemical reactivity and physical properties. In particular, $CHCl_2$ substituted six-membered heterocycles have important applications in medicinal and agricultural scientific fields.[5] Therefore, the development of synthetic methodologies for the regioselective introduction of $CHCl_2$ or CF_3 groups into heterocyclic rings is of current interest.[73]

3.2.2 Synthesis of 2-(dichloromethyl)pyran-4-ones

The cyclization reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5** with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one **34**, carried out in the presence of Me_3SiOTf (1.0 equiv.) rather than $TiCl_4$, results in the formation of 2-(dichloromethyl)pyran-4-ones in good yields **41a-k** (**Scheme 3-9**).[71]



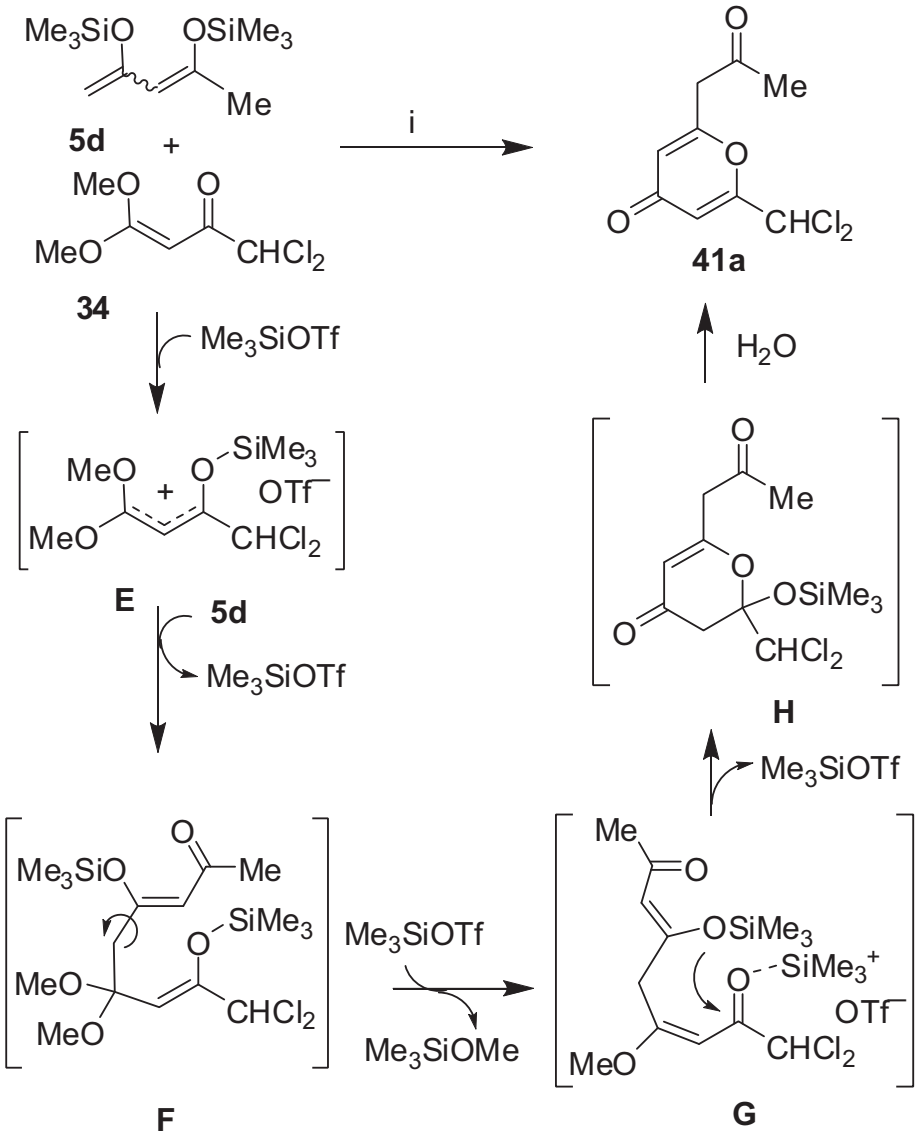
Scheme 3-9. Synthesis of 2-(dichloromethyl)pyran-4-ones **41a-k.** *Conditions i*: 1) Me_3SiOTf, CH_2Cl_2, -78 → 20 °C, 20 h; 2) aqueous solution of HCl (10%)

The best yield was obtained when the solution was slowly warmed from -78 °C to 20 °C during 20 h, when the reaction was carried out in a diluted solution (10 mL / 1.0 mmol of **34**), and when an excess (2.0 equiv.) of 1,3-bis(silyloxy)-1,3-butadiene **5** and 1.0 equivalent of Me_3SiOTf was employed. For the work-up of the reaction mixture the aqueous solution of hydrochloric acid (10%) was employed.

3.2.3 Mechanistic pathway

The reaction of **34** with 1,3-bis(silyloxy)-1,3-butadiene **5b**, carried out in the presence of Me_3SiOTf (1.0 equiv.) resulted in the formation of 2-(dichloromethyl)pyran-4-one **41a** (**Scheme 3-10**). The formation of **41a** presumably proceeds by formation of allylic cation **E**. The attack of the terminal carbon atom of **5d** onto **E** gave intermediate **F**. The elimination of Me_3SiOMe (intermediate **C**) and subsequent cyclization via the oxygen rather than the carbon atom gave intermediate **H**. The elimination of silanol (before or during the aqueous work-up)

resulted in the formation of pyran-4-one **41a**. The formation of 6-dichloromethyl-4-methoxysalicylate **36a** was *not* observed.



Scheme 3-10. Possible mechanism of the formation of **41a.** *Conditions i*: 1) Me_3SiOTf, CH_2Cl_2, -78 → 20 °C, 20 h; 2) aqueous solution of HCl (10%)

3.2.4 Products and yields

The Me_3SiOTf-mediated cyclization of **34** with 1,3-bis(silyloxy)-1,3-butadienes **5** afforded the functionalized 2-(dichloromethyl)pyran-4-ones **41a-k** (**Scheme 3-11, Table 3-6**) in moderate yields. The yields of the esters **41c-k** are higher than the yields of the ketones

41a,b. This can be explained by the higher nucleophilicity of β-ketoester-derived 1,3-bis(silyloxy)-1,3-butadienes compared to those derived from 1,3-diketones. The best yield was obtained for product **41c** which is derived from the simple diene **5b**.

Table 3-6. Synthesis of 2-(dichloromethyl)pyran-4-ones **41a-k**

41	5	R^1	R^2	% (41)[a]
a	**a**	Me	H	21
b	**j**	Ph	H	25
c	**d**	OEt	H	61
d	**f**	O*i*-Pr	H	47
e	**e**	O*i*-Bu	H	35
f	**i**	OBn	H	30
g	**g**	$O(CH_2)_2OMe$	H	35
h	**ab**	OMe	Me	35
i	**ah**	OMe	Et	33
j	**m**	OEt	*n*-Hept	30
k	**af**	OMe	*n*-Oct	25

[a] Yields of isolated products

The structures of all products were confirmed by spectroscopic methods. Typical for the ^{1}H-NMR spectra are the two doublets of the vinyl protons at 6.24-6.56 ppm. The coupling over four bonds is verified by a $^4J_{H\text{-}H}$ constant of 2 Hz.The structures of **41g** and **41i** were independently confirmed by X-ray crystal structure analyses (**Figures 3-9** and **Figure 3-10**).

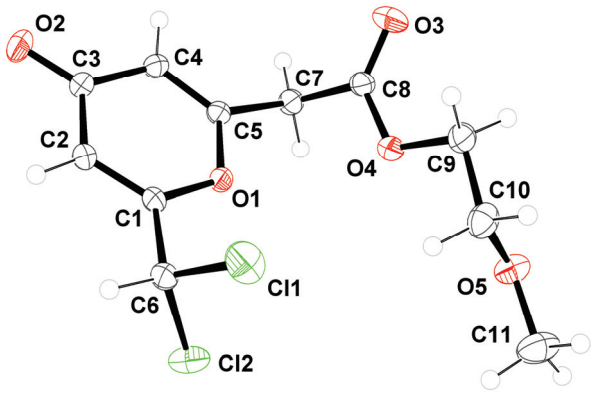


Figure 3-9. Ortep plot of **41g** (50% probability level)

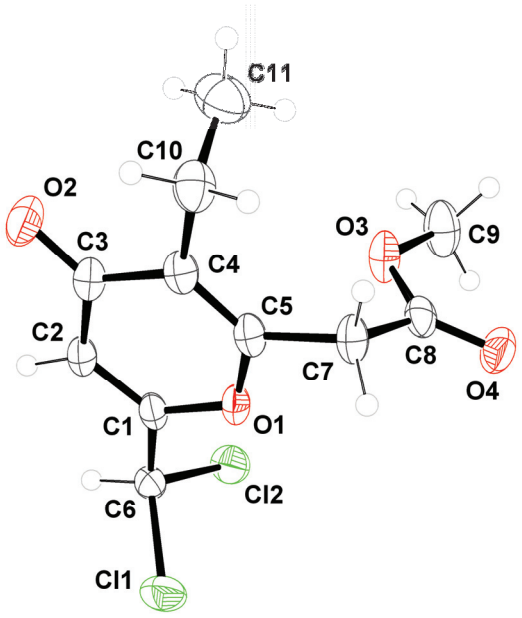
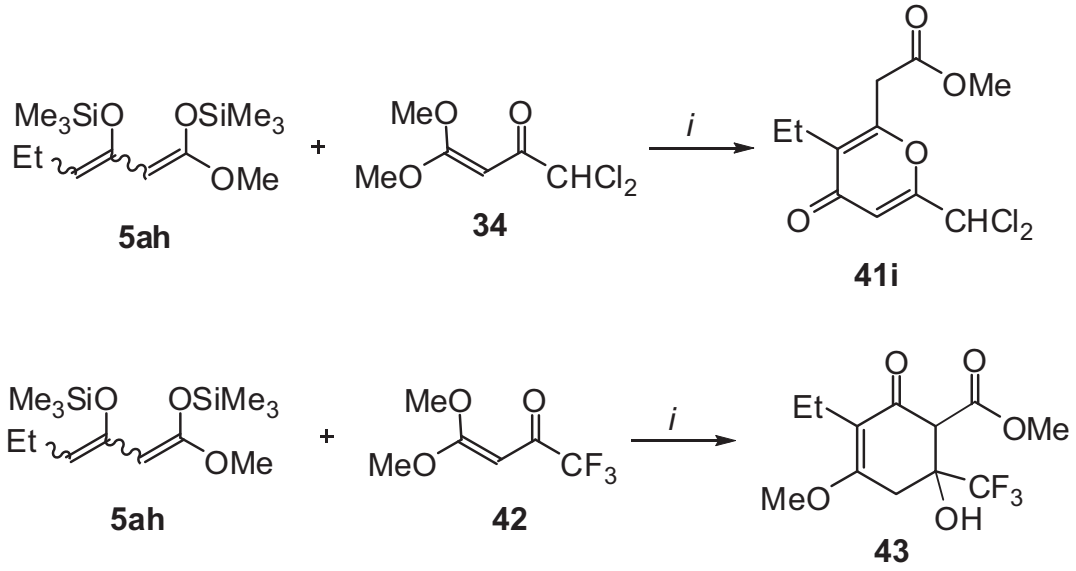


Figure 3-10. Ortep plot of **41i** (50% probability level)

It is important to note that the Me_3SiOTf-mediated formation of $CHCl_2$-substituted pyran-4-ones was generally observed for *all* dienes employed. This result is in contrast to the Me_3SiOTf-mediated synthesis of CF_3-substituted pyran-4-ones which were formed only for 1,3-bis(trimethylsilyloxy)-1,3-butadienes containing no substituent located at carbon atom C-4.[66] For substituted dienes the formation of cyclohexanones was observed.[66] This is illustrated by the reactions shown in **Scheme 3-11**.



Scheme 3-11. Different selectivity of the cyclization of **5ah** with **34** and **42.** *Conditions i*, Me_3SiOTf, CH_2Cl_2, –78 → 20 °C

The Me_3SiOTf-mediated cyclization of **5ah** with **34** afforded pyran-4-one **41i**, while the cyclization of **5ah** with **42** gave under identical conditions the cyclohexanone **43**. The latter did not undergo aromatization under the conditions employed because of the low stability of a cation located next to the CF_3 group. The different regioselectivity of the formation of **41i** and **43** might be explained by the assumption that the (more reactive) trifluoroacetyl group undergoes a rapid and irreversible C-cyclization. In addition, the steric influence of the dichloromethyl group (which should be higher than that of the trifluoromethyl group) may play a role (steric interaction with the ester group).

3.3 *Conclusions*

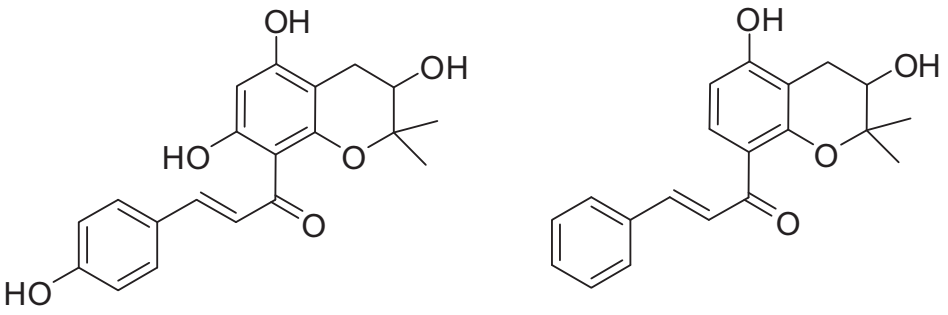
In conclusion, it is reported the $TiCl_4$-mediated formal [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones and 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one. These reactions allow the convenient synthesis of a variety of functionalized 6-(dichloromethyl)salicylates with very good regioselectivity in moderate yields. Some of the products were successfully converted to novel formylsalicylates in good yields. Furthermore, the synthesis of novel 7-formyl-8-(methoxycarbonyl)chromanes is shown. First, the corresponding 6-(dichloromethyl)salicylates were synthesized by $TiCl_4$-mediated cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene and 1,1-dichloro-4-ethoxy-3-buten-2-ones. The reaction of the latter with NaOMe/MeOH and subsequent addition of hydrochloric acid afforded the 7-formyl-8-(methoxycarbonyl)chromanes in high yields.

During the reaction of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one, the use of Me_3SiOTf instead of $TiCl_4$ results in a dramatic change of the selectivity to give novel functionalized 2-(dichloromethyl)pyran-4-ones. A different selectivity was observed for $CHCl_2$ compared to CF_3-substituted substrates.

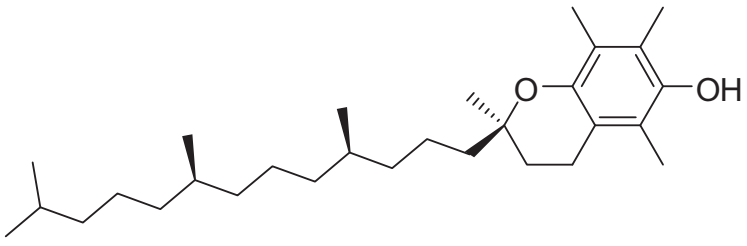
4. Chelation control in the [3+3] annulation reaction of alkoxy-substituted 1,1-diacylcyclopropanes with 1,3-bis(silyloxy)-1,3-butadienes. Synthesis of Chromanes and Isochromanes.

4.1.1 Introduction

3,4-Dihydro-2H-chromenes (chromanes) represent pharmacologically relevant heterocycles, which occur in a variety of natural products (**Figure 4-1**).[74,75] For example, *bavachromanol* has been isolated from leaves of *Maclura tinctoria L.* (Venezuela).[75a] The chromanol moiety of vitamin E (*a-tocopherol*) exhibits anti-androgen properties.[21]



Bavachromanol **XIV** *Flemistrictin F* **XV**

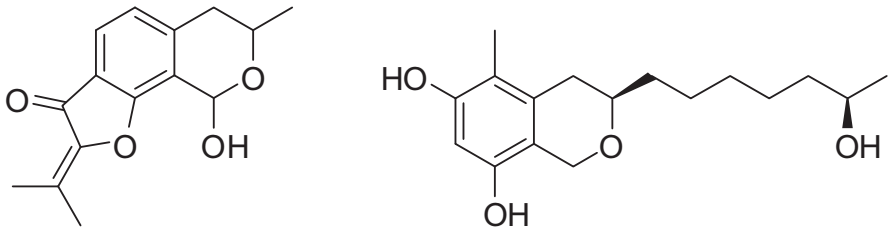


Vitamin E (alpha-tocopherol) **XVI**

Figure 4-1. Bavachromanol, Flemistrictin F, Vitamin E

Natural products containing Isochromane substructure are also of pharmacological relevance. For example, the natural product *pseudodeflectusine* which has been isolated from *Aspergillus*

pseudodeflectus exhibits selective cytotoxic activity against human several cancer cell lines.[76] The two new isochromane derivatives *pseudoanguillosporine A* and *B* which have been isolated first time by Kock *et al*. from *Pseudoanguillospora* show antibacterial and antifungal activity (**Figure 4-2**).[77]



Pseudodeflectosin **XVII** *Pseudoanguillosporin B* **XVIII**

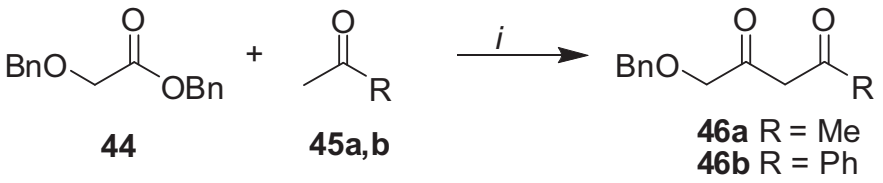
Figure 4-2. Pseudodeflectusine, Pseudoanguillosporine B

Finn *et al*. have prepared chromanes from salicylic aldehydes and vinylboronic acids in the presence of catalytic amounts of dibenzylamine.[78] Jones *et al*. reported the synthesis of chromanes by Diels–Alder reactions of o-quinone methides, which were generated from salicylic aldehydes and alcohols.[79] Recently Langer *et al.* reported the synthesis of 6-(2-hydroxybenzoyl)-3,4-dihydro-2*H*-chromenes based on sequential ′[3+3]-cyclization / Williamson′ reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-formylchromones.[65] Langer and Bose have reported [80] the synthesis of functionalized phenols by $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes. Although symmetrical cyclopropanes were employed in most cases, some unsymmetrical substrates have also been studied. The cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-acetyl-1-formylcyclopropane and with 1-acetyl-1-benzoylcyclopropane proceeded by regioselective attack of the terminal carbon atom of the diene onto the more reactive carbonyl group (i.e., the formyl and the acetyl group, respectively).[80,81]

In this chapter I report an efficient synthetic approach to functionalized chromanes and isochromanes based on the formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes.[82] Noteworthy, the annulation reactions reported provide a convenient and regioselective approach to a variety of sterically encumbered and highly functionalized phenols, which are not readily available by other methods.

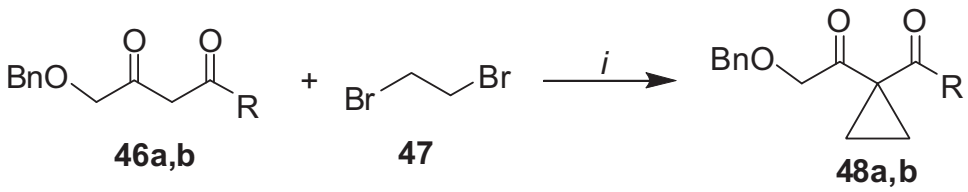
4.1.2 Synthesis of starting materials

First of all two 1,3-dicarbonyl compounds (1-benzyloxypentane-2,4-dione **46a** and 4-benzyloxy 1-phenylbutane-1,3-dion **46b**) were prepared by Claisen condensation of 1.0 equivalent of benzyl-2-(benzyloxy)acetate **44** with 1.0 equivalent of aceton **45a**, or acetophenone **45b** (**Scheme 4-1**).[83]



Scheme 4-1. Synthesis of 1-benzyloxypentane-2,4-dione **46a** and 4-benzyloxy-1-phenylbutane-1,3-dion **46b**. *Conditions i*: 1) Na (4.0 equiv), toluene, 80 °C, 2 h; 2) Et_2O, aqueous solution of HCl (10%)

The potassium carbonate-mediated reaction of the 1-benzyloxypentane-2,4-dione and 4-benzyloxy-1-phenylbutane-1,3-dione **46a,b** with 1,2-dibromoethane **47** in DMSO afforded the substituted cyclopropanes **48a,b** in moderate yields (**Scheme 4-2**).[84]

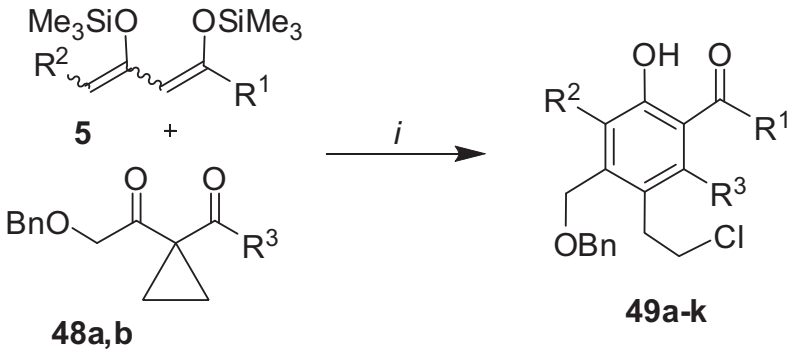


Scheme 4-2. Synthesis of substituted cyclopropanes **48a,b**. *Conditions i*: 1) K_2CO_3 (3.0 equiv.), 1,2-dibromoethane **47** (1.3 equiv.), DMSO, 20 °C, 18 h

1,3-Bis(trimethylsilyloxy)-1,3-butadienes **5** were prepared according to the literature from the corresponding β-diketones or β-ketoesters in one or two steps, respectively (see **Chapter 1**).[12,16]

4.1.3 Synthesis of functionalized Phenols by Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Diacylcyclopropanes

The cyclization of 1-benzyloxypentane-3-cyclopropyl-2,4-dion and 4-benzyloxy-2-cyclopropyl-1-phenylbutane-1,3-dion **48a,b** with 1,3-bis(silyloxy)-1,3-butadienes **5**, in the presence of $TiCl_4$, afforded the functionalized phenols **49a-k** (**Scheme 4-3, Table 4-1**) which are intermediate products for the synthesis of chromanes and isochromanes. All products were formed with very good regioselectivity by attack of the terminal carbon atom of the diene **5** onto the carbonyl group located next to the alkoxy group of dione **48**.[82]



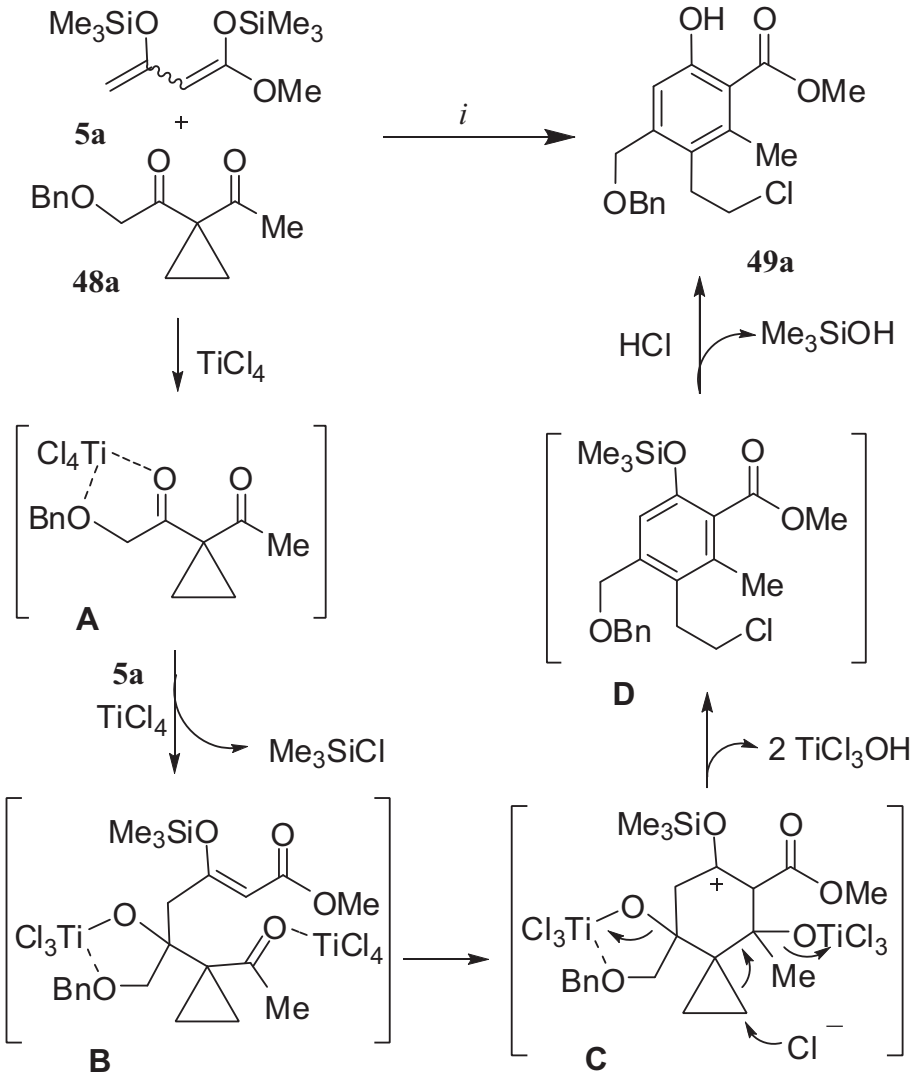
Scheme 4-3. Synthesis of functionalized phenols **49a-k.** *Conditions i*: 1) $TiCl_4$ (2.0 equiv.), CH_2Cl_2, -78 → 20 ºC, 18 h; 2) aqueous solution of HCl (10%)

During the optimization of the reaction, the following parameters proved to be important. The best yields of products **49** were obtained when 1.0 equiv. of dicarbonyl **48**, 1.5 equiv. of 1,3-bis(trimethylsilyloxy)-1,3-butadiene **5** and 2.0 equiv of $TiCl_4$ were employed. The low concentration (c(**48**) = 0.01 M) and the presence of molecular sieves (4 Å) also played an important role.

4.1.4 Mechanistic pathway of the synthesis of functionalized phenols

The $TiCl_4$-mediated cyclization of **48a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **5a** afforded the 5-chloroethyl-4-(benzyloxymethyl)salicylate **49a** (**Scheme 4-4**). The regioselective formation of **49a** can be explained by chelation of $TiCl_4$ by the benzyloxy and the neighboring carbonyl group (intermediate **A**). The $TiCl_4$-mediated attack of the terminal carbon atom of **5a** onto **48a** gives rise to the formation of intermediate **B**, which undergoes a

cyclization via the central carbon atom of the 1,3-dicarbonyl unit (intermediate **C**). The product is subsequently formed by Lewis acid-assisted cleavage of the spirocyclopropane moiety and aromatization by attack of a chloride ion onto the cyclopropane (intermediate **D**) and hydrolysis upon aqueous work-up. The process can be regarded as a domino '[3+3] cyclization/homo-Michael' reaction.[85,86] The regioselectivity can be explained by the Lewis acid-directing effect of the methoxy group of the substrate.



Scheme 4-4. Possible mechanism of the formation of **49a.** *Conditions i*: 1) $TiCl_4$, CH_2Cl_2, -78 → 20 °C, 20 h; 2) aqueous solution of HCl (10%)

4.1.5 Products and yields

The cyclization of **48a,b** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5**, in the presence of $TiCl_4$, afforded the functionalized phenols **49a–k** in moderate to good yields (**Scheme 4-3, Table 4-1**).

Table 4-1. Synthesis of functionalized phenols **49a-k**

5	48	49	R^1	R^2	R^3	% (49)[a]
a	**a**	**a**	OMe	H	Me	46[b]
f	**a**	**b**	O*i*-Pr	H	Me	53
e	**a**	**c**	O*i*-Bu	H	Me	48
ab	**a**	**d**	OMe	Me	Me	68[b]
o	**a**	**e**	OMe	Allyl	Me	35
ai	**a**	**f**	OMe	$Cl(CH_2)_3$	Me	47[b]
a	**b**	**g**	OMe	H	Ph	40[b]
e	**b**	**h**	O*i*-Bu	H	Ph	58
ah	**b**	**i**	OMe	Et	Ph	64[b]
o	**b**	**j**	OMe	Allyl	Ph	46
ai	**b**	**k**	OMe	$Cl(CH_2)_3$	Ph	63

[a] Yields of isolated products
[b] Products were synthesized by Jennifer Hefner

The structure of all products were confirmed by spectroscopic methods. The structure of **49c and 49h** were independently confirmed by X-ray crystral structure analyses (**Figure 4-3 and Figure 4-4**).

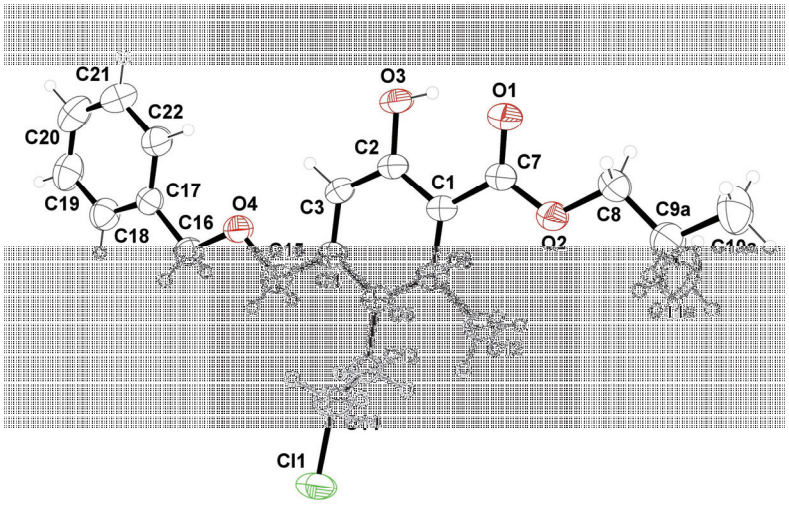


Figure 4-3. Crystal structure of **49c** (35% probability level)

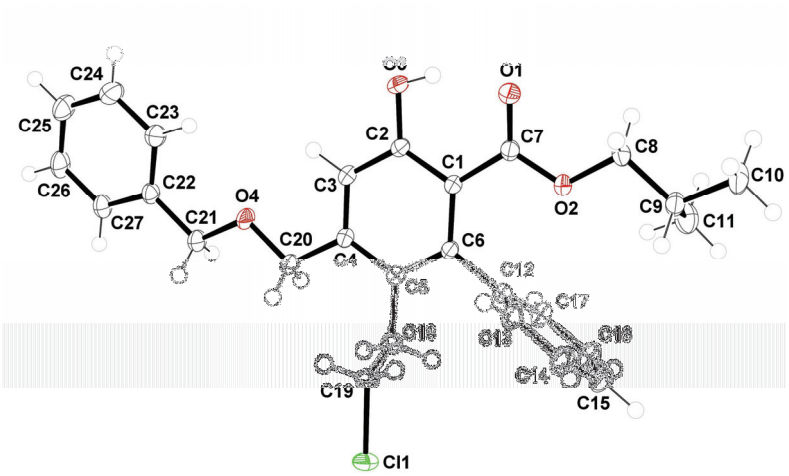
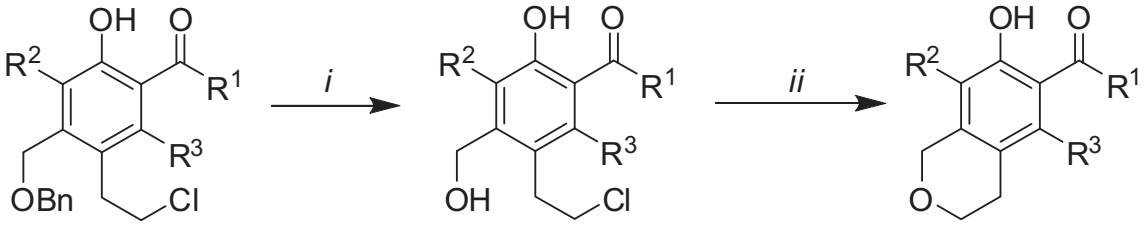


Figure 4-4. Crystal structure of **49h** (60% probability level)

4.1.6 Synthesis of Isochromanes and Chromanes

The substituted arenes **49** prepared by formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) **5** with 1,1-diacylcyclopropanes **48** represent useful synthetic building blocks. For example, benzyloxy-substituted phenoles **49** can be transformed into dihydrobenzopyranes **51** by debenzylation with H_2 and Pd/C (products **50**) and subsequent Williamson reaction (**Scheme 4-5, Table 4-2**).



49 **50** **51a-h**

Scheme 4-5. Synthesis of isochromanes **51a-h**. *Conditions i*: 1) H_2, Pd/C (10 mol%), MeOH, 20 °C, 48 h; *ii*: 1) TBAI (2.0 equiv.), NaH (2.3 equiv.), DMF, 0 °C, 18 h, 2) aqueous solution of HCl (10%)

Table 4-2. Synthesis of Isochromanes **51a-h**

49	**50**	**51**	R^1	R^2	R^3	% (**50**)[a]	% (**51**)[a]
a	**a**	**a**	OMe	H	Me	61[b]	62[b]
b	**b**	**b**	O*i*-Pr	H	Me	75	52
c	**c**	**c**	O*i*-Bu	H	Me	87	54
e	**d**	**d**	OMe	Allyl	Me	85	44
g	**e**	**e**	OMe	H	Ph	96[b]	72[b]
h	**f**	**f**	O*i*-Bu	H	Ph	78	50
j	**g**	**g**	OMe	Allyl	Ph	68	57

[a] Yields of isolated products
[b] Products were synthesized by Jennifer Hefner

The structures of all products were established by spectroscopic methods. The structures of **51c,d,g** were independently confirmed by X-ray crystral structure analyses (**Figures 4-5, 4-6, 4-7**).

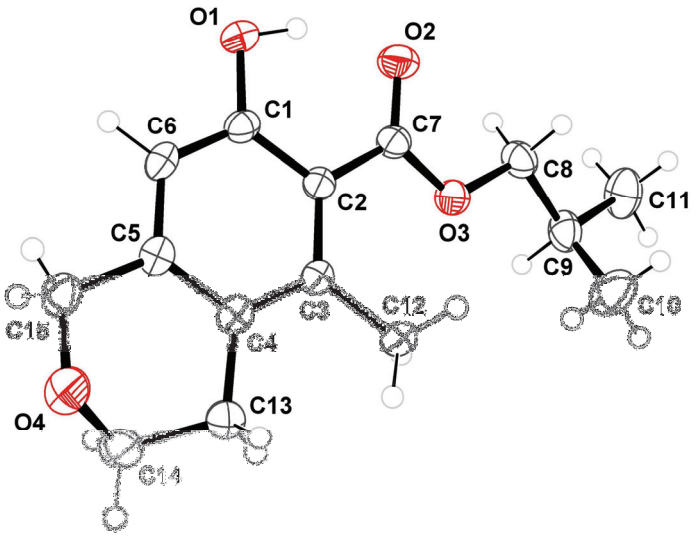


Figure 4-5. Crystal structure of **51c** (50% probability level)

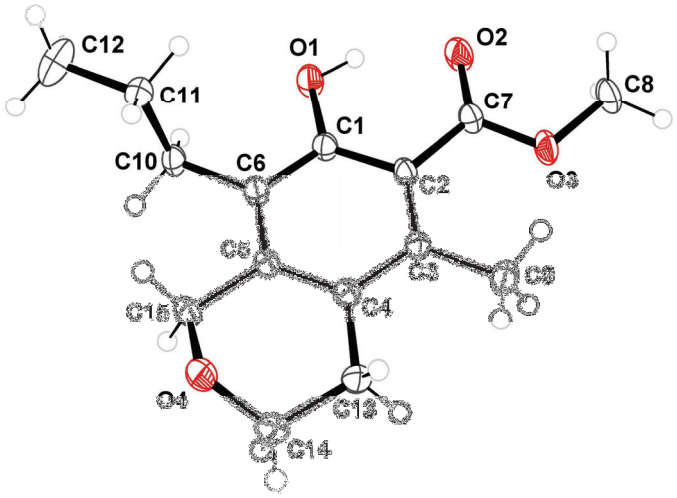


Figure 4-6. Crystal structure of **51d** (50% probability level)

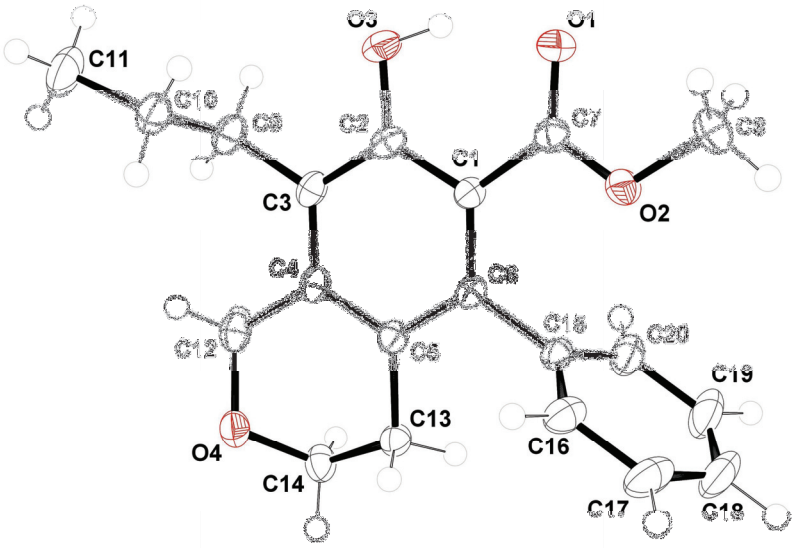
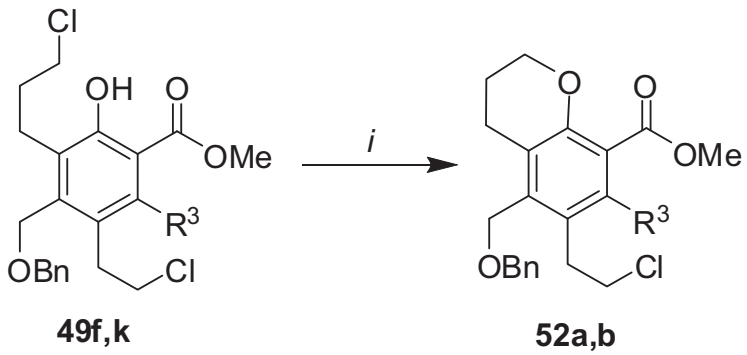


Figure 4-7. Crystal structure of **51g** (50% probability level)

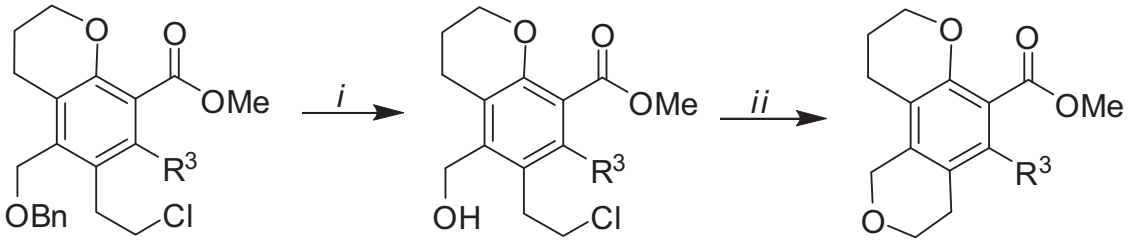
The salicylates **49f,k** prepared by cyclization of **48a** and **48b** with 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **5ai**, containing a second chlorinated side-chain, are transferred to chromanes **52a,b** by treatment of a DMF solution of **49f,k** with sodium hydride (NaH), in the presence of tetrabutylammonium iodide (TBAI) **(Scheme 4-6, Table 4-3).**



49f,k **52a,b**

Scheme 4-6. Synthesis of chromanes **52a,b**. *Conditions i*: 1) TBAI (2.0 equiv.), NaH (2.3 equiv.), DMF, 0 °C, 18 h, 2) aqueous solution of HCl (10%)

The debenzylation of chromanes **52a,b** with H_2 and Pd/C afforded new chromanes **53a,b**. Subsequent treatment of **53** with sodium hydride (NaH), in the presence of tetrabutylammonium iodide (TBAI) (Williamson reaction) afforded tricylic compounds **54a,b** (**Scheme 4-7, Table 4-3**).



52a,b **53a,b** **54a,b**

Scheme 4-7. Synthesis of chromanes **53** and **54**. *Conditions i*: 1) H_2, Pd/C (10 mol%), MeOH, 20 °C, 48 h; *ii*: 1) TBAI (2.0 equiv.), NaH (2.3 equiv.), DMF, 0 °C, 18 h, 2) aqueous solution of HCl (10%)

Table 4-3. Synthesis of chromanes **52, 53** and **54**

49	**52**	**53**	**54**	**R^3**	% (**52**)[a]	% (**53**)[a]	% (**54**)[a]
f	**a**	**a**	**a**	Me	73[b]	96[b]	50[b]
k	**b**	**b**	**b**	Ph	63	61	80

[a] Yields of isolated products
[b] Products were synthesized by Jennifer Hefner

The structures of all products were established by spectroscopic methods. The structures of **53b** and **54b** were independently confirmed by X-ray crystral structure analyses (**Figure 4-8** and **Figure 4-9**).

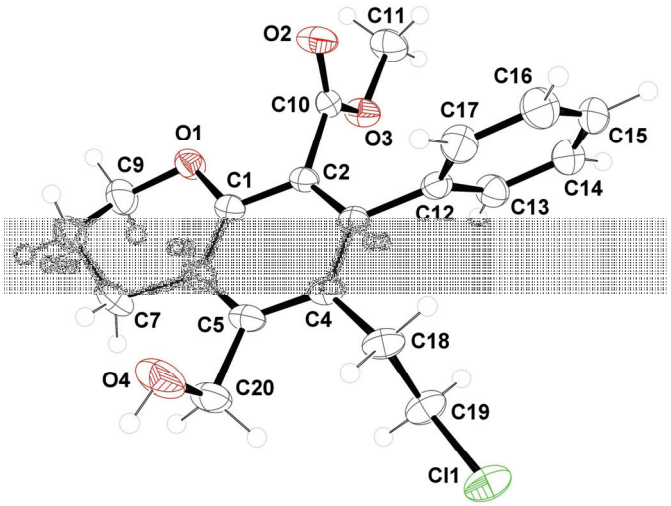


Figure 4-8. Crystal structure of **53b** (50% probability level)

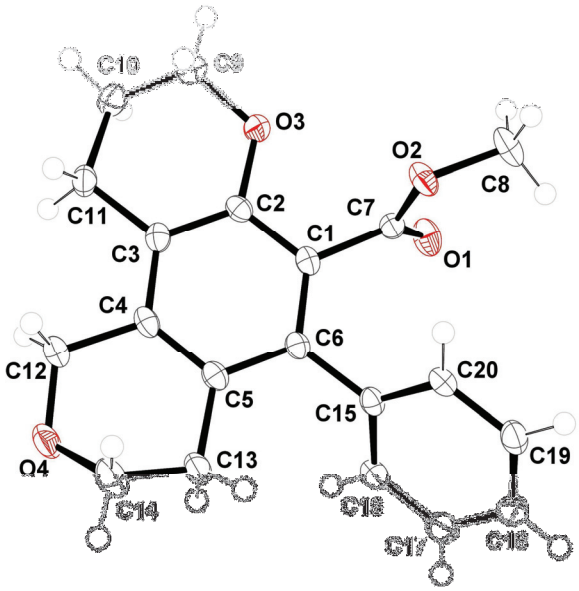


Figure 4-9. Crystal structure of **54b** (50% probability level)

4.1.7 Conclusions

In conclusion, substrate-directed chelation-controlled domino '[3+3] cyclization/homo-Michael' reaction of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes was reported. These reactions provide a convenient approach to highly functionalized phenols, which are not readily available by other methods. The substituted arenes were transformed into isochromanes and chromanes by debenzylation and subsequent Williamson reaction.

5. Regioselective Synthesis of 6-Halomethyl-5,6-dihydro-4*H*-1,2-oxazines based on Cyclizations of Arylalkenyl-oximes

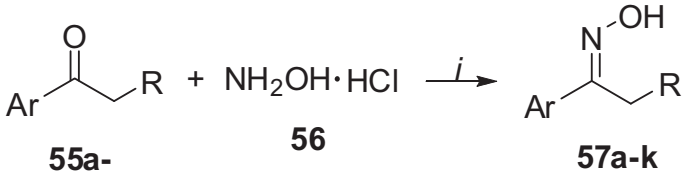
5.1.1 Introduction

1,2-Oxazines are of pharmacological relevance and represent useful synthetic building blocks. They have been used, for instance, as intermediates during the synthesis of glycosidase inhibitor analogues [87] and of functionalized pyrroles.[88] 1,2-Oxazines have been prepared, for example, by hetero-Diels-Alder reactions of alkenes with ene-nitroso compounds derived from α-haloximes [89] and by hetero-Diels-Alder reactions of dienes with nitroso compounds.[90] 1,2-Oxazines are also available by NBS-,[91] acid-,[92] and UV-mediated [93] cyclization of alkenyl-substituted oximes. 1,2-Oxazines have also been prepared by base-mediated cyclizations of γ-chloroximes [94] and γ-sulfonyloximes.[95] Other synthetic approaches to 1,2-oxazines rely on Lewis-acid catalyzed reactions of allenoximes,[96] acid-catalyzed cyclization of cyclopropyloximes,[97] and on cyclizations of γ-nitroketones.[98] Recently, *Langer at el*.[99] reported the synthesis of 1,2-oxazines by cyclization of oxime dianions with epibromohydrin.

In this chapter I report the first syntheses of 6-halomethyl-5,6-dihydro-4*H*-1,2-oxazines by condensation of oxime dianions with allylbromide and subsequent *O*-regioselective iodine- or NBS-mediated cyclization.[100]

5.1.2 Synthesis of arylalkenyl-oximes

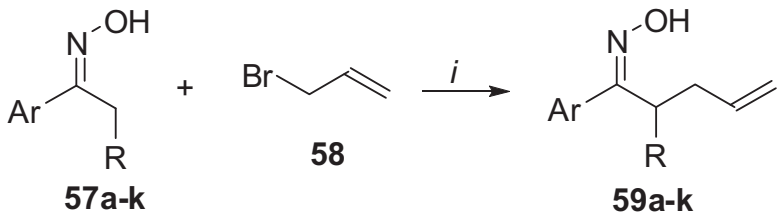
The reactions of ketones **55a-k** with hydroxylamine hydrochloride (1.2 equiv.) **56** afforded, following a known procedure, the corresponding acetophenone oximes **57** (**Scheme 5-1**).[101]



55a- **56** **57a-k**

Scheme 5-1. Synthesis of oximes **57a-k**. *Conditions i*: 1) NaOH (1.2 equiv.), EtOH/H_2O (2:1, 1mL/mmol) reflux, 5 h

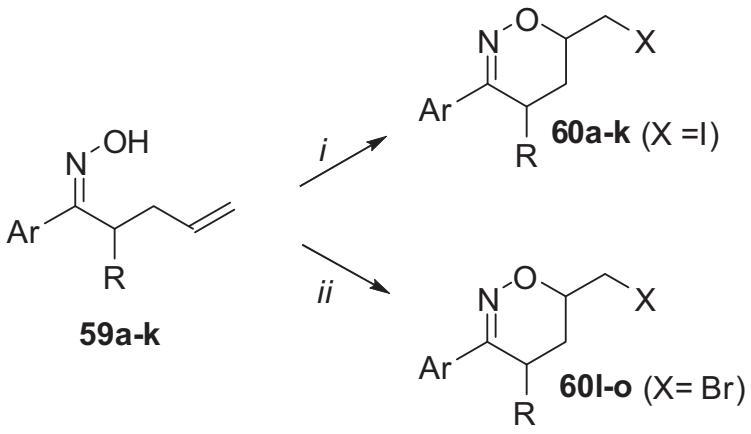
The reaction of the dianions of oximes **57a-k**, generated by means of *n*-butyllithium (2.5 equiv.), with allyl bromide **58** (2.0 equiv.) afforded the arylalkenyl-oximes **59a-k** in good yields (**Scheme 5-2, Table 5-1**).



Scheme 5-2: Synthesis of arylalkenyl-oximes **59a-k**. *Conditions i*: 1) *n*BuLi (2.5 equiv), THF, 1 h, −78 °C, then 10 min, 20 °C; 2) **58** (2.0 equiv), -78 → 20 °C, 16 h

5.1.3 Synthesis of 6-halomethyl-5,6-dihydro-4*H*-1,2-oxazines

The reaction of arylalkenyl-oximes **59a-k** with iodine afforded the 6-iodomethyl-5,6-dihydro-4*H*-1,2-oxazines **60a-k** in moderate to excellent yields (**Scheme 5-3, Table 5-1**).



Scheme 5-3. Synthesis of 1,2-oxazines **60a-o**. *Conditions* for **60a-k** *i*: 1) I_2 (2.0 equiv), CH_2Cl_2, $NaHCO_3$ (sat. aq. sol.), 20 °C, 12 h, 2) Na_2SO_3 (sat. aq. sol.) *Conditions* for **60l-o** *ii*: NBS (1.0 equiv), CH_2Cl_2, 20 °C, 2 h

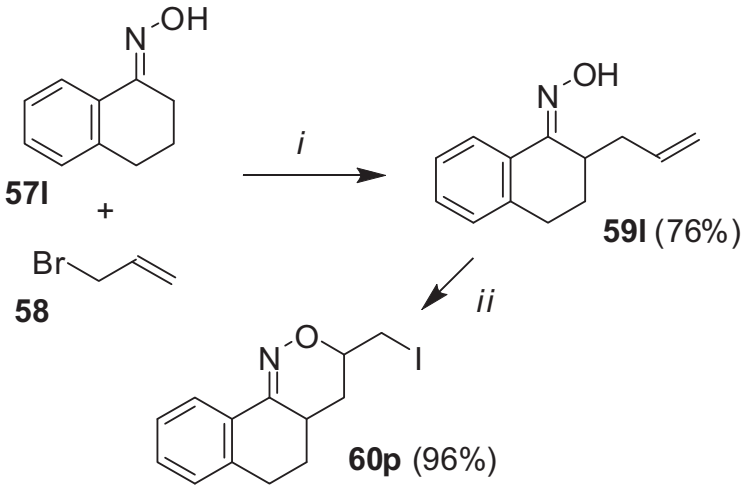
The best yields were obtained when the reaction was carried out in CH_2Cl_2 using a saturated aqueous solution of sodium bicarbonate as the base. The reaction of **59e,f,j,k** with *N*-bromosuccinimide (NBS) afforded the 6-bromomethyl-5,6-dihydro-4*H*-1,2-oxazines **60l-o** (**Scheme 5-3, Table 5-1**).

Table 5-1. Synthesis of arylalkenyl-oximes **59a-k** and 1,2-oxazines **60a-o**

57,59	60	X	R	Ar	% (59)[a]	% (60)[a]
a	**a**	I	H	Ph	85	95
b	**b**	I	H	4-MeC_6H_5	69	83
c	**c**	I	H	3-(MeO)C_6H_5	68	66
d	**d**	I	H	4-(MeO)C_6H_5	71	67
e	**e**	I	H	2-(EtO)C_6H_5	64	96
f	**f**	I	H	4-(EtO)C_6H_5	69	61
g	**g**	I	H	4-FC_6H_5	67	81
h	**h**	I	H	4-ClC_6H_5	60	52
i	**i**	I	H	1-Naphthyl	65	66
j	**j**	I	Me	Ph	63	50[b]
k	**k**	I	Me	4-(MeO)C_6H_5	60	43[b]
e	**l**	Br	H	2-(EtO)C_6H_5	64	57
f	**m**	Br	H	4-(EtO)C_6H_5	69	87
j	**n**	Br	Me	Ph	63	73[b]
k	**o**	Br	Me	4-(MeO)C_6H_5	60	25[b]

[a] Yields of isolated product; [b] dr = 1:1

The tricyclic oxazine **60p** was prepared in high yield from tetralone oxime **57l** (**Scheme 5-4**).



Scheme 5-4. Synthesis of 1,2-oxazine **60p**. *Reagents and conditions*: *i*, 1) **57l** (1.0 equiv), *n*BuLi (2.5 equiv), THF, 1 h, −78 °C, then 10 min, 20 °C, 2) **58** (2.0 equiv), −78 → 20 °C, 16 h; *ii*, 1) $\mathbf{I_2}$ (2.0 equiv), CH_2Cl_2, $NaHCO_3$ (sat. aq. sol.), 20 °C, 12 h, 2) Na_2SO_3 (sat. aq. sol.)

The structure of all products was established by spectroscopic methods. The structures of **60d**,**f,j** were independently confirmed by X-ray crystal structure analyses (**Figures 5-1,2,3**).

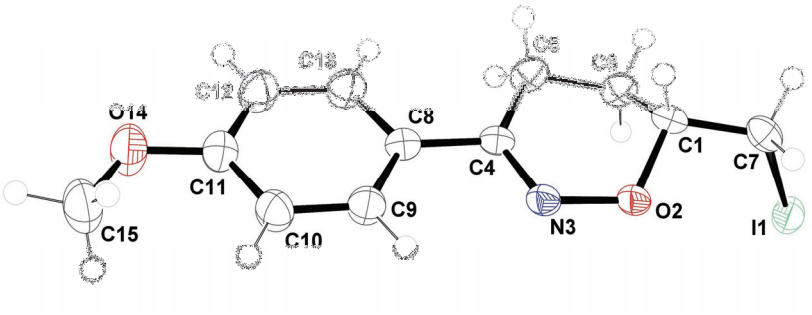


Figure 5-1. Ortep plot of **60d** (50% probability level)

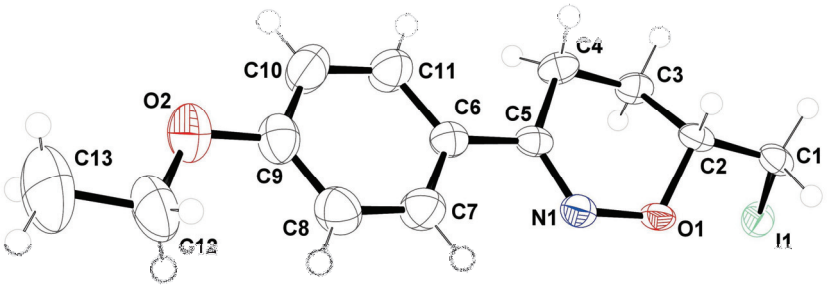


Figure 5-2. Ortep plot of **60f** (50% probability level)

Products **60j,k** and **60n-p** were isolated as 1:1 mixtures of diastereomers. In case of **60j**, one of the two diastereomers could be separated by crystallization (**Figure 5-3**).

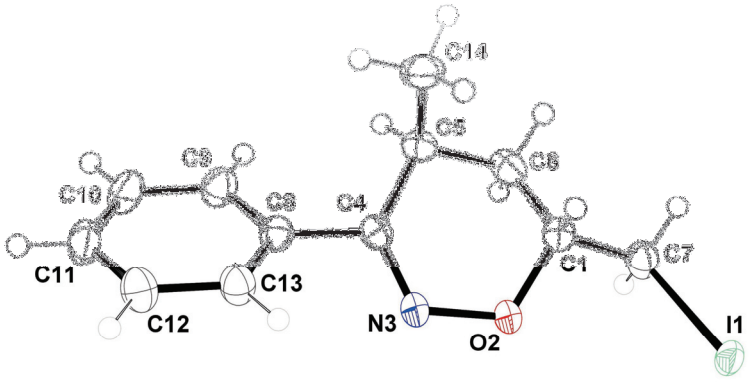
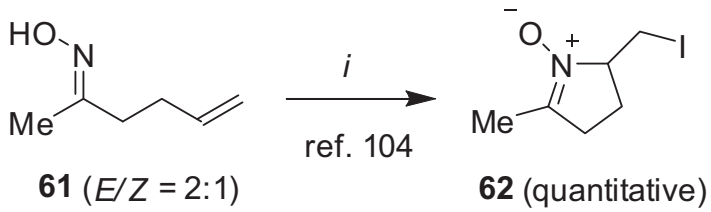


Figure 5-3. Ortep plot of **60j** (50% probability level)

The regioselectivity of cyclization requires some discussion. Oximes are ambident nucleophiles which can react with electrophiles either at the oxygen or at the nitrogen atom. Grigg and coworkers showed that the regioselectivity is controlled by the *E*/*Z*-configuration of the oxime and by the rate of *E*/*Z*-isomerization with respect to the *N*- or *O*-nucleophilic attack.[102-105] The intramolecular reaction of oximes with halonium ions has been reported to result in *N*-alkylation and formation of nitrones. For example, treatment of a CH_2Cl_2-solution of alkenyl-oxime **61** with iodine and anhydrous potassium carbonate quantitatively afforded nitrone **62** which was trapped by a subsequent [3+2] cycloaddition (**Scheme 5-5**).[104]



Scheme 5-5. Synthesis of nitrone **62** by Grigg *et al.*(ref. 104). *Reagents and conditions i*: I_2 (2.0 equiv), CH_2Cl_2, K_2CO_3 (anhydrous), 25 °C, 12 h

Similar results were obtained for the oxime of ethyl 2-homoallyl-cyclohexanone-2-carboxylate. The *N*-regioselectivity was explained by a rapid *Z*→*E* isomerization and subsequent attack of the nitrogen atom onto the iodonium ion. The reaction of **61** with *N*-bromosuccinimide (NBS) was reported to give a 2:1-mixture of nitrone and 1,2-oxazine which reflects the *E*/*Z*-ratio of **61**.[90] In this reaction, the *E*/*Z*-isomerization was slow compared to the *N*- and *O*-cyclization. Similar results have been reported for diphenyl diselenide-mediated cyclizations.[91] In contrast to **61**, the aryl-substituted oximes **59a-l** contain an *E*-configured C=N group, due to the steric effect of the aryl group.[105] The excellent *O*-regioselectivity of the formation of 1,2-oxazines **60a-p** can be explained by the assumption that the *E*→*Z* isomerization is slow compared to the *O*-regioselective 1,2-oxazine formation.

5.1.4 Conclusions

In conclusion, I developed the synthesis of 6-iodo- and 6-bromomethyl-5,6-dihydro-4*H*-1,2-oxazines by alkylation of dilithiated acetophenone-oximes with allylbromide and subsequent regioselective iodine- or NBS-mediated cyclization. The results reported herein show that oxazines are available from alkenyl-oximes containing sterically demanding substituents.

6. Abstract

The goal of the present thesis was an extension of the synthetic potential of 1,3-bis(silyl enol ethers) (**5**). Regioselective cyclization reactions of 1,3-bis(silyloxy)-1,3-butadienes (**5**) provide an elegant approach for the synthesis of various complex carba- and heterocycles from simple starting materials.

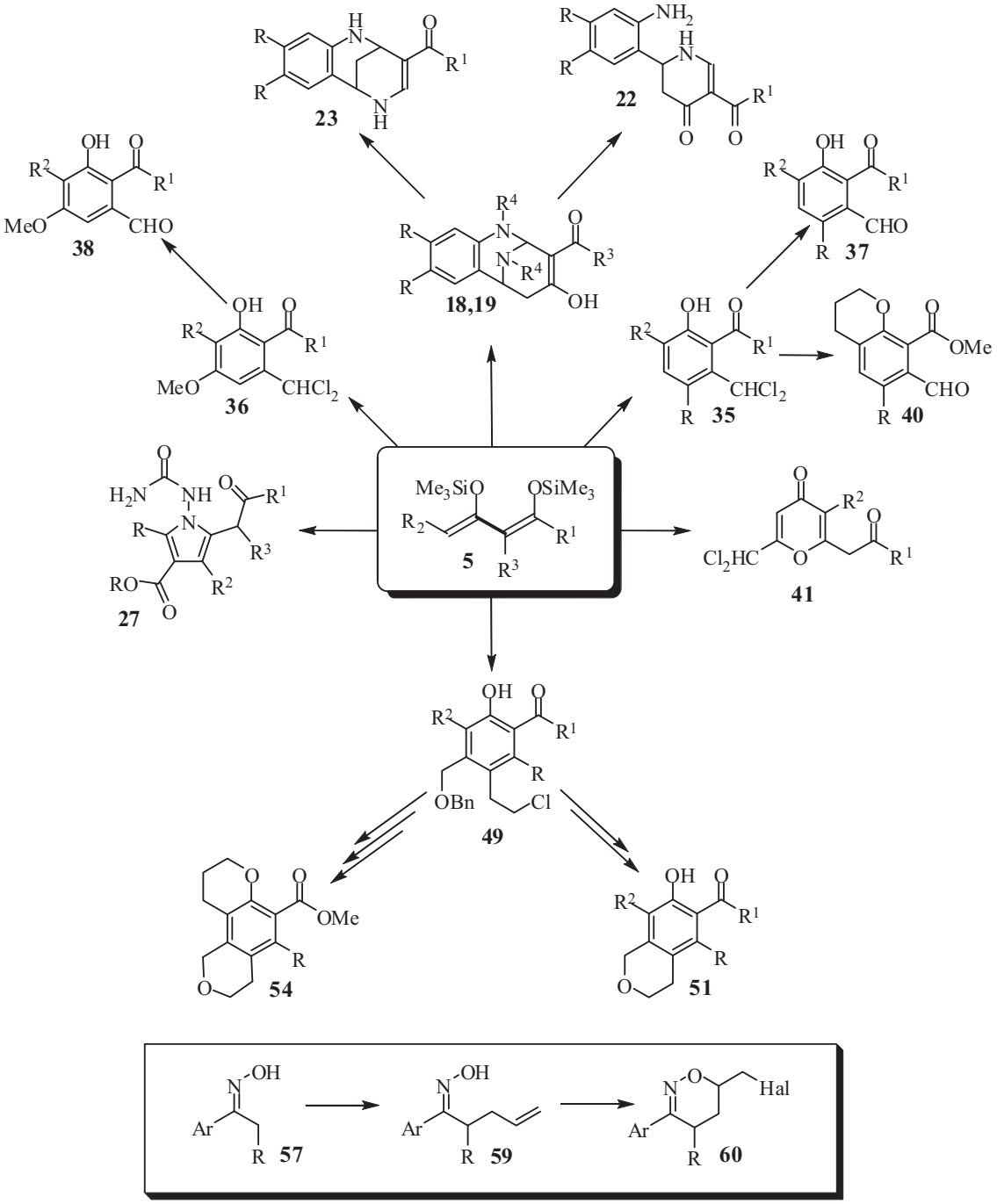
Thus, various bridged *N*-heterocycles (**18, 19**) were prepared by one-pot cyclization of 1,3-bis(silyloxy)-1,3-butadienes (**5**) with quinazolines. The Pd-catalyzed hydration of some products afforded novel functionalized bridged and non bridged *N*-heterocycles (**22, 23**). A variety of functionalized 1-aminopyrroles (**27**) was synthesized by $ZnCl_2$-catalyzed one-pot ′conjugate addition/cyclization′ reactions of 1,2-diaza-1,3-butadienes with 1,3-bis(silyloxy)-1,3-butadienes (**Chapter 2**).

The $TiCl_4$-mediated formal [3+3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dichloro-4-ethoxy-3-buten-2-ones and 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one allow for convenient synthesis of a variety of functionalized salicylates (**35, 36**). Some of the products were successfully converted to novel formylsalicylates (**37, 38**) and formylchromanes (**40**) in high yields. The Me_3SiOTf-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1,1-dimethoxy-4,4-dichlorobut-1-en-3-one results novel functionalized 2-(dichloromethyl)pyran-4-ones (**41**) (**Chapter 3**).

Furthermore, a variety of functionalized phenols with halogenated side chains (**49**) were prepared with very good regioselectivity by chelation-controlled domino '[3+3] cyclization/homo-MICHAEL' reaction. Follow-up reactions of the prepared compounds resulted in the formation of chromans, isochromans (**51, 54**) (**Chapter 4**).

In addition, 6-halomethyl-5,6-dihydro-4*H*-1,2-oxazines (**60**) are synthesized based on regioselective cyclization of arylalkenyl-oximes (**59**) (**Chapter 5**).

All products were thoroughly characterized by various analytical methods. The products reported herein are not readily available by other methods.



General Scheme: Reactions of masked (1,3-bis(silyloxy)-1,3-butadienes) and oxime dianions developed in this thesis

7. Experimental Section

7.1 *General: Equipment, chemicals and work technique*

NMR Spectroscopy: ^{1}H NMR spectra (250.13 MHz, 300.13 MHz and 500 MHz) and ^{13}C NMR spectra (62.9 MHz, 75.5 MHz and 125.8 MHz) were recorded on Bruker instruments AVANCE 250, ARX 300, and AVANCE 500, with $CDCl_3$, MeOH-d_4 and DMSO-d_6 as solvents. The calibration of spectra was carried out on solvent signals ($CDCl_3$: δ ^{1}H = 7.25, δ ^{13}C = 77.00; DMSO-d_6: δ ^{1}H = 2.50, δ ^{13}C = 39.50; MeOH-d_4: δ ^{1}H = 3.30, δ ^{13}C = 49.00). The ^{1}H and ^{13}C NMR signals were assigned by DEPT and two–dimensional ^{1}H,^{1}H COSY, ^{1}H,^{1}H NOESY and ^{1}H,^{13}C correlation spectra (HMBC and HSQC).
Characterization of the signal fragmentations: s = singlet, d = doublet, dd = double of doublet, ddd = doublet of a double doublet, t = triplet, q = quartet, quint = quintet; sext = Sextet, sept = Septet, m = multiplet, br = broadly. Spectra were evaluated according to first order rule. All coupling constants are indicated as (*J*).

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

High resolution mass spectroscopy (HRMS): Finnigan MAT 95 or Varian MAT 311; Bruker FT CIR, AMD 402 (AMD Intectra).

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

Elementary analysis: LECO CHNS-932, Thermoquest Flash EA 1112.

X-ray crystal structure analysis: Crystallographic data were collected on a Bruker X8Apex, Diffractometer with CCD-Kamera (MoK_a und Graphit Monochromator, λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-97 and refined against F^2 on all data by fullmatrix least-squares with SHELXL-97.

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

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

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

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

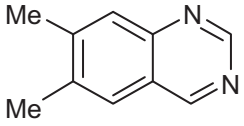
Computational details: The structures **28a-z** were optimized at the B3LYP/6-31G(d) level of density functional theory. All optimized structures were characterized by frequency calculation as energy minimums without imaginary frequencies (NImag = 0) or transition states with only one imaginary frequency (NImag = 1) at the same level of theory. The thermal corrections to Gibbs free energies at 298 K at B3LYP/6–31G* from the frequency calculations have been added to the total electronic energies for analyzing the selectivity, which has been estimated on the basis of the relationship of $\Delta\Delta G = -RT\ln K$, in which $\Delta\Delta G$ is the difference of the Gibbs free energy, and K presents the considered equilibrium constant of the two competing reactions. All calculations have been carried out by using the Gaussian 03 program package.

7.2 *Procedures and Spectroscopic Data:*

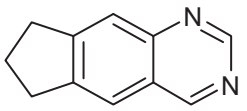
7.2.1 Synthesis of substituted Quinazolines

General procedure 1: To a solution of aniline **14** (10.0 mmol) in THF (100 mL) were added triethylamine (20.0 mmol) and ethyl chloroformate (20.0 mmol). The solution was stirred for 1 h at 20 ºC, filtered and concentrated in vacuo. To the residue was added ethyl acetate (100 mL) and the solution was washed with water (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. To the residue were added TFA (70 mL) and hexamethylenetetramine (HMTA) (9.800 g, 70.0 mmol) and the solution was heated under reflux for 1 h. After cooling, the mixture was diluted with 4 M HCl (400 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH, 1/1) 10% KOH (600 mL), added of $K_3Fe(CN)_6$ (25.0 g, 76.0 mmol) and refluxed for 4 h. After cooling, the mixture was diluted with water (600 mL), extracted with toluene (5 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane →heptane-EtOAc = 2:1).

6,7-Dimethylquinazoline (16h): Following **general procedure 1** and starting with 3,4-dimethylaniline **14e** (1.210 g, 10.0 mmol), triethylamine (2.020 g, 20.0 mmol) and ethyl chloroformate (2.170 g, 20.0 mmol) in THF (100 mL) and with HMTA (9.800 g, 70.0 mmol) in TFA (70 mL) **16h** was obtained as a red oil (0.550 g, 35%).[1] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.62 (s, 1H, CH_{Hetar}), 7.77 (s, 1H, CH_{Hetar}), 9.20 (s, 1H, NCH), 9.23 (s, 1H, NCH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.1, 20.9 (CH_3), 123.9, 126.1 (CH_{Hetar}), 127.5, 138.2, 145.4, 149.2 (C_{Hetar}), 154.6, 158.8 (NCH_{Hetar}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3253 (w), 3015 (w), 2974 (m), 2944 (m), 2923 (m), 2872 (w), 1671 (s), 1627 (m), 1576 (s), 1489 (s), 1455 (m), 1406 (w), 1370 (m), 1352 (w), 1178 (w), 1112 (w), 1025 (m), 1003 (w). MS (EI, 70 eV): *m/z* (%) = 158 (M^+, 100), 143 (25), 131 (14), 104 (31). HRMS (EI): Calcd for $C_{10}H_{10}N_2$ (M^+) 158.08385, found 158.083300.



7,8-Dihydro-6*H*-cyclopenta[*g*]quinazoline (16i). Following **general procedure 1** and

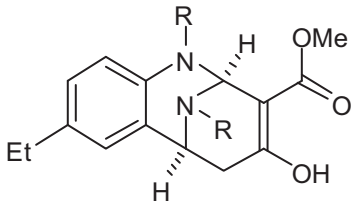


starting with 5-aminoindane **14f** (1.330 g, 10.0 mmol), triethylamine (2.020 g, 20.0 mmol) and ethyl chloroformate (2.170 g, 20.0 mmol) in THF (100 mL) and with HMTA (9.800 g, 70.0 mmol) in TFA (70 mL), **16i** was obtained as a slightly yellow solid (0.910 g, 54%); mp 97 – 98 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15 (m, 2H, $CH_2CH_2CH_2$), 3.08 (m, 4H, $CH_2CH_2CH_2$), 7.65 (s, 1H, CH_{Hetar}), 7.79 (s, 1H, CH_{Hetar}), 9.18 (s, 1H, NCH), 9.23 (s, 1H, NCH). ^{13}C NMR (250 MHz, $CDCl_3$): δ = 25.9 ($CH_2CH_2CH_2$), 32.4, 33.2 ($CH_2CH_2CH_2$), 121.0, 122.5 (CH_{Hetar}) 124.4, 145.7, 153.0, 149.8 (C_{Hetar}), 154.4, 159.1 (NCH_{Hetar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3018 (w), 2976 (w), 2954 (m), 2910 (m), 2873 (w), 1653 (w), 1626 (m), 1570 (m), 1421 (m), 1357 (m), 1281 (w), 1039 (w), 937 (m), 871 (m). MS (EI, 70 eV): *m/z* (%) = 170 (M^+, 100), 142 (17), 115 (46), 89 (8). HRMS (EI): Calcd for $C_{11}H_{10}N_2$ (M^+) 170.08385, found 170.083376.

7.2.2 Synthesis of 3,4-Benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes and by Cyclization of 1,3-Bis(silyloxy)-1,3-butadiens with Quinazolines

General procedure 2: To a solution of quinazoline **16** (4.0 mmol) in CH_2Cl_2 (40 mL) were added at 0 °C the 1,3-bis(silyloxy)-1,3-butadiene **5** (5.6 mmol) and the chloroformate (16.0 mmol). The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, heptane → heptane-EtOAc =2:1).

4-Ethyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-

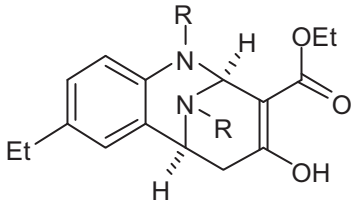


(R = CO_2Me)

tricarboxylic acid trimethyl ester (18f). Following **general procedure 2** and starting with 6-ethylquinazoline **16d** (0.316 g, 2.0 mmol), **5a** (0.728 g, 2.8 mmol) and methyl chloroformate (0.756 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **18f** was obtained as a slightly yellow solid (0.330 g, 43%); mp. 137 – 139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t ^{3}J = 7.6 Hz, 3H, CH_2CH_3), 2.40 (dd, ^{2}J = 17.6 Hz, ^{3}J = 1.7 Hz, 1H NCHCH_2), 2.58 (q, ^{3}J = 7.6 Hz, 2H, CH_2CH_3), 2.97 (dd, ^{2}J = 17.6 Hz, ^{3}J = 4.7 Hz, 1H, NCHCH_2), 3.75, 3.79, 3.86 (s, 9H, OCH_3), 5.36 (br, 1H, NCHCH$_2$), 6.87 (s, 1H, Ar), 7.06 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.7 Hz, 1H, Ar), 7.36 (br, 1H, NCHN), 7.64 (br, 1H, Ar), 12.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.4 (CH_2CH_3), 28.1 (CH_2CH_3), 38.1

(br, NCH*C*H$_2$), 48.8 (br, N*C*HCH$_2$), 52.0, 53.1, 53.2 (OCH$_3$), 58.9 (br, NCHN), 98.0 (NCH*C*CO), 124.3, 125.5, 126.6 (CH$_{Ar}$), 127.3, 132.0 (br), 140.2 (C$_{Ar}$), 153.5, 154.1 (NCOO), 170.6 (C*C*OO), 173.3 (br, COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3073 (w), 2962 (m), 2873 (w), 1721 (s), 1700 (s), 1659 (s), 1619 (m), 1500 (m), 1446 (s), 1412 (s), 1379 (s), 1328 (m), 1286 (s), 1196 (m), 1164 (m), 1136 (m), 1047 (m), 842 (m), 769 (m), 753 (m). MS (EI, 70eV): *m/z* (%) = 391 (M$^+$, 100), 371 (63), 341 (20), 177 (25), 113 (17). Anal. Calcd for $C_{19}H_{22}N_2O_7$ (390.39): C, 58.46; H, 5.68; N, 7.18. Found: C, 58.71; H, 5.87; N, 6.64.

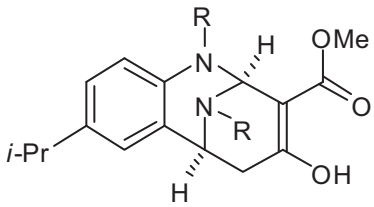
4-Ethyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 10-ethyl ester 8,13-dimethyl ester (18g).



(R = CO$_2$Me)

Following **general procedure 2** and starting with 6-ethylquinazoline **16d** (0.400 g, 2.5 mmol), **5d** (0.971 g, 3.5 mmol) and methyl chloroformate (0.945 g, 10.0 mmol) in CH_2Cl_2 (25 mL), **18g** was obtained as a yellowish solid (0.379 g, 37%); mp. 127 – 130 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.6 Hz, 3H, CH$_2$C*H*$_3$), δ = 1.33 (t, ^3J = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 2.40 (dd, ^2J = 17.6 Hz, ^3J = 1.4 Hz, 1H, NCHC*H*$_2$), 2.58 (q, ^3J = 7.6 Hz, 2H, CH$_3$C*H*$_2$), 2.97 (dd, ^2J = 17.6 Hz, ^3J = 4.9 Hz, 1H, NCHC*H*$_2$), 3.75, 3.85 (s, 6H, OCH$_3$), 4.23 (q, ^3J = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 5.36 (br, 1H, NC*H*CH$_2$), 6.87 (s, 1H, Ar), 7.06 (dd, ^3J = 8.5 Hz, ^2J = 1.7 Hz, 1H, CH$_{Ar}$), 7.36 (br, 1H, NCHN), 7.68 (br, 1H, CH$_{Ar}$), 12.34 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.03, 15.38 (CH$_2$*C*H$_3$), 28.1 (CH$_3$*C*H$_2$C$_{Ar}$), 38.2 (br, NCH*C*H$_2$), 49.0 (br, N*C*HCH$_2$), 53.0, 53.1 (OCH$_3$), 58.9 (br, NCHN), 61.0 (OC*H*$_2$CH$_3$), 98.2 (NCH*C*CO), 124.2, 125.4, 126.6 (CH$_{Ar}$), 127.3, 132.1 (br), 140.1 (C$_{Ar}$), 153.6, 154.1 (NCOO), 170.3 (C*C*OO), 173.0 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3069 (w), 2962 (m), 2930 (w), 1708 (s), 1655 (s), 1455 (s), 1413 (m), 1381 (s), 1327 (m), 1286 (s), 1262 (m), 1236 (s), 1220 (m), 1151 (m), 1105 (m), 1068 (m), 1044 (m), 773 (m). MS (EI, 70 eV): *m/z* (%) = 404 (M$^+$, 11), 345 (100), 299 (45), 267 (15), 226 (41), 180 (27). HRMS (EI): Calcd for $C_{20}H_{24}N_2O_7$ (M$^+$) 404.15780, found 404.157772.

11-Hydroxy-4-isopropyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid trimethyl ester (18h).

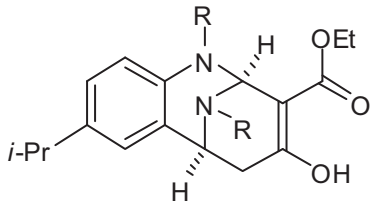


(R = CO$_2$Me)

Following **general procedure 2** and starting with 6-isopropylquinazoline **16e** (0.626 g, 3.5 mmol), **5a** (1.275 g, 4.9 mmol) and methyl chloroformate (1.323 g, 14.0 mmol) in CH_2Cl_2 (35 mL), **18h** was obtained as light yellow solid (0.620 g, 44%); mp. 151 ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, ^3J = 7.0 Hz, 3H, CHCH_3), 1.21 (d, ^3J = 6.9 Hz, 3H, CHCH_3), 2.40 (dd, ^2J = 17.7 Hz, ^3J = 1.1 Hz, 1H, NCHCH_2), 2.84 (m, 1H, CH(CH_3)$_2$), 2.97 (dd, ^2J = 17.7 Hz, ^3J = 4.4 Hz, 1H, NCHCH_2), 3.74, 3.79, 3.85 (s, 9H, OCH_3), 5.37 (br, 1H, NC$H$$CH_2$), 6.88 (s, 1H, CH_{Ar}), 7.09 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H, Ar), 7.36 (br, 1H, NCHN), 7.65 (br, 1H, CH_{Ar}), 12.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.8, 22.0 (CH(*C*H_3)$_2$), 31.4 (*C*H(CH_3)$_2$), 36.2 (br, NCH*C*H_2), 46.9 (br, N*C*HCH_2), 50.0, 51.1, 51.2 (O*C*H_3), 56.9 (br, N*C*HN), 96.1 (NCH*C*CO), 122.0, 122.3, 123.9 (CH_{Ar}), 124.5, 130.1 (br), 142.8 (C_{Ar}), 151.5, 152.1 (N*C*OO), 168.6 (C*C*OO), 171.2 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2958 (m), 2931 (w), 1723 (s), 1658 (s), 1618 (m), 1445 (s), 1412 (m), 1378 (s), 1330 (m), 1287 (s), 1264 (s), 1240 (s), 1225 (s), 1195 (m), 1114 (m), 1044 (m), 1009 (m), 835 (m), 768 (m). MS (EI, 70 eV): *m/z* (%) = 404 (M^+, 12), 345 (100), 313 (44), 281 (16), 212 (50), 180 (25). HRMS (EI): Calcd for $C_{20}H_{24}N_2O_7$ (M^+) 404.15780, found 404.158017.

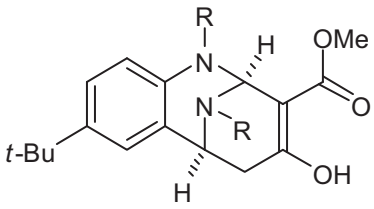
11-Hydroxy-4-isopropyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 10-ethyl ester 8,13-dimethyl ester (18i). Following **general procedure 2** and starting with 6-isopropylquinazoline **16e** (0.344 g, 2.0 mmol), **5d** (0.768 g, 2.8 mmol) and methyl chloroformate (0.756 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **18i** was obtained as a slightly yellow solid (0.368 g, 44%); mp. 134–136 ºC.



(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, ^3J = 1.4 Hz, 3H, CH(CH_3)$_2$), 1.22 (d, ^3J = 1.4 Hz, 3H, CH(CH_3)$_2$), 1.33 (t, ^3J = 7.1 Hz, 3H, C$H_3$$CH_2$), 2.40 (dd, ^2J = 17.6 Hz, ^3J = 1.3 Hz, 1H, NCHCH_2), 2.84 (m, 1H, CH(CH_3)$_2$), 2.97 (br dd, ^2J = 17.6 Hz, ^3J = 4.8 Hz, 1H, NCHCH_2), 3.74, 3.85 (s, 6H, OCH_3), 4.22 (q, ^3J = 7.1 Hz, 2H, OC$H_2$$CH_3$), 5.37 (br, 1H, NC$H$$CH_2$), 6.88 (s, 1H, CH_{Ar}), 7.01 (dd, ^3J = 8.6 Hz, ^2J = 1.8 Hz, 1H, CH_{Ar}), 7.35 (br, 1H, NCHN), 7.69 (br, 1H, CH_{Ar}), 12.35 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (*C*$H_3$$CH_2$), 23.8, 24.0 (CH(*C*$H_3$)$_2$), 33.4 (*C*H($CH_3$)$_2$), 38.2 (br, NCH*C*$H_2$), 49.0 (br, N*C*HC$H_2$), 53.0, 53.1 ($OCH_3$), 58.9 (br, NCHN), 61.0 (O*C*$H_2$$CH_3$), 98.2 (NCH*C*CO), 124.1, 125.8 (CH_{Ar}), 126.5, 132.1, 144.8, (C_{Ar}), 153.6, 154.1 (NCOO), 170.3 (C*C*OO), 173.0 (br, COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3048 (w), 2957 (m), 1706 (s), 1658 (s), 1618 (m), 1502 (m), 1453 (s), 1402 (s), 1377 (s), 1328 (s), 1296 (s), 1260 (s), 1236 (m), 1217 (s), 1192 (m), 1120 (m), 1044 (m), 1003 (m), 771 (m). MS (EI, 70 eV): *m/z* (%) = 418 (M^+, 9), 359 (100), 313 (30), 281 (10), 226 (29), 180 (17). HRMS (EI): Calcd for $C_{21}H_{26}N_2O_7$ (M^+) 418.17345, found 418.173096.

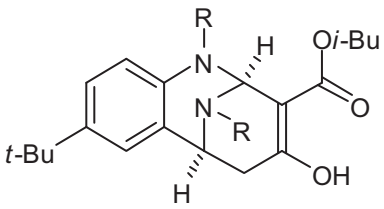
4-*tert*-Butyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid trimethyl ester (18j). Following **general procedure 2** and starting with 6-*tert*-butylquinazoline **16f** (0.372 g, 2.0 mmol), **5a** (0.728 g, 2.8 mmol) and methyl chloroformate (0.756 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **18j** was obtained as a slightly yellow solid (0.422 g, 50%); mp. 150 – 151 °C.



(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 9H, C(CH_3)$_3$), 2.41 (dd, ^2J = 17.6 Hz, ^3J = 1.1 Hz, 1H, NCHCH_2) 3.0 (dd, ^2J = 17.6 Hz, ^3J = 4.7 Hz, 1H, NCHCH_2), 3.75, 3.79, 3.86 (s, 9H, OCH_3), 5.39 (br, 1H, NCHCH_2), 7.03 (br, 1H, Ar), 7.25 (dd, ^3J = 8.6 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.37 (br, 1H, NCHN), 7.67 (br, 1H, CH_{Ar}), 12.28 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.2 (C(*C*H$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 38.2 (br, NCH*C*H$_2$), 49.0 (br, N*C*HCH$_2$), 52.0, 53.1, 53.2 (OCH_3), 58.9 (br, NCHN), 98.1 (NCH*C*CO), 122.9 (br), 124.0, 125.0 (CH_{Ar}), 126.2, 131.8 (br), 147.2 (C_{Ar}), 153.5, 154.1 (NCOO), 170.7 (C*C*OO), 173.2 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2957 (m), 2907 (w), 1716 (s), 1659 (s), 1620 (m), 1444 (s), 1380 (m), 1333 (s), 1295 (s), 1267 (s), 1232 (s), 1195 (m), 1146 (m), 1067 (m), 835 (m). MS (EI, 70 eV): *m/z* (%) = 418 (M^+, 10), 359 (100), 327 (38), 295 (13), 212 (43), 180 (21). HRMS (EI): Calcd for $C_{21}H_{26}N_2O_7$ ([M]$^+$) 418.17345, found 418.173725.

4-*tert*-Butyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 10-isobutyl ester 8,13-dimethyl ester (18k). Following **general procedure 2** and starting with 6-*tert*-butylquinazoline **16f** (0.372 g, 2.0 mmol), **5e** (0.847 g, 2.8 mmol) and methyl chloroformate (0.756 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **18k** was obtained as a slightly yellow solid (0.500 g, 54%); mp. 104-106 ºC.

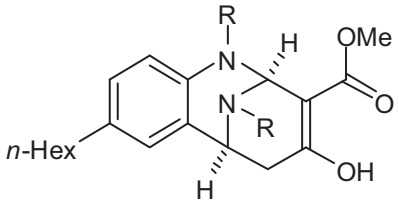


(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 6.5 Hz, 6H, CH(CH_3)$_2$), 1.28 (s, 9H, C(CH$_3$)$_3$), 2.00 (m, 1H, CH(CH$_3$)$_2$), 2.40 (dd, ^2J = 17.6 Hz, ^3J = 1.3 Hz, 1H, NCHCH_2), 2.97 (br dd, ^2J = 17.6 Hz, ^3J = 4.8 Hz, 1H, NCHCH_2), 3.75, 3.83 (s, 6H, OCH_3), 3.89 (m, 1H, OCH_2), 4.05 (m, 1H, OCH_2), 5.38 (br, 1H, NCHCH_2), 7.03 (m, 1H, Ar), 7.25 (m, 1H, Ar), 7.37 (br, 1H, NCHN), 7.62 (br, 1H, CH_{Ar}), 12.44 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.9, 18.9 (CH(*C*H$_3$)$_2$), 27.6 (*C*H(CH$_3$)$_2$), 31.2 (C(*C*H$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 38.3 (br, NCH*C*H$_2$), 49.0 (br, N*C*HCH$_2$), 53.1 (2 OCH_3), 58.9 (br, NCHN), 71.1 (OCH_2), 98.2 (NCH*C*CO), 122.8 (br), 124.1, 124.9 (CH_{Ar}), 126.3, 131.9, 147.2 (C_{Ar}), 153.5, 154.2 (NCOO), 170.5 (C*C*OO), 173.0 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2960 (m), 2907 (w), 1709

(s), 1653 (s), 1622 (m), 1455 (s), 1414 (s), 1380 (m), 1330 (s), 1287(s), 1263(s), 1231 (s), 1182 (m), 1144 (m), 1064 (m), 1048 (m), 1012 (m), 834 (m). MS (EI): *m/z* (%) = 460 (M^+, 9), 401 (100), 327 (37), 302 (15), 254 (23), 198 (23). HRMS (EI): Calcd for $C_{24}H_{32}N_2O_7$ (M^+) 460.22040, found 460.220738.

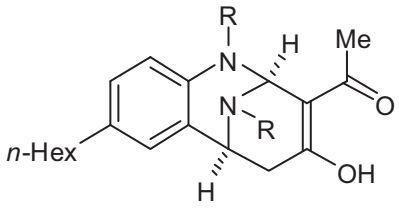
4-Hexyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid trimethyl ester (18l). Following **general procedure 2** and starting with 6-hexylquinazoline **16g** (0.419 g, 2.0 mmol), **5a** (0.714 g, 2.7 mmol) and methyl chloroformate (0.749 g, 7.8 mmol) in CH_2Cl_2 (20 mL), **18l** was obtained as a yellowish solid (0.322 g, 37%); mp. 118-120 ºC.



(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 3H, $CH_2CH_2CH_3$), 1.28 (m, 6H, $CH_2CH_2C_2H_6CH_3$), 1.56 (m, 2H, $CH_2CH_2C_4H_9$), 2.40 (dd, ^2J = 17.6 Hz, ^3J = 1.4 Hz, 1H, NCHCH_2), 2.53 (t, ^3J = 7.8 Hz, 2H, $CH_2C_5H_{11}$), 3.0, (dd, ^2J = 17.6 Hz, ^3J = 4.6 Hz, 1H, NCHCH_2), 3.75, 3.79, 3.85 (s, 9H, OCH_3), 5.36 (br, 1H, NCHCH$_2$), 6.84 (br, 1H, CH_{Ar}), 7.04 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H, CH_{Ar}), 7.36 (br, 1H, NCHN), 7.63 (br, 1H, CH_{Ar}), 12.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 ($CH_3CH_2CH_2$), 22.5, 28.9, 31.3, 31.6, 35.2 ($C_5H_{11}CH_3$), 38.1 (br, NCHCH$_2$), 48.9 (br, NCHCH$_2$), 52.0, 53.1, 53.2 (OCH_3), 58.9 (br, NCHN), 98.0 (NCHCCO), 124.2, 126.0, 126.5 (CH_{Ar}), 127.8, 132.0 (br), 139.0 (C_{Ar}), 153.5, 154.1 (NCOO), 170.6 (CCOCH$_3$), 173.0 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (m), 2929 (m), 2856 (w), 1716 (s), 1656 (m), 1618 (m), 1501 (m), 1412 (w), 1379 (m), 1289 (m), 1264 (m), 1237 (m), 1194 (w), 1172 (w), 1067 (w), 1011 (w). MS (EI, 70 eV): *m/z* (%) = 446 (M^+, 10), 387 (100), 355 (40), 330 (28), 212 (44), 180 (20). HRMS (EI): Calcd for $C_{23}H_{30}N_2O_7$ ([M]$^+$) 446.20475, found 446.205676.

10-Acetyl-4-hexyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-dicarboxylic acid dimethyl ester (18m). Following **general procedure 2** and starting with 6-hexylquinazoline **16g** (0.647 g, 3.0 mmol), **5b** (1.026 g, 4.2 mmol) and methyl chloroformate (1.134 g, 12.0 mmol) in CH_2Cl_2 (30 mL), **18m** was obtained as a yellowish, highly viscous oil (0.684 g, 53%).

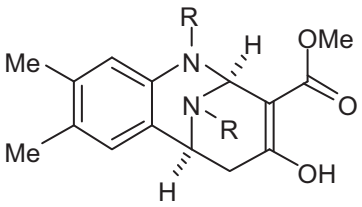


(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (br t, ^3J = 6.6 Hz, 3H, $CH_2CH_2CH_3$), 1.27 (br m, 6H, $CH_2CH_2(CH_2)_3CH_3$), 1.56 (br m, 2H, $CH_2CH_2C_4H_9$), 2.33 (s, 3H, CCH_3), 2.51 (m, 3H,

(2H, $C_{Ar}CH_2$ and 1H, NCHCH_2)), 3.00 (dd, ^2J = 22.9 Hz, ^3J = 5.2 Hz, 1H, NCHCH_2), 3.76, 3.85 (s, 6H, OCH_3), 5.37 (br, 1H, NC$H$$CH_2$), 6.86 (m, 1H, CH_{Ar}), 7.03 (m, 1H, CH_{Ar}), 7.39 (br, 2H, (1H, CH_{Ar} and 1H, NCHN), 16.35 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 ($CH_3CH_2CH_2$), 22.5, 28.9, 31.2, 31.6, 35.2 (CH_2), 24.3 (CH_3CO), 40.7 (br, NCHCH_2), 48.6 (br, NCHCH$_2$), 53.2, 53.5 (OCH_3), 60.3 (br, NCHN), 107.2 (NCHCCO), 125.2, 126.0, 127.8 (CH_{Ar}), 126.9, 131.3, 139.8 (C_{Ar}), 153.4, 154.5 (NCOO), 184.8 (br CCOCH$_3$), 196.3 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (m), 2927 (s), 2856 (m), 1715 (s), 1605 (m), 1501 (s), 1452 (s), 1410 (s), 1372 (s), 1337 (s), 1286 (s), 1193(m), 1136(m), 1110 (m), 1048 (m), 1016 (m), 941 (m), 830 (m). MS (EI, 70 eV): *m/z* (%) = 430 (M^+, 19), 371 (100), 339 (38), 329 (16), 196 (57), 43 (23). HRMS (EI): Calcd for $C_{23}H_{30}N_2O_6$ ([M]$^+$) 430.20984, found 430.210108.

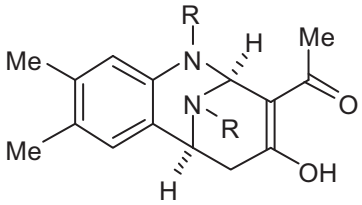
11-Hydroxy-4,5-dimethyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-tricarboxylic acid trimethyl ester (18n). Following **general procedure 2** and starting with 6,7-dimethylquinazoline **16h** (0.237 g, 1.5 mmol), **5a** (0.546 g, 2.1 mmol) and methyl chloroformate (0.567 g, 6.0 mmol) in CH_2Cl_2 (15 mL), **18n** was obtained as a yellowish solid (0.270 g, 46%); mp. 173–175 °C.



(R = CO_2Me)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19, 2.21, 2.22 (s, 6H, $C_{Ar}CH_3$, rotamers), 2.38 (dd, ^2J = 17.6 Hz, ^3J = 1.3 Hz, 1H, NCHCH_2), 2.95 (br dd, ^2J = 17.6 Hz, ^3J = 4.3 Hz, 1H, NCHCH_2), 3.74-3.86 (m, 9H, OCH_3), 5.32, 5.59 (br, 1H, NC$H$$CH_2$, rotamers), 6.80, 7.03, 7.05 (s, 1H, CH_{Ar}), 7.35 (br, 1H, NCHN), 7.52 (br, 1H, CH_{Ar}), 12.23, 12.26 (s, 1H, OH, rotamers). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.1, 19.8, 20.1 (CH_3), 35.9, 38.2 (br, NCHCH_2, rotamers), 47.0, 48.5 (br, NCHCH$_2$, rotamers), 51.9, 52.0, 53.1, 53.2 (OCH_3, rotamers), 58.3, 58.9 (br, NCHN, rotamers), 97.7, 98.0 (br, NCHCCO, rotamers), 122.4, 124.1, 125.0, 127.1 (CH_{Ar}, rotamers), 128.7, 132.0 (br), 132.8, 136.2, (C_{Ar}), 153.5, 154.2 (NCOO), 170.6 (CCOO), 173.3 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2998 (w), 2955 (m), 2923 (w), 2859 (s), 1716 (s), 1658 (s), 1618 (m), 1445 (s), 1414 (m), 1380 (m), 1332 (s), 1296 (s), 1252 (s), 1223 (m), 1197 (m), 1172 (m), 1068 (m), 1017 (m), 773 (m). MS (EI, 70 eV): *m/z* (%) = 390 (M^+, 18), 331 (100), 299 (56), 267 (19), 212 (62), 180 (33). HRMS (EI): Calcd for $C_{19}H_{22}N_2O_7$ (M^+) 390.14215, found 390.141802.

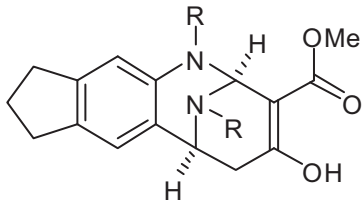
10-Acetyl-11-hydroxy-4,5-dimethyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-dicarboxylic acid dimethyl ester (18o).



(R = CO_2Me)

Following **general procedure 2** and starting with 6,7-dimethylquinazoline **16h** (0.237 g, 1.5 mmol), **5b** (0.513 g, 2.1 mmol) and methyl chloroformate (0.567 g, 6.0 mmol) in CH_2Cl_2 (15 mL), **18o** was obtained as a yellowish solid (0.268 g, 48 %) mp. 87–89 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18-2.23 (m, 6H, 2 CH_3), 2.33, 2.35 (s, 3H, $COCH_3$, rotamers), 2.47 (dd, ^2J = 17.8 Hz, ^3J = 1.5 Hz, 1H, NCHCH_2), 2.97 (br dd, ^2J = 17.8 Hz, ^3J = 4.9 Hz, 1H, NCHCH_2), 3.76, 3.77, 3.83, 3.86 (s, 6H, OCH_3, rotamers), 5.33, 5.58 (br, 1H, NC$H$$CH_2$, rotamers), 6.81, 7.03, 7.05, 7.36 (br, 3H, 2H, CH_{Ar} and 1H, NCHN) 16.28, 16.35 (s, 1H, OH, rotamers). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.2, 19.8, 20.1 (CH_3, rotamers), 24.3, 24.4 (CO$C$$H_3$, rotamers), 38.4, 40.75 (br, NCH$C$$H_2$, rotamers), 46.9, 48.4 (br, N$C$$HCH_2$, rotamers), 53.2, 53.3, 53.5 (OCH_3, rotamers), 59.9, 60.4 (br, NCHN, rotamers), 106.9, 107.3 (NCHCCO, rotamers), 124.6, 131.3 (br), 133.7, 136.2 (C_{Ar}), 126.1 (d), 127.1 (CH_{Ar}), 153.5, 154.6, 154.8 (NCOO, rotamers), 184.9 (CCOO), 196.3 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956 (m), 2922 (w), 2858 (w), 1716 (s), 1605 (m), 1505 (m), 1450 (s), 1412 (m), 1376 (m), 1337 (m), 1297 (s), 1195 (m), 1019 (m). MS (EI, 70 eV): *m/z* (%) = 374 (M^+, 22), 315 (100), 340 (11), 283 (35), 196 (42), 177 (19). HRMS (EI): Calcd for $C_{19}H_{22}N_2O_6$ (M^+) 374.14724, found 374.146557.

11-Hydroxy-4,5(1′,3′)-propylene-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid trimethyl ester (18p).

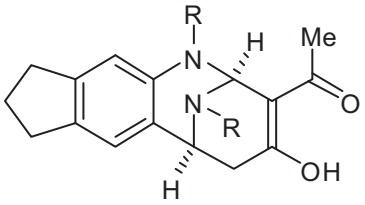


(R = CO_2Me)

Following **general procedure 2** and starting with 7,8-dihydro-6*H*-cyclopenta[g]quinazoline **16i** (0.400 g, 2.3 mmol), **5a** (0.838 g, 3.22 mmol) and methyl chloroformate (0.870 g, 9.2 mmol) in CH_2Cl_2 (23 mL), **18p** was obtained as a slightly yellow solid. (0.415 g, 51 %); mp. 159 ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (m, 2H, $CH_2C$$H_2$$CH_2$), 2.39 (dd, ^2J = 17.6 Hz, ^3J = 1.2 Hz, 1H, NCHCH_2), 2.88 (m, 5H, (4H, C$H_2$$CH_2CH_2$ and 1H, NCHCH_2), 3.74, 3.79, 3.86 (s, 9H, OCH_3), 5.34 (br, 1H, NC$H$$CH_2$), 6.89 (s, 1H, CH_{Ar}), 7.35 (br, 1H, NCHN), 7.57 (br, 1H, CH_{Ar}), 12.26 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.6, 32.3, 32.9 ($C$$H_2$$C$$H_2$$C$$H_2$), 38.3 (br, NCH$C$$H_2$), 49.0 (br, N$C$$HCH_2$), 51.2, 53.1, 53.2 ($OCH_3$), 58.9 (br, NCHN), 98.0 (NCHCCO), 120.3, 121.8 (CH_{Ar}), 124.6, 132.4 (br), 140.4, 144.0 (C_{Ar}), 153.5, 154.3 (NCOO), 170.6 (CCOO), 173.2 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3081 (w), 2998 (w), 2956 (m), 1722 (s), 1707 (s), 1654 (s), 1613 (m), 1487

(m), 1455 (s), 1445 (s), 1412 (m), 1390 (m), 1360 (m), 1333 (s), 1295 (s), 1283 (s), 1264 (s), 1241 (s), 1221 (s), 1195 (m), 1177 (m), 1119 (m), 1089 (m), 1023 (m), 774 (m). MS (EI, 70 eV): *m/z* (%) = 402 (M^+, 20), 343 (100), 311 (64), 279 (24), 212 (46), 180 (32). HRMS (EI): Calcd for $C_{20}H_{22}N_2O_7$ ([M]$^+$) 402.14215, found 402.141755.

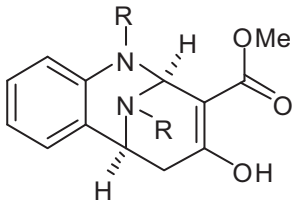
10-Acetyl-11-hydroxy-4,5(1′,3′)-propylene-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-dicarboxylic acid dimethyl ester (18q).



(R = CO_2Me)

Following **general procedure 2** and starting with 7,8-dihydro-6*H*-cyclopenta[g]quinazoline **16i** (0.340 g, 2.0 mmol), **5b** (0.684 g, 2.8 mmol) and methyl chloroformate (0.756 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **18q** was obtained as a slightly yellow solid (0.415 g, 53%); mp. 98–99 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (m, 2H, $CH_2CH_2CH_2$), 2.33 (s, 3H, CCH_3O), 2.48 (dd, ^2J = 17.7 Hz, ^3J = 1.2 Hz, 1H, $NCHCH_2$), 2.83 (m, 4H, $CH_2CH_2CH_2$), 2.97 (dd, ^2J = 17.7 Hz, ^3J = 5.0 Hz, 1H, $NCHCH_2$), 3.76, 3.86 (s, 6H, OCH_3), 5.35 (br, 1H, $NCHCH_2$), 6.90 (s, 1H, CH_{Ar}), 7.31 (br, 1H, NCHN), 7.37 (br, 1H, CH_{Ar}), 16.34 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.3 ($COCH_3$), 25.6, 32.3, 32.8 ($CH_2CH_2CH_2$), 40.9 (br, $NCHCH_2$), 48.8 (br, $NCHCH_2$), 53.2, 53.5 (OCH_3), 60.4 (br, NCHN), 107.3 (NCHCCO), 121.1, 121.2 (CH_{Ar}, rotamers), 121.8 (CH_{Ar}), 125.0, 131.7 (br), 141.4, 144.1 (C_{Ar}), 153.5, 154.7 (NCOO), 185.0 (CCOO), 196.2 (COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2955 (m), 2845 (w), 1716 (s), 1605 (m), 1576 (m), 1489 (m), 1440 (s), 1410 (m), 1377 (m), 1339 (m), 1289 (s), 1252 (m), 1196 (m), 1154 (w), 1112 (m), 1089 (m), 1039 (w). MS (EI, 70 eV): *m/z* (%) = 386 (M^+, 12), 327 (100), 295 (27), 196 (21), 156 (5). HRMS (EI): calcd for $C_{20}H_{22}N_2O_6$ (M^+) 386.14724, found 386.147092.

11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-methyl ester (19b)



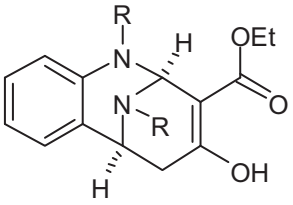
(R = CO_2Bn)

Following **general procedure 2** and starting with quinazoline **16a** (0.260 g, 2.0 mmol), **5a** (0.782 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19b** was obtained as yellowish, highly viscous oil (0.617 g, 60%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.33 (d, ^2J = 17.7 Hz, 1H, $NCHCH_2$), 2.88 (br d, ^2J = 17.7 Hz, 1H, $NCHCH_2$), 3.38 (s, 3H, OCH_3), 4.99 - 5.38 (m, 5H, OCH_2 and $NCHCH_2$), 6.97 - 7.03 (m, 2H, CH_{Ar}), 7.14 - 7.39 (m, 12H, CH_{Ar}, NCHN), 7.76 (d, ^3J = 8.3 Hz, 1H, CH_{Ar}), 12.21 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 38.1 ($NCHCH_2$), 48.5 (br), 49.1

(br) (N*C*HCH$_2$, rotamers), 51.5 (O*C*H$_3$), 58.8 (br, NCHN), 67.6, 67.8 (OCH$_2$), 97.8 (NCH*C*CO), 124.2, 126.3, 127.6, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7 (CH$_{Ar}$), 129.2 (NCHN), 133.2, 134.4 (br), 135.8, 136.1 (C$_{Ar}$), 152.8, 153.1 (br), (NCOO), 170.5 (C), 173.3 (br, C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3064 (w), 3032 (w), 2952 (w), 1703 (s), 1652 (m), 1490 (w), 1445 (m), 1382 (m), 1258 (s), 1224 (s), 1132 (m), 1102 (m), 1064 (m), 1022 (m), 1000 (m), 909 (m), 763 (m), 728 (s), 695 (s), 648 (w). MS (EI, 70 eV): *m/z* (%) = 514 (M$^+$, 5), 379 (65), 335 (11), 303 (12), 91 (100), 65 (9). HRMS (EI): calcd for $C_{29}H_{26}O_7N_2$ (M$^+$) 514.17345, found 514.173948.

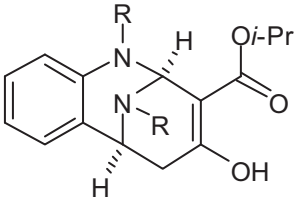
11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-ethyl ester (19c)



(R = CO$_2$Bn)

Following **general procedure 2** and starting from quinazoline **16a** (0.260 g, 2.0 mmol), **5d** (0.818 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19c** was obtained as a light yellow viscous (0.539 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.41 (d, ^3J = 17.6 Hz, 1H, NCHC*H*$_2$), 2.93 (d, ^3J = 16.1 Hz, 1H, NCHC*H*$_2$), 4.04 (q, ^3J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 5.00-5.54 (br m, 5H, OCH$_2$ and NC*H*CH$_2$), 7.05-7.13 (m, 2H, CH$_{Ar}$), 7.27-7.51 (br m, 12H, CH$_{Ar,}$ NCHN), 7.82 (d, ^3J = 8.2 Hz, 1H, CH$_{Ar}$), 12.38 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (OCH$_2$*C*H$_3$), 38.2 (br, NCH*C*H$_2$), 48.7 (br, N*C*HCH$_2$), 58.9 (br, NCHN), 60.9 (O*C*H$_2$CH$_3$), 67.7(br, OCH$_2$C$_{Ar}$), 98.2 (NCH*C*CO), 124.3, 124.5, 126.3, 126.9, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5 (CH$_{Ar}$), 134.6, 136.0, 136.1, 152.8, 153.2 (C), 170.2 (C), 173.3 (br, C). IR (Kapillar, cm^{-1}): $\tilde{\nu}$ = 3033 (m), 2981 (w), 1709 (s), 1653 (s), 1620 (s), 1491 (m), 1429 (s), 1386 (s), 1327 (s), 1295 (s), 1261 (s), 1228 (s), 1181 (m), 1135 (s), 1065 (m), 1024 (m), 1004 (m), 948 (w), 827 (w), 738 (m). MS (EI): *m/z* (%) = 528 (M$^+$, 11), 456 (2), 393 (88), 349 (25), 303 (30), 258 (11), 212 (10), 91 (100), 65 (14). HRMS (EI): calcd for $C_{30}H_{28}N_2O_7$ (M$^+$) 528.18910, found 528.188792.

11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-isopropyl ester (19d)

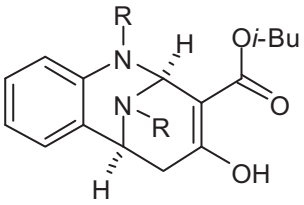


(R = CO$_2$Bn)

Following **general procedure 2** and starting with quinazoline **16a** (0.260 g, 2.0 mmol), **5f** (0.866 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19d** was

obtained as yellowish, highly viscous oil (0.619 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00, 1.03 (d, ^{3}J = 6.3 Hz, 6H, OCH(CH_3)$_2$), 2.31 (d, ^{2}J = 17.8 Hz, 1H, NCHCH_2), 2.90 (br d, ^{2}J = 16.9 Hz, 1H, NCHCH_2), 4.95 (m, 1H, OCH(CH_3)$_2$), 5.00 - 5.38 (br m, 5H, OCH_2 and NC$H$$CH_2$), 6.97 - 7.03 (m, 2H, CH_{Ar}), 7.15 - 7.44 (m, 12H, CH_{Ar}, NCHN), 7.71 (d, ^{3}J = 8.4 Hz, 1H, CH_{Ar}), 12.38 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.5, 21.6 (OCH(CH_3)$_2$), 38.2 (NCHCH_2), 48.8 (br) (NCHCH_2), 58.9 (br, NCHN), 67.6, 67.8 (OCH_2), 68.7 (OCH(CH_3)$_2$), 98.4 (NCHCCO), 124.3, 124.5, 126.3 (CH_{Ar}), 126.9 (C_{Ar}), 127.6, 127.9, 128.0, 128.2, 128.4 (CH_{Ar}), 128.5 (NCHN), 134.6, 136.0 (C_{Ar}), 152.6, 153.3 (br), (NCOO), 169.8 (C), 172.3 (br, C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3064 (w), 3032 (w), 2939 (w), 1704 (m), 1643 (m), 1552 (w), 1490 (w), 1402 (m), 1323 (m), 1257 (s), 1224 (s), 1133 (m), 1100 (m), 1022 (m), 998 (m), 946 (w), 764 (w), 733 (s), 695 (s), 662 (w). MS (EI, 70 eV): *m/z* (%) = 542 (M^+, 7), 456 (1), 407 (81), 365 (18), 303 (14), 91 (100), 65 (10). HRMS (EI): calcd for $C_{31}H_{30}O_7N_2$ (M^+) 542.20475, found 542.204531.

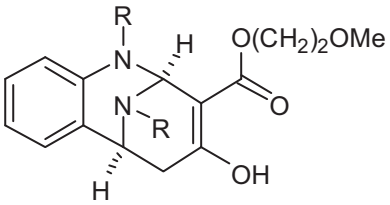
11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-isobutyl ester (19e)



(R = CO_2Bn)

Following **general procedure 2** and starting with quinazoline **16a** (0.260 g, 2.0 mmol), **5e** (0.902 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19e** was obtained as colourless solid (0.589 g, 53%), mp 104-105°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80 (d, ^{3}J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 1.76 ($CH_2CH(CH_3)_2$), 2.41 (d, ^{2}J = 17.5 Hz, 1H, NCHCH_2), 2.99 (br d, ^{2}J = 16.2 Hz, 1H, NCHCH_2), 3.67-3.74 (m, 1H, CH_2CH(CH_3)$_2$), 3.92-3.99 (m, 1H, CH_2CH(CH_3)$_2$), 5.18-5.45 (br m, 5H, OCH_2, NC$H$$CH_2$), 7.08-7.11 (m, 2H, CH_{Ar}), 7.20-7.53 (br m, 12H, $CH_{Ar,}$ NCHN), 7.73 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 12.43 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.6, 18.7 ($CH_2CH(CH_3)_2$), 27.4 ($CH_2CH(CH_3)_2$), 38.1 (NCHCH_2), 48.7 (br) (NCHCH_2), 58.9 (br, NCHN), 67.7, 67.9 (OCH_2), 70.9 (CH_2CH(CH_3)$_2$), 98.1 (NCHCCO), 124.4, 124.8, 126.3, 126.9 (CH_{Ar}), 127.0 (C_{Ar}), 127.6, 128.1, 128.4, 128.5 (CH_{Ar}), 134.6 (NCHN), 136.0 (C_{Ar}), 152.7, 153.4 (br), (NCOO), 170.3 (C), 173.4 (br, C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3071 (w), 2873 (w), 1711 (m), 1688 (s), 1650 (m), 1612 (m), 1454 (w), 1440 (m), 1415 (m), 1379 (m), 1262 (s), 1220 (br, s), 1168 (m), 1131 (s), 1062 (m), 1010 (s), 974 (m), 851 (s), 824 (m), 761 (m), 734 (s), 710 (m), 693 (s), 624 (m). MS (EI, 70 eV): *m/z* (%) = 556 (M^+, 8), 421 (68), 377 (13), 347 (14), 321 (22), 303 (38), 241 (14), 213 (21), 108 (26), 91 (100), 79 (23). HRMS (EI): calcd for $C_{32}H_{32}O_7N_2$ (M^+) 556.22040, found 556.219914.

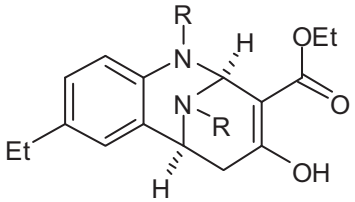
11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-(2-methoxy-ethyl) ester (19f)



(R = CO_2Bn)

Following **general procedure 2** and starting with quinazoline **16a** (0.260 g, 2.0 mmol), **5g** (0.914 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19f** was obtained as yellowish, highly viscous oil (0.551 g, 49%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41 (d, ^2J = 17.5 Hz, 1H, NCHCH_2), 2.98 (br d, ^2J = 16.5 Hz, 1H, NCHCH_2), 3.24 (s, 3H, CH_2OCH_3), 3.35 (m, 2H, CH_2OCH_3), 4.19 (m, 2H, OCH_2CH_2O), 5.11 – 5.45 (br m, 5H, OCH_2 and NC$H$$CH_2$), 7.05 – 7.09 (m, 2H, CH_{Ar}), 7.19-7.54 (br m, 12H, $CH_{Ar,}$ NCHN), 7.81 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 12.25 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 38.2 (br, NCH$C$$H_2$), 48.8 (br, N$CHCH_2$), 58.8 ($CH_2OCH_3$) 58.9 (br, NCHN), 63.8 (OCH_2CH_2O), 67.7 (br, OCH_2C_{Ar}), 69.9 (O$C$$H_2CH_2O$), 98.0 (NCH$C$CO), 124.3, 124.5, 126.3 (CH_{Ar}), 126.8 (C_{Ar}), 127.7, 127.9, 128.1, 128.2, 128.5, 128.5 (CH_{Ar}), 134.6, 135.9, 136.1 (C_{Ar}), 152.8, 153.2, 169.9, 173.5 (br), (C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3063 (w), 3032 (w), 2949 (w), 1703 (s), 1651 (m), 1499 (w), 1416 (m), 1384 (m), 1323 (m), 1255 (s), 1222 (m), 1178 (w), 1130 (m), 1022 (m), 1001 (m), 912 (w), 762 (m), 695 (s), 615 (w). MS (EI, 70 eV): *m/z* (%) = 558 (M^+, 9), 423 (87), 379 (17), 347 (11), 303 (32), 241 (14), 108 (59), 91 (100), 79 (48). HRMS (EI): calcd for $C_{31}H_{30}O_8N_2$ (M^+) 558.19967, found 558.200307.

4-Ethyl-11-hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-ethyl ester (19g)

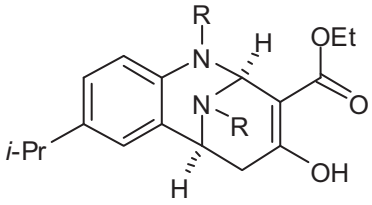


(R = CO_2Bn)

Following **general procedure 2** and starting from 6-ethylquinazoline **19d** (0.315 g, 2.0 mmol), **5d** (0.822 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19g** was obtained as yellowish, highly viscous oil (0.490 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.20 (t, ^3J = 7.6 Hz, 3H, CH_2CH_3), 2.41 (d, ^3J = 17.7 Hz, 1H, NCHCH_2), 2.59 (q, ^3J = 7.6 Hz, 2H, CH_2CH_3), 2.97 (br, d, ^3J = 16.1 Hz, 1H, NCHCH_2), 4.04 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 5.12-5.43 (br, m, 5H, OCH_2C_{Ar}, OCH_2C_{Ar}, NC$H$$CH_2$), 6.88 (s, 1H, CH_{Ar}), 7.07 (dd, ^3J = 8.6 Hz, ^4J = 1.9 Hz, 1H, CH_{Ar}), 7.27-7.50 (m, 11H, CH_{Ar}, NCHN), 7.72 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 12.39 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 15.4 (CH_2CH_3), 28.1 (CH_2CH_3), 38.2 (br, NCH$C$$H_2$), 48.7 (br, N$CHCH_2$), 58.9 (br, NCHN), 60.9 (OCH_2CH_3), 67.7 (OCH_2), 98.2 (CCO), 124.2, 125.5 (CH_{Ar}), 126.7 (C), 126.9, 127.3, 127.9, 128.0, 128.2,

128.4, 128.5 (CH_{Ar}), 132.1, 136.0, 136.2, 140.2, 152.8, 153.3, 170.2 (C), 173.3 (br, COH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3031 (w), 2969 (w), 2929 (w), 2871 (w), 1703 (s), 1650 (m), 1416 (m), 1383 (m), 1324 (m), 1280 (m), 1258 (s), 1222 (s), 1178 (w), 1133 (m), 1103 (m), 1065 (m), 1004 (m), 827 (w). MS (EI): *m/z* (%) = 556 (M^+, 7), 448 (3), 421 (79), 377 (14), 331 (15), 286 (9), 108 (24), 91 (100), 79 (21). HRMS (EI): calcd for $C_{32}H_{32}N_2O_7$ (M^+) 556.22040, found 556.219580.

11-Hydroxy-4-isopropyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-ethyl ester (19h)

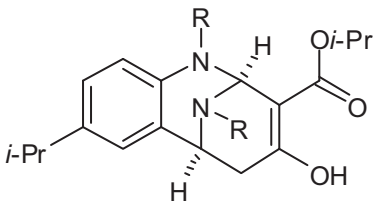


(R = CO_2Bn)

Following **general procedure 2** and starting from 6-isopropylquinazoline **16e** (0.340, 2.0 mmol), **5d** (0.822 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19h** was obtained as yellowish, highly viscous oil (0.537 g, 47%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.22 (d, ^3J = 6.9 Hz, 3H, $CH(CH_3)_2$), 1.23 (d, ^3J = 6.9 Hz, 3H, $CH(CH_3)_2$), 2.42 (d, ^3J = 17.5 Hz, 1H, $NCHCH_2$), 2.86 (m, ^3J = 6.9 Hz, 1H, $CCH(CH_3)_2$), 2.99 (br, d, ^3J = 16.1 Hz, 1H, $NCHCH_2$), 4.05 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 5.13-5.45 (br, m, 5H, OCH_2C_{Ar}, OCH_2C_{Ar}, $NCHCH_2$), 6.91 (s, 1H, CH_{Ar}), 7.12 (dd, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.27-7.51 (m, 11H, CH_{Ar}, NCHN), 7.75 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 12.42 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9 (OCH_2CH_3), 23.7, 23.9 ($CH(CH_3)_2$), 33.4 ($CH(CH_3)_2$), 38.2 (br, $NCHCH_2$), 48.8 (br, $NCHCH_2$), 58.8 (br, NCHN), 60.8 (OCH_2CH_3), 67.6 (br, OCH_2C_{Ar}), 98.2 (*C*CO), 124.0, 125.8 (CH_{Ar}), 126.6 (C), 126.9, 127.9, 128.0, 128.2, 128.4, 128.5 (CH_{Ar}), 132.1, 136.0, 136.1, 144.8, 152.8, 153.3 (C), 170.2 (*C*COO), 173.2 (br, COH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 2960 (w), 2872 (w), 1701 (br, s), 1651 (w), 1504 (w), 1406 (m), 1390 (m), 1312 (m), 1271 (s), 1233 (s), 1148 (m), 1095 (m), 1026 (s), 986 (w), 829 (w), 735 (w), 697 (m). MS (EI): *m/z* (%) = 570 (M^+, 2), 435 (22), 345 (5), 108 (18), 91 (100), 79 (18). HRMS (EI): calcd for $C_{33}H_{34}N_2O_7$ (M^+) 570.23605, found 570.236153.

11-Hydroxy-4-isopropyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-isopropyl ester (19i)

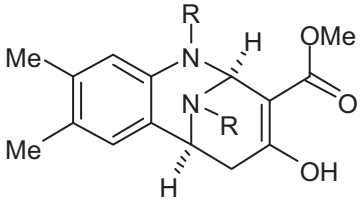


(R = CO_2Bn)

Following **general procedure 2** and starting from 6-isopropylquinazoline **16e** (0.340, 2.0 mmol), **5f** (0.866 g,

3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19i** was obtained as yellowish, highly viscous oil (0.526 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, ^3J = 6.3 Hz, 3H, OCH(CH_3)$_2$), 1.12 (d, ^3J = 6.3 Hz, 3H, OCH(CH_3)$_2$), 1.22 (d, ^3J = 6.9 Hz, 3H, CH(CH_3)$_2$), 1.23 (d, ^3J = 6.9 Hz, 3H, CH(CH_3)$_2$), 2.41 (d, ^3J = 17.6 Hz, 1H, NCHCH_2), 2.85 (m, ^3J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 2.98 (br, d, ^3J = 16.1 Hz, 1H, NCHCH_2), 5.04 (m, ^3J = 6.3 Hz, 1H, OCH(CH$_3$)$_2$), 5.09-5.42 (br, m, 5H, OCH_2C$_{Ar}$, OCH_2C$_{Ar}$, NCHCH$_2$), 6.90 (s, 1H, CH$_{Ar}$), 7.11 (dd, ^3J = 8.6 Hz, ^4J = 1.9 Hz, 1H, CH$_{Ar}$), 7.27-7.52 (m, 11H, CH$_{Ar}$, NCHN), 7.72 (d, ^3J = 8.6 Hz, 1H, CH$_{Ar}$), 12.49 (s, 1H, OH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.5, 23.7, 24.0 (*C*H$_3$), 33.4 (*C*H(CH$_3$)$_2$), 38.2 (br, NCH*C*H$_2$), 49.1 (br, N*C*HCH$_2$), 58.9 (br, NCHN), 67.7 (br, OCH$_2$C$_{Ar}$), 68.7 (O*C*H(CH$_3$)$_2$), 98.4 (C), 124.0, 124.3, 125.8, 126.7, 127.9, 128.0, 128.2, 128.4, 128.5 (CH$_{Ar}$), 132.2, 136.1, 144.8, 153.3 (C), 169.9 (C*C*OO), 173.1 (br, COH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3032 (w), 2956 (w), 1703 (br, s), 1644 (m), 1498 (w), 1401 (m), 1259 (s), 1224 (s), 1101 (s), 1057 (m), 1000 (m), 909 (m), 826 (m), 729 (s), 694 (s), 597 (w). MS (EI): *m/z* (%) = 584 (M$^+$, 19), 449 (100), 407 (24), 345 (22), 263 (13), 172 (5), 91 (68), 65 (13). HRMS (EI): calcd for $C_{34}H_{36}N_2O_7$ (M$^+$) 584.25170, found 584.252239.

11-Hydroxy-4,5-dimethyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-methyl ester (19j)

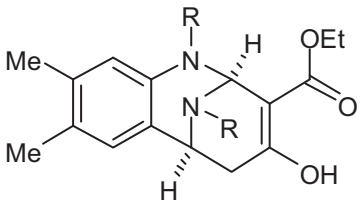


(R = CO_2Bn)

Following **general procedure 2** and starting with 6,7-dimethylquinazoline **16h** (0.315 g, 2.0 mmol), **5a** (0.780 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19j** was obtained as yellowish, highly viscous oil (0.467 g, 43%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 3H, CCH$_3$), 2.21 (s, 3H, CCH$_3$), 2.40 (d, ^2J = 18.0 Hz, 1H, NCHCH_2), 2.94 (br d, ^2J = 13.5 Hz, 1H, NCHCH_2), 3.48, 3.50 (s, 3H, OCH$_3$), 5.07 - 5.65 (m, 5H, OCH$_2$, NCHCH$_2$), 6.80 (br, s, 1H, CH$_{Ar}$), 7.27 - 7.60 (m, 12H, CH$_{Ar}$, 11H, CH$_{Ar}$, NCHN), 12.26, 12.29 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.1 (CCH$_3$), 19.8 (CCH$_3$), 38.2 (NCH*C*H$_2$), 48.5 (br) (N*C*HCH$_2$), 51.5, 51.6 (O*C*H$_3$, rotamers), 58.9 (br, NCHN), 67.5, 67.8 (OCH$_2$), 98.0 (NCH*C*CO), 125.1, 127.0, 127.2, 127.6, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9 (CH$_{Ar}$), 131.9, 132.8, 136.0 (br), 136.2, 136.3 (C$_{Ar}$), 152.9, 153.4 (br), 170.6, 173.5 (C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3063 (w), 3031 (w), 2923 (w), 1702 (m), 1652 (m), 1615 (w), 1445 (m), 1383 (m), 1326 (m), 1248 (br, s), 1220 (s), 1170 (w), 1110 (br, m), 1065 (m), 1011 (m), 951 (w), 783 (w), 730 (m), 695 (s), 597 (w). MS (EI, 70 eV): *m/z* (%) = 542

(M^+, 9), 407 (72), 363 (10), 331 (13), 91 (100), 65 (8). HRMS (EI): calcd for $C_{31}H_{30}O_7N_2$ (M^+) 542.20475, found 542.205401.

11-Hydroxy-4,5-dimethyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-ethyl ester (19k)

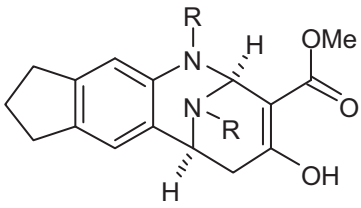


(R = CO_2Bn)

Following **general procedure 2** and starting with 6,7-dimethylquinazoline **16h** (0.315 g, 2.0 mmol), **5d** (0.822 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19k** was obtained as yellowish, highly viscous oil (0.467 g, 42%).

IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3032 (w), 2923 (w), 1702 (s), 1650 (m), 1620 (w), 1384 (m), 1368 (w), 1325 (m), 1247 (br, s), 1219 (s), 1176 (m), 1150 (w), 1110 (br, m), 1064 (m), 1013 (m), 994 (m), 953 (w), 820 (m), 785 (m), 695 (s), 597 (w). MS (EI, 70 eV): *m/z* (%) = 556 (M^+, 18), 421 (99), 377 (20), 331 (26), 286 (19), 249 (14), 91 (100), 65 (11). HRMS (EI): calcd for $C_{32}H_{32}O_7N_2$ (M^+) 556.22040, found 556.220884.

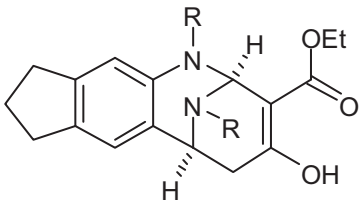
11-Hydroxy-4,5(1′,3′)-propylene-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-methyl ester (19l)



(R = CO_2Bn)

Following **general procedure 2** and starting with 7,8-dihydro-6*H*-cyclopenta[*g*]quinazoline **16i** (0.340 g, 2.0 mmol), **5a** (0.782 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19l** was obtained as yellowish, highly viscous oil (0.588 g, 53%).^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99-2.10 (m, 2H, $CH_2CH_2CH_2$), 2.41 (d, ^3J = 17.6 Hz, 1H, NCHCH_2), 2.81-2.98 (m, 5H, $CH_2CH_2CH_2$, NCHCH_2), 3.48 (s, 3H, OCH_3), 5.07-5.43 (br m, 5H, OCH_2, NC*H*CH_2), 6.91 (s, 1H, CH_{Ar}), 7.26-7.45 (br m, 11H, $CH_{Ar,}$ NCHN), 7.67 (s, 1H, CH_{Ar}), 12.30 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.5 ($CH_2CH_2CH_2$), 32.2, 32.8 ($CH_2CH_2CH_2$), 38.4 (br, NCHCH_2), 48.7 (br, N$CHCH_2$), 51.5 (OCH_3), 58.8 (br, NCHN), 67.4, 67.7 (OCH_2C_{Ar}), 97.9 (NCH*C*CO), 120.2, 121.8 (CH_{Ar}), 124.6 (C_{Ar}), 127.9, 128.0, 128.1, 128.2, 128.4, 128.5 (CH_{Ar}), 132.3, 135.9, 136.3, 140.4, 144.0, 152.9, 153.4, 170 (C), 173.4 (br, COH). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3031 (w), 2951 (w), 1699 (s), 1651 (m), 1488 (w), 1427 (m), 1326 (m), 1278 (m), 1238 (s), 1108 (m), 1064 (m), 1008 (m), 943 (w), 823 (w), 695 (s), 585 (w). MS (EI, 70 eV): *m/z* (%) = 554 (M^+, 5), 446 (3), 419 (33), 343 (8), 108 (17), 91 (100), 79 (16). HRMS (EI): calcd for $C_{32}H_{30}O_7N_2$ (M^+) 554.20475, found 554.204275.

11-Hydroxy-4,5(1′,3′)-propylene-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid 8,13-dibenzyl ester 10-ethyl ester (19m)



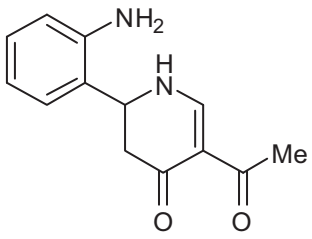
(R = CO_2Bn)

Following **general procedure 2** and starting with 7,8-dihydro-6*H*-cyclopenta[*g*]quinazoline **16i** (0.340 g, 2.0 mmol), **5d** (0.822 g, 3.0 mmol) and benzyl chloroformate (1.365 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **19m** was obtained as yellowish, highly viscous oil (0.591 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.04 (m, 2H, $CH_2CH_2CH_2$), 2.39 (d, ^3J = 17.7 Hz, 1H, $NCHCH_2$), 2.77-2.98 (m, 5H, $CH_2CH_2CH_2$, $NCHCH_2$), 4.04 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 4.97-5.41 (br m, 5H, OCH_2, $NCHCH_2$), 6.90 (s, 1H, CH_{Ar}), 7.31-7.64 (br m, 12H, CH_{Ar}, NCHN), 12.38 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 25.6 ($CH_2CH_2CH_2$), 32.3, 32.9 ($CH_2CH_2CH_2$), 38.4 (br, $NCHCH_2$), 49.0 (br, $NCHCH_2$), 58.9 (br, NCHN), 60.9 (OCH_2CH_3), 67.7 (br, OCH_2C_{Ar}), 98.2 ($NCHCCO$), 120.3, 121.8 (CH_{Ar}), 124.7 (C_{Ar}), 127.9, 128.0, 128.2, 128.4, 128.5 (CH_{Ar}), 132.5, 136.1, 136.2, 140.5, 144.0, 152.6, 153.6, 170.3, 172.9 (br, C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3063 (w), 3032 (w), 2842 (w), 1702 (s), 1649 (m), 1616 (w), 1426 (m), 1386 (m), 1325 (m), 1280 (s), 1255 (s), 1238 (s), 1219 (s), 1181 (m), 1108 (m), 1086 (m), 1062 (m), 945 (w), 730 (br, s), 695 (s), 585 (w). MS (EI, 70 eV): *m/z* (%) = 568 (M^+, 6), 433 (39), 389 (8), 343 (8), 298 (8), 237 (10), 108 (47), 91 (100), 79 (50). HRMS (EI): calcd for $C_{33}H_{32}O_7N_2$ (M^+) 568.22040, found 568.220118.

7.2.3 Synthesis of 6-(2-aminophenyl)-4-oxo-1,4,5,6-tetrahydropyridines and 8,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraenes by reductive cleavage of the benzyloxycarbonyl moiety as a protective group

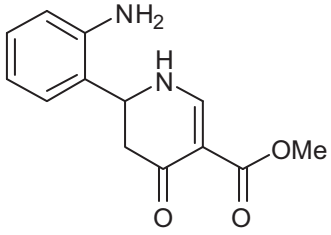
General procedure 3: Pd on activated carbon (10 wt. % Pd, 10 mol %) was added to a MeOH solution (10 mL) of **19** (1.0 mmol) at room temperature (20 ºC) under argon atmosphere. The flask was evacuated and filled with H_2 (3x) and the mixture was stirred under hydrogen atmosphere for 12 h. The mixture was filtered (Celite), washed with MeOH (50 mL) and the filtrate was concentrated in vacuo. The residue was purified by crystallization (EtOAc for **22**), or by colunm chromatography (for **23**), (silica gel, heptane/EtOAc = 10:1→5:1).

5-Acetyl-2-(2-aminophenyl)-2,3-dihydro-1*H*-pyridin-4-one (22a)



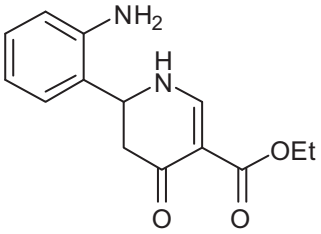
Following **general procedure 3** and starting with **19a** (0.498 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22a** was obtained as a colourless solid (0.102 g, 44%), mp 163-165 °C. ^{1}H NMR (250 MHz, DMSO): δ = 2.31 (s, 3H, CH_3), 2.52-2.57 (m, 2H, CH_2), 5.06 (t, ^3J = 8.2 Hz, 1H, C*H*CH_2), 5.16 (s, 2H, NH_2), 6.57 (t, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 6.68 (d, ^3J = 7.4 Hz, 1H, CH_{Ar}), 6.98-7.04 (m, 2H, CH_{Ar}), 8.29 (d, ^3J = 7.4 Hz, 1H, NHC*H*), 9.44 (d, ^3J = 7.4 Hz, 1H, N*H*CH). ^{13}C NMR (75.5 MHz, DMSO): δ = 30.0 (CH_3), 41.1 (CH*C*H_2), 51.0 (*C*HCH_2), 108.8 (CO*C*CO), 115.6, 116.2 (CH_{Ar}), 121.4 (C_{Ar}), 126.0, 128.4 (CH_{Ar}), 145.4 (C_{Ar}), 157.3 (CHNH), 188.2, 192.4 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3413 (w), 3335 (w), 3201 (w), 2834 (w), 1614 (m), 1567 (br, s), 1497 (s), 1459 (m), 1309 (m), 1241 (s), 1153 (m), 1025 (m), 957 (m), 761 (s), 722 (m). MS (EI, 70 eV): *m/z* (%) = 230 (M^+, 82), 229 (100), 211 (23), 198 (17), 145 (26), 131 (65), 119 (34), 76 (11). HRMS (EI): calcd for $C_{13}H_{14}O_2N_2$ (M^+) 230.10498, found 230.104384.

6-(2-Aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester



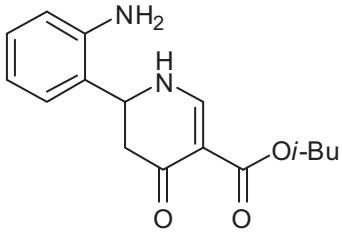
(22b) Following **general procedure 3** and starting with **19b** (0.514 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22b** was obtained as a colourless solid (0.221 g, 90%), mp 199-200°C. ^{1}H NMR (250 MHz, DMSO): δ = 2.47-2.51 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 5.02 (t, ^3J = 8.1 Hz, 1H, C*H*CH_2), 5.13 (s, 2H, NH_2), 6.56 (t, ^3J = 7.5 Hz, 1H, CH_{Ar}), 6.67 (d, ^3J = 7.7 Hz, 1H, CH_{Ar}), 6.97-7.05 (m, 2H, CH_{Ar}), 8.25 (s, 1H, NHC*H*), 9.17 (s, 1H, N*H*CH). ^{13}C NMR (62.9 MHz, DMSO): δ = 41.6 (CH*C*H_2), 50.3 (OCH_3), 51.0 (*C*HCH_2), 98.7 (CO*C*CO), 115.9, 116.4 (CH_{Ar}), 121.9 (C_{Ar}), 126.3, 128.6 (CH_{Ar}), 145.7 (C_{Ar}), 158.0 (CHNH), 165.0 (COO), 186.3 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3404 (w), 3297 (w), 2802 (w), 1699 (s), 1610 (m), 1592 (m), 1571 (s), 1533 (m), 1364 (s), 1318 (m), 1271 (s), 1209 (m), 1194 (m), 1054 (s), 1006 (m), 827 (w), 742 (s). MS (EI, 70 eV): *m/z* (%) = 246 (M^+, 81), 214 (100), 186 (37), 154 (38), 131 (89), 103 (26), 77 (14). HRMS (EI): calcud for $C_{13}H_{14}O_3N_2$ (M^+) 246.09989, found 246.099483.

6-(2-Aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (22c)



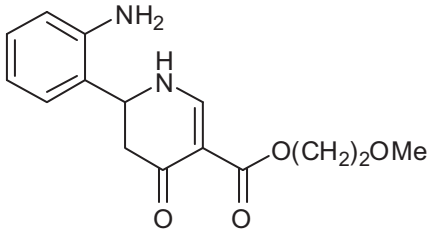
Following **general procedure 3** and starting with **19c** (0.529 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22c** was obtained as a colourless solid (0.242 g, 93%), mp 165-166°C. ^{1}H NMR (500 MHz, DMSO): δ = 1.19 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 2.46 (dd, ^2J = 15.8 Hz, ^3J = 6.3 Hz, 1H, $CHCH_2$), 2.52 (dd, ^2J = 15.8 Hz, ^3J = 10.1 Hz, 1H, $CHCH_2$), 4.05 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 5.02 (dd, ^3J = 10.1 Hz, ^3J = 6.3 Hz, 1H, $CHCH_2$), 5.13 (s, 2H, NH_2), 6.57 (d't', ^3J = 7.7 Hz, ^3J = 7.3 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 6.68 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.00 (ddd, ^3J = 7.9 Hz, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 7.05 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, CH_{Ar}), 8.24 (s, 1H, CHNH), 9.09 (s, 1H, NH). ^{13}C NMR (125.8 MHz, DMSO): δ = 14.6 (CH_3), 41.6 ($CHCH_2$), 51.0 ($CHCH_2$), 58.4 (OCH_2CH_3), 98.9 (COCCO), 115.8, 116.4 (CH_{Ar}), 121.9 (C_{Ar}), 126.3, 128.6 (CH_{Ar}), 145.6 (C_{Ar}), 157.8 (CHNH), 164.3 (COO), 186.3 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3306 (w), 2890 (w), 1683 (m), 1615 (m), 1398 (m), 1384 (m), 1323 (w), 1276 (s), 1210 (m), 1090 (m), 1049 (m), 950 (m), 838 (m), 748 (s), 622 (m) MS (EI, 70 eV): *m/z* (%) = 260 (M^+, 33), 214 (74), 186 (19), 168 (17), 145 (28), 131 (100), 103 (37), 76 (17). HRMS (EI): calcd for $C_{14}H_{16}O_3N_2$ (M^+) 260.11554, found 260.115360.

6-(2-Aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid isopropyl ester (22d) Following **general procedure 3** and starting with **19d** (0.543 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22d** was obtained as a colourless solid (0.227 g, 83%), mp 107-108°C.^{1}H NMR (250 MHz, DMSO): δ = 1.18 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 2.39-2.51 (m, 2H, CH_2), 4.91 (m, ^3J = 6.3 Hz, 1H, $CH(CH_3)_2$), 5.00 (dd, ^3J = 10.1 Hz, ^3J = 6.4 Hz, 1H, $CHCH_2$), 5.14 (s, 2H, NH_2), 6.57 (t, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 6.67 (d, ^3J = 8.0 Hz, ^4J = 1.1 Hz, 1H, CH_{Ar}), 6.97-7.06 (m, 2H, CH_{Ar}), 8.21 (s, 1H, NHCH), 9.08 (br s, 1H, NHCH). ^{13}C NMR (62.8 MHz, DMSO): δ = 22.2 ($CH(CH_3)_2$), 41.7 ($CHCH_2$), 51.1 ($CHCH_2$), 65.3 ($OCH(CH_3)_2$), 99.2 (COCCO), 115.8, 116.4 (CH_{Ar}), 122.0 (C_{Ar}), 126.4, 128.6 (CH_{Ar}), 145.7 (C_{Ar}), 157.7 (CHNH), 163.6 (COO), 186.5 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3203 (w), 2977 (w), 1693 (m), 1574 (s), 1495 (m), 1382 (m), 1372 (m), 1276 (s), 1179 (m), 1158 (m), 1036 (s), 980 (w), 953 (w), 922 (w), 747 (s), 627 (m). MS (EI, 70 eV): *m/z* (%) = 274 (M^+, 12), 215 (35), 187 (24), 155 (100), 128 (21), 91(9), 76 (14). HRMS (EI): calcd for $C_{15}H_{18}O_3N_2$ (M^+) 274.13174, found 274.1317605.

6-(2-Aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid isobutyl ester (22e) 

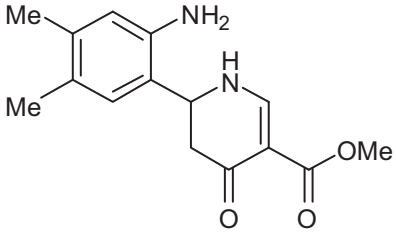
Following **general procedure 3** and starting with **19e** (0.556 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22e** was obtained as a colorless solid (0.231 g, 80%), mp 199-200 ºC. ^{1}H NMR (300 MHz, DMSO): δ = 0.91 (d, ^{3}J = 6.7 Hz, 6H, CH(CH_3)$_2$), 1.87 (m, ^{3}J = 6.7 Hz, 1H, CH(CH$_3$)$_2$), 2.41-2.52 (m, 2H, CHCH_2), 3.80 (d, ^{3}J = 6.5 Hz, 2H, OCH_2), 5.00-5.05 (m, 1H, CHCH$_2$), 5.14 (s, 2H, NH$_2$), 6.57 (d't', ^{3}J = 7.4 Hz, ^{4}J = 1.0 Hz, 1H, CH$_{Ar}$), 6.67 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, 1H, CH$_{Ar}$), 6.98-7.07 (m, 2H, CH$_{Ar}$), 8.24 (d, ^{3}J = 7.4 Hz, 1H, NHCH), 9.05 (d, ^{3}J = 7.4 Hz, 1H, NHCH). ^{13}C NMR (75.5 MHz, DMSO): δ = 19.3 (CH(*C*H$_3$)$_2$), 27.7 (*C*H(CH$_3$)$_2$), 41.7 (CH*C*H$_2$), 51.1 (*C*HCH$_2$), 68.6 (O*C*H$_2$CH), 99.0 (CO*C*CO), 115.8, 116.4 (CH$_{Ar}$), 121.9 (C$_{Ar}$), 126.3, 128.6 (CH$_{Ar}$), 145.7 (C$_{Ar}$), 157.8 (CHNH), 164.4 (COO), 186.3 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3396 (w), 2967 (w), 1683 (m), 1564 (s), 1494 (m), 1407 (m), 1386 (m), 1365 (m), 1275 (s), 1235 (m), 1207 (m), 1156 (m), 1045 (m), 987 (w), 826 (m), 747 (s), 666 (m). MS (EI, 70 eV): *m/z* (%) = 288 (M$^+$, 288 (64), 214 (100), 186 (26(, 158 (23), 146 (30), 131 (72), 103 (28), 76 (12). HRMS (EI): calcd for C$_{16}$H$_{20}$O$_3$N$_2$ (M$^+$) 288.14684, found 288.146106.

6-(2-Aminophenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid 2-methoxy-ethyl ester (22f)



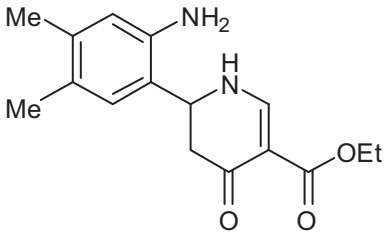
Following **general procedure 3** and starting with **19f** (0.558 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22f** was obtained as a colourless solid (0.235 g, 81%), mp 158-159 ºC. ^{1}H NMR (300 MHz, MeOD): δ = 2.62 (dd, ^{2}J = 16.2 Hz, ^{3}J = 6.0 Hz, 1H, CHCH_2), 2.79 (dd, ^{2}J = 16.2 Hz, ^{3}J = 11.9 Hz, 1H, CHCH_2), 3.38 (s, 3H, OCH$_3$), 3.63-3.66 (m, 2H, CH_2OCH$_3$), 4.24-4.27 (m, 2H, COOCH_2), 5.08 (dd, ^{3}J = 11.9 Hz, ^{3}J = 6.0 Hz, 1H, CHCH$_2$), 6.69-6.78 (m, 2H, CH$_{Ar}$), 7.08 (d't', ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, 1H, CH$_{Ar}$), 7.18 (dd, ^{3}J = 7.6 Hz, ^{4}J = 1.0 Hz, 1H, CH$_{Ar}$), 8.46 (s, 1H, NHCH). ^{13}C NMR (62.9 MHz, MeOD): δ = 42.4 (CH*C*H$_2$), 53.4 (*C*HCH$_2$), 59.1 (OCH$_3$), 63.4 (*C*H$_2$OCH$_3$), 71.9 (COO*C*H$_2$), 100.0 (CO*C*CO), 118.0, 119.3 (CH$_{Ar}$), 123.5 (C$_{Ar}$), 127.5, 130.2 (CH$_{Ar}$), 146.3 (C$_{Ar}$), 160.3 (CHNH), 166.0 (COO), 190.8 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3388 (w), 3153 (m), 2983 (w), 1681 (m), 1615 (m), 1564 (s), 1495 (m), 1395 (m), 1290 (m), 1274 (s), 1204 (m), 1161 (m), 1089 (m), 1050 (m), 833 (m), 752 (s). MS (EI, 70 eV): *m/z* (%) = 290 (M$^+$, 17), 214 (81), 145 (45), 131 (100), 103 (79), 76 (54). HRMS (EI): calcd for C$_{15}$H$_{18}$O$_4$N$_2$ (M$^+$) 290.12611, found 290.126013.

6-(2-Amino-4,5-dimethyl-phenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (22g)



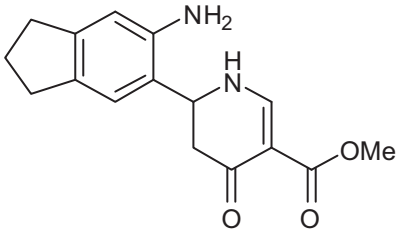
Following **general procedure 3** and starting with **19j** (0.542 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22g** was obtained as a colourless solid (0.181 g, 66%), mp 167-169 ºC. ^{1}H NMR (250 MHz, DMSO): δ = 2.05 (s, 3H, CCH_3), 2.07 (s, 3H, CCH_3), 2.34-2.49 (m, 2H, CHCH_2), 3.57 (s, 3H, OCH_3), 4.83 (s, 2H, NH_2), 4.96 (dd, ^{3}J = 10.8 Hz, ^{3}J = 6.6 Hz 1H, CHCH_2), 6.48 (s, 1H, CH_{Ar}), 6.82 (s, 1H, CH_{Ar}), 8.22 (d, ^{3}J = 7.4 Hz, 1H, NHCH), 9.07 (d, ^{3}J = 7.4 Hz, 1H, NHCH). ^{13}C NMR (62.9 MHz, DMSO): δ = 18.7, 19.4 ($C_{Ar}CH_3$), 42.0 (CHCH$_2$), 50.3 (OCH_3), 50.9 (CHCH$_2$), 98.7 (COCCO), 117.4, 119.6 (CH_{Ar}), 123.8, 127.3, 136.2, 143.4 (C_{Ar}), 157.9 (CHNH), 165.0 (COO), 186.4 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3432 (w), 3171 (w), 2950 (w), 1704 (m), 1688 (m), 1614 (m), 1567 (s), 1439 (m), 1320 (m), 1273 (s), 1274 (m), 1194 (m), 1157 (m), 1095 (m), 809 (w), 773 (m). MS (EI, 70 eV): *m/z* (%) = 274 (M^+, 37), 242 (56), 213 (21), 197 (13), 186 (15), 173 (31), 158 (100), 143 (25), 130 (19), 104 (21), 77 (15). HRMS (EI): calcd for $C_{15}H_{18}O_3N_2$ (M^+) 274.13119, found 274.130591.

6-(2-Amino-4,5-dimethyl-phenyl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (22h)



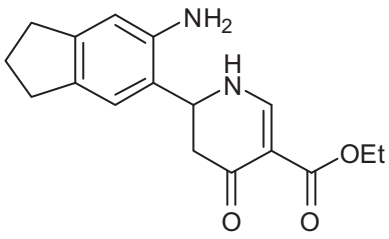
Following **general procedure 3** and starting with **19k** (0.556 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22h** was obtained as a colourless solid (0.172 g, 60%), mp 152-154°C.^{1}H NMR (250 MHz, MeOD): δ = 1.29 (t, ^{3}J = 7.1 Hz, 3H, CH_2CH_3), 2.14 (s, 3H, CCH_3), 2.15 (s, 3H, CCH_3), 2.57 (dd, ^{2}J = 16.2 Hz, ^{3}J = 5.8 Hz, 1H, CHCH_2), 2.79 (dd, ^{2}J = 16.2 Hz, ^{3}J = 12.5 Hz, 1H, CHCH_2), 4.19 (q, ^{3}J = 7.1 Hz, 2H, CH_2CH$_3$), 5.03 (dd, ^{3}J = 12.5 Hz, ^{3}J = 5.8 Hz 1H, CHCH_2), 6.61 (s, 1H, CH_{Ar}), 6.94 (s, 1H, CH_{Ar}), 8.40 (d, ^{3}J = 1.1 Hz, 1H, NHCH). ^{13}C NMR (62.9 MHz, DMSO): δ = 14.7 (OCH_2CH_3), 18.7, 19.4 ($C_{Ar}CH_3$), 42.0 (CHCH$_2$), 50.9 (CHCH$_2$), 58.4 (OCH$_2$CH$_3$), 98.8 (COCCO), 117.4, 119.6 (CH_{Ar}), 123.8, 127.3, 136.2, 143.4 (C_{Ar}), 157.8 (CHNH), 164.3 (COO), 186.5 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3369 (w), 3165 (w), 2978 (w), 1694 (m), 1575 (m), 1505 (m), 1404 (m), 1383 (m), 1355 (w), 1319 (w), 1273 (s), 1196 (w), 1164 (m), 1051 (m), 1018 (w). MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 60), 242 (79), 213 (32), 186 (21), 173 (37), 159 (100), 143 (22), 130 (23), 104 (20), 69 (27). HRMS (EI): calcd for $C_{16}H_{20}O_3N_2$ (M^+) 288.14684, found 288.146207.

6-(6-Amino-indan-5-yl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (22i)



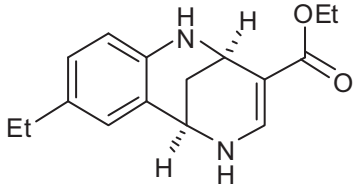
Following **general procedure 3** and starting with **19l** (0.544 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22i** was obtained as a colourless solid (0.187 g, 65%), mp 182-183°C. ^{1}H NMR (300 MHz, DMSO): δ = 1.90-2.02 (m, 2H, $CH_2CH_2CH_2$), 2.46-2.52 (m, 2H, $CHCH_2$), 2.69-2.77 (m, 4H, $CH_2CH_2CH_2$), 3.62 (s, 3H, OCH_3), 4.91 (s, 2H, NH_2), 5.04 (t, ^3J = 7.9 Hz, 1H, $CHCH_2$), 6.61 (s, 1H, CH_{Ar}), 6.94 (s, 1H, CH_{Ar}), 8.28 (d, ^3J = 6.6 Hz, 1H, NHC*H*), 9.27 (d, ^3J = 5.6 Hz, 1H, N*H*CH). ^{13}C NMR (62.9 MHz, DMSO): δ = 25.5, 31.8, 32.4 ($CH_2CH_2CH_2$), 41.8 ($CHCH_2$), 50.3 (OCH_3), 51.1 ($CHCH_2$), 98.5 (COCCO), 112.0 (CH_{Ar}), 120.4 (C_{Ar}), 121.6 (CH_{Ar}), 131.7, 144.0, 144.2 (C_{Ar}), 157.9 (CHNH), 165.0 (COO), 186.6 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3405 (w), 3211 (w), 2943 (w), 1705 (s), 1593 (s), 1432 (m), 1364 (s), 1286 (s), 1187 (m), 1050 (s), 949 (w), 869 (w), 769 (m). MS (GS, 70 eV): *m/z* (%) = 286 (M^+,8), 227 (62), 211 (100), 180 (26), 143 (12), 119 (32), 91 (28), 76 (12). HRMS (EI): calcd for $C_{16}H_{18}O_3N_2$ (M^+) 286.131744, found 286.131646.

6-(6-Amino-indan-5-yl)-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (22j)



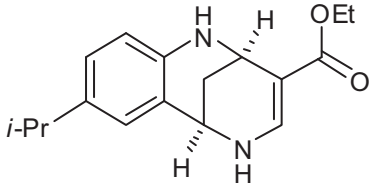
Following **general procedure 3** and starting with **19m** (0.556 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **22j** was obtained as a colourless solid (0.204 g, 68%), mp 163-165°C. ^{1}H NMR (250 MHz, DMSO): δ = 1.18 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.88-1.99 (m, 2H, $CH_2CH_2CH_2$), 2.40-2.49 (m, 2H, $CHCH_2$), 2.66-2.73 (m, 4H, $CH_2CH_2CH_2$), 4.05 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 4.88 (s, 2H, NH_2), 5.03 (dd, ^3J = 9.9 Hz, ^3J = 6.8 Hz, 1H, $CHCH_2$), 6.57 (s, 1H, CH_{Ar}), 6.92 (s, 1H, CH_{Ar}), 8.22 (d, ^3J = 7.4 Hz, 1H, NHC*H*), 9.06 (d, ^3J = 7.4 Hz, 1H, N*H*CH). ^{13}C NMR (62.9 MHz, DMSO): δ = 14.7 (OCH_2CH_3), 25.5, 31.8, 32.4 ($CH_2CH_2CH_2$), 42.0 ($CHCH_2$), 51.2 ($CHCH_2$), 58.4 (OCH_2CH_3), 98.8 (COCCO), 111.9 (CH_{Ar}), 120.4 (C_{Ar}), 121.7 (CH_{Ar}), 131.6, 144.1, 144.2 (C_{Ar}), 157.7 (CHNH), 164.3 (COO), 186.5 (CO). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3407 (w), 3307 (w), 2971 (w), 2545 (w), 1699 (s), 1616 (m), 1567 (s), 1490 (m), 1428 (m), 1368 (m), 1321 (m), 1280 (s), 1150 (m), 1062 (m), 1048 (m), 849 (m). MS (GS, 70 eV): *m/z* (%) = 300 (M^+, 5) 255 (15), 211 (100), 186 (16), 116 (23), 76 (12). HRMS (ESI): calcd for $C_{17}H_{21}O_3N_2$ ($(M+H)^+$) 301.15467, found 301.15461.

4-Ethyl-8,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-10-carboxylic acid ethyl ester (23a)



Following **general procedure 3** and starting with **19g** (0.556 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **23a** was obtained as a colourless solid (0.150 g, 55%), mp 149-151°C. ^{1}H NMR (300 MHz, DMSO): δ = 1.17 (t, ^{3}J = 7.5 Hz, 3H, CH_2CH_3), 1.23 (t, ^{3}J = 7.2 Hz, 3H, OCH_2CH_3), 1.94 (ddd, ^{2}J = 12.4 Hz, ^{3}J = 9.3 Hz, ^{3}J = 9.3 Hz, 1H, $CHCH_2CH$), 2.15 (ddd, ^{2}J = 12.4 Hz, ^{3}J = 9.5 Hz, ^{3}J = 9.5 Hz, 1H, $CHCH_2CH$), 2.50 (q, ^{3}J = 7.5 Hz, 2H, CH_2CH_3), 4.12 (q, ^{3}J = 7.2 Hz, 2H, OCH_2CH_3), 4.16 (br, 1H, NH), 4.32-4.34 (m, 2H, $CHCH_2CH$), 5.31 (s, 1H, NH), 6.55 (d, ^{3}J = 8.1 Hz, 1H, CH_{Ar}), 6.83 (d, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 6.89 (dd, ^{3}J = 8.1 Hz, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 7.52 (d, ^{3}J = 5.6 Hz, 1H, NHCH). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 14.6 (CH_3), 15.8 (CH_3), 26.3 ($CHCH_2$), 27.8 ($C_{Ar}CH_2$), 42.3 (CHN), 47.3 (CHN), 59.1 (OCH_2), 103.2 (CCOO), 126.3 (CH_{Ar}), 124.4 (C_{Ar}), 128.2, 128.3 (CH_{Ar}), 133.3, 141.7 (C_{Ar}), 143.1 (COO), 168.0 (CHN). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3339 (m), 2957 (w), 2928 (w), 1619 (m), 1584 (s), 1505 (s), 1464 (m), 1374 (m), 1338 (w), 1286 (m), 1220 (s), 1181 (m), 1153 (w), 1088 (s), 1046 (m), 997 (w), 898 (w), 818 (m). MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 100), 243 (42), 226 (73), 197 (33), 158 (39), 106 (48), 77 (7). HRMS (EI): calcd for $C_{16}H_{20}O_2N_2$ (M^+) 272.15193, found 272.151571.

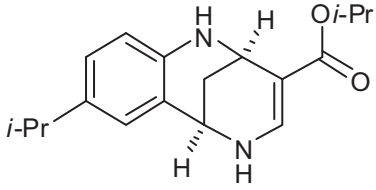
4-Isopropyl-8,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-10-carboxylic acid ethyl ester (23b)



Following **general procedure 3** and starting with **19h** (0.570 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **23b** was obtained as a colourless solid (0.129 g, 45%), mp 165-166 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (d, ^{3}J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.23 (t, ^{3}J = 7.1 Hz, 3H, OCH_2CH_3), 1.94 (ddd, ^{2}J = 12.4 Hz, ^{3}J = 9.3 Hz, ^{3}J = 9.3 Hz, 1H, $CHCH_2CH$), 2.12-2.18 (m, 1H, $CHCH_2CH$), 2.76 (m, ^{3}J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.12 (q, ^{3}J = 7.1 Hz, 2H, OCH_2CH_3), 4.32-4.35 (m, 2H, $CHCH_2CH$), 4.67 (br, 1H, NH), 5.25 (s, 1H, NH), 6.55 (d, ^{3}J = 8.2 Hz, 1H, CH_{Ar}), 6.85 (d, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 6.93 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.0 Hz, 1H, CH_{Ar}), 7.52 (d, ^{3}J = 5.9 Hz, 1H, NHCH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6 (CH_3), 24.2, 24.3 ($CH(CH_3)_2$), 26.3 ($CHCH_2$), 33.1 ($CH(CH_3)_2$), 42.3 (CHN), 47.5 (CHN), 59.1 (OCH_2), 103.4 (CCOO), 116.2 (CH_{Ar}), 124.3 (C_{Ar}), 126.8, 126.9 (CH_{Ar}), 138.0, 141.8 (C_{Ar}), 143.1 (COO), 168.0 (CHN). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (m), 2957 (m), 1618 (m), 1586 (s), 1506 (m), 1374 (m), 1339 (m), 1286 (m), 1220 (s), 1161 (w), 1089 (s), 1048 (m),

997 (w), 902 (w). MS (EI, 70 eV): *m/z* (%) = 286 (M^+, 100), 257 (32), 240 (50), 211 (21), 172 (28), 156 (27), 120 (27), 77 (5). HRMS (EI): calcd for $C_{17}H_{22}O_2N_2$ (M^+) 286.16758, found 286.166644.

4-Isopropyl-8,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-10-carboxylic acid isopropyl ester (23c)

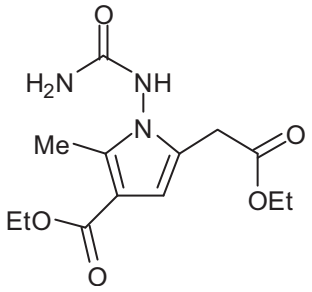


Following **general procedure 3** and starting with **19i** (0.582 g, 1.0 mmol), Pd/C (0.106 g, 0.1 mmol) in methanol (10 mL), **23c** was obtained as a colourless solid (0.150 g, 50%), mp 172-174 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, ^3J = 6.9 Hz, 6H, CH(CH_3)$_2$), 1.20 (d, ^3J = 6.2 Hz, 3H, OCH(CH_3)$_2$), 1.23 (d, ^3J = 6.2 Hz, 3H, OCH(CH_3)$_2$), 1.94 (ddd, ^2J = 12.4 Hz, ^3J = 9.2 Hz, ^3J = 9.2 Hz, 1H, CHCH_2CH), 2.17 (ddd, ^2J = 12.4 Hz, ^3J = 9.8 Hz, ^3J = 9.8 Hz, 1H, CHCH_2CH), 2.77 (m, ^3J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 4.33-4.35 (m, 2H, CHCH$_2$CH), 5.02 (m, ^3J = 6.2 Hz, 1H, CH(CH$_3$)$_2$), 5.24 (s, 1H, NH), 6.55 (d, ^3J = 8.2 Hz, 1H, CH_{Ar}), 6.85 (d, ^4J = 2.1 Hz, 1H, CH_{Ar}), 6.93 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1H, CH_{Ar}), 7.50 (d, ^3J = 5.8 Hz, 1H, NHCH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.2, 22.3, 24.2, 24.3 (CH_3), 26.3 (CHCH$_2$), 33.1 (CH(CH$_3$)$_2$), 42.4 (CHN), 47.4 (CHN), 66.0 (OCH), 103.6 (CCOO), 116.3 (CH_{Ar}), 124.5 (C_{Ar}), 126.8, 126.9 (CH_{Ar}), 138.1, 141.7 (C_{Ar}), 143.0 (COO), 167.5 (CHN). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3314 (w), 2957 (w), 2867 (w), 1586 (s), 1514 (m), 1461 (w), 1379 (m), 1286 (m), 1223 (s), 1178 (w), 1089 (s), 1046 (m), 998 (m), 948 (w), 826 (w). MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 100), 257 (76), 240 (83), 211 (15), 172 (34), 156 (23), 124 (28), 91 (3). HRMS (ESI): Calculated for $C_{18}H_{25}O_2N_2$ ((M+H)$^+$) 301.19105, found 301.19082.

7.2.4 Regioselective Synthesis of New 1-Aminopyrroles and 1-Amino-4,5,6,7-tetrahydroindoles by One-Pot ′Conjugate Addition/Cyclization′ Reactions of 1,3-Bis(silyloxy)-1,3-butadienes with 1,2-Diaza-1,3-butadienes

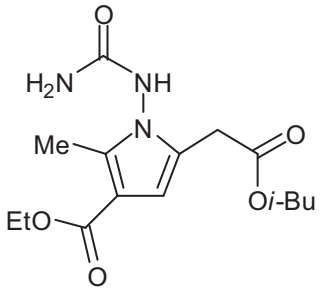
General procedure 4: To a CH_2Cl_2 solution (12 mL) of 1,2-diaza-1,3-butadiene **24** (2.0 mmol) was added 1,3-bis(silyloxy)-1,3-butadiene **5** (2.4 mmol) and freshly dried $ZnCl_2$ (0.055 g, 0.4 mmol) at 20 °C. The solution was stirred for 12 h at room temperature and subsequently TFA (0.3 mL) was added. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, heptane → heptane/EtOAc = 1:2).

5-Ethoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28b)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5d** (0.658 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), 3b was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.550 g, 92%); mp = 155–158 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.20 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 1.25 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 2.29 (s, 3H, $C_{Hetar}CH_3$), (ABq, ^2J = 17.0 Hz, 2H, CH_2CO), 4.08 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 4.16 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 6.20 (br, 2H, NH_2), 6.24 (s, 1H, CH_{Hetar}), 9.11 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 10.5 ($C_{Hetar}CH_3$), 14.2, 14.6 (OCH_2CH_3), 31.2 (CH_2CO), 59.0, 60.7 (OCH_2CH_3), 106.5 (CH_{Hetar}), 108.7 ($C_{Hetar}CO$), 126.2, 136.8, (C_{Hetar}), 157.2 (CO), 164.4 (CONH), 169.9 ($COOCH_2CH$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3411 (s), 3305 (s), 3206 (w), 2981 (w), 1717 (s), 1678 (s), 1596 (s), 1534 (s), 1351 (m), 1282 (m), 1237 (s), 1221 (s), 1129 (m), 1075 (s), 1029 (m), 772 (w). MS (EI, 70 eV): *m/z* (%) = 297 (M^+, 42), 280 (13), 252 (24), 238 (100), 224 (77), 207 (58), 181 (68), 166 (14), 136 (26), 108 (18), 77 (13). HRMS (EI): Calcd. for $C_{13}H_{19}N_3O_5$ (M^+) 297.13192, found 297.131203.

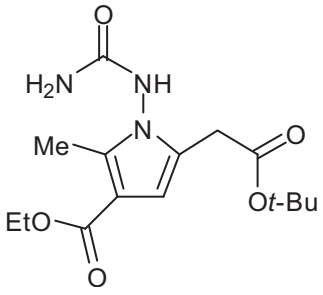
5-Isobutoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28c)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5e** (0.726 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28c** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.517 g, 80%); mp = 131–133 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.88 (d, ^3J = 6.7 Hz, 6H, $CH(CH_3)_2$), 1.25 (t, ^3J = 7.0 Hz, 3H, OCH_2CH_3), 1.89 (m, 1H, $CH(CH_3)_2$), 2.29 (s, 3H, $C_{Hetar}CH_3$), 3.51 (ABq, ^2J = 16.9 Hz, 2H, CH_2CO), 3.84 (dd, ^2J = 1.8 Hz, 2H, CH_2CH), 4.16 (q, ^3J = 7.0 Hz, 2H, OCH_2CH_3), 6.20 (br, 2H, NH_2), 6.25 (s, 1H, CH_{Hetar}), 9.11 (s, 1H, NH). ^{13}C NMR (250 MHz, DMSO-d_6): δ = 10.3 ($C_{Hetar}CH_3$), 14.4 (OCH_2CH_3), 18.8 ($CHCH_3$), 27.1 (CH_2CH), 30.8 (CH_2CO), 58.7 (OCH_2CH_3), 70.2 (OCH_2CH), 106.2 (CH_{Hetar}), 108.5, 125.9, 136.5 (C_{Hetar}), 156.9 ($C_{Hetar}CO$), 164.2 (CONH), 169.7 ($COOCH_2CH$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (m), 3314 (m), 3211 (w), 2959 (m), 1722 (s), 1702 (s), 1678 (s), 1541 (m), 1525 (m), 1342 (m), 1226 (s), 1189 (m), 1078 (s), 994 (w), 771 (w). MS (EI, 70 eV): *m/z* (%) = 325 (M^+, 43), 280 (23), 266 (71), 224 (100), 207 (58), 181

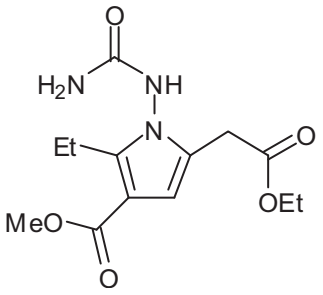
(58), 166 (18), 136 (19), 108 (15) 57 (16). HRMS (EI): calcd. for $C_{15}H_{23}N_3O_5$ (M^+) 325.16322, found 325.163068.

5-*tert*-Butoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28d)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5h** (0.726 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28d** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.527 g, 81%); mp. = 178–180 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.42 (s, 9H, $C(CH_3)_3$), 2.29 (s, 3H, $C_{Hetar}CH_3$), 3.34 (ABq, ^2J = 16.9 Hz, 2H, CH_2CO), 4.16 (q, ^3J = 7.1 Hz, 2H, CH_2CH_3), 6.19 (br, 2H, $CONH_2$), 6.23 (s, 1H, CH_{Hetar}), 9.06 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.5 (CH_2CH_3), 14.6 ($NCCH_3$), 27.9 ($C(CH_3)_3$), 32.2 (CCH_2CO), 58.9 (OCH_2), 80.6 ($OC(CH_3)_3$), 106.2 (CH_{Hetar}), 108.7, 126.5, 136.6 (C_{Hetar}), 157.2, 164.4, 169.1 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3405 (s), 3270 (m), 2981 (m), 2934 (w), 2907 (w), 1740 (s), 1675 (s), 1576 (m), 1531 (m), 1457 (m), 1414 (m), 1388 (m), 1229 (s), 1146 (s), 1081 (s), 1021 (w), 849 (w), 773 (w), 602 (w). MS (EI, 70 eV): *m/z* (%) = 325 (M^+, 11), 269 (18), 224 (100), 207 (26), 166 (27), 57 (79). HRMS (EI, 70 eV): calcd. for $C_{15}H_{23}N_3O_5$ ($[M]^+$) 325.16322, found 325.162992.

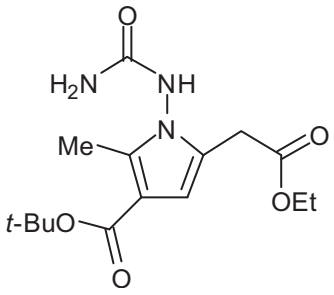
5-Ethoxycarbonylmethyl-2-ethyl-1-ureido-1*H*-pyrrole-3-carboxylic acid methyl ester (28e)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24b** (0.250 g, 1.35 mmol), **5d** (0.445 g, 1.62 mmol) and $ZnCl_2$ (0.037 g, 0.37 mmol) in CH_2Cl_2 (12 mL), **28e** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.304 g, 60%); mp. = 201–203 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.06 (t, ^3J = 7.4 Hz, 3H, CCH_2CH_3), 1.20 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 2.70 (m, 1H, CCH_2CH_3), 2.81 (m, 1H, CCH_2CH_3), 3.47 (ABq, ^2J = 17.0 Hz, 2H, CH_2CO), 3.69 (s, 3H, CH_3O), 4.09 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 6.19 (br, 2H, NH_2), 6.25 (s, 1H, CH_{Hetar}), 9.14 (s, 1H, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.8 ($C_{Hetar}CH_2CH_3$), 14.2 (OCH_2CH_3), 17.9 ($C_{Hetar}CH_2CH_3$), 31.2 ($C_{Hetar}CH_2$), 50.7 (CH_3O), 60.7 (OCH_2CH_3), 106.5 (CH_{Hetar}), 107.8 ($C_{Hetar}CO$), 126.2, 142.5, (C_{Hetar}), 157.1 (CO), 164.6

(CONH), 169.8 (*C*OOCH$_2$CH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437 (s), 3325 (m), 3250 (m), 3207 (m), 2978 (w), 1736 (s), 1677 (s), 1592 (m), 1540 (s), 1439 (m), 1392 (m), 1239 (s), 1212 (s), 1167 (s), 1135 (m), 1093 (s), 1055 (m), 1029 (m), 771 (w). MS (EI, 70 eV): *m/z* (%) = 297 (M$^+$, 18), 280 (3), 254 (12), 238 (100), 224 (21), 207 (14), 181 (42), 164 (35), 149 (17), 132 (19), 106 (9), 77 (7). HRMS (EI): Calcd. for $C_{13}H_{19}N_3O_5$ (M$^+$) 297.13192, found 297.131448.

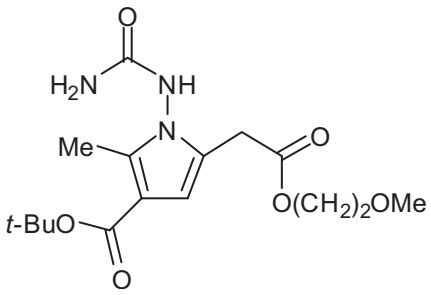
5-Ethoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (28f)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24c** (0.290 g, 1.36 mmol), **5d** (0.447 g, 1.63 mmol) and $ZnCl_2$ (0.037 g, 0.27 mmol) in CH_2Cl_2 (12 mL), **28f** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.270 g, 61%); mp. = 165–167 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.23 (t, ^3J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.51 (s, 9H, C(CH$_3$)$_3$), 2.29 (s, 3H, C$_{Hetar}$CH$_3$), 3.50 (ABq, ^2J = 17.1 Hz, 2H, CH$_2$CO), 4.11 (q, ^3J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 6.21 (s, 3H, CON*H*$_2$, CH$_{Hetar}$), 9.1 (s, 1H, NNHCO). ^{13}C NMR (75.5 MHz, DMSO-d$_6$): δ = 10.5 (C$_{Hetar}$*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 31.2 (C*C*H$_2$CO), 60.6 (O*C*H$_2$CH$_3$), 78.7 (O*C*(CH$_3$)$_3$), 106.7 (CH$_{Hetar}$), 110.2 (*C*$_{Hetar}$CO), 125.8, 136.1 (C$_{Hetar}$), 157.2 (CO), 164.0 (CONH), 169.9 (*C*OOCH$_2$CH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3418 (s), 3176 (broad, m), 2930 (m), 1744 (s), 1697 (broad, s), 1610 (m), 1401 (s), 1366 (s), 1246 (s), 1218 (s), 1158 (s), 1070 (s), 1036 (w), 855 (w), 778 (m), 619 (w). MS (EI, 70 eV): *m/z* (%) = 325 (M$^+$, 19), 269 (9), 252 (47), 210 (100), 196 (57), 180 (39), 153 (64), 107 (11), 77 (10). Anal. calcd for $C_{15}H_{23}N_3O_5$ (325.36): C, 55.37; H, 7.13; N, 12.91. Found: C, 55.44; H, 6.97; N, 12.75.

5-(2-Methoxy-ethoxycarbonylmethyl)-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (28g)

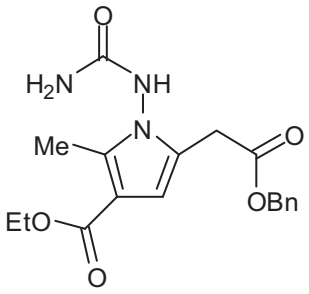


Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24c** (0.426 g, 2.0 mmol), **5g** (0.730 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28g** was isolated as a yellow solid (0.418 g, 60%); mp. = 99–101 °C.

^{1}H NMR (250 MHz, CDCl$_3$-d$_6$): δ = 1.51 (s, 9H, C(CH$_3$)$_3$), 2.41 (s, 3H, C$_{Hetar}$CH$_3$), 3.35 (s, 3H, OCH$_3$), 3.48-3.68 (m, 4H, C$_{Hetar}$C*H*$_2$, C*H*$_2$OCH$_3$), 4.09-4.32 (m, 2H, COOCH$_2$), 5.26 (br, 2H, CON*H*$_2$), 6.37 (s, 1H, CH$_{Hetar}$), 8.31 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ =

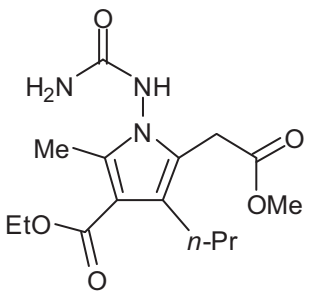
10.3 ($C_{Hetar}CH_3$), 28.4 ($C(CH_3)_3$), 31.4 ($C_{Hetar}CH_2$), 58.7 (OCH_3), 63.9, 70.1 (OCH_2CH_2O), 79.9 ($C(CH_3)_3$), 108.8 (CH_{Hetar}), 112.4, 124.3, 136.6 (C_{Hetar}), 158.8 (CONH), 164.2 ($COOCH_2$), 170.4 ($COOCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3169 (w), 2974 (w), 2926 (w), 1691 (s), 1609 (m), 1588 (m), 1541 (w), 1392 (m), 1364 (m), 1246 (m), 1199 (m), 1147 (s), 1068 (s), 1036 (m), 994 (w), 852 (w), 774 (m). MS (EI, 70 eV): *m/z* (%) = 355 (M^+, 24), 312 (6), 282 (27), 265 (9), 240 (39), 223 (24), 207 (11), 196 (58), 180 (100), 164 (31), 153 (61), 138 (19), 107 (11), 59 (16). HRMS (EI): Calcd for $C_{16}H_{25}N_3O_6$ (M^+) 355.17379, found 355.172879.

5-Benzyloxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28h)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5i** (0.806 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28h** was purified by column chromatography and crystallization (EtOH) as a colourless solid (0.432 g, 60%); mp. = 178–181 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, $C_{Hetar}CH_3$), 3.57 (ABq, ^2J = 17.1 Hz, 2H, CH_2CO), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 5.12 (s, 2H, OCH_2C_{Ar}), 6.25 (s, 3H, CH_{Hetar}, NH_2), 7.37 (s, 5H, CH_{Ar}), 9.18 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.5 ($C_{Hetar}CH_3$), 14.6 (OCH_2CH_3), 31.1 (CCH_2CO), 59.0 (OCH_2CH_3), 66.2 (OCH_2C_{Ar}), 106.5 (CH_{Hetar}), 108.7 ($C_{Hetar}CO$), 126.0 (C), 128.2, 128.3, 128.6 (CH_{Ar}), 136.2, 136.8 (*C*), 157.2 (CONH), 164.4 ($COOCH_2$), 169.8 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 3269 (w), 3204 (w), 2969 (broad, w), 22927 (w), 2872 (w), 1713 (m), 1699 (m), 1672 (s), 1589 (m), 1538 (m), 1454 (w), 1405 (w), 1352 (m), 1338 (m), 1249 (w), 1231 (m), 1191 (s), 1142 (s), 1076 (s), 1029 (w), 952 (w), 839 (w), 772 (w). MS (EI, 70 eV): *m/z* (%) = 359 (M^+, 4), 316 (15), 268 (30), 224 (29), 207 (25), 181 (45), 166 (14), 149 (21), 108 (22), 91 (100), 79 (17), 65 (14). HRMS (EI): Calcd for $C_{18}H_{21}N_3O_5$ (M^+) 359.14757, found 359.147171.

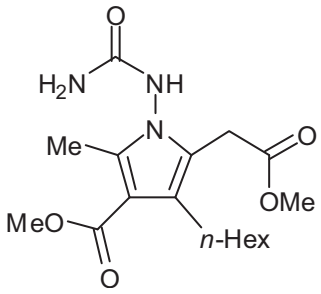
5-Methoxycarbonylmethyl-2-methyl-4-propyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28j)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5k** (0.75 g, 2.5 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28j** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.420 g, 63%); mp. = 184–189 °C.

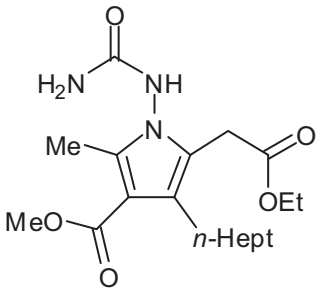
^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 0.84 (t, ^3J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.26 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.41 (m, 2H, $CH_2CH_2CH_3$), 2.25 (s, 3H, $C_{Hetar}CH_3$), 2.49 (m, 2H, $CH_2CH_2CH_3$), 3.47 (ABq, ^2J = 16.9 Hz, 2H, CH_2CO), 3.58 (s, 3H, OCH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.15 (br, 2H, NH_2), 9.06 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ = 11.0 ($C_{Hetar}CH_3$), 14.1, 14.5 (OCH_2CH_3, $CH_2CH_2CH_3$), 24.3, 27.4 (CH_2), 29.1 (CCH_2CO), 52.0 (OCH_3), 58.8 (OCH_2CH_3), 107.8, 120.0, 123.4, 136.6 (C_{Hetar}), 157.3 (CONH), 165.0 ($COOCH_2$), 170.6 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3412 (w), 3321 (w), 3207 (w), 2955 (m), 2868 (w), 1726 (m), 1676 (s), 1624 (m), 1531 (m), 1519 (m), 1439 (m), 1396 (w), 1353 (m), 1265 (s), 1210 (s), 1113 (s), 1095 (m), 1060 (m), 1008 (w), 856 (w), 785 (w). MS (EI, 70 eV): *m/z* (%) = 325 (M^+, 24), 282 (10), 266 (100), 250 (18), 223 (23), 206 (10), 177 (10), 97 (6), 69 (10). HRMS (EI): Calcd for $C_{15}H_{23}N_3O_5$ (M^+) 325.16322, found 325.162781.

4-Hexyl-5-methoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid methyl ester (28k)



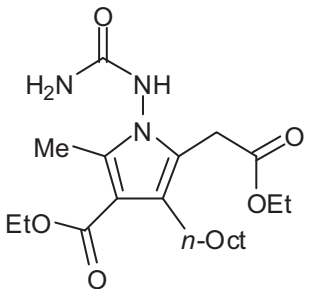
Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.257 g, 1.5 mmol), **5l** (0.620 g, 1.8 mmol) and $ZnCl_2$ (0.04 g, 0.3 mmol) in CH_2Cl_2 (12 mL), **28k** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.345 g, 65%); mp. = 192–194 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 0.86 (t, ^3J = 6.5 Hz, 3H, $C_5H_{10}CH_3$), 1.19-1.36 (m, 8H, $CH_2C_4H_8CH_3$), 2.26 (s, 3H, $C_{Hetar}CH_3$), 2.45 (m, 2H, $C_{Hetar}CH_2C_5H_{11}$), 3.46 (ABq, ^2J = 17.0 Hz, 2H, CH_2CO), 3.59 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.12 (br, 2H, NH_2), 9.02 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ = 11.0 ($C_{Hetar}CH_3$), 14.1 ($C_5H_{10}CH_3$), 22.3, 25.2, 28.9, 29.1, 31.0, 31.3 (CH_2), 50.4, 51.9 (OCH_3), 107.6, 120.3, 123.3, 136.6 (C_{Hetar}), 157.2 (CONH), 165.4 ($COOCH_2$), 170.5 ($COOCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3420 (m), 3328 (s), 3212 (w), 2953 (m), 2929 (m), 2855 (w), 1724 (s), 1689 (s), 1676 (s), 1622 (w), 1533 (m), 1438 (m), 1387 (w), 1356 (m), 1266 (m), 1220 (m), 1190 (m), 1122 (m), 1106 (m), 1063 (w), 1009 (w), 786 (w). MS (EI, 70 eV): *m/z* (%) = 353 (M^+, 36), 310 (17), 294 (100), 278 (15), 239 (23), 224 (68), 207 (41), 181 (12), 166 (17), 147 (7), 108 (10), 79 (8). Anal. Calcd. for $C_{17}H_{27}N_3O_5$ (353.41): C, 57.77; H, 7.70; N, 11.89. Found: C, 57.86; H, 7.72; N, 11.77.

5-Ethoxycarbonylmethyl-4-heptyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid methyl ester (28l)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.225 g, 1.3 mmol), **5m** (0.580 g, 1.56 mmol) and $ZnCl_2$ (0.03 g, 0.2 mmol) in CH_2Cl_2 (12 mL), **28l** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.372 g, 75%); mp. = 168–171 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.85 (t, 3H, $C_6H_{12}CH_3$), 1.18 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.24-1.36 (m, 10H, $CH_2C_5H_{10}CH_3$), 2.25 (s, 3H, $C_{Hetar}CH_3$), 2.51 (m, 2H, $C_{Hetar}CH_2C_6H_{13}$), 3.44 (ABq, ^2J = 16.8 Hz, 2H, CH_2CO), 3.68 (s, 3H, OCH_3), 4.05 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.14 (br, 2H, NH_2), 9.04 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 11.1 ($C_{Hetar}CH_3$), 14.1, 14.2 (CH_3), 22.3, 25.2, 28.9, 29.2, 29.3, 31.1, 31.5 (CH_2), 50.5 (OCH_3), 60.6 (OCH_2CH_3), 107.6, 120.3, 123.4, 136.5 (C_{Hetar}), 157.2 (CONH), 165.4 ($COOCH_2$), 170.1 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3330 (w), 3206 (w), 2921 (broad, w), 2851 (w), 1725 (s), 1698 (s), 1676 (s), 1623 (m), 1526 (m), 1423 (w), 1402 (m), 1254 (m), 1200 (s), 1186 (s), 1124 (m), 1100 (s), 1021 (m), 852 (w), 785 (w). MS (EI, 70 eV): *m/z* (%) = 381 (M^+, 57), 350 (11), 338 (22), 322 (100), 308 (37), 253 (35), 238 (82), 224 (57), 207 (96), 181 (34), 166 (33), 122 (17), 77 (11). HRMS (EI): Calcd for $C_{19}H_{31}N_3O_5$ (M^+) 381.22582, found 381.225604.

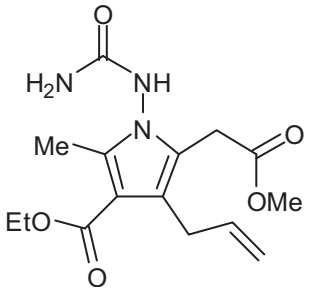
5-Ethoxycarbonylmethyl-2-methyl-4-octyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28m)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5n** (0.926 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28m** was purified by column chromatography and crystallization (EtOH) as a colourless solid (0.381 g, 47%); mp. = 131–133 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 0.85 (t, ^3J = 6.6 Hz, 3H, $C_7H_{14}CH_3$), 1.18 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.23-1.37 (m, 15H, OCH_2CH_3, $CH_2C_6H_{12}CH_3$), 2.26 (s, 3H, $C_{Hetar}CH_3$), 2.51 (m, 2H, $C_{Hetar}CH_2C_7H_{15}$), 3.44 (ABq, ^2J = 16.8 Hz, 2H, CH_2CO), 4.05 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.14 (br, 2H, NH_2), 9.02 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 11.0 ($C_{Hetar}CH_3$), 14.1, 14.2, 14.5 (CH_3), 22.3, 25.4, 28.9, 29.2, 29.26, 29.3, 31.2, 31.5 (CH_2), 58.8, 60.6 (OCH_2CH_3), 107.7 ($C_{Hetar}CO$), 120.2, 123.3, 136.6 (C_{Hetar}), 157.2 (CONH), 165.0 ($COOCH_2$), 170.1 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3314 (m), 3274 (m), 3215 (w), 2953 (w), 2921 (m), 2870 (w), 2850 (w), 1715 (s), 1679 (s), 1614

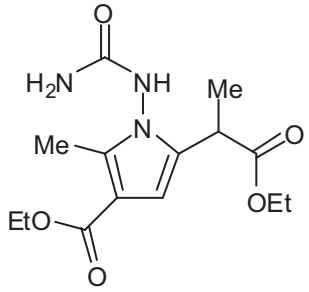
(m), 1531 (m), 1410 (w), 1377 (m), 1345 (m), 1263 (m), 1232 (m), 1211 (s), 1115 (s), 1103 (s), 1059 (m), 1038 (m), 851 (w), 783 (w), 686 (w). MS (EI, 70 eV): *m/z* (%) = 409 (M^+, 50), 364 (26), 350 (100), 336 (45), 320 (29), 293 (30), 267 (27), 252 (88), 238 (54), 207 (73), 180 (34), 122 (17). HRMS (EI): Calculated for $C_{21}H_{35}N_3O_5$ (M^+) 409.25712, found 409.258327.

4-Allyl-5-methoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28n)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.430 g, 2.5 mmol), **5o** (0.900 g, 3.0 mmol) and $ZnCl_2$ (0.068 g, 0.5 mmol) in CH_2Cl_2 (12 mL), **28n** was purified by column chromatography and crystallization (EtOH) as a colourless solid (0.355 g, 44%); mp. = 166–170 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.27 (s, 3H, $C_{Hetar}CH_3$), 3.47 (ABq, ^2J = 16.9 Hz, 2H, CH_2CO), 3.50 (br, m, 2H, $C_{Hetar}CH_2CH$), 3.57 (s, 3H, OCH_3), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 4.89 (m, 2H, $CHCH_2$), 5.82 (m, 1H, $CHCH_2$), 6.17 (br, 2H, NH_2), 9.10 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.0 ($C_{Hetar}CH_3$), 14.5 (OCH_2CH_3), 29.0, 29.4 ($C_{Hetar}CH_2$), 51.9 (OCH_3), 58.9 (OCH_2CH_3), 107.8 ($C_{Hetar}CO$), 114.0 ($CHCH_2$), 117.2, 123.9 (C_{Hetar}), 136.6 ($C_{Hetar}CH_3$), 138.3 ($CHCH_2$), 157.2 (CONH), 164.9 ($COOCH_2$), 170.4 ($COOCH_3$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3415 (m), 3321 (m), 3263 (w), 3205 (m), 3078 (w), 2978 (w), 2952 (m), 2930 (w), 1721 (s), 1676 (s), 1619 (m), 1525 (m), 1438 (m), 1352 (m), 1265 (s), 1244 (m), 1206 (s), 1169 (m), 1118 (s), 1103 (s), 1055 (m), 1008 (m), 993 (m), 904 (w), 863 (w), 784 (m). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 69), 278 (11), 264 (100), 247 (20), 218 (20), 204 (14), 190 (20), 176 (24), 158 (26), 132 (44), 117 (17), 91 (19). HRMS (EI): Calcd for $C_{15}H_{21}O_5N_3$ (M^+) 323.14757, found 323.146924.

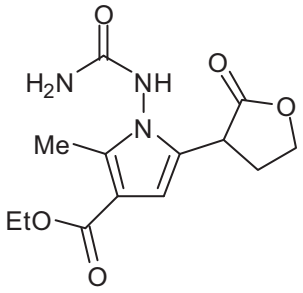
5-(1-Ethoxycarbonyl-ethyl)-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28o)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5p** (0.700 g, 2.40 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (16 mL), **28o** was isolated by column chromatography and crystallized (EtOH) as a colourless solid (0.280 g, 45%); mp = 152–158 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.16, 1.17 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3, diastereomers), 1.25 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.33, 1.36 (d, ^3J = 7.2 Hz, 3H, $CHCH_3$, diastereomers), 2.27 (s, 3H, $C_{Hetar}CH_3$), 3.62 (m, 1H, $C_{Hetar}CH$), 4.00-4.20 (m, 4H, OCH_2CH_3,

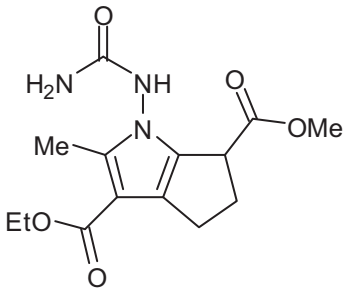
OC*H*$_2$CH$_3$), 6.16, 6.19 (s, 1H, CH$_{Hetar}$, diastereomers), 6.25 (br, 2H, NH$_2$), 9.18 (s, 1H, NNHCO). ^{13}C NMR (62.9 MHz, DMSO-d$_6$): δ = 10.4 (C$_{Hetar}$*C*H$_3$), 14.1, 14.2, 14.7 (OCH$_2$*C*H$_3$), 16.7, 17.5 (CH*C*H$_3$, diastereomers), 36.3 (*C*HCH$_3$), 59.0, 60.7 (OCH$_2$CH$_3$), 104.1, 104.5 (CH$_{Hetar}$, diastereomers), 108.7 (*C*$_{Hetar}$CO), 132.1, 132.4 (*C*$_{Hetar}$, diastereomers), 136.8, 137.1 (*C*$_{Hetar}$, diastereomers), 157.2 (CONH), 164.4 (C$_{Hetar}$*C*OO), 172.8, 173.2 (CH*C*OO, diastereomers). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3402 (br, w), 3291 (br, w), 3209 (w), 2987 (w), 2940 (w), 1727 (m), 1690 (s), 1670 (s), 1594 (m), 1534 (m), 1442 (br, m), 1383 (m), 1367 (w), 1321 (m), 1229 (s), 1202 (s), 1173 (m), 1163 (s), 1075 (s), 1022 (m), 896 (w), 857 (w), 832 (w), 800 (w), 771 (m), 724 (w), 689 (w), 574 (br, m). MS (GC/MS, 70 eV): m/z (%) = 311 (M$^+$, 20), 266 (18), 238 (100), 222 (49), 192 (16), 165 (12), 149 (31), 106 (13), 91 (7), 77 (8). HRMS (EI): Calculated for C$_{14}$H$_{21}$N$_3$O$_5$ (M$^+$) 311.14757, found 311.147297.

2-Methyl-5-(2-oxo-tetrahydro-furan-3-yl)-1-ureido-1*H*-pyrrole-3-carboxylic acid ethyl ester (28p)



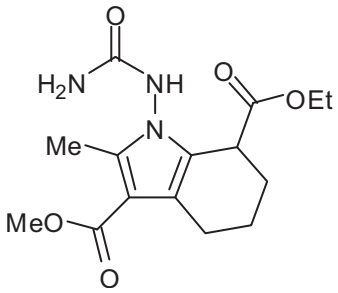
Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.463 g, 2.5 mmol), **5q** (0.816 g, 3.0 mmol) and ZnCl$_2$ (0.069 g, 0.5 mmol) in CH$_2$Cl$_2$ (12 mL), **28p** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.367 g, 50%); mp. = 166–168 °C. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.18–2.39 (m, 4H, C$_{Hetar}$C*H*$_3$, CHC*H*$_2$), 2.49 (m, 1H, CHC*H*$_2$), 3.94 (m, 1H, C*H*CH$_2$), 4.16 (q, ^3J = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.33 (m, 2H, CH$_2$C*H*$_2$O), 6.22, 6.25 (s, 1H, CH$_{Hetar}$, diastereomers), 6.32 (s, 2H, N*H*$_2$), 9.20, 9.21 (s, 1H, NHCO, diastereomers). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 10.3, 10.4 (C$_{Hetar}$*C*H$_3$, diastereomers), 14.6 (OCH$_2$*C*H$_3$), 29.2, 29.4 (CH*C*H$_2$, diastereomers), 36.8, 37.5 (C$_{Hetar}$*C*H, diastereomers), 59.1 (O*C*H$_2$CH$_3$), 66.7, 66.9 (O*C*H$_2$CH$_2$, diastereomers), 104.5, 106.3 (CH$_{Hetar}$, diastereomers), 108.8, 108.9 (C$_{Hetar}$, diastereomers), 129.0, 129.1 (C$_{Hetar}$, diastereomers), 137.4, 137.5 (C$_{Hetar}$, diastereomers), 157.1, 157.4 (CONH, diastereomers), 164.3, 164.4 (CO, diastereomers) 176.3, 176.5 (CO, diastereomers). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3391 (broad, w), 3292 (w), 3207 (w), 1761 (m), 1674 (s), 1593 (m), 1538 (m), 1445 (m), 1398 (w), 1353 (w), 1241 (s), 1187 (s), 1142 (s), 1080 (s), 1020 (s), 992 (m), 950 (m), 822 (w), 771 (m). MS (EI, 70 eV): *m/z* (%) = 295 (M$^+$, 50), 278 (74), 236 (100), 208 (53), 179 (30), 149 (26), 137 (28), 97 (80). HRMS (EI): Calcd for C$_{13}$H$_{17}$N$_3$O$_5$ (M$^+$) 295.11627, found 295.117050.

2-Methyl-1-ureido-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole-3,6-dicarboxylic acid 3-ethyl ester 6-methyl ester (28q)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.463 g, 2.5 mmol), **5r** (0.858 g, 3.0 mmol) and $ZnCl_2$ (0.069 g, 0.5 mmol) in CH_2Cl_2 (12 mL), **28q** was isolated by column chromatography and crystallization (EtOH) as a brownish solid (0.305 g, 40%); mp. = 185-190°C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.23 (m, 3H, OCH_2CH_3), 2.27 (s, 3H, $C_{Hetar}CH_3$), 2.41-2.61 (m, 4H, $C_{Hetar}CH_2CH_2$), 3.59 (s, 3H, OCH_3), 3.77 (br, 1H, $C_{Hetar}CH$), 4.13 (m, 2H, OCH_2CH_3), 6.17, 6.40 (s, 2H, NH_2, diastereomers), 9.13, 9.30 (s, 1H, NNHCO, diastereomers). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.0, 10.8 ($C_{Hetar}CH_3$, diastereomers), 14.3, 14.6 (OCH_2CH_3, diastereomers), 25.9, 33.0 (CH_2), 43.0 ($C_{Hetar}CH$,), 52.0 (OCH_3), 58.8, 59.7 (OCH_2CH_3, diastereomers), 105.5 (C_{Hetar}), 126.2 (C_{Hetar}), 133.3, 134.7 (C_{Hetar}, diastereomers), 140.6 (C_{Hetar}), 157.3 (CONH), 164.5, 173.2 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (broad, m), 3200 (w), 2979 (w), 2953 (w), 2908 (w), 1727 (m), 1693 (s), 1670 (s), 1598 (m), 1526 (m), 1436 (m), 1344 (m), 1277 (m), 1195 (s), 1173 (s), 1121 (s), 1105 (s), 1061 (m), 1023 (w), 842 (w), 780 (w). MS (EI, 70 eV): *m/z* (%) = 309 (M^+, 12), 277 (29), 264 (10), 250 (100), 233 (20), 207 (19), 177 (8), 162 (11), 133 (7), 77 (7). HRMS (EI): Calcd for $C_{14}H_{19}N_3O_5$ (M^+) 309.13192, found 309.131337.

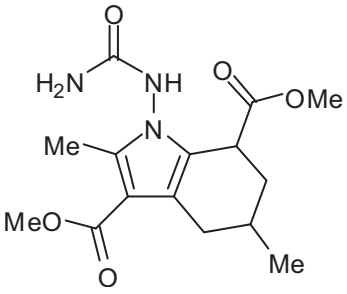
2-Methyl-1-ureido-4,5,6,7-tetrahydro-1*H*-indole-3,7-dicarboxylic acid 7-ethyl ester 3-methyl ester (28r). Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.342 g, 2.0 mmol), **5s** (0.761 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28r** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.562 g, 87%); mp. = 213–215 °C.



^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.20 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.66 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.27 (s, 3H, $C_{Hetar}CH_3$), 2.60 (m, 2H, $C_{Hetar}CH_2$), 3.39 (t, ^3J = 5.3 Hz, 1H, $C_{Hetar}CH$), 3.68 (s, 3H, OCH_3), 4.10 (m, 2H, OCH_2CH_3), 6.15 (s, 2H, NH_2), 8.93, 9.02 (s, 1H, NNHCO, diastereomers). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.5, 10.6 ($C_{Hetar}CH_3$, diastereomers), 14.2, 14.3 (OCH_2CH_3, diastereomers), 20.1, 21.0 (CH_2, diastereomers), 22.9, 27.0 (CH_2), 37.2, 37.8 ($C_{Hetar}CH$, diastereomers), 50.5 (OCH_3), 60.6 (OCH_2CH_3), 107.0 (C_{Hetar}), 117.0, 117.4, 125.5, 126.0, 136.5, 137.3 (C_{Hetar},

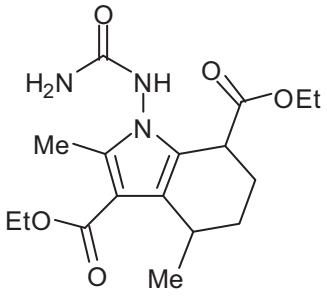
diastereomers), 157.2 (CONH), 165.5 (CO), 172.9, 173.4 (CO, diastereomers). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3421 (s), 3338 (broad, s), 3279 (m), 3216 (m), 2946 (m), 2854 (w), 1735 (s), 1678 (s), 1619 (m), 1593 (m), 1540 (m), 1441 (m), 1396 (m), 1366 (m), 1325 (w), 1261 (s), 1187 (m), 1129 (s), 1074 (m), 1026 (w), 854 (w), 784 (w). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 19), 292 (6), 277 (28), 264 (64), 250 (100), 233 (43), 207 (19), 191 (16), 158 (18), 130 (16), 69 (13). HRMS (EI): Calcd for $C_{15}H_{21}N_3O_5$ (M^+) 323.14757, found 323.147006.

2,5-Dimethyl-1-ureido-4,5,6,7-tetrahydro-1*H*-indole-3,7-dicarboxylic acid dimethyl ester (28s)



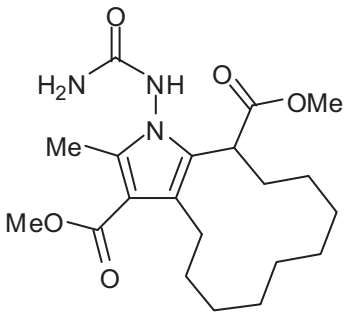
Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.342 g, 2.0 mmol), **5t** (0.754 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28s** was isolated by column chromatography and crystallization (EtOH) as a colourless solid (0.396 g, 61%); mp. = 199–203°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.02 (d, ^3J = 6.8 Hz, 3H, CHC*H*$_3$), 1.44 (m, 1H, CHC*H*$_2$CH), 1.72 (br, 1H, C*H*CH$_3$), 2.02-2.12 (m, 2H, C_{Hetar}C*H*$_2$, CHC*H*$_2$CH), 2.25, 2.27 (s, 3H, C_{Hetar}C*H*$_3$, diastereomers), 2.82 (m, 1H, C_{Hetar}C*H*$_2$), 3.49 (m, 1H, C_{Hetar}C*H*), 3.63, 3.65 (s, 3H, OCH$_3$, diastereomers), 3.68 (s, 3H, OCH$_3$), 6.11, 6.16 (s, 2H, NH$_2$, diastereomers), 8.92, 8.96, 9.00 (s, 1H, NH, diastereomers). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.7, 10.8 (C_{Hetar}*C*H$_3$, diastereomers), 21.6, 21.8 (*C*H$_3$CH, diastereomers), 29.4, 29.6 (*C*HCH$_3$, diastereomers), 31.6, 31.7 (C_{Hetar}*C*H$_2$, diastereomers), 36.1 (CH*C*H$_2$CH), 37.4, 39.8 (C_{Hetar}*C*H, diastereomers), 50.7 (OCH$_3$), 52.3, 52.4 (OCH$_3$, diastereomers), 107.0 (C_{Hetar}), 117.0, 117.2 (C_{Hetar}, diastereomers), 125.7, 126.4 (C_{Hetar}, diastereomers), 136.8, 137.1 (C_{Hetar}, diastereomers), 157.3, 157.4 (CO, diastereomers), 165.6, 165.7 (CO, diastereomers), 173.7, 174.6 (CO, diastereomers). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268 (broad, w), 2980 (w), 2913 (w), 1667 (s), 1596 (m), 1538 (m), 1449 (m), 1415 (m), 1360 (m), 1291 (m), 1262 (s), 1189 (s), 1130 (s), 1063 (m), 845 (w), 799 (w), 785 (m). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 13), 291 (22), 264 (100), 247 (15), 221 (10), 205 (8), 172 (14), 144 (13), 115 (3), 91 (4), 77 (4). HRMS (EI): Calcd for $C_{15}H_{21}N_3O_5$ (M^+) 323.14757, found 323.146991.

2,4-Dimethyl-1-ureido-4,5,6,7-tetrahydro-1*H*-indole-3,7-dicarboxylic acid diethyl ester (28t)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.370 g, 2.0 mmol), **5u** (0.785 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28t** was isolated by column chromatography and crystallization (EtOH) as a yellow solid (0.345 g, 49%), mp. = 81–83 °C. ^{1}H NMR (300 MHz, DMSO): δ = 1.13–1.29 (m, 9H, OCH_2CH_3, $CHCH_3$, OCH_2CH_3), 1.45–2.03 (m, 4H, $CHCH_2CH_2CH$), 2.25, 2.27 (s, 3H, $C_{Hetar}CH_3$, diastereomers), 3.08 (m, 1H, $CHCH_3$), 3.38 (m, 1H, $C_{Hetar}CH$), 4.06–4.20 (m, 4H, OCH_2CH_3, OCH_2CH_3), 6.15 (s, 2H, CNH_2), 8.90, 8.95, 9.03 (s, 1H, NH, diastereomers). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.5, 10.6 ($C_{Hetar}CH_3$, diastereomers), 14.2, 14.3, 14.5 (OCH_2CH_3, diastereomers), 21.2, 21.7 ($CHCH_3$, diastereomers), 21.8, 23.5 (CH_2, diastereomers), 26.2, 26.5 ($CHCH_3$, diastereomers), 27.4, 29.6 (CH_2, diastereomers), 36.9, 39.2 ($C_{Hetar}CH$, diastereomers), 58.8 (OCH_2CH_3), 60.5, 60.6 (OCH_2, diastereomers), 106.7, 106.8 (C_{Hetar}, diastereomers), 122.1 (C_{Hetar}), 125.4, 125.7 (C_{Hetar}, diastereomers), 136.5, 136.8, 137.6 (C_{Hetar}, diastereomers), 157.2 (CO), 164.8 (CO), 173.0, 174.1 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305 (broad, w), 2978 (w), 2956 (w), 2931 (w), 2870 (w), 1674 (s), 1590 (w), 1531 (w), 1443 (w), 1402 (w), 1370 (m), 1250 (m), 1180 (s), 1134 (s), 1094 (m), 1067 (m), 1021 (m), 840 (w), 786 (w). MS (EI, 70 eV): *m/z* (%) = 351 (M^+, 19), 305 (30), 292 (64), 278 (100), 261 (21), 235 (35), 218 (9), 172 (14), 146 (14), 91 (7), 77 (7). HRMS (EI): Calcd for $C_{17}H_{25}N_3O_5$ (M^+) 351.17887, found 351.179282.

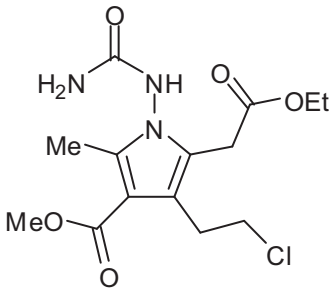
2-Methyl-1-ureido-4,5,6,7,8,9,10,11,12,13-decahydro-1*H*-cyclododeca[*b*]pyrrole-3,13-dicarboxylic acid dimethyl ester (28u)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.342 g, 2.0 mmol), **5v** (0.922 g, 2.4 mmol) and $ZnCl_2$ (0.055 g, 0.4 mmol) in CH_2Cl_2 (12 mL), **28u** was isolated by column chromatography and crystallization (EtOH) as a yellow solid (0.364 g, 46%), mp. = 110–112 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.09–1.70 (m, 16H, CH_2), 2.19, 2.20 (s, 3H, $C_{Hetar}CH_3$, diastereomers), 2.39 (m, 1H, CH_2), 2.76 (m, 1H, CH_2), 3.58 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.80 (m, 1H, $C_{Hetar}CH$), 6.07, 6.20 (br s, 2H, NH_2, diastereomers), 8.83, 9.03 (s, 1H, NH, diastereomers). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.8, 10.9 ($C_{Hetar}CH_3$, diastereomers), 21.3, 21.7, 22.4, 22.5, 22.9, 23.2, 23.4, 24.1, 24.2, 24.5, 25.3, 25.4, 25.7, 27.4, 27.7, 28.5, 28.6 (CH_2,

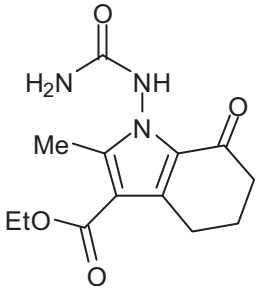
diastereomers), 37.0, 37.4 ($C_{Hetar,}CH$), 50.5 (OCH_3), 51.7, 52.1 (OCH_3, diastereomers), 107.6 (br, C_{Hetar}), 119.4 (C_{Hetar}), 128.8, 129.4 (C_{Hetar}, diastereomers), 137.3 (C_{Hetar}), 157.3 (br, CO), 165.4 (CO), 171.7, 173.0 (CO, diastereomers). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (broad w), 2928 (m), 2858 (w), 1674 (s), 1582 (w), 1531 (w), 1436 (s), 1373 (m), 1256 (m), 1238 (s), 1199 (s), 1171 (s), 1145 (s), 1108 (s), 1093 (s), 996 (w), 849 (w), 784 (w). MS (EI, 70 eV): *m/z* (%) = 393 (M^+, 70), 350 (11), 334 (100), 318 (62), 291 (25), 259 (25), 224 (19), 211 (20), 152 (13), 97 (19), 69 (31). HRMS (EI): Calcd for $C_{20}H_{31}N_3O_5$ (M^+) 393.22582, found 393.226575.

4-(2-Chloro-ethyl)-5-ethoxycarbonylmethyl-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylic acid methyl ester (28v)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.342 g, 2.0 mmol), **5w** (0.809 g, 2.40 mmol) and $ZnCl_2$ (0.055 g, 0.40 mmol) in CH_2Cl_2 (12 mL), **28v** was isolated by column chromatography and crystallization (EtOH) as a brownish solid (0.110 g, 20%); mp. = 184–186 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.18 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.27 (s, 3H, $C_{Hetar}CH_3$), 3.02 (m, 2H, CH_2), 3.44-3.68 (m, 4H, $C_{Hetar}CH_2$, CH_2), 3.72 (s, 3H, OCH_3), 4.05 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.19 (br, 2H, NH_2), 9.12 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 11.1 ($C_{Hetar}CH_3$), 14.2 (OCH_2CH_3), 29.2, 29.3 (CH_2CH_2), 44.9 ($C_{Hetar}CH_2C$), 50.7 (OCH_3), 60.7 (OCH_2CH_3), 107.6, 115.9, 125.3, 137.1 (C_{Hetar}), 157.1 (CONH), 165.2 ($C_{Hetar}COO$), 169.9 (CH_2COO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3331 (m), 3252 (m), 3211 (m), 2971 (w), 1725 (s), 1688 (s), 1675 (s), 1575(m), 1544 (s), 1449 (s), 1398 (s), 1366 (s), 1340 (m), 1288 (m), 1223 (s), 1185 (m), 1118 (s), 1021 (m), 987 (w), 736 (w). MS (EI, 70 eV): *m/z* (%) = 345 (M^+, 38), 309 (16), 286 (86), 272 (100), 256 (42), 236 (33), 207 (31), 193 (27), 161 (23), 133 (20), 97 (49). HRMS (EI): Calcd for $C_{14}H_{20}N_3O_5Cl$ (M^+) 345.10860, found 345.109202.

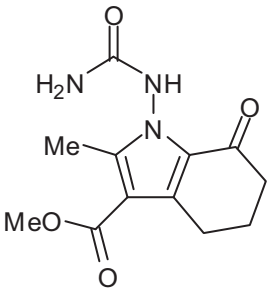
2-Methyl-6-oxo-1-ureido-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester (28aa)



Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24a** (0.463 g, 2.5 mmol), **5aa** (0.768 g, 3.0 mmol) and $ZnCl_2$ (0.069 g, 0.5 mmol) in CH_2Cl_2 (12 mL), **28aa** was isolated by column chromatography and crystallization (EtOH) as a brownish solid (0.279 g, 50%); mp. = 166–168 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.26 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.30 (s, 3H, $C_{Hetar}CH_3$), 2.56 (t, ^3J = 6.8 Hz, 2H,

$C_{Hetar}CH_2CH_2$), 2.96 (t, ^3J = 6.8 Hz, 2H, $C_{Hetar}CH_2CH_2$), 3.21 (ABq, ^2J = 20.1 Hz, 2H, CH_2CO), 4.17 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.31 (s, 2H, NH_2), 9.19 (s, 1H, NHCO). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.6 ($C_{Hetar}CH_3$), 14.6 (OCH_2CH_3), 22.0, 36.3, 39.3 (CH_2), 58.9 (OCH_2CH_3), 106.8, 114.4, 125.2, 137.4 (C_{Hetar}), 157.5, 164.9, 207.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268 (broad, w), 2980 (w), 2913 (w), 1667 (s), 1596 (m), 1538 (m), 1449 (m), 1415 (m), 1360 (m), 1291 (m), 1262 (s), 1189 (s), 1130 (s), 1063 (m), 845 (w), 799 (w), 785 (m). MS (EI, 70 eV): *m/z* (%) = 279 (M^+, 77), 236 (45), 220 (100), 192 (30), 179 (30), 163 (31), 146 (12), 135 (29), 122 (12), 107 (5), 69 (14). HRMS (EI): Calcd for $C_{13}H_{17}N_3O_4$ (M^+) 279.12136, found 279.121776.

2-Methyl-6-oxo-1-ureido-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid methyl ester (28ab)

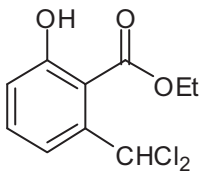


Following **general procedure 4** and starting with 1,2-diaza-1,3-butadiene **24d** (0.428 g, 2.5 mmol), **5aa** (0.768 g, 3.0 mmol) and $ZnCl_2$ (0.069 g, 0.5 mmol) in CH_2Cl_2 (12 mL), **28ab** was isolated by column chromatography and crystallization (EtOH) as a brownish solid (0.215 g, 32%); mp. = 215–217 ºC. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.30 (s, 3H, $C_{Hetar}CH_3$), 2.56 (t, ^3J = 6.6 Hz, 2H, $C_{Hetar}CH_2CH_2$), 2.95 (t, ^3J = 6.6 Hz, 2H, $C_{Hetar}CH_2CH_2$), 3.21 (ABq, ^2J = 20.2 Hz, 2H, CH_2CO), 3.70 (s, 3H, OCH_3), 6.32 (s, 2H, NH_2), 9.21 (s, 1H, NHCO). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 10.7 ($C_{Hetar}CH_3$), 22.0, 36.3, 39.3 (CH_2), 50.6 (OCH_3), 106.7, 114.3, 125.3, 137.5 (C_{Hetar}), 157.4, 165.4, 207.6 (CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3308 (broad, w), 3253 (w), 3200 (w), 2951 (w), 2923 (w), 1672 (s), 1573 (m), 1537 (m), 1439 (m), 1394 (m), 1339 (m), 1252 (m), 1185 (s), 1129 (s), 1008 (w), 852 (w), 800 (m), 785 (m). MS (EI, 70 eV): *m/z* (%) = 265 (M^+, 68), 222 (23), 206 (100), 178 (40), 162 (13), 146 (35), 133 (14), 118 (13), 91 (11), 77 (21). HRMS (EI): Calcd for $C_{12}H_{15}N_3O_4$ (M^+) 265.10571, found 265.105589.

7.2.5 Synthesis of 6-Dichloromethylsalicylates based on Regioselective [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dichloro-4-ethoxy-3-buten-2-ones

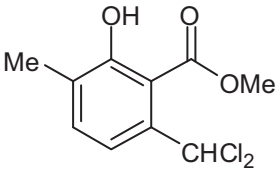
General procedure 5: To CH_2Cl_2 solution (4.00 ml) of **31** (2.00 mmol) and 1,3-bis(silyloxy)-1,3-butadiene **5** (4.00 mmol) was added $TiCl_4$ (2.00 mmol) at -78 ºC under argon atmosphere. The temperature of solution was allowed to rise to 20 ºC during 20 h. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3x) 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 (silica gel, heptane-EtOAc = 15:1).

2-Dichloromethyl-6-hydroxy-benzoic acid ethyl ester (35a)



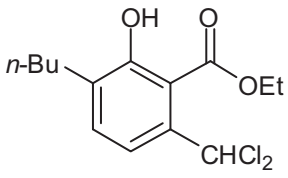
Following **general procedure 5** and starting with 1,1-dichloro-4-ethoxy-but-3-en-2-one **31a** (0.366 g, 2.00 mmol), **5d** (1.098 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35a** was obtained as yellow viscous (0.259 g, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.49 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 4.52 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 7.04 (dd, ^3J = 8.3 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.5 (t, ^3J = 8.2 Hz, 1H, CH_{Ar}), 7.64 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.75 (s, 1H, $CHCl_2$), 11.09 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 62.9 (OCH_2CH_3), 69.0 ($CHCl_2$), 109.2 (C_{Ar}), 119.7, 120.3, 134.7 (CH_{Ar}), 141.4, 161.8 (C_{Ar}), 169.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (s), 2854 (m), 1750 (w), 1713 (w), 1670 (m), 1607 (w), 1437 (m), 1417 (m), 1297 (m), 1255 (s), 1232 (s), 1195 (m), 1143 (s), 1005 (w), 984 (w), 836 (w), 802 (w), 768 (s), 745 (s), 714 (s), 642 (w). MS (GC, 70 eV): *m/z* (%) = 248 (M^+, 27), 204 (65), 202 (100), 167 (16), 149 (51), 139 (35), 111 (8), 93 (6), 75 (16). HRMS (EI): calcd for $C_{10}H_{10}O_3Cl_2$ (M^+) 248.00015, found 247.999670.

6-Dichloromethyl-2-hydroxy-3-methyl-benzoic acid methyl ester (35b)



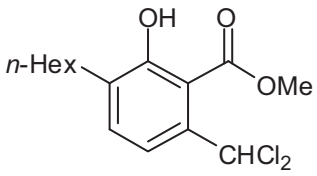
Following **general procedure 5** and starting with **31a** (0.366 g, 2.00 mmol), **5ab** (1.098 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35b** was obtained as colourless oil (0.293 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): 2.27 (s, 3H, $C_{Ar}CH_3$), 4.04 (s, 3H, OCH_3), 7.38 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.55 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.68 (s, 1H, $CHCl_2$), 11.28 (s, 1H, OH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.2 ($C_{Ar}CH_3$), 53.0 (OCH_3), 69.4 ($CHCl_2$), 108.2 (C_{Ar}), 119.6 (CH_{Ar}), 129.2 (C_{Ar}), 135.5 (CH_{Ar}), 138.8, 160.0, (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034 (w), 2954 (w), 2899 (w), 1725 (w), 1671 (m), 1608 (w), 1593 (w), 1438 (w), 1411 (m), 1380 (w), 1326 (w), 1293 (m), 1251 (s), 1221 (w), 1195 (m), 1145 (s), 1051 (w), 1033 (w), 1008 (m), 951 (w), 833 (s), 794 (br, s), 767 (s), 732 (br, s), 704 (s), 677 (s), 637 (m), 611 (w). MS (GC, 70 eV): *m/z* (%) = 248 (M^+, 42), 216 (100), 180 (67), 153 (41), 125 (18), 89 (33), 63 (14). HRMS (EI): calcd for $C_{10}H_{10}O_3Cl_2$ (M^+) 248.00015, found 247.999629.

3-Butyl-6-dichloromethyl-2-hydroxy-benzoic acid ethyl ester (35e)



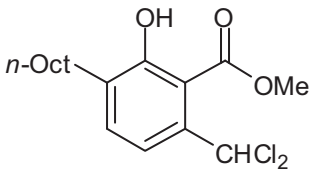
Following **general procedure 5** and starting **31a** (0.366 g, 2.00 mmol), **5ad** (1.320 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35e** was obtained as yellow viscous (0.153 g, 25%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.39 (m, 2H, CH_2), 1.49 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.55 (m, 2H, CH_2), 2.65 (t, ^3J = 7.6 Hz, 2H, CH_2C_{Ar}), 4.52 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 7.36 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.71 (s, 1H, $CHCl_2$), 11.34 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9, 14.0 (CH_2CH_3, OCH_2CH_3), 22.6, 29.8, 31.2 (CH_2), 62.8 (OCH_2CH_3), 69.4 ($CHCl_2$), 108.6 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.7, 159.8 (C_{Ar}), 170.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (s), 2855 (m), 1751 (w), 1714 (w), 1660 (m), 1600 (w), 1430 (m), 1416 (m), 1321 (m), 1268 (s), 1232 (s), 1196 (m), 1155 (s), 1024 (w), 984 (w), 846 (w), 816 (w), 789 (s), 744 (s), 716 (s), 648 (w), 580 (w). MS (EI, 70 eV): *m/z* (%) = 304 (M^+, 49), 258 (18), 241 (11), 222 (23), 205 (66), 180 (91), 159 (9), 89 (15), 77 (10). HRMS (EI): calcd for $C_{14}H_{18}O_3Cl_2$ (M^+) 304.06275, found 304.062748.

6-Dichloromethyl-3-hexyl-2-hydroxy-benzoic acid methyl ester (35g)



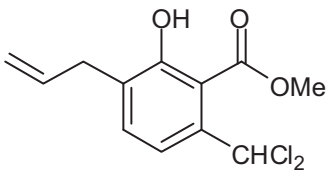
Following **general procedure 5** and starting with **31a** (0.366 g, 2.00 mmol), **5l** (1.315 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35g** was obtained as yellow oil (0.325 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.9 Hz, 3H, CH_2CH_3), 1.26-1.38 (m, 6H, $CH_3(CH_2)_3CH_2CH_2C$), 1.60 (m, 2H, $CH_3(CH_2)_3CH_2CH_2C$), 2.65 (t, ^3J = 7.7 Hz, 2H, CH_2C_{Ar}), 4.04 (s, 3H, OCH_3), 7.37 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.57 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.68 (s, 1H, $CHCl_2$), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 22.6, 29.0, 29.2, 30.1, 31.7 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.3 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.6, 159.7 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 2926 (m), 2856 (w), 1934 (w), 1746 (w), 1709 (br, w), 1671 (w), 1650 (w), 1620 (w), 1436 (m), 1417 (m), 1299 (m), 1232 (br, s), 1195 (m), 1146 (m), 1030 (w), 907 (w), 841 (s), 768 (m), 724 (w). MS (GC, 70 eV): *m/z* (%) = 318 (M^+, 30), 255 (26), 222 (100), 180 (75), 159 (11), 89 (22), 77 (11). HRMS (EI): calcd for $C_{15}H_{20}O_3Cl_2$ (M^+) 318.04710, found 318.047046.

6-Dichloromethyl-2-hydroxy-3-octyl-benzoic acid methyl ester (35h)



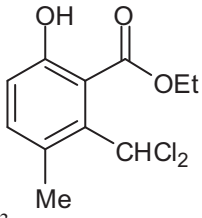
Following **general procedure 5** and starting with **31a** (0.366 g, 2.00 mmol), **5af** (1.491 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35h** was obtained as yellow viscous (0.312 g, 45%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.5 Hz, 3H, CH_2CH_3), 1.24-1.32 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.59 (m, 2H, $CH_2CH_2C_{Ar}$), 2.64 (t, ^3J = 7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.03 (s, 3H, OCH_3), 7.36 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.56 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 22.6, 27.2, 29.0, 29.2, 29.5, 29.7, 30.1 (CH_2), 53.0 (OCH_3), 69.5 ($CHCl_2$), 108.4 (C_{Ar}), 119.6 (CH_{Ar}), 133.6 (C_{Ar}), 134.6 (CH_{Ar}), 138.6, 159.7 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (s), 2854 (m), 1750 (w), 1670 (m), 1607 (w), 1437 (m), 1417 (m), 1297 (m), 1255 (s), 1232 (s), 1195 (m), 1143 (s), 1005 (w), 984 (w), 836 (w), 768 (s), 745 (s), 714 (s), 642 (w). MS (GC, 70 eV): *m/z* (%) = 346 (M^+, 18), 271 (14), 263 (25), 231 (100), 215 (26), 180 (24), 159 (9), 115 (5), 89 (10). HRMS (EI): calcd for $C_{17}H_{24}O_3Cl_2$ (M^+) 346.10970, found 346.109276.

3-Allyl-6-dichloromethyl-2-hydroxy-benzoic acid methyl ester (35j)



Starting with **31a** (0.366 g, 2.00 mmol), **5o** (1.200 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35j** was obtained as colourless oil (0.253 g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (d, ^3J = 6.6 Hz, 2H, CH_2C_{Ar}), 4.05 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2CHCH_2), 5.98 (ddt, ^3J = 6.6 Hz, ^3J = 7.9 Hz, ^3J = 9.6 Hz, 1H, CH_2CHCH_2), 7.40 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.59 (d, ^3J = 8.1 Hz, 1H, CH_{Ar}), 7.69 (s, 1H, $CHCl_2$), 11.31 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.0 (CH_2C_{Ar}), 53.1 (OCH_3), 69.3 ($CHCl_2$), 108.5 (C_{Ar}), 116.5 (CH_2CH), 119.8 (CH_{Ar}), 131.0 (C_{Ar}), 134.7 (CH_{Ar}), 135.4 (CH_2CHCH_2), 139.2, 159.5 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036(w), 2954 (w), 2856 (w), 1667 (s), 1640 (w), 1606 (w), 1588 (w), 1436 (m), 1417 (s), 1332 (m), 1301 (m), 1254 (s), 1225 (m), 1208 (m), 1195 (m), 1139 (s), 1007 (w), 987 (m), 915 (m), 874 (w), 816 (w), 802 (m), 738 (br, s), 708 (s), 628 (w), 586 (m). MS (GC, 70 eV): *m/*z (%) = 274 (M^+, 44), 239 (44), 206 (100), 178 (25), 143 (41), 115 (66), 89 (22), 77 (18). HRMS (EI): calcd for $C_{12}H_{12}O_3Cl_2$ (M^+) 274.01580, found 274.015869.

2-Dichloromethyl-6-hydroxy-3-methyl-benzoic acid ethyl ester (35k)



Following **general procedure 5** and starting with 1,1-dichloro-4-ethoxy-3-methyl-but-3-en-2-one **31b** (0.394 g, 2.00 mmol), **5d** (1.098 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35k** was obtained as colourless oil (0.158 g, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 2.65 (s, 3H, $C_{Ar}CH_3$), 4.49 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 6.95 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 7.27 (d, ^3J = 8.6 Hz, 1H, CH_{Ar}), 7.61 (s, 1H, $CHCl_2$), 9.96 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9 (OCH_2CH_3), 20.0 ($C_{Ar}CH_3$), 62.9 (OCH_2CH_3), 67.7 ($CHCl_2$), 111.8 (C_{Ar}), 119.2 (CH_{Ar}), 130.8, 136.7 (C_{Ar}), 138.3 (CH_{Ar}), 158.2 (C_{Ar}), 169.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092 (w), 2981 (w), 2929 (w), 1718 (w), 1668 (s), 1589 (w), 1467 (s), 1396 (w), 1372 (m), 1315 (m), 1297 (s), 1259 (m), 1201 (s), 1176 (s), 1132 (m), 1040 (m), 1010 (m), 983 (w), 912 (w), 857 (m), 829 (m), 752 (s), 717 (m), 697 (m), 657 (m), 657 (w), 624 (w), 590 (s), 545 (w). MS (GC, 70 eV): *m/*z (%) = 262 (M^+, 26), 216 (100), 181 (62), 163 (47), 153 (35), 125 (8), 89 (22), 77 (15). HRMS (EI): calcd for $C_{11}H_{12}Cl_2O_3$ (M^+) 262.01580, found 262.015223.

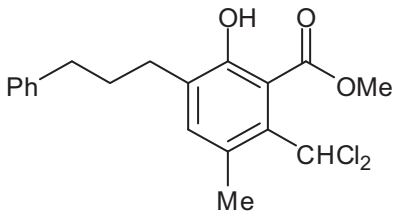
2-Dichloromethyl-6-hydroxy-3,5-dimethyl-benzoic acid methyl ester (35l)

Following **general procedure 5** and starting with **31b** (0.394 g, 2.00 mmol), **5ab** (1.098 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35l** was obtained as colourless oil (0.149 g, 27%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3H, $C_{Ar}CH_3$), 2.61 (s, 3H, $C_{Ar}CH_3$), 4.02 (s, 3H, OCH_3), 7.15 (s, 1H, CH_{Ar}), 7.53 (s, 1H, $CHCl_2$), 10.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.0 ($C_{Ar}CH_3$), 19.9 ($C_{Ar}CH_3$), 53.0 (OCH_3), 68.0 ($CHCl_2$), 110.8 (C_{Ar}), 128.7, 129.9, 134.2 (C_{Ar}), 139.2 (CH_{Ar}), 156.5 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091 (w), 2954 (w), 2929 (w), 1721 (w), 1670 (s), 1589 (w), 1461 (w), 1436 (s), 1407 (m), 1379 (w), 1331 (m), 1293 (s), 1235 (m), 1217 (m), 1194 (s), 1163 (s), 1077 (w), 1016 (br, m), 903 (w), 880 (w), 844 (w), 805 (w), 791 (w), 752 (s), 740 (s), 710 (s), 627 (m), 548 (w). MS (GC, 70 eV): *m/*z (%) = 262 (M^+, 35), 230 (100), 195 (82), 167 (52), 103 (22), 77 (30). HRMS (EI): calcd for $C_{11}H_{12}Cl_2O_3$ (M^+) 262.01580, found 262.015669.

3-Allyl-6-dichloromethyl-2-hydroxy-5-methyl-benzoic acid methyl ester (35o)

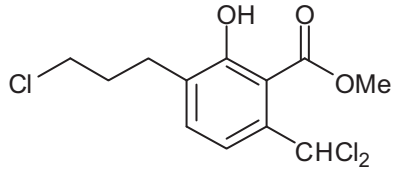
Following **general procedure 5** and starting with **31b** (0.394 g, 2.00 mmol), **5o** (1.200 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35o** was obtained as colourless oil (0.145 g, 25%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.63 (s, $C_{Ar}CH_3$), 3.39 (d, ^3J = 6.7 Hz, 2H, CH_2C_{Ar}), 4.02 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2CHCH_2), 5.97 (ddt, ^3J = 6.6 Hz, $^3J_{cys}$ = 8.0 Hz, $^3J_{anti}$ = 9.6 Hz, 1H, CH_2CHCH_2), 7.15 (s, 1H, CH_{Ar}), 7.52 (s, 1H, $CHCl_2$), 10.11 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.0 (CH_3C_{Ar}), 34.0 (CH_2C_{Ar}), 53.0 (OCH_3), 67.9 ($CHCl_2$), 111.3 (C_{Ar}), 116.5 (CH_2CH), 130.1, 130.5, 134.7 (C_{Ar}), 135.5 (CH_{Ar}), 138.4 (CH_2CHCH_2), 155.9 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2954 (w), 1934 (w), 1671 (s), 1640 (w), 1587 (w), 1435 (s), 1382 (w), 1333 (br, m), 1296 (m), 1194 (s), 1161 (s), 1024 (m), 989 (m), 912 (m), 876 (w), 843 (m), 808 (w), 750 (s), 727 (br, s), 631 (m). MS (GC, 70 eV): *m/*z (%) = 288 (M^+, 42), 256 (44), 22 (100), 193 (24), 185 (35), 157 (30), 128 (36), 115 (33), 91 (19), 77 (18). HRMS (EI): calcd for $C_{13}H_{14}O_3Cl_2$ (M^+) 288.03145, found 288.031106.

2-Dichloromethyl-6-hydroxy-3-methyl-5-(3-phenyl-propyl)-benzoic acid methyl ester (35p)



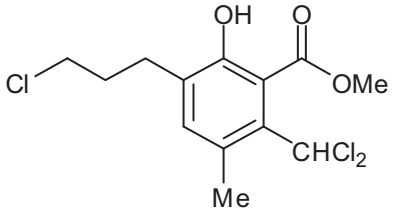
Following **general procedure 5** and starting with **31b** (0.394 g, 2.00 mmol), **5ag** (1.515 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **35p** was obtained as yellow oil (0.308 g, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (m, 2H, $CH_2CH_2CH_2$), 2.62 (s, 3H, $C_{Ar}CH_3$), 2.68 (m, 4H, $C_{Ar}CH_2$), 4.02 (s, 3H, OCH_3), 7.13-7.31 (m, 6H, CH_{Ar}), 7.52 (s, 1H, $CHCl_2$), 10.10 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.0 ($C_{Ar}CH_3$), 29.7, 30.6, 35.7 ($CH_2CH_2CH_2$), 53.0 (OCH_3), 68.0 ($CHCl_2$), 111.1 (C_{Ar}), 125.7, 128.3, 128.4 (CH_{Ar}), 129.9, 132.6, 134.3 (C_{Ar}), 134.4 (CH_{Ar}), 142.1 (C_{Ar}), 156.2 (COH), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084 (w), 3061 (w), 2929 (w), 2858 (w), 1933 (w), 1698 (w), 1671 (m), 1603 (w), 1586 (w), 1435 (s), 1382 (w), 1334 (m), 1297 (m), 1245 (br., m), 1194 (s), 1165 (s), 1079 (w), 1028 (w), 981 (w), 886 (w), 749 (s), 725 (s), 697 (s), 628 (m), 591 (w). MS (EI, 70 eV): *m/*z (%) = 366 (M^+, 27), 334 (10), 298 (11), 230 (57), 230 (12), 194 (100), 160 (11), 103 (23), 77 (26). HRMS (EI): calcd for $C_{19}H_{20}O_3Cl_2$ (M^+) 366.00813, found 366.007726.

3-(3-Chloro-propyl)-6-dichloromethyl-2-hydroxy-benzoic acid methyl ester (39a)



Following **general procedure 5** and starting with **31a** (0.366 g, 2.00 mmol), **5ai** (1.348 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **39a** was obtained as yellow oil (0.355 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.09 (m, 2H, $CH_2CH_2CH_2$), 2.83 (t, ^3J = 7.4 Hz, 2H, $C_{Ar}CH_2$), 3.54 (t, ^3J = 6.5 Hz, 2H, CH_2Cl), 4.05 (s, 3H, OCH_3), 7.41 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.58 (d, ^3J = 8.0 Hz, 1H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 11.31 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.6, 31.5, 44.5 ($CH_2CH_2CH_2$), 53.1 (OCH_3), 69.3 ($CHCl_2$), 108.6 (C_{Ar}), 119.8 (CH_{Ar}), 131.4 (C_{Ar}), 135.2 (CH_{Ar}), 139.4, 159.8 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 1934 (w), 1701 (w), 1669 (s), 1607 (w), 1586 (w), 1436 (m), 1416 (s), 1335 (br, m), 1289 (br, m), 1252 (br, s), 1195 (s), 1150 (s), 1134 (m), 1047 (w), 1004 (br, w), 961 (w), 837 (s), 801 (s), 767 (s), 740 (s), 708 (s), 640 (br, m). MS (EI, 70 eV): *m/*z (%) = 310 (M^+, 19), 275 (21), 243 (100), 207 (25), 180 (60), 161 (13), 115 (18), 89 (24), 69 (18). HRMS (EI): Calculated for $C_{12}H_{13}O_3Cl_3$ (M^+) 309.99248, found 309.991699.

3-(3-Chloro-propyl)-6-dichloromethyl-2-hydroxy-5-methyl-benzoic acid methyl ester (39b)

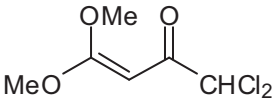


Following **general procedure 5** and starting with **31b** (0.394 g, 2.00 mmol), **5ai** (1.348 g, 4.00 mmol) and $TiCl_4$ (0.379 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml), **39b** was obtained as colourless oil (0.345 g, 53%). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.07 (m, 2H, $CH_2CH_2CH_2$), 2.62 (s, 3H, $C_{Ar}CH_3$), 2.78 (t, ^3J = 7.3 Hz, 2H, $C_{Ar}CH_2$), 3.53 (t, ^3J = 6.5 Hz, 2H, CH_2Cl), 4.02 (s, 3H, OCH_3), 7.17 (s, 1H, CH_{Ar}), 7.51 (s, 1H, $CHCl_2$), 10.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.0 ($C_{Ar}CH_3$), 27.5, 31.7, 44.5 ($CH_2CH_2CH_2$), 53.1 (OCH_3), 67.9 ($CHCl_2$), 111.3 (C_{Ar}), 130.0, 131.0, 134.8 (C_{Ar}), 138.8 (CH_{Ar}), 156.2 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954 (w), 1934 (w), 1673 (m), 1588 (w), 1436 (m), 1382 (w), 1336 (w), 1292 (m), 1249 (m), 1195 (s), 1166 (s), 1079 (w), 1010 (br, w), 967 (w), 905 (w), 840 (s), 753 (s), 726 (s), 679 (m), 649 (m). MS (GC, 70 eV): *m/z* (%) = 326 (M^+, 17), 292 (20), 257 (100), 230 (12), 194 (44), 103 (14), 77 (13). HRMS (EI): Calculated for $C_{13}H_{15}O_3Cl_2$ (M^+) 324.00813, found 324.007726.

7.2.6 Synthesis of 6-Dichloromethylsalicylates based on Regioselective [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dimethoxy-4,4-dichlorobut-1-en-3-one

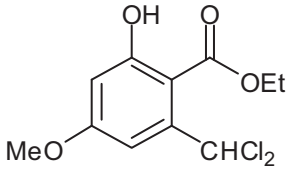
General procedure 6: To a CH_2Cl_2 solution (4.0 mL) of 1,1-dichloro-4,4-dimethoxy-but-3-en-2-one **34** (2.0 mmol) and 1,3-bis(silyloxy)-1,3-butadiene **5** (4.0 mmol) was added $TiCl_4$ (2.0 mmol) at −78 °C under argon atmosphere. The temperature of the solution was allowed to rise to 20 °C during 20 h. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3 x 30 mL) 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 (silica gel, heptane-EtOAc = 15:1).

The starting material *1,1-Dichloro-4,4-dimethoxy-but-3-en-2-one* **34** was prepared following a known procedure.[67]



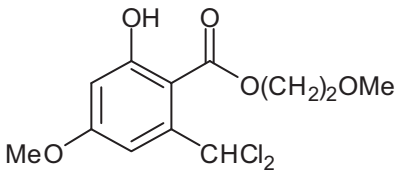
Starting with methyl orthoacetate **33** (1.202 g, 10.0 mmol), dichloroacetyl anhydride **32** (4.800 g, 20.0 mmol) and dry pyridine (1.820 g, 23.0 mmol) in CH_2Cl_2 (15.0 ml), **34** was obtained as a colourless solid (1.33 g, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.02 (s, 1H, CCH), 5.89 (s, 1H, $CHCl_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.3, 57.3 (OCH_3), 70.8 (*C*HC), 73.1 (*C*HCl_2), 171.2 (CO), 183.8 (*C*$O(CH_3)_2$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (w), 3002 (w), 1731 (w), 1664 (m), 1531 (s), 1477 (s), 1427 (s), 1306 (s), 1275 (s), 1178 (m), 1137 (m), 1047 (s), 1014 (s), 937 (w), 719 (s). MS (EI, 70 eV): *m/z* (%) = 198 (M^+, 0.2), 135 (5), 115 (100), 89 (11), 69 (32), 47 (9). HRMS (EI): calcd for $C_6H_8O_3Cl_2$ (M^+) 197.98450, found 197.984007.

2-Dichloromethyl-6-hydroxy-4-methoxy-benzoic acid ethyl ester (36a)



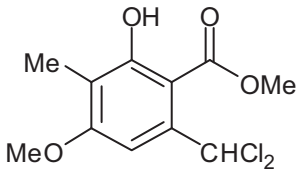
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5d** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36a** was obtained as a colourless solid (0.251 g, 45%); mp. 65-66 ºC.^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 4.48 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.49 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.22 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.65 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 55.6 (OCH_3), 62.4 (OCH_2CH_3), 68.9 ($CHCl_2$), 102.0 (C_{Ar}), 102.2, 109.5 (CH_{Ar}), 143.1, 164.3, 164.9 (C_{Ar}), 169.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3075 (w), 2982 (w), 1656 (s), 1615 (s), 1574 (m), 1463 (w), 1434 (m), 1366 (s), 1327 (m), 1249 (s), 1205 (s), 1160 (s), 1109 (m), 1014 (s), 954 (m), 852 (s), 760 (s), 738 (s), 683 (m). MS (EI, 70 eV): *m/z* (%) = 278 (M^+, 27), 232 (100), 197 (12), 179 (43), 126 (7), 95 (4). HRMS (EI): calcd for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.010586.

2-Dichloromethyl-6-hydroxy-4-methoxy-benzoic acid 2-methoxy-ethyl ester (36b)



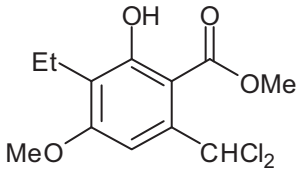
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5g** (1.218 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36b** was obtained as a colourless oil (0.277 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.45 (s, 3H, $CH_2OC\mathit{H}_3$), 3.74 (m, ^3J = 4.6 Hz, 2H, $C\mathit{H}_2OCH_3$), 3.84 (s, 3H, OCH_3), 4.49-4.53 (m, 2H, $OC\mathit{H}_2CH_2$), 6.47 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.21 (d, ^4J = 2.6 Hz, 1H, CH_{Ar}), 7.82 (s, 1H, $CHCl_2$), 11.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 59.0 (OCH_3), 64.7 ($OCH_2\mathit{C}H_2$), 69.0 ($CHCl_2$), 69.7 ($COOCH_2$), 102.1 (C_{Ar}), 102.2, 109.5 (CH_{Ar}), 143.6, 164.3, 164.4 (C_{Ar}), 169.2 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 2893 (w), 1715 (w), 1657 (m), 1615 (s), 1574 (m), 1436 (w), 1368 (m), 1323 (m), 1242 (s), 1200 (s), 1158 (s), 1114 (s), 1045 (s), 954 (m), 842 (w), 726 (s), 621 (m). MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 15), 232 (100), 198 (10), 169 (21), 135 (8), 59 (31). HRMS (EI): calcd for $C_{12}H_{14}O_5Cl_2$ (M^+) 308.02128, found 308.021193.

6-Dichloromethyl-2-hydroxy-4-methoxy-3-methyl-benzoic acid methyl ester (36c)



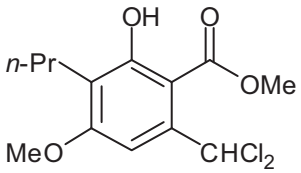
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5ab** (1.096 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36c** was obtained as a colourless solid (0.118 g, 32%). ^{1}H NMR (250 MHz, $CDCl_3$): 2.11 (s, 3H, $C_{Ar}C\mathit{H}_3$), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.54 (s, 1H, OH). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 55.0 (OCH_3), 69.5 ($CHCl_2$), 102.2 (C_{Ar}), 103.5 (CH_{Ar}), 115.6, 140.3, 161.0, 161.8 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2954 (w), 1722 (w), 1662 (s), 1574 (m), 1506 (w), 1436 (m), 1402 (m), 1373 (w) 1279 (s), 1226 (m), 1194 (m), 1157 (s), 1125 (br, s), 994 (s), 930 (w), 789 (s), 717 (s), 667 (m). MS (EI, 70 eV): *m/z* (%) = 278 (M^+, 36), 246 (64), 210 (100), 183 (19), 149 (5), 77 (15). HRMS (EI): calcd for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.010448.

6-Dichloromethyl-3-ethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (36d)



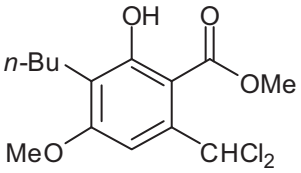
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5ah** (1.152 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36d** was obtained as a colourless solid (0.281 g, 48%); mp. 63-65 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.08 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3), 2.68 (q, ^3J = 7.5 Hz, 2H, CH_2CH_3), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.48 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.9 (CH_2CH_3), 16.4 (CH_2CH_3), 52.8 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.4 (C_{Ar}), 103.7 (CH_{Ar}), 121.6, 140.4, 160.8, 161.6 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3083 (w), 2956 (w), 2851 (w), 1659 (s), 1603 (m), 1569 (w), 1437 (m), 1406 (m), 1275 (s), 1218 (s), 1154 (s), 1129 (s), 1001 (s), 943 (w), 724 (s), 587 (m). MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 23), 260 (20), 224 (100), 206 (10), 161 (16), 125 (2), 77 (7). HRMS (EI): calcd for $C_{12}H_{14}O_4Cl_2$ (M^+) 292.02637, found 292.026341.

6-Dichloromethyl-2-hydroxy-4-methoxy-3-propyl-benzoic acid methyl ester (36e)



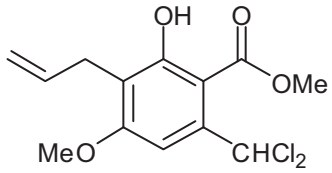
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5k** (1.098 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36e** was obtained as a yellow solid (0.325 g, 53%); mp. 68-71 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): 0.94 (t, ^3J = 7.4 Hz, 3H, CH_2CH_3), 1.43-1.61 (m, 2H, CH_2CH_3), 2.60-2.66 (m, 2H, $C_{Ar}CH_2$), 3.92 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.20 (s, 1H, CH_{Ar}), 7.75 (s, 1H, $CHCl_2$), 11.49 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 21.7, 25.0 (CH_2CH_2), 52.8 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.4 (C_{Ar}), 103.7 (CH_{Ar}), 120.2, 140.4, 161.0, 161.8 (C_{Ar}), 170.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3083 (w), 2959 (m), 1715 (w), 1652 (s), 1602 (m), 1511 (w), 1435 (w), 1270 (s), 1193 (m), 1132 (m), 994 (m), 729 (s), 601 (w). MS (EI, 70 eV): *m/z* (%) = 306 (M^+, 40), 274 (32), 238 (100), 210 (40), 175 (15), 111 (15), 69 (32). HRMS (EI): calcd for $C_{13}H_{16}O_4Cl_2$ (M^+) 306.04202, found 306.041499.

3-Butyl-6-dichloromethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (36f)



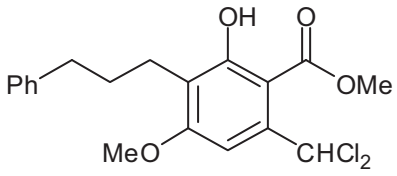
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5ac** (1.212 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36f** was obtained as a colourless solid (0.294 g, 46%); mp. 91-92 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): 0.92 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 1.30-1.39 (m, 2H, CH_2), 1.40-1.52 (m, 2H, CH_2), 2.63-2.68 (m, 2H, $C_{Ar}CH_2$), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (s, 1H, CH_{Ar}), 7.76 (s, 1H, $CHCl_2$), 11.48 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 22.7, 22.8, 30.7 (CH_2), 52.7 (OCH_3), 55.7 (OCH_3), 69.6 ($CHCl_2$), 102.3 (C_{Ar}), 103.7 (CH_{Ar}), 120.4, 140.3, 161.0, 161.7 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 2925 (m), 1657 (s), 1605 (m), 1573 (w), 1435 (m), 1404 (m), 1287 (s), 1270 (s), 1190 (m), 1138 (s), 1077 (m), 1004 (s), 991 (s), 851 (m), 725 (s), 644 (m). MS (EI, 70 eV): *m/z* (%) = 320 (M^+, 35), 277 (22), 245 (65), 210 (100), 179 (12), 145 (5), 89 (8). HRMS (EI): calcd for $C_{14}H_{18}O_4Cl_2$ (M^+) 320.05767, found 320.057681.

3-Allyl-6-dichloromethyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (36g)



Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5o** (1.204 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36g** was obtained as a colourless oil (0.316 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.41-3.44 (m, 2H, $C_{Ar}CH_2$), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.94-5.06 (m, 2H, CH_2CHCH_2), 5.86-5.99 (m, 1H, CH_2CHCH_2), 7.23 (s, 1H, CH_{Ar}), 7.77 (s, 1H, $CHCl_2$), 11.54 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.1 ($C_{Ar}CH_2$), 52.8 (OCH_3), 55.8 (OCH_3), 69.4 ($CHCl_2$), 102.5 (C_{Ar}), 103.8 (CH_{Ar}), 114.8 (CH_2CH), 117.2 (C_{Ar}), 135.2 (CH_2CH), 141.0, 160.9, 161.6 (C_{Ar}), 170.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2955 (w), 1788 (w), 1720 (w), 1659 (s), 1605 (m), 1510 (w), 1403 (m), 1360 (w), 1276 (s), 1195 (s), 1153 (s), 1133 (s), 999 (m), 912 (m), 724 (s), 630 (m). MS (EI, 70 eV): *m/z* (%) = 304 (M^+, 40), 269 (29), 236 (100), 203 (13), 173 (59), 115 (12), 77 (14). HRMS (EI): calcd for $C_{13}H_{14}O_4Cl_2$ (M^+) 304.02637, found 304.026251.

6-Dichloromethyl-2-hydroxy-4-methoxy-3-(3-phenyl-propyl)-benzoic acid methyl ester (36h)



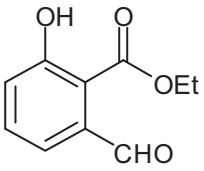
Following **general procedure 6** and starting with **34** (0.400 g, 2.0 mmol), **5ag** (1.515 g, 4.0 mmol) and $TiCl_4$ (0.379 g, 2.0 mmol) in CH_2Cl_2 (4.0 mL), **36h** was obtained as a colourless oil (0.329 g, 43%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.89-2.00 (m, 2H, $C_{Ar}CH_2CH_2$), 2.76-2.86 (m, 4H, $C_{Ar}CH_2$), 4.02 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 7.28-7.38 (m, 6H, CH_{Ar}), 7.87 (s, 1H, $CHCl_2$), 11.62 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.9, 29.8, 35.9 ($CH_2CH_2CH_2$), 52.7 (OCH_3), 55.7 (OCH_3), 69.5 ($CHCl_2$), 102.4 (C_{Ar}), 103.6 (CH_{Ar}), 119.8 (C_{Ar}), 125.5, 128.1, 128.3 (CH_{Ar}), 140.5, 142.6, 161.0, 161.7 (C_{Ar}), 170.4 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3025 (w), 2939 (w), 1934 (w), 1804 (w), 1703 (w), 1661 (m), 1605(m), 1496 (w), 1405 (m), 1359 (w), 1280 (s), 1226 (m), 1157 (s), 1116 (s), 1002 (m), 843 (w), 733 (m), 699 (m). MS (EI, 70 eV): *m/z* (%) = 382 (M^+, 40), 347 (14), 314 (7), 245 (32), 210 (100), 176 (16), 91 (31). HRMS (EI): calcd for $C_{19}H_{20}O_4Cl_2$ (M^+) 382.07332, found 382.073284.

7.2.7 Synthesis of 6-Formylsalicylates and Formylchromanes

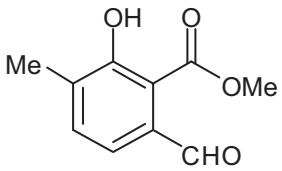
General procedure 7: To a methanol or ethanol (10 mL) solution of sodium methanolate (3.0 mmol) was added dichloromethyl-substituted salicylate (**35, 36** or **39**) (1.0 mmol) under argon atmosphere and the solution was stirred for 24 h at room temperature. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3 x 30 mL) 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 (silica gel, heptane-EtOAc = 15:1).

2-Formyl-6-hydroxy-benzoic acid ethyl ester (37a)



Following **general procedure 7** and starting with **35a** (0.239 g, 0.96 mmol), NaOEt (0.196 g, 2.88 mmol) in dry EtOH (4.8 ml), **37a** was obtained as colourless solid (0.130 g, 70%); mp. 47-49 °C.^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 4.52 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 7.20 (dd, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.27 (dd, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, CH_{Ar}), 7.52 (m, 1H, CH_{Ar}), 10.50 (s, 1H, CHO), 10.94 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_3), 62.8 (OCH_2CH_3), 111.6 (C_{Ar}), 120.0, 122.6, 134.8 (CH_{Ar}), 139.1, 161.9 (C_{Ar}), 169.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2990 (w), 2991 (w), 2376 (w), 2282 (w), 2046 (w), 1986 (w), 1688 (m), 1664 (s), 1597 (w), 1447 (m), 1349 (m), 1373 (m), 1327 (s), 1288 (m), 1231 (s), 1209 (s), 1162 (s), 1132 (s), 1111 (s), 1066 (m) 1015 (s), 971 (m), 915 (w), 861 (m), 818 (s), 780 (s), 737 (br, s), 634 (s), 542 (m). MS (EI, 70 eV): *m/z* (%) = 194 (M^+, 25), 165 (42), 148 (42), 120 (100), 92 (55), 63 (19). HRMS (EI): calcd for $C_{10}H_{10}O_4$ (M^+) 194.05736, found 194.057014.

6-Formyl-2-hydroxy-3-methyl-benzoic acid methyl ester (37b)

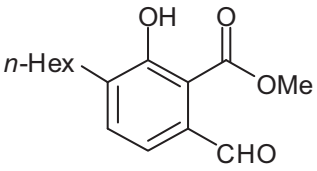


Following **general procedure 7** and starting with **35b** (0.273 g, 1.04 mmol), NaOMe (0.168 g, 3.12 mmol) in dry MeOH (5.2 ml), **37b** was obtained as colourless solid (0.170 g, 85%); mp. 63-65 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.31 (s, 3H, $C_{Ar}CH_3$), 4.01 (s, 3H, OCH_3), 7.24 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.40 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 10.43 (s, 1H, CHO), 11.13 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.2 ($C_{Ar}CH_3$), 53.0 (OCH_3), 110.6 (C_{Ar}), 119.7 (CH_{Ar}), 133.0 (C_{Ar}), 135.3 (CH_{Ar}), 136.6, 160.2, (C_{Ar}), 170.5 (C=O), 192.0

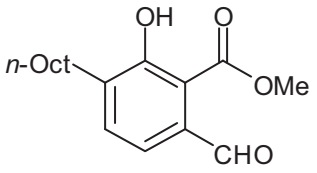
(CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3047 (w), 2960 (w), 2917 (w), 2849 (w), 1666 (s), 1577 (w), 1492 (w), 1440 (m), 1417 (m), 1381 (m), 1340 (s), 1290 (m), 1246 (s), 1196 (m), 1142 (s), 1033 (m), 1010 (w), 960 (m), 952 (m), 870 (m), 775 (s), 731 (s), 714 (s), 689 (m), 587 (m). MS (EI, 70 eV): *m/z* (%) = 194 (M^+, 47), 179 (15), 166 (25), 148 (26), 134 (100), 106 (76), 77 (41). HRMS (EI): calcd for $C_{10}H_{10}O_4$ (M^+) 194.05736, found 194.057224.

6-Formyl-3-hexyl-2-hydroxy-benzoic acid methyl ester (37f)



Following **general procedure 7** and starting with **37g** (0.300 g, 0.94 mmol), NaOMe (0.152 g, 2.82 mmol) in dry MeOH (4.7 ml), **37f** was obtained as yellow oli (0.170 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.8 Hz, 3H, CH_2CH_3), 1.27-1.37 (m, 6H, $CH_3(CH_2)_3CH_2CH_2C_{Ar}$), 1.61 (m, 2H, $CH_3(CH_2)_3CH_2CH_2C_{Ar}$), 2.69 (t, ^3J = 7.7 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 7.27 (d, ^3J = 7.7 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J = 7.7 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.11 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 22.6, 29.0, 29.1, 30.3, 31.7 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7, 134.5 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2926 (w), 2856 (w), 1738 (w), 1670 (s), 1614 (w), 1578 (w), 1492 (w), 1439 (m), 1420 (m), 1336 (m), 1288 (m), 1239 (s), 1196 (m), 1141 (s), 1099 (w), 1053 (w), 1011 (w), 982 (w), 875 (w), 812 (w), 781 (m), 747 (m), 582 (w). MS (EI, 70 eV): *m/z* (%) = 264 (M^+, 23), 249 (18), 235 (21), 205 (13), 194 (17), 175 (13), 162 (100), 147 (14), 134 (40), 105 (21), 77 (24). HRMS (EI): calcd for $C_{15}H_{20}O_4$ (M^+) 264.13561, found 264.135677.

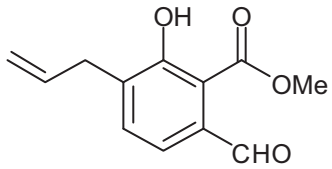
6-Formyl-2-hydroxy-3-octyl-benzoic acid methyl ester (37g)



Following **general procedure 7** and starting with **35h** (0.290 g, 0.84 mmol), NaOMe (0.135 g, 2.50 mmol) in dry MeOH (4.2 ml), **37g** was obtained as colourless solid (0.178 g, 73%); mp. 48-50 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.5 Hz, 3H, CH_2CH_3), 1.24-1.35 (m, 10H, $CH_3(CH_2)_5CH_2CH_2$), 1.60 (m, 2H, $CH_2CH_2C_{Ar}$), 2.68 (t, ^3J = 7.6 Hz, 2H, $CH_2CH_2C_{Ar}$), 4.01 (s, 3H, OCH_3), 7.27 (d, ^3J = 7.7 Hz, 1H, CH_{Ar}), 7.39 (d, ^3J = 7.7 Hz, 1H, CH_{Ar}), 10.42 (s, 1H, CHO), 11.12 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 22.6, 29.0, 29.2, 29.4, 29.5, 30.3, 31.9 (CH_2), 53.0 (OCH_3), 110.8 (C_{Ar}), 119.7 (CH_{Ar}), 134.6 (CH_{Ar}), 136.5, 137.4, 160.0 (C_{Ar}), 170.5 (C=O), 192.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3037 (w), 2950 (w), 1217 (m), 2849 (m), 1745 (w), 1689 (s), 1661 (s), 1575 (w), 1494 (w), 1439 (m), 1419 (m), 1392 (w), 1341 (m), 1292 (m), 1243 (s),

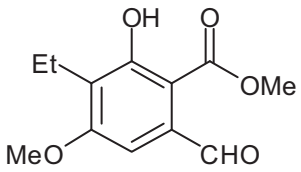
1147 (s), 1092 (w), 980 (w), 939 (w), 813 (w), 780 (m), 757 (m), 724 (m). MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 22), 277 (19), 263 (23), 233 (12), 194 (24), 162 (100), 147 (13), 134 (36), 105 (16), 77 (17). HRMS (EI): calcd for $C_{17}H_{24}O_4$ (M^+) 292.16691, found 292.166507.

3-Allyl-6-formyl-2-hydroxy-benzoic acid methyl ester (37i)



Following **general procedure 7** and starting with **35j** (0.233 g, 0.85 mmol), NaOMe (0.137 g, 2.54 mmol) in dry MeOH (4.3 ml), **37i** was obtained as yellow oil (0.152 g, 81%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.46 (d, ^3J = 6.7 Hz, 2H, CH_2C_{Ar}), 4.01 (s, 3H, OCH_3), 5.09 (m, 2H, CH_2CHCH_2), 5.98 (m, 1H, CH_2CHCH_2), 7.28 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 7.42 (d, ^3J = 7.6 Hz, 1H, CH_{Ar}), 10.43 (s, 1H, CHO), 11.16 (s, 1H, OH). ^{3}C NMR (62.9 MHz, $CDCl_3$): δ = 34.1 (CH_2C_{Ar}), 53.0 (OCH_3), 110.9 (C_{Ar}), 116.8 (CH_2CH), 119.8 (CH_{Ar}), 134.5 (C_{Ar}), 134.6 (CH_{Ar}), 135.0 (CH_2CHCH_2), 137.0, 159.7 (C_{Ar}), 170.4 (C=O), 192.0 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2921 (w), 1669 (s), 1577 (w), 1486 (w), 1437 (m), 1421 (s), 1336 (m), 1303 (br, m), 1241 (s), 1196 (s), 1139 (s), 989 (m), 916 (m), 872 (w), 836 (m), 813 (m), 781 (s), 746 (br, m). MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 55), 205 (19), 173 (38), 159 (49), 145 (16), 131 (100), 115 (15), 103 (48), 77 (60). HRMS (EI): calcd for $C_{12}H_{12}O_4$ (M^+) 220.07301, found 220.072813.

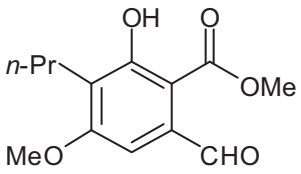
3-Ethyl-6-formyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (38a)



Following **general procedure 7** and starting with **36d** (0.295 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **38a** was obtained as a colourless solid (0.167 g, 70%); mp. 57-58 ºC.

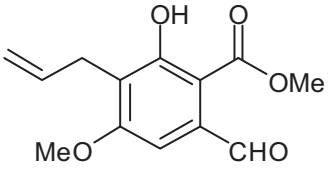
^{1}H NMR (300 MHz, $CDCl_3$): 1.09 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3), 2.71 (q, ^3J = 7.5 Hz, 2H, CH_2CH_3), 3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.93 (s, 1H, CH_{Ar}), 10.47 (s, 1H, CHO), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.8 (CH_2CH_3), 16.6 (CH_2CH_3), 52.7 (OCH_3), 55.9 (OCH_3), 103.2 (CH_{Ar}), 105.3, 125.0, 137.5, 161.0, 161.6 (C_{Ar}), 170.4 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2875 (w), 1662 (s), 1596 (m), 1570 (m), 1503 (w), 1437 (m), 1390 (m), 1346 (m), 1276 (s), 1251 (s), 1196 (m), 1155 (s), 1131 (s), 1058 (m), 1003 (m), 957 (m), 806 (m), 729 (m). MS (EI, 70eV): *m/z* (%) = 238 (M^+, 65), 209 (41), 191 (26), 179 (100), 150 (63), 135 (31), 107 (16), 77 (29). HRMS (EI): calcd for $C_{12}H_{14}O_5$ (M^+) 238.08358, found 238.083399.

6-Formyl-2-hydroxy-4-methoxy-3-propyl-benzoic acid methyl ester (38b)



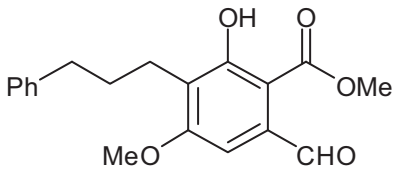
Following **general procedure 7** and starting with **36e** (0.306 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **38b** was obtained as a colourless solid (0.194 g, 77%); mp. 72-73 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): 0.93 (t, ^{3}J = 7.4 Hz, 3H, CH_2CH_3), 1.46-1.58 (m, 2H, CH_2CH_3), 2.63-2.68 (m, 2H, $C_{Ar}CH_2$), 3.89 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.92 (s, 1H, CH_{Ar}), 10.47 (s, 1H, CHO), 11.27 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 21.6, 25.1 (CH_2CH_2), 52.7 (OCH_3), 55.8 (OCH_3), 103.1 (CH_{Ar}), 105.2, 123.6, 137.6, 161.2, 161.8 (C_{Ar}), 170.4 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (w), 2867 (w), 1686 (m), 1660 (s), 1570 (m), 1503 (w), 1435 (m), 1386 (m), 1346 (m), 1298 (s), 1285 (s), 1217 (s), 1135 (s), 1077 (m), 1036 (w), 999 (w), 951 (w), 795 (m), 754 (s), 610 (m). MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 66), 223 (52), 193 (100), 177 (42), 135 (18), 105 (17), 77 (28). HRMS (EI): calcd for $C_{13}H_{16}O_5$ (M^+) 252.09923, found 252.099149.

3-Allyl-6-formyl-2-hydroxy-4-methoxy-benzoic acid methyl ester (38c)



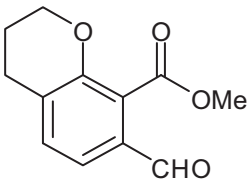
Following **general procedure 7** and starting with **36g** (0.304 g, 1.0 mmol), NaOMe (0.165 g, 3.0 mmol) in dry MeOH (10 mL), **38c** was obtained as a colourless solid (0.202 g, 81%); mp. 54-55 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 3.44-3.47 (m, 2H, $C_{Ar}CH_2$), 3.91 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.95-5.04 (m, 2H, CH_2CHCH_2), 5.85-5.98 (m, 1H, CH_2CH), 6.94 (s, 1H, CH_{Ar}), 10.49 (s, 1H, CHO), 11.32 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.2 ($C_{Ar}CH_2$), 52.8 (OCH_3), 56.0 (OCH_3), 103.2 (CH_{Ar}), 105.4 (C_{Ar}), 115.1 (CH_2CH), 120.6 (C_{Ar}), 134.9, (CH_2CH), 138.1, 161.1, 161.7 (C_{Ar}), 170.3 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3077 (w), 2946 8w), 2845 (w), 1661 (s), 1602 (w), 1570 (s), 1504 (w), 1435 (m), 1408 (m), 1344 (m), 1284 (s), 1212 (s), 1158 (s), 1131 (s), 1035 (m), 995 (s), 910 (m), 876 (m), 797 (s), 750 (s), 631 (m). MS (EI, 70 eV): *m/z* (%) = 250 (M^+, 75), 222 (61), 191 (100), 175 (74), 147 (12), 119 (24), 91 (41). HRMS (EI): calcd for $C_{13}H_{14}O_5$ (M^+) 250.08358, found 250.083807.

6-Formyl-2-hydroxy-4-methoxy-3-(3-phenyl-propyl)-benzoic acid methyl ester (38d)



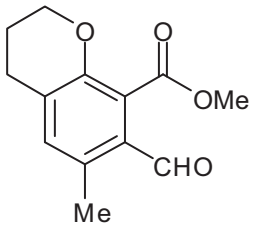
Following **general procedure 7** and starting with **36h** (0.153 g, 0.4 mmol), NaOMe (0.083 g, 1.5 mmol) in dry MeOH (5 mL), **38d** was obtained as a colourless solid (0.110 g, 72%); mp. 65-67 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.80-1.90 (m, 2H, $C_{Ar}CH_2CH_2$), 2.65-2.79 (m, 4H, $C_{Ar}CH_2$), 3.89 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.93 (s, 1H, CH_{Ar}), 7.15-7.26 (m, 5H, CH_{Ar}), 10.48 (s, 1H, CHO), 11.31 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.1, 29.7, 35.9 ($CH_2CH_2CH_2$), 52.7 (OCH_3), 55.8 (OCH_3), 103.1 (CH_{Ar}), 105.2, 123.2 (C_{Ar}), 125.6, 128.1, 128.3 (CH_{Ar}), 137.7, 142.5, 161.2, 161.7 (C_{Ar}), 170.4 (C=O), 192.2 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937 (w), 2856 (w), 1746 (w), 1657 (s), 1569 (m), 1494 (w), 1438 (m), 1387 (m), 1341 (m), 1294 (s), 1273 (s), 1255 (s), 1200 (s), 1146 (s), 1107 (s), 1000 (s), 948 (m), 846 (m), 746 (s), 699 (s). MS (EI, 70 eV): *m/z* (%) = 328 (M^+, 2), 269 (19), 224 (100), 192 (99), 164 (18), 105 (16), 77 (17). HRMS (EI): calcd for $C_{19}H_{20}O_5$ (M^+) 328.13053, found 328.130587.

7-Dichloromethyl-chroman-8-carboxylic acid methyl ester (40a)



Following **general procedure 7** and starting with **39a** (0.335 g, 1.08 mmol), NaOMe (0.233 g, 4.32 mmol) in dry MeOH (5.4 ml), **40a** was obtained as colourless solid (0.198 g, 83%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04 (m, 2H, CH_2CH_2O), 2.86 (t, ^{3}J = 6.5 Hz, 2H, $C_{Ar}CH_2$), 3.95 (s, 3H, OCH_3), 4.26 (t, ^{3}J = 5.3 Hz, 2H, CH_2O), 7.23 (d, ^{3}J = 7.8 Hz, 1H, CH_{Ar}), 7.33 (d, ^{3}J = 7.8 Hz, 1H, CH_{Ar}), 9.87 (s, 1H, CHO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.4, 25.4 ($CH_2CH_2CH_2O$), 52.8 (OCH_3), 67.1 (CH_2O), 122.7 (C_{Ar}), 122.7 (CH_{Ar}), 130.1 (C_{Ar}), 131.0 (CH_{Ar}), 132.5, 152.2 (C_{Ar}), 167.5 (C=O), 190.1 (CHO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2956 (w), 2921 (w), 1669 (s), 1577 (w), 1486 (w), 1437 (m), 1421 (s), 1336 (m), 1303 (br, m), 1241 (s), 1196 (s), 1139 (s), 989 (m), 916 (m), 872 (w), 836 (m), 813 (m), 781 (s), 746 (br, m), 587 (m). MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 24), 205 (9), 191 (58), 161 (100), 147 (14), 133 (28), 105 (22), 77 (30). HRMS (EI): calcd for $C_{12}H_{12}O_4$ (M^+) 220.07301, found 220.072913.

7-Dichloromethyl-6-methyl-chroman-8-carboxylic acid methyl ester (40b)

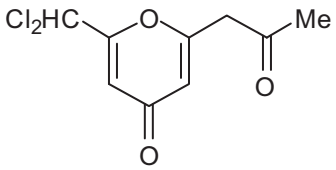


Following **general procedure 7** and starting with **39b** (0.325 g, 1.00 mmol), NaOMe (0.216 g, 4.00 mmol) in dry MeOH (5.0 ml), **40b** was obtained as colourless solid (0.198 g, 83%); mp. 81-82 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.03 (m, 2H, CH_2CH$_2$O), 2.25 (s, 3H, CH_3C$_{Ar}$), 2.79 (t, ^{3}J = 6.4 Hz, 2H, C$_{Ar}$CH_2), 3.52 (s, 3H, OCH$_3$), 4.34 (t, ^{3}J = 5.2 Hz, 2H, CH_2O), 6.15 (CHO), 7.10 (s, 1H, CH$_{Ar}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.1 (*C*H$_3$C$_{Ar}$), 21.6, 24.7 (*C*H$_2$*C*H$_2$CH$_2$O), 55.6 (O*C*H$_3$), 67.3 (*C*H$_2$O), 101.5 (CHO), 113.4, 124.7, 125.2 (C$_{Ar}$), 137.9 (CH$_{Ar}$), 142.6, 152.0 (C$_{Ar}$), 167.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2957 (w), 2924 (w), 1669 (s), 1615 (m), 1576 (w), 1468 (w), 1436 (m), 1422 (s), 1332 (m), 1304 (br, m), 1241 (s), 1196 (s), 1140 (s), 987 (m), 918 (m), 871 (w), 813 (m), 781 (s), 748 (br, m). MS (EI, 70 eV): *m/*z (%) = 234 (M$^+$, 44), 203 (100), 175 (60), 147 (12), 115 (7), 91 (13), 77 (7). HRMS (EI): calcd for $C_{13}H_{14}O_4$ (M$^+$) 234.08866, found 234.088260.

7.2.8 Synthesis of Dichloromethyl-Substituted Pyran-4-ones by Me_3SiOTf-mediated Cyclocondensation of 1,3-Bis(silyloxy)-1,3-butadienes with 1,1-Dimethoxy-4,4-dichlorobut-1-en-3-one.

General procedure 8: To a CH_2Cl_2 solution (10 mL) of **34** (1.0 mmol) was added 1,3-bis(silyloxy)-1,3-butadiene **5** (2.0 mmol) and, subsequently, Me_3SiOTf (0.244 g, 1.1 mmol) at -78 °C. The temperature of the solution was allowed to warm to 20 °C during 12-14 h with stirring. The solution was poured into an aqueous solution of HCl (10%). The organic and the aqueous layers were separated and the latter was extracted (3 x 30 mL) 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 (silica gel, heptane-EtOAc = 15:1).

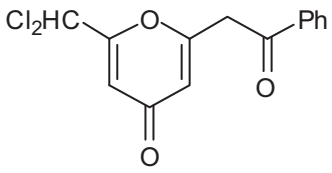
2-Dichloromethyl-6-(2-oxo-propyl)-pyran-4-one (41a)



Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5b** (0.978 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41a** was obtained as a brown viscous (0.099 g, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 6.24 (d, ^{4}J = 2.1 Hz, 1H, CHCO), 6.32 (s, 1H, $CHCl_2$), 6.52 (d,

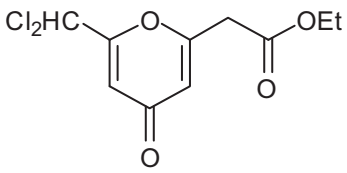
^4J = 2.1 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.0 (CH_3), 47.8 (CH_2CO), 65.2 ($CHCl_2$), 112.9, 116.9 (*C*HCO), 161.3, 161.9 (O*C*CH), 178.7 (CH*C*=O), 200.1 (CH_2CO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2922 (w), 1725 (m), 1656 (s), 1603 (m), 1394 (m), 1314 (m), 1213 (w), 1156 (s), 975 (w), 928 (s), 873 (m), 761 (s), 741 (s), 655 (m), 621 (w). MS (EI, 70 eV): *m/z* (%) = 234 (M^+, 1), 192 (100), 157 (27), 128 (7), 109 (8), 69 (17). HRMS (EI): calcd for $C_9H_8O_3Cl_2$ (M^+) 233.98450, found 233.984907.

2-Dichloromethyl-6-(2-oxo-2-phenyl-ethyl)-pyran-4-one (41b)



Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5j** (1.224 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41b** was obtained as a colourless solid (0.148 g, 25%); mp. 76-77 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.25 (s, 2H, CH_2), 6.29 (d, ^4J = 2.2 Hz, 1H, CHCO), 6.31 (s, 1H, $CHCl_2$), 6.53 (d, ^4J = 2.2 Hz, 1H, CHCO), 7.49-7.54 (m, 2H, CH_{Ar}), 7.64 (ddd, ^3J = 7.4 Hz, ^3J = 6.2 Hz, ^4J = 2.0 Hz, 1H, CH_{Ar}), 7.97-8.00 (m, 2H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 43.2 (CH_2CO), 65.2 ($CHCl_2$), 113.0, 117.2 (*C*HCO), 128.4, 129.0, 134.2 (CH_{Ar}), 135.5 (C_{Ar}), 161.3, 162.4 (O*C*CH), 178.6 (C=O), 192.2 ($C_{Ar}CO$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076 (w), 2979 (m), 2662 (w), 2476 (w), 1668 (s), 1632 (s), 1609 (m), 1449 (w), 1392 (s), 1338 (m), 1299 (m), 1196 (m), 1149 (m), 978 (m), 964 (m), 923 (s), 879 (m), 824 (w), 767 (s), 734 (s), 690 (s), 666 (m). MS (EI, 70 eV): *m/z* (%) = 297 (M^+, 6), 218 (32), 192 (15), 176 (100), 94 (32), 78 (8). HRMS (ESI^+): calcd for $C_{14}H_{11}O_3Cl_2$ ($(M+H)^+$) 297.00798, found 297.00788.

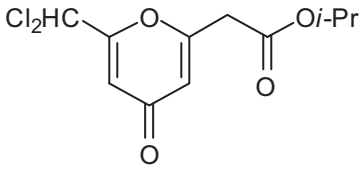
(6-Dichloromethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid ethyl ester (41c)



Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5d** (1.096 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41c** was obtained as an orange oil (0.321 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 3.59 (s, 2H, CCH_2C), 4.21 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 6.27 (d, ^4J = 2.1 Hz, 1H, CHCO), 6.33 (s, 1H, $CHCl_2$), 6.51 (d, ^4J = 2.1 Hz, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 39.4 (CH_2CO), 62.0 (OCH_2CH_3), 65.1 ($CHCl_2$), 112.9, 116.6 (*C*HCO), 161.2, 161.5 (O*C*CH), 166.7 (COO), 178.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2983 (w), 1734 (s), 1659 (s), 1627 (s), 1465 (w), 1393 (s), 1331 (w), 1250 (m), 1162 (m), 1026 (m), 975 (w), 928 (s), 873 (m), 760 (s), 734 (s), 621 (m). MS (EI, 70 eV): *m/z*

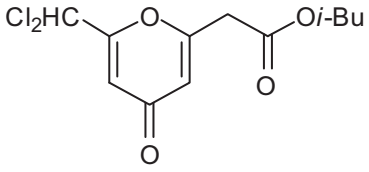
(%) = 264 (M^+, 56), 192 (80), 157 (53), 128 (100), 109 (17), 69 (56). HRMS (EI): calcd for $C_{10}H_{10}O_4Cl_2$ (M^+) 263.99507, found 263.995087.

(6-Dichloromethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid isopropyl ester (41d)



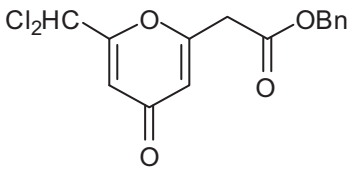
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5f** (1.114 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41d** was obtained as an orange oil (0.262 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, ^3J = 6.3 Hz, 6H, OCH(CH_3)$_2$), 3.56 (s, 2H, CCH_2C), 5.01-5.10 (m, ^3J = 6.3 Hz, 1H, OCH(CH$_3$)$_2$), 6.26 (d, ^4J = 2.2 Hz, 1H, CHCO), 6.33 (s, 1H, $CHCl_2$), 6.51 (d, ^4J = 2.2 Hz, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.6 (CH(*C*H$_3$)$_2$), 39.7 (*C*H$_2$CO), 65.1 ($CHCl_2$), 69.9 (COO*C*H), 112.7, 116.4 (*C*HCO), 161.3, 161.8 (O*C*CH), 166.2 (COO), 178.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2982 (w), 1730 (m), 1659 (s), 1627 (m), 1454 (w), 1394 (s), 1321 (m), 1258 (m), 1172 (m), 1101 (s), 996 (m), 928 (s), 873 (m), 761 (m), 680 (w), 621 (m). MS (EI, 70 eV): *m/z* = 278 (M^+, 11), 219 (14), 192 (27), 163 (11), 128 (12), 69 (15), 43 (100). HRMS (EI): calcd for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01072, found 278.010826.

(6-Dichloromethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid isobutyl ester (41e)



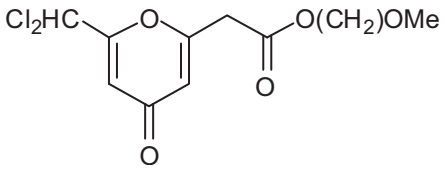
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5e** (1.202 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41e** was obtained as an orange oil (0.205 g, 35%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (d, ^3J = 6.8 Hz, 6H, CH(CH_3)$_2$), 1.80-1.96 (m, ^3J = 6.8 Hz, 1H, CH(CH$_3$)$_2$), 3.58 (s, 2H, CCH_2C), 3.88 (d, ^3J = 6.7 Hz, 2H, OCH_2CH), 6.25 (d, ^4J = 2.2 Hz, 1H, CHCO), 6.36 (s, 1H, $CHCl_2$), 6.48 (d, ^4J = 2.2 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.8 (CH(*C*H$_3$)$_2$), 27.4 (*C*H(CH$_3$)$_2$), 39.2 (*C*H$_2$CO), 65.0 ($CHCl_2$), 71.8 (COO*C*H$_2$), 112.7, 116.4 (*C*HCO), 161.3, 161.7 (O*C*CH), 166.7 (COO), 178.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 2962 (w), 1736 (m), 1660 (s), 1629 (m), 1469 (w), 1393 (s), 1321 (w), 1246 (br, m), 1163 (s), 1104 (w), 1005 (m), 928 (s), 874 (m), 761 (s), 683 (w), 622 (m). MS (EI, 70 eV): *m/z* = 292 (M^+, 41), 237 (77), 192 (55), 163 (15), 128 (30), 99 (11), 69 (28), 57 (100), 41 (60). HRMS (EI): calcd for $C_{12}H_{14}O_4Cl_2$ (M^+) 292.02637, found 292.026605.

(6-Dichloromethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid benzyl ester (41f)



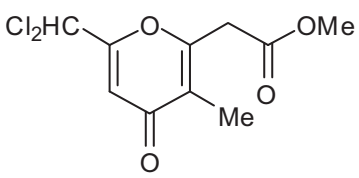
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5i** (1.344 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41f** was obtained as an orange oil (0.197 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 2H, CCH_2C), 5.19 (s, 2H, OCH_2C), 6.26 (s, 1H, $CHCl_2$), 6.29 (d, ^4J = 2.1 Hz, 1H, CHCO), 6.52 (d, ^4J = 2.1 Hz, 1H, CHCO), 7.33-7.38 (m, 5H, CH_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 39.3 (*C*H_2CO), 65.0 ($CHCl_2$), 67.8 (C_{Ar}*C*H_2O), 112.9, 116.9 (*C*HCO), 128.5, 128.7 (CH_{Ar}), 134.1 (C_{Ar}), 161.3, 161.4 (O*C*CH), 166.5 (COO), 178.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066 (w), 3004 (w), 1738 (m), 1659 (s), 1605 (br., m), 1455 (w), 1395 (m), 1321 (w), 1256 (m), 1210 (m), 1159 (s), 1142 (s), 1000 (m), 929 (m), 874 (m), 730 (s), 696 (s), 620 (m). MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 3), 219 (2), 192 (15), 158 (3), 91 (100), 65 (8). HRMS (EI): calcd for $C_{15}H_{12}O_4Cl_2$ (M^+) 326.01072, found 326.010851.

(6-Dichloromethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid 2-methoxy-ethyl ester (41g)



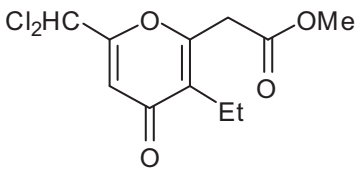
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5g** (1.216 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41g** was obtained as a colourless solid (0.206 g, 35 %); mp. 60-61 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (s, 3H, OCH_3), 3.54-3.57 (m, 2H, CH_2OCH_3), 3.61 (s, 2H, CCH_2C), 4.25-4.28 (m, 2H, $COCH_2$), 6.25 (d, ^4J = 2.1 Hz, 1H, CHCO), 6.34 (s, 1H, $CHCl_2$), 6.48 (d, ^4J = 2.1 Hz, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 39.0 (*C*H_2CO), 58.8 (OCH_3), 64.7 (OCH_2CH_2), 65.0 ($CHCl_2$), 69.9 ($COOCH_2$), 112.9, 116.5 (*C*HCO), 161.2 (O*C*CH), 166.7 (COO), 178.5 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3085 (w), 3006 (w), 2888 (w), 1732 (s), 1653 (s), 1617 (s), 1419 (w), 1400 (s), 1366 (m), 1280 (s), 1229 (m), 1181 (m), 1124 (s), 1098 (m), 1032 (s), 993 (m), 933 (s), 894 (s), 856 (s), 759 (s), 733 (s), 625 (m). MS (EI, 70 eV): *m/z* = 294 (M^+, 12), 228 (59), 192 (51), 158 (30), 128 (34), 99 (12), 69 (33), 45 (100). HRMS (EI): calcd for $C_{11}H_{12}O_5Cl_2$ (M^+) 294.00563, found 294.05227.

(6-Dichloromethyl-3-methyl-4-oxo-4*H*-pyran-2-yl)-acetic acid methyl ester (41h)



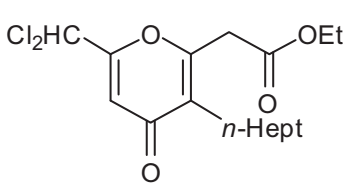
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5ab** (1.096 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41h** was obtained as an orange oil (0.184 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CCH_3), 3.70 (s, 2H, CCH_2C), 3.74 (s, 3H, OCH_3), 6.33 (s, 1H, $CHCl_2$), 6.54 (s, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.8 (C*C*H$_3$), 37.3 (*C*H$_2$CO), 52.8 (OCH_3), 65.1 ($CHCl_2$), 111.2 (*C*HCO), 124.3 (*C*CH$_3$), 157.4, 160.6 (OC), 167.5 (COO), 179.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084 (w), 3002 (w), 1740 (m), 1656 (s), 1605 (m), 1411 (m), 1381 (m), 1322 (m), 1271 (m), 1204 (m), 1155 (s), 1092 (m), 1044 (w), 1006 (m), 909 (w), 868 (w), 758 (s), 729 (s), 619 (m). MS (EI, 70 eV): *m/z* (%) = 264 (M^+, 92), 233 (25), 196 (100), 155 (86), 142 (58), 83 (4), 69 (34), 53 (27). HRMS (EI): calcd for $C_{10}H_{10}O_4Cl_2$ (M^+) 263.99507, found 263.994553.

(6-Dichloromethyl-3-ethyl-4-oxo-4*H*-pyran-2-yl)-acetic acid methyl ester (41i)



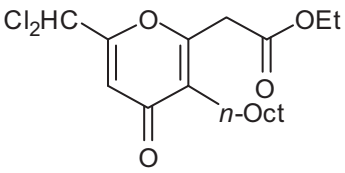
Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5ah** (1.152 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41i** was obtained as a colourless solid (0.183 g, 33%); mp 64-65 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.5 Hz, 3H, CH_2CH_3), 2.37 (q, ^3J = 7.5 Hz, 2H, CH_2CH_3), 3.65 (s, 2H, CCH_2C), 3.70 (s, 3H, OCH_3), 6.32 (s, 1H, $CHCl_2$), 6.47 (s, 1H, CHCO). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.6 (CH_2CH_3), 17.9 (CH_2CH_3), 36.8 (*C*H$_2$CO), 52.6 (OCH_3), 65.1 ($CHCl_2$), 111.7 (*C*HCO), 129.4 (*C*CH$_2$CH$_3$), 157.0, 160.2 (OC), 167.7 (COO), 178.3 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2995 (w), 2959 (w), 1739 (s), 1654 (s), 1601 (s), 1461 (w), 1415 (s), 1289 (w), 1263 (s), 1186 (m), 1131 (m), 1108 (m), 1015 (m), 978 (m), 907 (w), 850 (m), 788 (m), 758 (s), 637 (m). MS (EI, 70 eV): *m/z* (%) = 278 (M^+, 21), 242 (99), 210 (100), 184 (21), 169 (51), 143 (21), 101 (11), 69 (24). HRMS (EI): calcd for $C_{11}H_{12}O_4Cl_2$ (M^+) 278.01157, found 278.011483.

(6-Dichloromethyl-3-heptyl-4-oxo-4*H*-pyran-2-yl)-acetic acid ethyl ester (41j)



Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5m** (1.492 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41j** was obtained as an orange oil (0.217 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.8 Hz, 3H, CH_2CH_3), 1.27 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.29-1.46 (m, 10H, $(CH_2)_5CH_3$), 2.36-2.41 (m, 2H, CCH_2CH_2), 3.68 (s, 2H, CCH_2C), 4.21 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.31 (s, 1H, $CHCl_2$), 6.57 (s, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 14.1 (CH_3), 22.6, 24.7, 28.4, 29.1, 29.6, 31.7 ($(CH_2)_6CH_3$), 37.3 (CH_2CO), 62.0 (OCH_2CH_3), 65.2 ($CHCl_2$), 111.6 (*C*HCO), 128.4 (CCH_2CH_2), 157.8, 160.4 (OC), 167.3 (COO), 179.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926 (w), 2855 (w), 1739 (s), 1645 (s), 1464 (w), 1418 (m), 1267 (m), 1175 (s), 1107 (m), 1025 (m), 867 (w), 763 (s), 676 (m), 637 (w). MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 2), 316 (15), 275 (100), 241 (34), 206 (24), 155 (14), 91 (6). HRMS (EI): calcd for $C_{17}H_{24}O_4Cl_2$ (M^+) 362.10462, found 362.104263.

(6-Dichloromethyl-3-octyl-4-oxo-4*H*-pyran-2-yl)-acetic acid ethyl ester (41k)

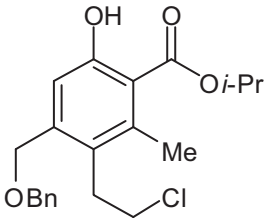


Following **general procedure 8** and starting with **34** (0.400 g, 2.0 mmol), **5af** (1.548 g, 4.0 mmol) and TMSOTf (0.488 g, 2.2 mmol) in CH_2Cl_2 (20 mL), **41k** was obtained as an orange oil (0.188 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.8 Hz, 3H, CH_2CH_3), 1.27 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.28-1.61 (m, 12H, $(CH_2)_6CH_3$), 2.36-2.41 (m, 2H, CCH_2CH_2), 3.67 (s, 2H, CCH_2C), 4.21 (q, ^3J = 7.2 Hz, 2H, OCH_2CH_3), 6.30 (s, 1H, $CHCl_2$), 6.50 (s, 1H, CHCO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 14.1 (CH_3), 22.6, 24.7, 28.4, 29.2, 29.4, 29.7, 31.8 ($(CH_2)_7CH_3$), 37.3 (CH_2CO), 61.9 (OCH_2CH_3), 65.3 ($CHCl_2$), 111.7 (*C*HCO), 128.4 (CCH_2CH_2), 157.5, 160.3 (OC), 167.4 (COO), 178.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (m), 2854 (w), 1740 (m), 1656 (s), 1602 (m), 1463 (w), 1415 (m), 1323 (w), 1252 (m), 1176 (s), 1107 (m), 1027 (m), 911 (w), 848 (w), 762 (s), 672 (w). MS (EI, 70eV): *m/z* (%) = 376 (M^+, 5), 330 (19), 289 (100), 278 (33), 255 (18), 206 (23), 177 (12), 155 (12), 69 (20). HRMS (EI): calcd for $C_{18}H_{26}O_4Cl_2$ (M^+) 376.12027, found 376.120015.

7.2.9 Synthesis of functionalized Phenols by Cyclizations of 1,3-Bis(silyloxi)-1,3-butadienes with 1,1-Diacylcyclopropanes

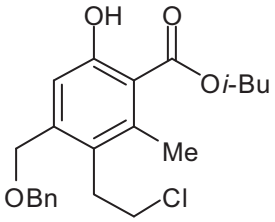
General procedure 9: To a CH_2Cl_2 solution (100 mL) of **1** (1.0 mmol) and of 1,3-bis(silyl enol ether) **2** (1.5 mmol) in the presence of molecular sieves (4 Å, 1.00 g) was dropwise added $TiCl_4$ (0.22 mL, 2.0 mmol) at -78 °C under argon atmosphere. The solution was allowed to warm to 20 °C within 18 h with stirring and subsequently filtered. The filtrate was poured into hydrochloric acid (10%, 100 mL), the organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 15:1→7:1).

4-Benzyloxymethyl-3-(2-chloro-ethyl)-6-hydroxy-2-methyl-benzoic acid isopropyl ester (49b)



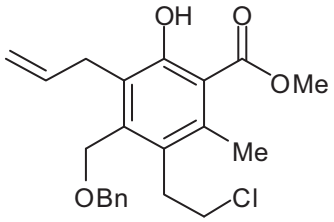
Following **general procedure 9** and starting with **48a** (0.464 g, 2.00 mmol), **5f** (1.156 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49b** was obtained as a yellow oil (0.400 g, 53 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 2.51 (s, 3H, $C_{Ar}CH_3$), 3.10 (m, 2H, $C_{Ar}CH_2$), 3.54 (m, 2H, CH_2Cl), 4.51 (s, 2H, CH_2O), 4.59 (s, 2H, CH_2O), 5.34 (m, ^3J = 6.3 Hz, 1H, $OCH(CH_3)_2$), 6.93 (s, 1H, CH_{Ar}), 7.30-7.38 (m, 5H, CH_{Ar}), 10.37 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.3 ($C_{Ar}CH_3$), 21.9 ($OCH(CH_3)_2$), 32.6, 42.9 (CH_2CH_2Cl), 69.9 ($OCH(CH_3)_2$), 70.9, 72.7, (CH_2O), 114.0 (C_{Ar}), 116.5 (CH_{Ar}), 126.9 (C_{Ar}), 127.7, 127.8, 128.4 (CH_{Ar}), 137.6, 139.5, 143.0 (C_{Ar}), 160.2 ($C_{Ar}OH$), 170.6 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 3031 (w), 2980 (w), 2954 (w), 1656 (m), 1601 (m), 1574 (m), 1454 (m), 1365 (m), 1309 (m), 1233 (s), 1197 (m), 1100 (s), 1088 (s), 1008 (m), 839 (s), 735 (m), 696 (m). MS (EI, 70eV): *m/z* (%) = 376 (M^+, 7), 270 (63), 228 (11), 210 (100), 175 (23), 161 (34), 105 (12), 91 (85), 77 (9). HRMS (EI): calcd for $C_{21}H_{25}O_4Cl_1$ (M^+) 376.14415, found 376.144093.

4-Benzyloxymethyl-3-(2-chloro-ethyl)-6-hydroxy-2-methyl-benzoic acid isobutyl ester (49c)



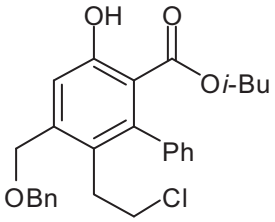
Following **general procedure 9** and starting with **48a** (0.464 g, 2.00 mmol), **5e** (1.208 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49c** was obtained as a colourless solid (0.375 g, 48 %); mp. 71-72 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, ^3J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 2.10 (m, ^3J = 6.7 Hz, 1H, $CH_2CH(CH_3)_2$), 2.54 (s, 3H, $C_{Ar}CH_3$), 3.10 (m, 2H, $C_{Ar}CH_2$), 3.54 (m, 2H, CH_2Cl), 4.17 (d, ^3J = 6.5 Hz, 2H, $OCH_2CH(CH_3)_2$), 4.51 (s, 2H, CH_2O), 4.60 (s, 2H, CH_2O), 6.94 (s, 1H, CH_{Ar}), 7.30-7.40 (m, 5H, CH_{Ar}), 10.81 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.6 ($C_{Ar}CH_3$), 19.4 ($CH_2CH(CH_3)_2$), 27.6 ($CH_2CH(CH_3)_2$), 32.6, 42.9 (CH_2CH_2Cl), 70.9, 72.2, 72.8 (CH_2O), 113.7 (C_{Ar}), 116.7 (CH_{Ar}), 126.9 (C_{Ar}), 127.8, 127.9, 128.5 (CH_{Ar}), 137.6, 139.6, 143.3 (C_{Ar}), 160.5 ($C_{Ar}OH$), 171.5 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 2967 (w), 2861 (w), 1646 (s), 1461 (m), 1321 (m), 1238 (s), 1196 (s), 1115 (s), 1073 (m), 975 (m), 778 (br, m), 731 (s), 695 (s). MS (EI, 70 eV): *m/z* (%) = 390 (M^+, 4), 317 (9), 284 (30), 210 (100), 190 (31), 161 (24), 91 (63), 77 (8). HRMS (EI): calcd for $C_{22}H_{27}O_4Cl$ (M^+) 390.15924, found 390.159031.

3-Allyl-4-benzyloxymethyl-5-(2-chloro-ethyl)-2-hydroxy-6-methyl-benzoic acid methyl ester (49e)



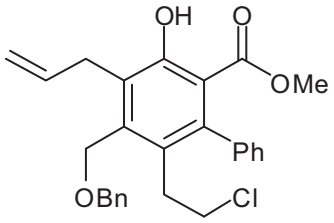
Following **general procedure 9** and starting with **48a** (0.464 g, 2.00 mmol), **5o** (1.204 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49e** was obtained as a yellow oil (0.273 g, 35 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H, $C_{Ar}CH_3$), 3.16 (m, 2H, $C_{Ar}CH_2CH_2$), 3.46-3.57 (m, 4H, CH_2Cl, $C_{Ar}CH_2CH$), 3.95 (s, 3H, OCH_3), 4.46 (s, 2H, CH_2O), 4.63 (s, 2H, CH_2O), 4.78 (dd, ^3J = 17.1 Hz, ^4J = 1.8 Hz, 1H, $CHCH_2$), 4.94 (dd, ^3J = 10.2 Hz, ^4J = 1.7 Hz, 1H, $CHCH_2$), 5.92 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 5.8 Hz, 1H, CH_2CHCH_2), 7.32-7.42 (m, 5H, CH_{Ar}), 10.75 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.4 ($C_{Ar}CH_3$), 30.2, 33.3, 43.3 (CH_2), 52.3 (OCH_3), 66.2, 73.6 (CH_2O), 114.0 (C_{Ar}), 114.7 (CH_2CH), 126.1 (C_{Ar}), 128.0, 128.3 (CH_{Ar}), 128.4 (C_{Ar}), 128.5 (CH_{Ar}), 136.5 (CH_2CHCH_2), 137.0, 137.5, 141.0 (C_{Ar}), 158.1 ($C_{Ar}OH$), 172.0 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 2853 (w), 1658 (s), 1438 (m), 1352 (m), 1274 (m), 1255 (s), 1243 (s), 1201 (s), 1178 (m), 1118 (m), 1065 (s), 961 (m), 735 (s), 697 (s). MS (EI, 70 eV): *m/z* (%) = 388 (M^+, 1), 297 (3), 248 (100), 199 (18), 128 (5), 91 (35). HRMS (EI): calcd for $C_{22}H_{25}O_4Cl$ (M^+) 388.14359, found 388.144068.

5-Benzyloxymethyl-6-(2-chloro-ethyl)-3-hydroxy-biphenyl-2-carboxylic acid isobutyl ester (49h)



Following **general procedure 9** and starting with **48b** (0.588 g, 2.00 mmol), **5e** (1.208 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49h** was obtained as a colourless solid (0.525 g, 58 %); mp. 73-74 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (d, ^3J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 1.23 (m, ^3J = 6.7 Hz, 1H, $CH_2CH(CH_3)_2$), 2.76 (m, 2H, $C_{Ar}CH_2$), 3.26 (m, 2H, CH_2Cl), 3.63 (d, ^3J = 6.8 Hz, 2H, $OCH_2CH(CH_3)_2$), 4.58 (s, 2H, CH_2O), 4.65 (s, 2H, CH_2O), 7.10-7.13 (m, 2H, CH_{Ar}), 7.17 (s, 1H, CH_{Ar}), 7.31-7.40 (m, 8H, CH_{Ar}), 11.05 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.0 ($CH_2CH(CH_3)_2$), 26.9 ($CH_2CH(CH_3)_2$), 32.5, 43.2 (CH_2CH_2Cl), 70.3, 71.9, 73.0 (CH_2O), 112.6 (C_{Ar}), 118.0 (CH_{Ar}), 126.6 (C_{Ar}), 127.0, 127.8, 127.9, 128.5, 128.6 (CH_{Ar}), 137.6, 130.7, 140.7, 143.7, 144.4 (C_{Ar}), 160.5 ($C_{Ar}OH$), 171.0 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (w), 2781 (w), 1650 (m), 1596 (m), 1452 (m), 1440 (m), 1323 (m), 1239 (s), 1200 (m), 1188 (m), 1113 (s), 812 (m), 774 (m), 754 (s), 734 (s), 716 (m), 702 (s). MS (EI, 70 eV): *m/z* (%) = 452 (M^+, 5), 346 (40), 326 (7), 284 (33), 272 (100), 252 (31), 235 (18), 210 (49), 165 (15), 91 (67). HRMS (EI): calcd for $C_{27}H_{29}O_4Cl$ (M^+) 452.17489, found 452.175081.

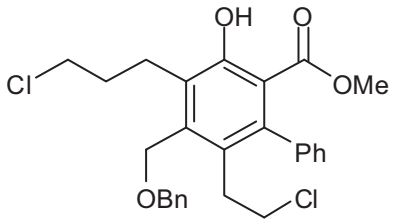
4-Allyl-5-benzyloxymethyl-6-(2-chloro-ethyl)-3-hydroxy-biphenyl-2-carboxylic acid methyl ester (49j)



Following **general procedure 9** and starting with **48b** (0.588 g, 2.00 mmol), **5o** (1.204 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49j** was obtained as a yellow oil (0.415 g, 46 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.88 (m, 2H, $C_{Ar}CH_2CH_2$), 3.33 (s, 3H, OCH_3), 3.36 (m, 2H, CH_2Cl), 3.56-3.59 (m, 2H, $C_{Ar}CH_2CH$), 4.53 (s, 2H, CH_2O), 4.67 (s, 2H, CH_2O), 4.88 (dd, ^3J = 17.2 Hz, ^4J = 1.8 Hz, 1H, $CHCH_2$), 5.01 (dd, ^3J = 10.2 Hz, ^4J = 1.6 Hz, 1H, $CHCH_2$), 5.99 (ddt, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^3J = 6.0 Hz, 1H, CH_2CHCH_2), 7.08-7.11 (m, 2H, CH_{Ar}), 7.33-7.44 (m, 8H, CH_{Ar}), 11.01 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.4, 33.4, 43.6 (CH_2), 51.8 (OCH_3), 66.1, 73.8 (CH_2O), 112.9 (C_{Ar}), 115.0 (CH_2CH), 126.8, 127.7 (CH_{Ar}), 128.0 (C_{Ar}), 128.1, (CH_{Ar}), 128.3 (C_{Ar}), 128.4, 128.5 (CH_{Ar}), 136.3 (CH_2CHCH_2), 137.4, 141.0, 141.1, 142.3 (C_{Ar}), 158.2 ($C_{Ar}OH$), 171.4 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2950 (w), 1660 (s), 1592 (w), 1563 (w), 1495 (w), 1439 (m), 1278 (m), 1256 (m), 1206 (m), 1174 (m), 1114 (w), 1073 (s), 1028 (m), 909 (m), 842 (w), 733 (br., m), 698 (s). MS (EI, 70 eV): *m/z* (%) = 450 (M^+, 1), 359 (4),

342 (20), 310 (100), 292 (28), 248 (31), 235 (16), 202 (12), 165 (12), 105 (14), 91 (55), 77 (16). HRMS (EI): calcd for $C_{27}H_{27}O_4Cl$ (M^+) 450.15924, found 450.160039.

5-Benzyloxymethyl-6-(2-chloro-ethyl)-4-(3-chloro-propyl)-3-hydroxy-biphenyl-2-carboxylic acid methyl ester (49k)



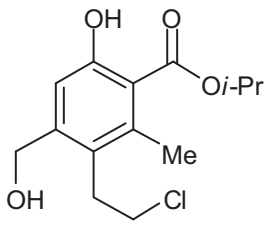
Following **general procedure 9** and starting with **48b** (0.588 g, 2.00 mmol), **5ai** (1.348 g, 4.00 mmol) and $TiCl_4$ (0.759 g, 4.00 mmol) in CH_2Cl_2 (200 mL), **49k** was obtained as a yellow oil (0.614 g, 63 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (m, 2H, $CH_2CH_2CH_2$), 2.84-2.96 (m, 4H, $C_{Ar}CH_2$), 3.33 (s, 3H, OCH_3), 3.35 (m, 2H, CH_2Cl), 3.60 (t, ^3J = 6.5 Hz, 2H, CH_2Cl), 4.57 (s, 2H, CH_2O), 4.69 (s, 2H, CH_2O), 7.07-7.14 (m, 2H, CH_{Ar}), 7.32-7.48 (m, 8H, CH_{Ar}), 11.03 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.1, 32.6, 33.4, 43.6, 45.3 (CH_2), 51.9 (OCH_3), 66.1, 73.8 (CH_2O), 112.8 (C_{Ar}), 126.9, 127.7 (CH_{Ar}), 127.9 (C_{Ar}), 128.1, 128.4, 128.5, 128.6 (CH_{Ar}), 130.0, 132.5, 137.3, 140.8, 140.9, 142.2 (C_{Ar}), 158.4 ($C_{Ar}OH$), 171.4 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2858 (w), 1659 (m), 1592 (m), 1439 (m), 1409 (m), 1313 (m), 1216 (m), 1175 (m), 1085 (m), 1064 (m), 1027 (m), 840 (w), 818 (m), 749 (s), 698 (s). MS (EI, 70 eV): *m/z* (%) = 486 (M^+, 1), 419 (9), 380 (10), 342 (35), 324 (47), 282 (89), 265 (41), 247 (30), 165 (25), 105 (34), 91 (100), 77 (34). HRMS (EI): calcd for $C_{27}H_{28}O_4Cl_2$ (M^+) 486.13592, found 486.136224.

7.2.10 Synthesis of Isochromanes and Chromanes

7.2.10.1 *Debenzylation of functionalized phenols*

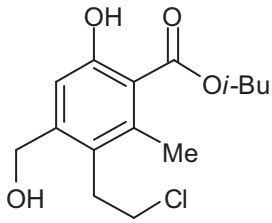
General procedure 10: To a EtOAc solution (10 mL) of **49** (1.0 mmol) was added Pd/C (10 wt. % Pd, 10 mol%) at 20 °C under argon atmosphere. The flask was evacuated and filled with hydrogen (3x) and the mixture was stirred under hydrogen atmosphere for 48 h. The mixture was filtered (Celite), washed with EtOAc (300 mL). The combined organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 10:1→5:1).

3-(2-Chloro-ethyl)-6-hydroxy-4-hydroxymethyl-2-methyl-benzoic acid isopropyl ester (50b)



Following **general procedure 10** and starting with **49b** (0.377 g, 1.00 mmol), Pd/C (0.106 g, 0.10 mmol Pd) in ethyl acetate (10 mL), **50b** was obtained as colourless viscous (0.215 g, 75 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, ^{3}J = 6.3 Hz, 6H, $CH(CH_3)_2$), 1.68 (br, 1H, CH_2OH), 2.51 (s, 3H, $C_{Ar}CH_3$), 3.12 (m, 2H, $C_{Ar}CH_2$), 3.56 (m, 2H, CH_2Cl), 4.47 (s, 2H, CH_2O), 5.33 (m, ^{3}J = 6.3 Hz, 1H, $OCH(CH_3)_2$), 6.94 (s, 1H, CH_{Ar}), 10.74 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.3 ($C_{Ar}CH_3$), 21.9 ($OCH(CH_3)_2$), 32.2, 42.9 (CH_2CH_2Cl), 63.6 (CH_2O), 70.0 ($OCH(CH_3)_2$), 113.9 (C_{Ar}), 115.1 (CH_{Ar}), 126.2, 139.5, 145.6 (C_{Ar}), 160.5 ($C_{Ar}OH$), 170.7 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2854 (w), 1658 (m), 1575 (w), 1454 (w), 1374 (w), 1257 (s), 1074 (s), 1008 (m), 864 (w), 788 (s), 701 (m). MS (EI, 70eV): *m/z* (%) = 286 (M^+, 13), 226 (84), 190 (10), 177 (100), 149 (3), 121 (3), 91 (6), 69 (6). HRMS (EI): calcd for $C_{14}H_{19}O_4Cl$ (M^+) 286.09664, found 286.096180.

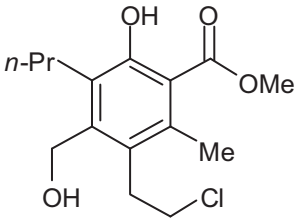
3-(2-Chloro-ethyl)-6-hydroxy-4-hydroxymethyl-2-methyl-benzoic acid isobutyl ester (50c)



Following **general procedure 10** and starting with **49c** (0.350 g, 0.90 mmol), Pd/C (0.096 g, 0.09 mmol Pd) in ethyl acetate (10 mL), **50c** was obtained as a colourless solid (0.237 g, 87 %); mp 60-61 ºC.

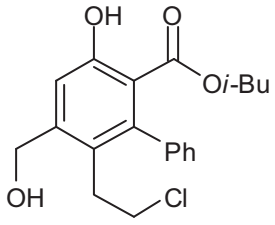
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, ^{3}J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 2.09 (m, 1H, $CH_2CH(CH_3)_2$), 2.11 (br, 1H, CH_2OH), 2.52 (s, 3H, $C_{Ar}CH_3$), 3.10 (m, 2H, $C_{Ar}CH_2$), 3.54 (m, 2H, CH_2Cl), 4.16 (d, ^{3}J = 6.5 Hz, 2H, $OCH_2CH(CH_3)_2$), 4.68 (s, 2H, CH_2O), 6.92 (s, 1H, CH_{Ar}), 10.81 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.5 ($C_{Ar}CH_3$), 19.3 ($CH_2CH(CH_3)_2$), 27.6 ($CH_2CH(CH_3)_2$), 32.2, 42.9 (CH_2CH_2Cl), 63.5, 72.2 (CH_2O), 113.4 (C_{Ar}), 115.1 (CH_{Ar}), 126.1, 139.6, 145.8 (C_{Ar}), 160.7 ($C_{Ar}OH$), 171.4 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3371 (w), 2962 (m), 1655 (m), 1600 (m), 1467 (m), 1397 (m), 1271 (m), 1230 (s), 1191 (m), 1157 (m), 1073 (s), 1032 (m), 867 (m), 802 (m), 705 (m). MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 21), 251 (6), 226 (97), 190 (23), 177 (100), 115 (6), 91 (11), 77 (12). HRMS (EI): calcd for $C_{15}H_{21}O_4Cl$ (M^+) 300.11229, found 300.112288.

3-(2-Chloro-ethyl)-6-hydroxy-4-hydroxymethyl-2-methyl-5-propyl-benzoic acid methyl ester (50d)



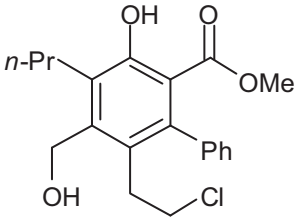
Following **general procedure 10** and starting with **49e** (0.250 g, 0.64 mmol), Pd/C (0.068 g, 0.064 mmol Pd) in ethyl acetate (6 mL), **50d** was obtained as a colourless solid (0.164 g, 85 %); mp. 130-131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, ^{3}J = 7.3 Hz, 3H, CH_2CH_3), 1.25 (br, 1H, CH_2OH), 1.53 (m, 2H, CH_2CH_3), 2.47 (s, 3H, $C_{Ar}CH_3$), 2.74 (m, 2H, $CH_2CH_2CH_3$), 3.24 (m, 2H, $C_{Ar}CH_2$), 3.60 (m, 2H, CH_2Cl), 3.96 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2O), 10.74 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 18.5 ($C_{Ar}CH_3$), 23.8, 28.5, 33.1, 43.5 (CH_2), 52.4 (OCH_3), 59.2 (CH_2O), 113.8, 127.7, 128.7, 136.6, 142.5 (C_{Ar}), 158.5 ($C_{Ar}OH$), 172.1 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3368 (w), 2926 (m), 1652 (s), 1440 (m), 1406 (m), 1384 (w), 1329 (s), 1253 (m), 1202 (s), 1114 (s), 1040 (s), 1019 (m), 996 (s), 843 (w), 812 (s), 776 (m), 750 (m). MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 21), 251 (6), 226 (97), 190 (23), 177 (100), 115 (6), 91 (11), 77 (12). HRMS (EI): calcd for $C_{15}H_{21}O_4Cl$ (M^+) 300.11229, found 300.112288.

6-(2-Chloro-ethyl)-3-hydroxy-5-hydroxymethyl-biphenyl-2-carboxylic acid isobutyl ester (50f)



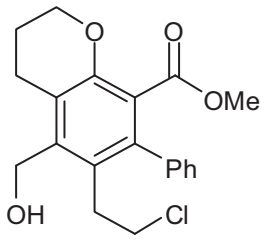
Following **general procedure 10** and starting with **49h** (0.455 g, 1.00 mmol), Pd/C (0.106 g, 0.10 mmol Pd) in ethyl acetate (10 mL), **50f** was obtained as a colourless solid (0.283 g, 87 %); mp. 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 (d, ^{3}J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 1.22 (m, 1H, $CH_2CH(CH_3)_2$), 1.82 (br, 1H, CH_2OH), 2.77 (m, 2H, $C_{Ar}CH_2$), 3.26 (m, 2H, CH_2Cl), 3.63 (d, ^{3}J = 6.8 Hz, 2H, $OCH_2CH(CH_3)_2$), 4.77 (s, 2H, CH_2O), 7.09-7.13 (m, 2H, CH_{Ar}), 7.18 (s, 1H, CH_{Ar}), 7.33-7.40 (m, 3H, CH_{Ar}), 11.07 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.1 ($CH_2CH(CH_3)_2$), 26.9 ($CH_2CH(CH_3)_2$), 32.2, 43.2 (CH_2CH_2Cl), 63.2, 71.9 (CH_2O), 112.5 (C_{Ar}), 116.7 (CH_{Ar}), 125.9 (C_{Ar}), 127.1, 127.9, 128.5 (CH_{Ar}), 140.7, 144.5, 146.2 (C_{Ar}), 160.8 ($C_{Ar}OH$), 171.0 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3278 (m), 2966 (m), 1688 (s), 1595 (m), 1359 (m), 1575 (w), 1427 (m), 1371 (m), 1311 (s), 1285 (s), 1241 (s), 1194 (s), 1071 (s), 853 (s), 768 (s), 707 (s). MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 22), 288 (100), 252 (9), 239 (64), 193 (13), 165 (9), 97 (8), 71 (12), 57 (16). HRMS (EI): calcd for $C_{20}H_{23}O_4Cl$ (M^+) 362.12794, found 362.127382.

6-(2-Chloro-ethyl)-3-hydroxy-5-hydroxymethyl-4-propyl-biphenyl-2-carboxylic acid methyl ester (50g)



Following **general procedure 10** and starting with **49j** (0.390 g, 0.86 mmol), Pd/C (0.092 g, 0.086 mmol Pd) in ethyl acetate (9 mL), **50g** was obtained as a colourless oil (0.212 g, 68 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, ^{3}J = 7.3 Hz, 3H, CH_2CH_3), 1.62 (m, 2H, CH_2CH_3), 1.69 (br, 1H, CH_2OH), 2.82 (m, 2H, $CH_2CH_2CH_3$), 2.95 (m, 2H, $C_{Ar}CH_2$), 3.32 (s, 3H, OCH_3), 3.36 (m, 2H, CH_2Cl), 4.79 (s, 2H, CH_2O), 7.07-7.11 (m, 2H, CH_{Ar}), 7.31-7.38 (m, 3H, CH_{Ar}), 10.95 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.5 (CH_2CH_3), 23.7, 28.6, 33.1, 43.9 (CH_2), 51.8 (OCH_3), 59.1 (CH_2O), 112.8 (C_{Ar}), 126.9 (CH_{Ar}), 127.2 (C_{Ar}), 127.7, 128.5 (CH_{Ar}), 130.9, 141.1, 141.9, 142.7 (C_{Ar}), 158.5 ($C_{Ar}OH$), 171.5 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 2954 (w), 1659 (s), 1494 (w), 1439 (s), 1408 (m), 1337 (s), 1210 (s), 1172 (s), 1105 (m), 1041 (m), 972 (m), 758 (m), 731 (s), 702 (s), 539 (m). MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 35), 330 (100), 294 (32), 267 (18), 249 (24), 223 (17), 195 (12), 165 (16), 115 (5). HRMS (EI): calcd for $C_{20}H_{23}O_4Cl$ (M^+) 362.12794, found 362.127382.

6-(2-Chloro-ethyl)-5-hydroxymethyl-7-phenyl-chroman-8-carboxylic acid methyl ester (53b)

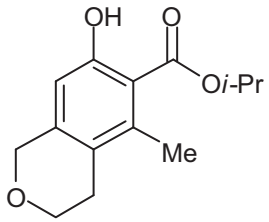


Following **general procedure 10** and starting with **52b** (0.250 g, 0.55 mmol), Pd/C (0.059 g, 0.055 mmol Pd) in ethyl acetate (6 mL), **53b** was obtained as a colourless solid (0.121 g, 61 %); mp 116-117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 1H, OH), 2.08 (m, 2H, CH_2CH_2O), 2.96-3.01 (m, 4H, $C_{Ar}CH_2$), 3.37 (m, 2H, CH_2Cl), 3.42 (s, 3H, OCH_3), 4.20 (m, 2H, CH_2CH_2O), 4.76 (s, 2H, $C_{Ar}CH_2O$), 7.17-7.22 (m, 2H, CH_{Ar}), 7.32-7.37 (m, 3H, CH_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.9, 22.3, 32.6, 44.1 (CH_2), 51.8 (OCH_3), 58.6, 66.3 (CH_2O), 122.3, 124.5, 127.0 (C_{Ar}), 127.7, 128.1, 129.3 (CH_{Ar}), 137.9, 138.9, 139.2 (C_{Ar}), 150.4 ($C_{Ar}O$), 167.0 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3447 (w), 2921 (w), 1702 (s), 1445 (m), 1426 (m), 1379 (w), 1290 (s), 1264 (m), 1213 (s), 1172 (s), 1092 (s), 1071 (s), 1016, (s), 964 (m), 770 (m), 728 (w), 703 (s). MS (EI, 70 eV): *m/z* (%) = 360 (M^+, 19), 324 (100), 279 (72), 234 (27), 178 (19), 115 (4). HRMS (EI): calcd for $C_{20}H_{21}O_4Cl_1$ (M^+) 360.11229, found 360.111720.

7.2.10.2 *Intramolecular Williamson reaction of debenzylated phenols*

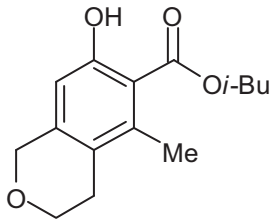
General procedure 11: To a DMF solution (20 mL) of **50** (and/or **49k, 53b**) (1.0 mmol) was added TBAI (2.0 mmol) under argon atmosphere and the reaction mixture was cooled to -78 °C. The cooling bath was replaced by an ice/NaCl-mixture and NaH (2.3 mmol) was added. After stirring for 14-20 h, EtOAc (5 mL) and ice water (5 mL) were added and the solution was neutralized with hydrochlorid acid (10%). The organic and the aqueous layers were separated and the latter was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuum. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 10:1→3:1).

7-Hydroxy-5-methyl-isochroman-6-carboxylic acid isopropyl ester (51b)



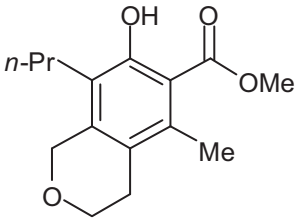
Following **general procedure 11** and starting with **50b** (0.187 g, 0.65 mmol), TBAI (0.554 g, 1.50 mmol) and NaH (0.031 g, 1.30 mmol) in DMFA (13 mL), **51b** was obtained as a colourless solid (0.084 g, 52 %); mp. 69-71 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 2.40 (s, 3H, $C_{Ar}CH_3$), 2.66 (t, ^3J = 5.8 Hz, 2H, $C_{Ar}CH_2CH_2$), 3.96 (t, ^3J = 5.8 Hz, 2H, OCH_2CH_2), 4.69 (s, 2H, CH_2O), 5.31 (m, ^3J = 6.3 Hz, 1H, $OCH(CH_3)_2$), 6.48 (s, 1H, CH_{Ar}), 10.72 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.3 ($C_{Ar}CH_3$), 22.0 ($OCH(CH_3)_2$), 26.4 ($C_{Ar}CH_2CH_2$), 65.8, 68.3 (CH_2O), 69.7 ($OCH(CH_3)_2$), 110.5 (CH_{Ar}), 112.7, 123.9, 139.4, 141.5 (C_{Ar}), 159.4 ($C_{Ar}OH$), 170.9 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979 (w), 2928 (w), 1723 (w), 1656 (s), 1465 (m), 1366 (s), 1245 (s), 1199 (m), 1145 (w), 1102 (s), 1067 (s), 988 (m), 875 (m), 802 (m). MS (EI, 70 eV): *m/z* (%) = 250 (M^+, 12), 190 (100), 160 (12), 132 (5), 104 (5). HRMS (EI): calcd for $C_{14}H_{18}O_4$ (M^+) 250.12051, found 250.120732.

7-Hydroxy-5-methyl-isochroman-6-carboxylic acid isobutyl ester (51c)



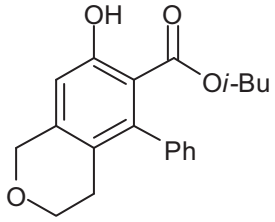
Following **general procedure 11** and starting with **50c** (0.196 g, 0.65 mmol), TBAI (0.554 g, 1.50 mmol) and NaH (0.031 g, 1.30 mmol) in DMFA (13 mL), **51c** was obtained as a colourless solid (0.093 g, 54 %); mp. 50-52 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (d, ^{3}J = 6.8 Hz, 6H, $CH_2CH(CH_3)_2$), 2.10 (m, 1H, $CH_2CH(CH_3)_2$), 2.43 (s, 3H, $C_{Ar}CH_3$), 2.67 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 3.96 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 4.16 (d, ^{3}J = 6.5 Hz, 2H, $OCH_2CH(CH_3)_2$), 4.69 (s, 2H, $C_{Ar}CH_2O$), 6.49 (s, 1H, CH_{Ar}), 10.81 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.8 ($C_{Ar}CH_3$), 19.4 ($CH_2CH(CH_3)_2$), 26.4 ($CH_2CH(CH_3)_2$), 27.7 ($C_{Ar}CH_2CH_2$), 63.8, 68.3 (CH_2O), 72.0 (OCH_2CH), 110.6 (CH_{Ar}), 112.4, 123.8, 139.4, 141.7 (C_{Ar}), 159.6 ($C_{Ar}OH$), 171.7 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2964 (w), 2932 (w), 1651 (s), 1600 (m), 1464 (m), 1250 (s), 1230 (s), 1201 (m), 1162 (m), 1066 (m), 1051 (m), 970 (m), 801 (s), 758 (m), 723 (m), 704 (m). MS (GC, 70eV): *m/z* (%) = 264 (M^+, 21), 190 (100), 175 (7), 160 (14), 133 (5), 104 (8), 77 (6). HRMS (EI): calcd for $C_{15}H_{20}O_4$ (M^+) 264.13561, found 264.135776.

7-Hydroxy-5-methyl-8-propyl-isochroman-6-carboxylic acid methyl ester (51d)



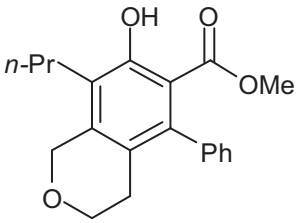
Following **general procedure 11** and starting with **50d** (0.142 g, 0.47 mmol), TBAI (0.400 g, 1.08 mmol) and NaH (0.023 g, 0.94 mmol) in DMFA (10 mL), **51d** was obtained as a colourless solid (0.055 g, 44 %); mp. 97-99 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, ^{3}J = 7.4 Hz, 3H, CH_2CH_3), 1.53 (m, 2H, CH_2CH_3), 2.36 (s, 3H, $C_{Ar}CH_3$), 2.46 (m, 2H, $CH_2CH_2CH_3$), 2.67 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 3.92 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 3.95 (s, 3H, OCH_3), 4.77 (s, 2H, CH_2O), 10.79 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (CH_2CH_3), 17.5 ($C_{Ar}CH_3$), 22.0, 26.8 (CH_2), 52.1 (OCH_3), 53.4 (CH_2), 65.2, 66.9 (CH_2O), 111.7, 123.5, 123.6, 136.0, 139.3 (C_{Ar}), 157.1 ($C_{Ar}OH$), 172.4 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 2871 (w), 1650 (m), 1409 (m), 1384 (m), 1260 (s), 1242 (m), 1194 (s), 1170 (m), 1096 (s), 1052 (m), 1039 (s), 1024 (m), 996 (m), 803 (s), 750 (m). MS (EI, 70 eV): *m/z* (%) = 264 (M^+, 32), 232 (48), 204 (100), 175 (18), 115 (11), 91 (12), 77 (6). HRMS (EI): calcd for $C_{15}H_{20}O_4$ (M^+) 264.13561, found 264.135746.

7-Hydroxy-5-phenyl-isochroman-6-carboxylic acid isobutyl ester (51f)



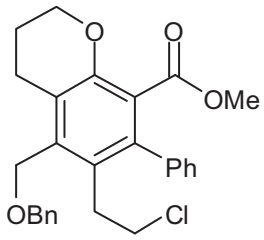
Following **general procedure 11** and starting with **50f** (0.254 g, 0.70 mmol), TBAI (0.594 g, 1.61 mmol) and NaH (0.034 g, 1.40 mmol) in DMFA (13 mL), **51f** was obtained as a colourless solid (0.115 g, 50 %); mp. 91-93 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.58 (d, ^{3}J = 6.7 Hz, 6H, $CH_2CH(CH_3)_2$), 1.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.23 (t, ^{3}J = 5.7 Hz, 2H, $C_{Ar}CH_2CH_2$), 3.65 (d, ^{3}J = 6.7 Hz, 2H, OCH_2CH), 3.78 (t, ^{3}J = 5.7 Hz, 2H, OCH_2CH_2), 4.75 (s, 2H, CH_2O), 6.67 (s, 1H, CH_{Ar}), 7.05-7.09 (m, 2H, CH_{Ar}), 7.28-7.38 (m, 3H, CH_{Ar}), 11.02 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.0 ($CH_2CH(CH_3)_2$), 27.0 ($C_{Ar}CH_2CH_2$, $CH_2CH(CH_3)_2$), 65.7, 68.1, 71.8 (CH_2O), 111.4 (C_{Ar}), 112.3 (CH_{Ar}), 123.8 (C_{Ar}), 126.7, 128.0, 128.3 (CH_{Ar}), 140.8, 142.0, 143.7 (C_{Ar}), 159.7 ($C_{Ar}OH$), 171.2 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2962 (w), 1654 (s), 1572 (m), 1348 (m), 1315 (s), 1296 (s), 1233 (s), 1226 (s), 1198 (s), 1173 (s), 1113 (m), 1067 (s), 992 (m), 973 (m), 946 (s), 920 (m), 874 (s), 809 (s), 750 (s), 698 (s). MS (EI, 70eV): *m/z* (%) = 326 (M^+, 25), 252 (100), 222 (8), 165 (25), 152 (6), 115 (2), 41 (4). HRMS (EI): calcd for $C_{20}H_{22}O_4$ (M^+) 326.15126, found 326.150885.

7-Hydroxy-5-phenyl-8-propyl-isochroman-6-carboxylic acid methyl ester (51g)



Following **general procedure 11** and starting with **50g** (0.182 g, 0.50 mmol), TBAI (0.424 g, 1.15 mmol) and NaH (0.024 g, 1.00 mmol) in DMFA (10 mL), **51g** was obtained as a colourless solid (0.092 g, 57 %); mp. 101-103 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.02 (t, ^{3}J = 7.4 Hz, 3H, CH_2CH_3), 1.58 (m, 2H, CH_2CH_3), 2.31 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 2.54 (m, 2H, $CH_2CH_2CH_3$), 3.35 (s, 3H, OCH_3), 3.75 (t, ^{3}J = 5.8 Hz, 2H, OCH_2CH_2), 4.83 (s, 2H, CH_2O), 7.04-7.08 (m, 2H, CH_{Ar}), 7.28-7.39 (m, 3H, CH_{Ar}), 10.96 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.6 (CH_2CH_3), 21.9, 26.9, 27.5 (CH_2), 51.6 (OCH_3), 65.2, 66.8 (CH_2O), 110.8, 123.2, 125.6 (C_{Ar}), 126.4, 127.8, 128.3 (CH_{Ar}), 139.5, 140.8, 141.1 (C_{Ar}), 157.2 ($C_{Ar}OH$), 171.8 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2953 (m), 1656 (s), 1435 (m), 1414 (m), 1339 (m), 1267 (s), 1246 (w), 1221 (m), 1208 (s), 1166 (m), 990 (m), 810 (s), 775 (m), 730 (s), 698 (s). MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 55), 294 (100), 265 (16), 237 (22), 223 (33), 195 (22), 165 (23), 152 (11), 115 (6), 89 (6). HRMS (EI): calcd for $C_{20}H_{22}O_4$ (M^+) 326.15126, found 326.150948.

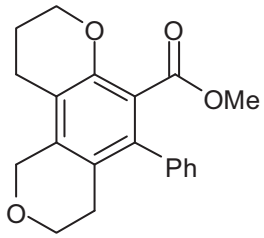
5-Benzyloxymethyl-6-(2-chloro-ethyl)-7-phenyl-chroman-8-carboxylic acid methyl ester (52b)



Following **general procedure 11** and starting with **49k** (0.550 g, 1.10 mmol) NaH (0.035 g, 1.43 mmol) in dry MeOH (5.0 ml), **52b** was obtained as a colourless oil (0.312 g, 63 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (m, 2H, C*H*$_2$CH$_2$O), 2.84-2.93 (m, 4H, $C_{Ar}CH_2$), 3.35 (m, 2H, CH_2Cl), 3.41 (s, 3H, OCH_3), 4.18 (m, 2H, CH_2CH_2O), 4.53 (s, 2H, CH_2O), 4.64 (s, 2H, CH_2O), 7.17-7.22 (m, 2H, CH_{Ar}), 7.31-7.39 (m, 8H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.9, 22.2, 33.1, 43.7 (CH_2), 51.8 (OCH_3), 65.8, 66.2, 73.4 (CH_2O), 124.5 (C_{Ar}), 127.6, 128.0, 128.2, 128.3, 128.5, 129.3 (CH_{Ar}), 137.6, 138.0, 139.0 (C_{Ar}), 150.4 ($C_{Ar}O$), 168.0 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2947 (w), 2872 (w), 1731 (s), 1566 (m), 1441 (m), 1352 (w), 1286 (s), 1172 (s), 1095 (s), 1074 (s), 1015 (m), 967 (m), 897 (w), 735 (m), 699 (s), 578 (m). MS (GC, 70 eV): *m/z* (%) = 450 (M^+, 5), 419 (11), 342 (45), 282 (100), 247 (20), 178 (19), 91 (68), 77 (7). HRMS (EI): calcd for $C_{27}H_{27}O_4Cl$ (M^+) 450.15924, found 450.159182.

9-Phenyl-2,3,4,5,7,8-hexahydro-1,6-dioxa-phenanthrene-10-carboxylic acid methyl ester (54b)



Following **general procedure 11** and starting with **53b** (0.108 g, 0.30 mmol), TBAI (0.255 g, 0.69 mmol) and NaH (0.015 g, 0.60 mmol) in DMFA (5 mL), **54b** was obtained as a colourless solid (0.078 g, 80 %); mp. 176-178 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (m, 2H, $CH_2CH_2CH_2$), 2.43 (t, ^3J = 5.7 Hz, 2H, $C_{Ar}CH_2CH_2O$), 2.53 (t, ^3J = 6.6 Hz, 2H, CH_2), 3.46 (s, 3H, OCH_3), 3.79 (t, ^3J = 5.7 Hz, 2H, OCH_2CH_2), 4.19 (m, 2H, CH_2O), 4.68 (s, 2H, CH_2O), 7.18-7.21 (m, 2H, CH_{Ar}), 7.30-7.39 (m, 3H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.6, 21.6, 27.0 (CH_2), 51.8 (OCH_3), 65.0, 66.2 (CH_2O), 117.4, 121.9, 123.2 (C_{Ar}), 127.3, 128.0, 129.2 (CH_{Ar}), 135.1, 137.8, 138.0 (C_{Ar}), 149.3 ($C_{Ar}OH$), 168.2 (COO). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3038 (w), 2927 (w), 1723 (s), 1567 (m), 1453 (m), 1431 (m), 1216 (m), 1194 (s), 1166 (m), 1130 (m), 1071 (s), 930 (m), 880 (m), 777 (s), 733 (m), 708 (s). MS (EI, 70eV): *m/z* (%) = 324 (M^+, 100), 293 (24), 262 (29), 234 (26), 209 (5), 178 (17), 89 (8). HRMS (EI): calcd for $C_{20}H_{20}O_4$ (M^+) 324.13561, found 324.135465.

7.2.11 Regioselective Synthesis of 6-Halomethyl-5,6-dihydro-4*H*-1,2-oxazines based on Cyclizations of Arylalkenyl-oximes

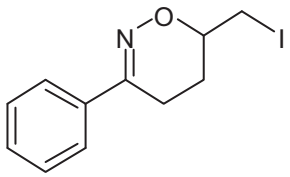
7.2.11.1 *Synthesis of arylalkenyl-oximes*

General procedure 12: To a THF solution (20 mL) of oxime **57** (2.0 mmol) was added *n*-butyllithium (5.0 mmol, 2.5 M) at −78 °C. After stirring for 1 h at −78 °C, the mixture was warmed to 20 °C and stirred for 10 min. Subsequently, allylbromide **58** (0.484 g, 4.0 mmol) was added at −78 °C. After warming of the mixture to 20 °C for 16 h, a saturated aqueous solution of NH_4Cl (30 mL) was added. The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 5:1)

7.2.11.2 *Synthesis of 6-iodomethyl-5,6-dihydro-4H-1,2-oxazines*

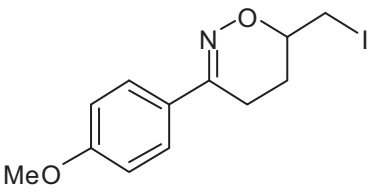
General procedure 13: To a CH_2Cl_2 solution (15 mL) of **59** (0.81 mmol) and of I_2 (0.406 g, 1.6 mmol) was added a saturated aqueous solution of $NaHCO_3$ (16 mL) and the solution was stirred for 12 h at 20 °C. The excess of iodine was removed by addition of a saturated aqueous solution of Na_2SO_3 (40 mL). The organic and the aqueous layer were separated and the latter was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane → *n*-heptane/EtOAc = 4:1)

6-Iodomethyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazine (60a)



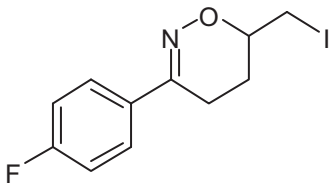
Following **general procedure 13** and starting with **59a** (0.141 g, 0.81 mmol), I_2 (0.412 g, 1.62 mmol), saturated aqueous solution of $NaHCO_3$ (8.1 mL) in CH_2Cl_2 (14 mL), **60a** was isolated as a brown solid (0.232 g, 95%); mp. 126-128 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (m, 1H, CHC*H*$_2$), 2.34 (m, 1H, CHC*H*$_2$), 2.68 (m, 2H, CC*H*$_2$), 3.27 (dd, ^2J = 10.3 Hz, ^3J = 7.3 Hz, 1H, CHC*H*$_2$I), 3.42 (dd, ^2J = 10.3 Hz, ^3J = 5.0 Hz, 1H, CHC*H*$_2$I), 3.85 (m, 1H, OC*H*CH$_2$), 7.38 (m, 3H, CH$_{Ar}$), 7.68 (m, 2H, CH$_{Ar}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 5.3 (CH$_2$I), 21.6, 24.2 (CH*C*H$_2$*C*H$_2$C), 74.1 (*C*HO), 125.4 (CH$_{Ar}$), 128.5 (CH$_{Ar}$), 129.7 (CH$_{Ar}$), 135.1 (C), 154.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3039 (br, w), 2959 (w), 2905 (br, w), 2853 (w), 1563 (w), 1490 (w), 1443 (w), 1404 (w), 1378 (w), 1330 (w), 1296 (w), 1260 (w), 1195 (m), 1161 (w), 1086 (m), 1012 (m), 997 (m), 982 (m), 799 (m), 750 (s), 685 (s), 603 (m). MS (EI, 70 eV): *m/z* (%) = 301 (M$^+$, 100), 207 (6), 174 (17), 156 (48), 144 (30), 128 (38), 118 (59), 104 (51), 77 (70). HRMS (EI): calcd for $C_{11}H_{12}INO$ (M$^+$): 300.99581, found 300.995322.

6-Iodomethyl-3-(4-methoxy-phenyl)-5,6-dihydro-4*H*-[1,2]oxazine (60d)



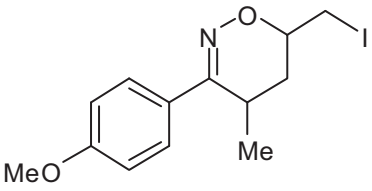
Following **general procedure 13** and starting with **59d** (0.478 g, 2.33 mmol), I_2 (1.184 g, 4.66 mmol), saturated aqueous solution of $NaHCO_3$ (23.3 mL) in CH_2Cl_2 (40.0 mL), **60d** was isolated as a red solid (0.517 g, 67%); mp. 140 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (m, 1H, CH$_2$), 2.31 (m, 1H, CHC*H*$_2$), 2.66 (m, 2H, CC*H*$_2$), 3.26 (dd, ^2J = 10.6 Hz, ^3J = 7.2 Hz, 1H, CHC*H*$_2$I), 3.41 (dd, ^2J = 10.6 Hz, ^3J = 5.0 Hz, 1H, CHC*H*$_2$I), 3.81 (s, 3H, OCH$_3$), 3.83 (m, 1H, OC*H*CH$_2$), 6.88 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 7.63 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 5.4 (CH$_2$I), 21.6 (CH$_2$), 24.3 (CH$_2$), 55.3 (OCH$_3$), 74.0 (*C*HO), 113.8, 126.8 (CH$_{Ar}$), 127.5, 154.5, 160.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 2905 (w), 2834 (w), 1611(s), 1514 (s), 1462 (w), 1334 (w), 1295 (m), 1258 (s), 1199 (m), 1175 (s), 1030 (m), 1016 (m), 920 (m), 823 (s). MS (EI, 70 eV): *m/z* (%) = 331 (M$^+$, 100), 187 (11), 172 (11), 133 (26), 90 (8), 77 (11). HRMS (EI): calculated for $C_{12}H_{14}INO_2$ (M$^+$): 331.00637, found 331.006054. Anal. calcd for $C_{12}H_{14}INO_2$ (331.15): C, 43.52; H, 4.26; N, 4.23. Found: C, 43.68; H, 4.30; N, 3.91.

3-(4-Fluoro-phenyl)-6-iodomethyl-5,6-dihydro-4*H*-[1,2]oxazine (60g)



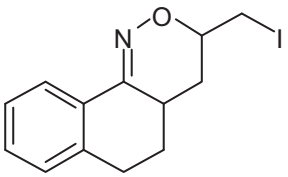
Following **general procedure 13** and starting with **59g** (0.290 g, 1.50 mmol), I_2 (0.762 g, 3.00 mmol), saturated aqueous solution of $NaHCO_3$ (15 mL) in CH_2Cl_2 (25 mL), **60g** was isolated as a brown solid (0.388 g, 81%); mp. 129-131 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86 (m, 1H, CHC*H*$_2$), 2.34 (m, 1H, CHC*H*$_2$), 2.65 (m, 2H, CC*H*$_2$), 3.27 (dd, ^2J = 10.4 Hz, ^3J = 7.2 Hz, 1H, CHC*H*$_2$I), 3.42 (dd, ^2J = 10.4 Hz, ^3J = 5.0 Hz, 1H, CHC*H*$_2$I), 3.84 (m, 1H, OC*H*CH$_2$), 7.05 (m, 2H, CH$_{Ar}$), 7.67 (m, 2H, CH$_{Ar}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.2 (CH_2I), 21.6, 24.1 (CH*C*H$_2$*C*H$_2$C), 74.1 (*C*HO), 115.5 (d, ^2J = 22.0 Hz, CH*C*HCF$_{Ar}$), 127.2 (d, ^3J = 8.5 Hz, *C*HCHCF$_{Ar}$), 131.3 (d, ^4J = 3.3 Hz, *C*CHCHCF$_{Ar}$), 153.8 (CN), 163.6 (d, ^1J = 249.7 Hz, *C*HCF$_{Ar}$). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053 (w), 2933 (br, w), 2904 (w), 1606 (m), 1508 (s), 1444 (w), 1405 (w), 1379 (w), 1331 (m), 1294 (w), 1232 (s), 1197 (s), 1099 (m), 1012 (m), 913 (s), 829 (s), 758 (w), 552 (s). MS (EI, 70 eV): *m/z* (%) = 319 (M$^+$, 100), 192 (16), 174 (37), 162 (16), 148 (14), 136 (47), 121 (40), 95 (19), 83 (18). HRMS (EI): calcd for $C_{11}H_{11}FINO$ (M$^+$): 318.98639, found 318.985435.

6-Iodomethyl-3-(4-methoxy-phenyl)-4-methyl-5,6-dihydro-4*H*-[1,2]oxazine (60k)



Following **general procedure 13** and starting with **59k** (0.657 g, 3.00 mmol), I_2 (1.524 g, 6.00 mmol), saturated aqueous solution of $NaHCO_3$ (30 mL) in CH_2Cl_2 (51 mL), **60k** was isolated as a colourless solid (0.445 g, 43%); mp. 100-102 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (d, ^3J = 7.3 Hz, 3H, CHC*H*$_3$), 1.86 (m, 1H, CHC*H*$_2$CH), 2.06 (m, 1H, CHC*H*$_2$CH), 3.03 (m, 1H, C*H*CH$_3$), 3.27 (dd, ^2J = 10.5 Hz, ^3J = 6.9 Hz, 1H, CHC*H*$_2$I), 3.44 (dd, ^2J = 10.5 Hz, ^3J = 5.1 Hz, 1H, CHC*H*$_2$I), 3.82 (s, 3H, OCH_3), 3.89 (m, 1H, OC*H*CH$_2$), 6.90 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$), 7.55 (d, ^3J = 9.0 Hz, 2H, CH$_{Ar}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.02 (CH_2I), 20.4 (CH*C*H$_3$), 25.7 (*C*HCH$_3$), 31.8 (CH*C*H$_2$CH), 55.3 (OCH_3), 70.9 (O*C*HCH$_2$), 113.9 (CH$_{Ar}$), 127.0 (C), 127.6 (CH$_{Ar}$), 158.6 (C), 160.6 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 2930 (w), 2881 (w), 2837 (w), 1606 (m), 1585 (w), 1511 (m), 1456 (m), 1411 (w), 1374 (w), 1346 (w), 1295 (m), 1244 (s), 1178 (m), 1110 (w), 1093 (w), 1074 (m), 1031 (m), 1007 (m), 899 (s), 860 (m), 831 (s), 814 (s), 749 (m), 725 (w), 639 (m), 628 (s), 608 (m). MS (EI, 70 eV): *m/z* (%) = 345 (M$^+$, 91), 256 (50), 239 (19), 201 (17), 186 (16), 133 (19), 111 (25), 102 (45), 83 (64), 69 (69), 57 (100). Anal. calcd for $C_{13}H_{16}INO_2$ (345.18): C, 45.23; H, 4.67; N, 4.06. Found: C, 45.38; H, 4.60; N, 3.86. HRMS (EI): calcd for $C_{13}H_{16}INO_2$ (M$^+$): 345.02202, found 345.022506.

3-Iodomethyl-4,4a,5,6-tetrahydro-3*H*-naphtho[1,2-*c*][1,2]oxazine (60p)



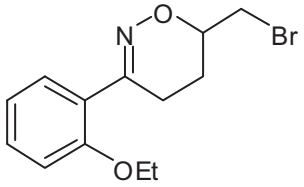
Following **general procedure 13** and starting with **59l** (0.221 g, 1.1 mmol), I_2 (0.559 g, 2.2 mmol), saturated aqueous solution of $NaHCO_3$ (11.0 mL) in CH_2Cl_2 (18.0 mL), **60p** was isolated as a colourless solid (0.345 g, 96%); mp. 105-107 ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37-1.65 (m, 2H, CH_2), 2.09 (m, 1H, CH_2), 2.33 (m, 1H, CH_2), 2.48 (m, 1H, CC*H*CH_2), 2.85 (m, 2H, CH_2), 3.20 (dd, ^2J = 10.6 Hz, ^3J = 7.0 Hz, 1H, CHC*H*$_2$I), 3.36 (dd, ^2J = 10.6 Hz, ^3J = 5.0 Hz, 1H, CHC*H*$_2$I), 3.88 (m, 1H, OCH), 7.14 (m, 3H, CH_{Ar}), 7.96 (d, ^3J = 7.8 Hz, 1H, CH_{Ar}). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 5.8 (CH_2I), 28.9 (CH_2), 29.0 (CH_2), 32.0 (*C*H_2), 33.0 (C*C*HCH_2), 73.6, 75.3 (O*C*H, diastereomers), 124.7 (CH_{Ar}), 126.5 (CH_{Ar}), 129.0 (CH_{Ar}), 129.6 (CH_{Ar}), 129.5 (C), 138.1 (C), 154.4 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3016 (br, w), 2924 (w), 2831 (w), 1728 (w), 1610 (w), 1479 (w), 1431 (w), 1372 (w), 1307 (w), 1291 (w), 1198 (s), 1151 (w), 1098 (w), 1079 (w), 1009 (s), 968 (m), 945 (m), 919 (s), 880 (s), 763 (s), 728 (s), 677 (m), 646 (m), 620 (w). MS (EI, 70 eV): *m/z* (%) = 327 (M^+, 100), 297 (4), 182 (13), 170 (15), 144 (16), 128 (50), 116 (23), 89 (11), 77 (13). HRMS (EI): calcd for $C_{13}H_{14}INO$ (M^+): 327.01146, found 327.010903.

7.2.11.3 *Synthesis of 6-bromomethyl-5,6-dihydro-4H-1,2-oxazines*

General procedure 14: To a CH_2Cl_2 solution (10 mL) of **59** (2.0 mmol) was added NBS (0.356 g, 2.0 mmol) portionwise over 15 min at 0 °C. The resultant solution stirred for 2 h at room temperature. The residue was purified by column chromatography (silica gel, *n*-heptane → *n*-heptane/EtOAc = 4:1)

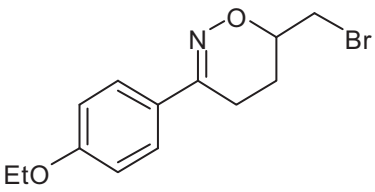
6-Bromomethyl-3-(2-ethoxy-phenyl)-5,6-dihydro-4*H*-[1,2]oxazine (60l)



Following **general procedure 14** and starting with **59e** (0.329 g, 1.50 mmol), NBS (0.267 g, 1.50 mmol) in CH_2Cl_2 (7.5 mL) **60l** was isolated as a brown viscous (0.256 g, 57%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (t, ^3J = 7.0 Hz, 3H, OCH_2CH_3), 1.89 (m, 1H, $CHCH_2CH_2$), 2.23 (m, 1H, $CHCH_2CH_2$), 2.69 (dd, ^2J = 8.2 Hz, ^3J = 5.7 Hz, 2H, CCH_2), 3.47 (dd, ^2J = 10.4 Hz, ^3J = 7.3 Hz, 1H, $CHCH_2Br$), 3.62 (dd, ^2J = 10.4 Hz, ^3J = 4.9 Hz, 1H, $CHCH_2Br$), 4.05 (q, ^3J = 7.0 Hz, 2H, OCH_2CH_3), 4.11 (m, 1H, $OCHCH_2$), 6.92 (m, 2H, CH_{Ar}), 7.32 (m, 2H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.8 (OCH_2CH_3), 22.7 (CH_2), 23.9 (CH_2), 32.5 (CH_2Br), 63.8 (OCH_2CH_3), 73.9 (*C*HO), 111.9 (CH_{Ar}), 120.6 (CH_{Ar}), 125.8 (C), 129.6 (CH_{Ar}), 130.4 (CH_{Ar}), 156.6, 158.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061 (br, w), 2976 (w), 2929 (w), 1600 (m), 1491 (m), 1475 (w), 1446 (s), 1391 (w), 1291 (m), 1236 (s), 1161 (w), 1122 (m), 1039 (s), 1023 (s), 924 (w), 897 (s), 800 (w), 750 (s), 682 (w). MS (EI, 70 eV): *m/z* (%) = 299 (M^+, ^{81}Br, 7), 297 (M^+, ^{79}Br, 7), 267 (4), 265 (4), 204 (34), 174 (24), 158 (60), 145 (100), 132 (21), 103 (9), 91 (35), 77 (18). HRMS (EI): calcd. for $C_{13}H_{16}O_2NBr$ (M^+): 297.03589, found 297.035775.

6-Bromomethyl-3-(4-ethoxy-phenyl)-5,6-dihydro-4*H*-[1,2]oxazine (60m)



Following **general procedure 14** and starting with **59f** (0.438 g, 2.00 mmol), NBS (0.356 g, 2.00 mmol) in CH_2Cl_2 (10.0 mL), **60m** was isolated as a colourless solid (0.519 g, 87%); mp. 130-135 ºC.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, ^3J = 7.0 Hz, 3H, OCH_2CH_3), 1.91 (m, 1H, $CHCH_2CH_2$), 2.28 (m, 1H, $CHCH_2CH_2$), 2.65 (m, 2H, CCH_2), 3.44 (dd, ^2J = 10.8 Hz, ^3J = 7.0 Hz, 1H, $CHCH_2Br$), 3.60 (dd, ^2J = 10.8 Hz, ^3J = 5.0 Hz, 1H, $CHCH_2Br$), 3.98 (m, 1H, $OCHCH_2$), 4.04 (q, ^3J = 7.0 Hz, 2H, OCH_2CH_3), 6.88 (d, ^3J = 9.0 Hz, 2H, CH_{Ar}), 7.61 (d, ^3J = 9.0 Hz, 2H, CH_{Ar}). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.7 ($OCHCH_3$), 21.2 (CH_2), 22.9

(CH_2), 32.4 (CH_2Br), 63.5 (OCH_2CH_3), 73.7 ($OCHCH_2$), 114.3 (CH_{Ar}), 126.7 (CH_{Ar}), 127.6, 154.5, 160.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2977 (w), 2909 (br, w), 1590 (m), 1511 (m), 1479 (m), 1449 (br, w), 1414 (w), 1392 (m), 1384 (m), 1356 (m), 1337 (m), 1292 (m), 1247 (s), 1225 (m), 1170 (m), 1116 (m), 1093 (w), 1043 (m), 1022 (m), 988 (m), 911 (m), 852 (m), 816 (s), 763 (m), 664 (m), 547 (s). MS (EI, 70 eV): *m/z* (%) = 299 (M^+, ^{81}Br, 98), 297 (M^+, ^{79}Br, 100) 268 (3), 204 (28), 176 (17), 148 (22), 147 (20), 134 (21), 119 (56), 91 (22), 77 (11), 65 (20). Anal. calcd for $C_{13}H_{16}BrNO_2$ (298.18): C, 52.36; H, 5.41; N, 4.70. Found: C, 52.01; H, 5.32; N, 4.52. HRMS (EI): calcd for $C_{13}H_{16}BrNO_2$ (M^+): 297.03589, found 297.035839.

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Appendix

Abbreviations

aq	aqueous
Ar	Aromatic
ATR	Attenuated total reflection
Bn	Benzyl
br.	broud
*n*BuLi	*n*-Butylithium
calcd	calculated
CI	Chemical ionization
COSY	Correlated spectroscopy
dd	doublet of doublets
DEPT	Distortionless enhancement by polarisation transfer
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dq	doublet of quartets
dt	doublet of triplets
E^+	Electrophile
EI	Electronic ionisation
equiv.	equivalent
ESI	Electrospray ionization
EtOAc	Ethylacetate
h	hour
Hal	Halogen
HMBC	Heteronuclear multiple bond correlation
HMTA	Hexamethylenetetramine
HRMS	High-resolution mass spectroscopy
Hz	Hertz
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
m	multiplet
Me_3SiOTf	Trimethylsilyl-trifluoromethanesulfonate

MHz	Megahertz
mp	melting point
MS	Mass spectroscopy
MS 4Å	Molecular siev 4 angstrem
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NEt_3	Triethylamine
NMDA	*N*-methyl *D*-aspartate
NMR	Nuclear magnetic resonance (spectroscopy)
NOESY	Nuclear overhauser effect spectroscopy
OTf	Triflat (Trifluoromethansulfonat)
pH	*pondus hydrogenii*
Ph	Phenyl
q	quartet
ref.	reference
R	organic moiety, rest
r.t.	room temperature
s	singlet
sat. aq. sol.	saturated aqueous solution
SET	Single electron transfer
t	triplet
TBAI	Tetrabutyl amonium iodie
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
UV	Ultraviolet spectroscopy
δ	chemical shift

Crystal Data and Structure Refinement

Identification code	**18h**	
Empirical formula	$C_{20}H_{24}N_2O_7$	
Formula weight	404.41	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.4794(5) Å	α = 102.5480(10)°.
	b = 12.6941(6) Å	β = 102.9830(10)°.
	c = 16.9496(9) Å	γ = 90.4220(10)°.
Volume	1936.59(17) $Å^3$	
Z	4	
Density (calculated)	1.387 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	856	
Crystal size	0.34 x 0.30 x 0.25 mm^3	
Θ range for data collection	2.21 to 30.00°.	
Index ranges	$-13\leq h\leq 12$, $-17\leq k\leq 14$, $-23\leq l\leq 23$	
Reflections collected	23764	
Independent reflections	11025 [R(int) = 0.0322]	
Completeness to Θ = 30.00°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9741 and 0.9650	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11025 / 0 / 536	
Goodness-of-fit on F^2	1.027	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0494, wR2 = 0.1163	
R indices (all data)	R1 = 0.0806, wR2 = 0.1334	
Extinction coefficient	0.0010(8)	
Largest diff. peak and hole	0.365 and -0.244 $e.Å^{-3}$	

Identification code	**18j**	
Empirical formula	$C_{21}H_{26}N_2O_7$	
Formula weight	418.44	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.44490(10) Å	α = 95.0010(10)°.
	b = 9.4430(2) Å	β = 100.0610(10)°.
	c = 13.2714(2) Å	γ = 99.2380(10)°.
Volume	1021.29(3) $Å^3$	
Z	2	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	444	
Crystal size	0.41 x 0.31 x 0.26 mm^3	
Θ range for data collection	2.49 to 30.00°.	
Index ranges	-11≤h≤11, -13≤k≤13, -18≤l≤18	
Reflections collected	16045	
Independent reflections	5871 [R(int) = 0.0227]	
Completeness to Θ = 30.00°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9738 and 0.9591	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5871 / 0 / 330	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ(I)]	R1 = 0.0537, wR2 = 0.1450	
R indices (all data)	R1 = 0.0680, wR2 = 0.1615	
Largest diff. peak and hole	0.495 and -0.375 $e.Å^{-3}$	

Identification code	**18n**	
Empirical formula	$C_{19}H_{22}N_2O_7$	
Formula weight	390.39	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.1758(16) Å	α = 103.88(3)°.
	b = 8.9304(18) Å	β = 96.73(3)°.
	c = 13.714(3) Å	γ = 105.83(3)°.
Volume	917.1(3) $Å^3$	
Z	2	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	412	
Crystal size	0.36 x 0.23 x 0.16 mm^3	
Θ range for data collection	2.47 to 27.50°.	
Index ranges	-10≤h≤10, -11≤k≤11, -17≤l≤17	
Reflections collected	20522	
Independent reflections	4169 [R(int) = 0.0188]	
Completeness to Θ = 30.00°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9828 and 0.9619	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3601 / 0 / 280	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2σ(I)]	R1 = 0.0463, wR2 = 0.1068	
R indices (all data)	R1 = 0.0542, wR2 = 0.1098	
Largest diff. peak and hole	0.428 and -0.357 $e.Å^{-3}$	

Identification code	**18p**	
Empirical formula	$C_{20}H_{22}N_2O_7$	
Formula weight	402.40	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.2926(2) Å	α = 91.2360(10)°.
	b = 8.4322(2) Å	β = 98.8450(10)°.
	c = 13.9059(3) Å	γ = 95.8850(10)°.
Volume	955.05(4) $Å^3$	
Z	2	
Density (calculated)	1.399 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	424	
Crystal size	0.6 x 0.54 x 0.18 mm^3	
Θ range for data collection	2.43 to 30.00°.	
Index ranges	-11≤h≤11, -11≤k≤11, -19≤l≤19	
Reflections collected	29775	
Independent reflections	5469 [R(int) = 0.0219]	
Completeness to Θ = 30.00°	98.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5469 / 0 / 301	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2σ(I)]	R1 = 0.0510, wR2 = 0.1447	
R indices (all data)	R1 = 0.0567, wR2 = 0.1528	
Extinction coefficient	0.000(4)	
Largest diff. peak and hole	1.064 and -0.230 $e.Å^{-3}$	

Identification code	**19e**	
Empirical formula	$C_{32}H_{32}N_2O_7$	
Formula weight	556.60	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 9.048(5) Å	α = 90.00°.
	b = 14.250(8) Å	β = 100.57(2)°.
	c = 21.378(13) Å	γ = 90.00°.
Volume	2710(3) $Å^3$	
Z	4	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	1176	
Crystal size	0.52 x 0.22 x 0.16 mm^3	
Θ range for data collection	4.64 to 27.50°.	
Index ranges	$-11 \le h \le 11$, $-18 \le k \le 18$, $-26 \le l \le 27$	
Reflections collected	24675	
Independent reflections	6179 [R(int) = 0.0369]	
Completeness to Θ = 30.00°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9847 and 0.9515	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4632 / 0 / 376	
Goodness-of-fit on F^2	1.060	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0412, wR2 = 0.1060	
R indices (all data)	R1 = 0.0627, wR2 = 0.1143	
Largest diff. peak and hole	0.280 and -0.281 $e.Å^{-3}$	

Identification code	**22f**	
Empirical formula	$C_{15}H_{18}N_2O_4$	
Formula weight	290.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 14.154(3) Å	α = 90.00°.
	b = 9.4094(19) Å	β = 114.41(3) °.
	c = 12.276(3) Å	γ = 90.00°.
Volume	1488.8(5) $Å^3$	
Z	4	
Density (calculated)	1.295 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	616	
Crystal size	0.35 x 0.22 x 0.06 mm^3	
Θ range for data collection	2.68 to 22.50°.	
Index ranges	-15≤h≤15, -10≤k≤10, -13≤l≤13	
Reflections collected	8534	
Independent reflections	1932 [R(int) = 0.0493]	
Completeness to Θ = 30.00°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9943 and 0.9676	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1295 / 0 / 205	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2σ(I)]	R1 = 0.0474, wR2 = 0.1107	
R indices (all data)	R1 = 0.0826, wR2 = 0.1237	
Largest diff. peak and hole	0.244 and -0.194 $e.Å^{-3}$	

Identification code	**23b**	
Empirical formula	$C_{17}H_{22}N_2O_2$	
Formula weight	286.37	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 10.072(2) Å	α = 65.83(3)°.
	b = 12.346(3) Å	β = 89.83(3) °.
	c = 13.799(3) Å	γ = 80.26(3)°.
Volume	1538.8(5) $Å^3$	
Z	4	
Density (calculated)	1.236 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	616	
Crystal size	0.64 x 0.16 x 0.10 mm^3	
Θ range for data collection	1.62 to 27.50°.	
Index ranges	-11≤h≤13, -16≤k≤16, -17≤l≤17	
Reflections collected	34725	
Independent reflections	7030 [R(int) = 0.0235]	
Completeness to Θ = 30.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9919 and 0.9497	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5590 / 0 / 412	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2σ(I)]	R1 = 0.0377, wR2 = 0.0966	
R indices (all data)	R1 = 0.0513, wR2 = 0.1034	
Largest diff. peak and hole	0.036 and -0.206 $e.Å^{-3}$	

Identification code	**28u**	
Empirical formula	$C_{23}H_{37}N_3O_6$	
Formula weight	451.56	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 10.389(2) Å	α = 90°.
	b = 8.5810(17) Å	β = 102.32(3)°.
	c = 28.412(8) Å	γ = 90°.
Volume	2474.5(10) $Å^3$	
Z	4	
Density (calculated)	1.212 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	976	
Crystal size	0.52 x 0.16 x 0.15 mm^3	
Θ range for data collection	2.22 to 25.93°.	
Index ranges	$-12 \le h \le 12$, $-10 \le k \le 10$, $-34 \le l \le 34$	
Reflections collected	42126	
Independent reflections	4799 [R(int) = 0.0383]	
Completeness to Θ = 30.00°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9870 and 0.9559	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3356 / 0 / 306	
Goodness-of-fit on F^2	1.040	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0467, wR2 = 0.1113	
R indices (all data)	R1 = 0.0753, wR2 = 0.1273	
Largest diff. peak and hole	0.294 and -0.178 $e.Å^{-3}$	

Identification code	**36e**	
Empirical formula	$C_{13}H_{16}ICl_2O_4$	
Formula weight	307.16	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 5.131(7) Å	α = 90°.
	b = 27.43(4) Å	β = 102.49(5)°.
	c = 10.191(13) Å	γ = 90°.
Volume	1400(3) $Å^3$	
Z	4	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	0.470 mm^{-1}	
F(000)	640	
Crystal size	0.70 x 0.27 x 0.14 mm^3	
Θ range for data collection	3.61 to 32.50°.	
Index ranges	$-7\leq h\leq 7$, $-41\leq k\leq 29$, $-15\leq l\leq 15$	
Reflections collected	19107	
Independent reflections	5007 [R(int) = 0.0198]	
Completeness to Θ = 30.00°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9371 and 0.7344	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4081 / 0 / 178	
Goodness-of-fit on F^2	1.049	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0388, wR2 = 0.1031	
R indices (all data)	R1 = 0.0510, wR2 = 0.1085	
Largest diff. peak and hole	0.511 and -0.419 $e.Å^{-3}$	

Identification code	**36f**	
Empirical formula	$C_{14}H_{18}Cl_2O_4$	
Formula weight	321.18	
Temperature	95(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.7761(5) Å	α = 111.807(4)°.
	b = 10.3822(11) Å	β = 108.868(3)°.
	c = 10.7838(7) Å	γ = 96.276(4)°.
Volume	738.33(10) $Å^3$	
Z	2	
Density (calculated)	1.445 Mg/m^3	
Absorption coefficient	0.449 mm^{-1}	
F(000)	336	
Crystal size	0.37 x 0.28 x 0.17 mm^3	
Θ range for data collection	2.21 to 30.00°.	
Index ranges	$-10 \le h \le 10$, $-14 \le k \le 14$, $-15 \le l \le 15$	
Reflections collected	20825	
Independent reflections	4255 [R(int) = 0.0254]	
Completeness to Θ = 30.00°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9275 and 0.8514	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4255 / 0 / 188	
Goodness-of-fit on F^2	1.055	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0291, wR2 = 0.0780	
R indices (all data)	R1 = 0.0336, wR2 = 0.0810	
Largest diff. peak and hole	0.428 and -0.339 $e.Å^{-3}$	

Identification code	**37a**	
Empirical formula	$C_{10}H_{10}O_4$	
Formula weight	194.18	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.1290(16) Å	α = 89.97(3) °.
	b = 8.2100(16) Å	β = 89.55(3) °.
	c = 14.135(3) Å	γ = 80.83(3) °.
Volume	931.3(3) $Å^3$	
Z	4	
Density (calculated)	1.385 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	408	
Crystal size	0.44 x 0.33 x 0.08 mm^3	
Θ range for data collection	1.44 to 27.50°.	
Index ranges	-9≤h≤10, -10≤k≤10, -18≤l≤14	
Reflections collected	10719	
Independent reflections	3967 [R(int) = 0.0302]	
Completeness to Θ = 30.00°	92.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9914 and 0.9541	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3152 / 0 / 263	
Goodness-of-fit on F^2	1.079	
Final R indices [I>2σ(I)]	R1 = 0.0546, wR2 = 0.1313	
R indices (all data)	R1 = 0.0708, wR2 = 0.1367	
Largest diff. peak and hole	0.327 and -0.319 $e.Å^{-3}$	

Identification code	**38b**	
Empirical formula	$C_{13}H_{16}O_5$	
Formula weight	252.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 11.77(3) Å	α = 90°.
	b = 4.873(14) Å	β = 98.91(5)°.
	c = 21.56(5) Å	γ = 90°.
Volume	1221(6) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	536	
Crystal size	0.91 x 0.14 x 0.02 mm^3	
Θ range for data collection	4.29 to 23.29 °.	
Index ranges	-8≤h≤12, -5≤k≤5, -23≤l≤22	
Reflections collected	5836	
Independent reflections	1709 [R(int) = 0.0431]	
Completeness to Θ = 30.00°	96.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9979 and 0.9101	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1177 / 0 / 170	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2σ(I)]	R1 = 0.0445, wR2 = 0.1010	
R indices (all data)	R1 = 0.0781, wR2 = 0.1103	
Largest diff. peak and hole	0.161 and -0.189 $e.Å^{-3}$	

Identification code	**41g**	
Empirical formula	$C_{11}H_{12}ICl_2O_5$	
Formula weight	295.11	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 9.023(9) Å	α = 90°.
	b = 8.491(7) Å	β = 95.63(2)°.
	c = 17.120(16) Å	γ = 90°.
Volume	1305(2) $Å^3$	
Z	4	
Density (calculated)	1.502 Mg/m^3	
Absorption coefficient	0.506 mm^{-1}	
F(000)	608	
Crystal size	0.62 x 0.32 x 0.29 mm^3	
Θ range for data collection	4.21 to 32.49°	
Index ranges	$-13 \le h \le 13$, $-12 \le k \le 12$, $-24 \le l \le 25$	
Reflections collected	17387	
Independent reflections	4691 [R(int) = 0.0215]	
Completeness to Θ = 30.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8671 and 0.7442	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4059 / 0 / 164	
Goodness-of-fit on F^2	1.081	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0330, wR2 = 0.0933	
R indices (all data)	R1 = 0.0394, wR2 = 0.0967	
Largest diff. peak and hole	0.464 and -0.451e.$Å^{-3}$	

Identification code	**41i**	
Empirical formula	$C_{11}H_{12}Cl_2O_4$	
Formula weight	279.11	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	C 2/c	
Space group (Hall)	-C 2yc	
Unit cell dimensions	a = 26.032(15) Å	α = 90°.
	b = 5.776(3) Å	β = 91.081(17) °.
	c = 16.876(9) Å	γ = 90°.
Volume	2537(2) $Å^3$	
Z	8	
Density (calculated)	1.462 Mg/m^3	
Absorption coefficient	0.511 mm^{-1}	
F(000)	1152	
Crystal size	0.31 x 0.20 x 0.09 mm^3	
Θ range for data collection	3.61 to 27.49 °.	
Index ranges	-33≤h≤33, -7≤k≤7, -21≤l≤21	
Reflections collected	11227	
Independent reflections	2883 [R(int) = 0.0282]	
Completeness to Θ = 30.00°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9555 and 0.8577	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2358 / 0 / 156	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2σ(I)]	R1 = 0.0359, wR2 = 0.0885	
R indices (all data)	R1 = 0.0472, wR2 = 0.0932	
Largest diff. peak and hole	0.434 and -0.247 $e.Å^{-3}$	

Identification code	**49c**	
Empirical formula	$C_{22}H_{27}ClO_4$	
Formula weight	390.89	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.0941(2) Å	α = 90.6100(10)°.
	b = 9.5955(2) Å	β = 97.1940(10)°.
	c = 12.3264(3) Å	γ = 96.300(2)°.
Volume	1060.39(4) $Å^3$	
Z	2	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.203 mm^{-1}	
F(000)	416	
Crystal size	0.55 x 0.28 x 0.26 mm^3	
Θ range for data collection	2.27 to 28.74°.	
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 12$, $-15 \le l \le 16$	
Reflections collected	19638	
Independent reflections	5297 [R(int) = 0.0200]	
Completeness to Θ = 28.74°	96.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9490 and 0.8964	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5297 / 0 / 262	
Goodness-of-fit on F^2	1.025	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0491, wR2 = 0.1300	
R indices (all data)	R1 = 0.0852, wR2 = 0.1530	
Largest diff. peak and hole	0.309 and -0.219 $e.Å^{-3}$	

Identification code	**49h**	
Empirical formula	$C_{27}\ H_{29}\ Cl\ O_4$	
Formula weight	452.95	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.3480(3) Å	α = 72.620(2)°.
	b = 11.2222(5) Å	β = 87.168(2)°.
	c = 13.2754(6) Å	γ = 84.864(2)°.
Volume	1181.80(9) $Å^3$	
Z	2	
Density (calculated)	1.273 Mg/m^3	
Absorption coefficient	0.192 mm^{-1}	
F(000)	480	
Crystal size	0.54 x 0.39 x 0.21 mm^3	
Θ range for data collection	2.84 to 32.50°.	
Index ranges	-12≤h≤12, -16≤k≤16, -20≤l≤20	
Reflections collected	35799	
Independent reflections	8386 [R(int) = 0.0225]	
Completeness to Θ = 32.50°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9607 and 0.9033	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8386 / 0 / 295	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2σ(I)]	R1 = 0.0339, wR2 = 0.0920	
R indices (all data)	R1 = 0.0405, wR2 = 0.0984	
Largest diff. peak and hole	0.513 and -0.207 $e.Å^{-3}$	

Identification code	**51c**	
Empirical formula	$C_{15}H_{20}O_4$	
Formula weight	264.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 8.379(8) Å	α = 90.00°.
	b = 13.745(8) Å	β = 97.538(19)°.
	c = 23.991(14) Å	γ = 90.00°.
Volume	2739(3) $Å^3$	
Z	8	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	1136	
Crystal size	1.18 x 0.44 x 0.07 mm^3	
Θ range for data collection	3.17 to 27.50 °.	
Index ranges	-10≤h≤10, -17≤k≤17, -31≤l≤31	
Reflections collected	24632	
Independent reflections	6249 [R(int) = 0.0330]	
Completeness to Θ = 30.00°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9936 and 0.8992	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4324 / 0 / 357	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2σ(I)]	R1 = 0.0456, wR2 = 0.1233	
R indices (all data)	R1 = 0.0737, wR2 = 0.1386	
Largest diff. peak and hole	0.226 and -0.344 $e.Å^{-3}$	

Identification code	**51d**	
Empirical formula	$C_{15}H_{20}O_4$	
Formula weight	264.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.312(10) Å	α = 94.35(6)°.
	b = 9.323(12) Å	β = 105.31(5)°.
	c = 10.196(13) Å	γ = 116.13(4)°.
Volume	667.1(15) $Å^3$	
Z	2	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	284	
Crystal size	0.77 x 0.18 x 0.11 mm^3	
Θ range for data collection	4.41 to 29.97°.	
Index ranges	-11≤h≤11, -13≤k≤12, -14≤l≤14	
Reflections collected	13637	
Independent reflections	3802 [R(int) = 0.0281]	
Completeness to Θ = 30.00°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9897 and 0.9308	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3209 / 0 / 179	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2σ(I)]	R1 = 0.0452, wR2 = 0.1314	
R indices (all data)	R1 = 0.0530, wR2 = 0.1391	
Largest diff. peak and hole	0.474 and -0.260 $e.Å^{-3}$	

Identification code	**51g**	
Empirical formula	$C_{20}H_{22}O_4$	
Formula weight	326.38	
Temperature	95(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.7822(4) Å	α = 75.911(2)°.
	b = 10.8752(6) Å	β = 86.172(2)°.
	c = 11.0605(6) Å	γ = 70.557(2)°.
Volume	856.04(8) $Å^3$	
Z	2	
Density (calculated)	1.266 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	348	
Crystal size	0.76 x 0.71 x 0.49 mm^3	
Θ range for data collection	2.04 to 30.00°.	
Index ranges	-10≤h≤10, -15≤k≤15, -15≤l≤15	
Reflections collected	24389	
Independent reflections	4936 [R(int) = 0.0317]	
Completeness to Θ = 30.00°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9585 and 0.9366	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4936 / 0 / 223	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2σ(I)]	R1 = 0.0441, wR2 = 0.1283	
R indices (all data)	R1 = 0.0494, wR2 = 0.1362	
Largest diff. peak and hole	0.460 and -0.233 $e.Å^{-3}$	

Identification code	**53b**	
Empirical formula	$C_{20}H_{21}ClO_4$	
Formula weight	360.82	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 18.021(10) Å	α = 90.00°.
	b = 10.002(5) Å	β = 93.308(10)°.
	c = 9.962(5) Å	γ = 90.00°.
Volume	1792.7(17) $Å^3$	
Z	4	
Density (calculated)	1.337 Mg/m^3	
Absorption coefficient	0.235 mm^{-1}	
F(000)	760	
Crystal size	0.48 x 0.41 x 0.22 mm^3	
Θ range for data collection	4.55 to 29.00°.	
Index ranges	-24≤h≤24, -13≤k≤13, -13≤l≤13	
Reflections collected	17347	
Independent reflections	4740 [R(int) = 0.0250]	
Completeness to Θ = 30.00°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9502 and 0.8957	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3698 / 0 / 241	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2σ(I)]	R1 = 0.0417, wR2 = 0.1162	
R indices (all data)	R1 = 0.0576, wR2 = 0.1252	
Largest diff. peak and hole	0.345 and -0.358 $e.Å^{-3}$	

Identification code	**54b**	
Empirical formula	$C_{20}\ H_{20}\ O_4$	
Formula weight	324.36	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1$	
Space group (Hall)	P 2yb	
Unit cell dimensions	a = 9.8489(7) Å	α = 90°.
	b = 7.9016(5) Å	β = 104.920(4)°.
	c = 10.7975(8) Å	γ = 90°.
Volume	811.95(10) $Å^3$	
Z	2	
Density (calculated)	1.327 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	344	
Crystal size	0.35 x 0.17 x 0.10 mm^3	
Θ range for data collection	2.14 to 29.19°.	
Index ranges	$-13\leq h\leq 13$, $-10\leq k\leq 10$, $-14\leq l\leq 14$	
Reflections collected	17806	
Independent reflections	2346 [R(int) = 0.0627]	
Completeness to Θ= 29.19°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9909 and 0.9686	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2346 / 1 / 218	
Goodness-of-fit on F^2	0.988	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0346, wR2 = 0.0805	
R indices (all data)	R1 = 0.0429, wR2 = 0.0837	
Absolute structure parameter	0(10)	
Largest diff. peak and hole	0.266 and -0.227 $e.Å^{-3}$	

Identification code	**60d**	
Empirical formula	$C_{12}H_{14}INO_2$	
Formula weight	331.14	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 27.4396(18) Å	α = 90°.
	b = 5.0875(3) Å	β = 97.1570(10)°.
	c = 8.6162(5) Å	γ = 90°.
Volume	1193.44(13) $Å^3$	
Z	4	
Density (calculated)	1.843 Mg/m^3	
Absorption coefficient	2.668 mm^{-1}	
F(000)	648	
Crystal size	0.51 x 0.34 x 0.06 mm^3	
Θ range for data collection	2.99 to 30.00°.	
Index ranges	-34≤h≤38, -7≤k≤7, -12≤l≤11	
Reflections collected	14972	
Independent reflections	3462 [R(int) = 0.0181]	
Completeness to Θ = 30.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8563 and 0.3431	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3462 / 0 / 146	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2σ(I)]	R1 = 0.0176, wR2 = 0.0452	
R indices (all data)	R1 = 0.0208, wR2 = 0.0477	
Largest diff. peak and hole	0.618 and -0.304 $e.Å^{-3}$	

Abstract

Regioselective cyclization reactions of 1,3-bis(silyloxy)-1,3-butadienes provide an elegant approach for the synthesis of various complex carba- and heterocycles from simple starting materials. Thus, various bridged and non-bridged *N*-heterocycles are prepared based on cyclization of 1,3-bis(silyl enol ethers) with quinazolines and 1,2-diaza-1,3-butadienes. The Lewis acid catalyzed cyclization of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles afforded a variety of functionalized pyran-4-ones and salicylates. Some of the products are transformed into novel formylsalicylates. Functionalized phenols are prepared by chelation-controlled cyclization reaction of 1,3-bis(silyl enol ethers). Follow-up reactions of the products resulted in the formation of chromans and isochromans. In addition, 6-halomethyl-5,6-dihydro-4*H*-1,2-oxazines are synthesized based on regioselective cyclization of arylalkenyl-oximes.

Regioselektive Cyclisierungen von 1,3-Bis(silyloxy)-1,3-butadienen ermöglichen einen eleganten Zugang zur Synthese einer Vielzahl komplexer Carba- und Heterocyclen ausgehend von einfachen Ausgangsmaterialien. Daher wurden diverse verbrückte und nicht-verbrückte *N*-Heterocyclen basierend auf der Cyclisierung von 1,3-Bis(silylenolethern) mit Chinazolinen und 1,2-Diaza-1,3-butadienen dargestellt. Die Lewissäure katalysierte Cyclisierung von 1,3-Bis(silylenolethern) mit 1,3-Dielektrophilen ergibt eine Reihe funktionalisierte Pyran-4-one und Salicylsäuren. Einige Produkte wurden in neuartige Formylsalicylate überführt. Funktionalisierte Phenole wurden durch eine chelat-kontrollierte Cyclisierung von 1,3-Bis(silylenolethern) dargestellt. Folgereaktionen der Produkte ergaben Chromane und *iso*-Chromane. Darüber hinaus wurden 6-Halomethyl-5,6-dihydro-4*H*-1,2-oxazine basierend auf der regioselektiven Cyclisierung von Arylalkenyloximen synthetisiert.

Erklärung

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

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Curriculum Vitae

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07.2005-08.2006	**Post graduate** in Pharmaceutical Chemistry, Yerevan State University, Armenia *Reasearch topic:* "Preparation of strains with *L*-aminoacylase activity and further investigation of the immobilized enzyme as a biocatalyst in different biochemical reactions"
06.2000-06.2005	**MSc.** in Pharmaceutical Chemistry, Yerevan State University, Armenia
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06.2005	M.S. Diploma with Honour, Yerevan State University, Armenia
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PUBLICATIONS:

1. Jennifer Hefner, **Vahuni Karapetyan**, Satenik Mkrtchyan, Alexander Villinger, Helmut Reinke, Christine Fischer, Peter Langer* 'Chelation Control in the [3+3] Annulation Reaction of Alkoxy-Substituted 1,1-Diacylcyclopropanes with 1,3-Bis(trimethylsilyloxy)-1,3-butadienes' *Manuscript in preparation*.

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7. **Vahuni Karapetyan**, Satenik Mkrtchyan, Tung T. Dang, Alexander Villinger, HelmutReinke, Peter Langer* 'Regioselective synthesis of 6-halomethyl-5,6-dihydro-4H-1,2-oxazines based on cyclizations of arylalkenyl-oximes' *Tetrahedron* **2008**, *64*. 8010-8015.

8. Muhammad A. Rashid, Nasir Rasool, Bettina Appel, Muhammad Adeel, **Vahuni Karapetyan,** Satenik Mkrtchyan, Helmut Reinke, Christine Fischer, Peter Langer* 'Synthesis of 1-azaxanthones by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-(cyano)benzopyrylium triflates and subsequent domino 'retro-Michael/nitrile-addition/heterocyclization' reaction' *Tetrahedron* **2008**, *64*, 5416-5425

9. Andreas Schmidt, **Vahuni Karapetyan**, Orazio A. Attanasi, Gianfranco Favi, Helmar Görls, Fabio Mantellini, Peter Langer* 'Regioselective Synthesis of New 1-Aminopyrroles and 1-Amino-4,5,6,7-tetrahydroindoles by One-Pot ′Conjugate Addition/Cyclization′ Reactions of 1,3-Bis(silyl enol ethers) with 1,2-Diaza-1,3-butadienes' *Synlett* **2007**, *19*, 2965-2968.