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I INTRODUCTION AND GOAL

The role of organic synthesis in the development of new physiologically active compounds is of paramount importance either by de novo synthesis of active compounds or by derivatization of lead compounds found in nature. Nature is an inexhaustible source of physiologically active molecules, which sometimes display weak activities in biotesting or in contrast, are too cytotoxic. Among others, it is the task of synthetic organic chemists to fine-tune this activity by changing molecular structures of these lead compounds. In that respect, 23% of the small molecules introduced as drugs worldwide, and in particular 78% of the antibiotics, are chemically designed on the basis of knowledge gained from a natural product.1 Today’s problems of resistance of micro-organisms due to antibiotic overuse, justify the unabated search for new active compounds more than ever.2 In the same context, the development of new agrochemicals (herbicides, insecticides, etc.) is of importance to assure future crop protection and prevent economical losses due to pests in general.

It is the main objective of this work to evaluate halogenated cyclobutanones as precursors for physiologically active compounds, especially small carbocyclic and five-membered heterocyclic compounds. Heterocycles are sometimes compared with jewellery rings studded with precious stones.3 Several carbon atoms make up the setting of the molecular ring, while the role of the jewel is played by a heteroatom which is responsible for its distinctive physiological properties. Heterocycles as a group still dominate modern organic chemistry and have established their market position in agrochemical and pharmaceutical industry.

![Heterocyclic compounds](image)

1a Pyrrolnitrin (R¹ = R³ = Cl, R² = NO₂)
1b Fenpiclonil (R¹ = CN, R² = R³ = Cl)
1c Fludioxonil (R¹ = CN, R², R³ = OCF₂O)

2 Rolipram (both R and S)
3 Captopril

As an example, pyrrolnitrin 1a, a metabolite from Pseudomonas pyrrocinia,4 has served as a lead compound for the development of the antifungals fenpiclonil (Beret®) 1b and fludioxonil (Celeste®, Maxim®, Saphire®) 1c, both used in agriculture.5,6 Rolipram 2 is a
well-known inhibitor of phosphodiesterase type IV, an anti-inflammatory agent and antidepressant.\(^7\) Captopril 3, an angiotensin converting enzyme inhibitor, is used as an antihypertensive agent and as adjunct in the therapy of heart failure.\(^8\)

The most famous examples of carbocyclic small ring compounds that are used today are the insecticidal pyrethroids. Pyrethrum, the common name for the dried flowers of *Chrysanthemum cinerariaefolium* (Benth. & Hook) (synonyms: *Chrysanthemum cinerariifolium* (Trevir. Sch. Bip.); *Tanacetum cinerariifolium* (Trevir. Sch. Bip.)), was used many centuries ago as an insecticide in Eastern Europe (“Dalmatian insect powder”) and in the Caucasian regions (“Persian dust”).\(^9\) Thanks to the chemical analysis of pyrethrum and the derivatization of (+)-trans-chrysanthemic acid 4, one of the active constituents, the application of pyrethroids as insecticides turned out to be a success story. The annual world production of dried flower-heads is about 25,000 tonnes and the insecticidal synthetic derivatives, which possess better physical and biological properties, are widely used predominantly as indoor applications, e.g. deltamethrin 5.\(^10\)

\[
\begin{align*}
\text{4 Chrysanthemic acid} \\
\text{5 Deltamethrin}
\end{align*}
\]

Cyclobutanones, which emerged from academic interest, play an important role as key intermediates in numerous synthetic pathways. These four-membered carbocyclic ring ketones 6 are currently used in the synthesis of tropolones, e.g. 7,\(^11\) compounds with renewed interest as insecticides\(^12\) and cancer cell proliferation inhibitors.\(^13\) Cyclobutanones are also used in the synthesis of the insecticidal pyrethroids, e.g. 5,\(^14\) the herbicide heptenophos 8\(^15\) and various natural products.\(^16\) The inherent ring strain and electrophilicity of cyclobutanones are interesting features that invite for further organic synthesis.
In a first part of this work, 3-aryl-2,2-dichlorocyclobutanones 12 will be evaluated as starting material for the synthesis of various azaheterocyclic compounds. Earlier work performed at the Department of Organic Chemistry (Faculty of Agricultural and Applied Biological Sciences, Ghent University) resulted already in the synthesis of such compounds via a cyclobutanone ring opening - ring closing methodology (12 → 13 → 14). This work will be optimized and extended to develop a general pathway towards 3-pyrrolin-2-ones 14 and pyrroles 15 with a variety of substituents.

3-Arylpyrrolinones are a class of compounds of particular importance as physiologically active compounds and as synthons for further transformation into various azaheterocycles. 3,4-Diarylpyrrolinones 9 were patented a few years ago and show anti-inflammatory (R = alkyl) and cyclooxygenase-2 inhibitor (R = aryl) activities. N-Unsubstituted pyrrolinones 10 are blood pressure reducing agents, while 4-[4-(1H-imidazol-1-yl)phenyl]pyrrolinones 11 possess selective positive inotropic properties.
Attempts will be made to develop a new, general method for pyrrole synthesis by reduction of the corresponding pyrrolinones 14. Various 3-arylpyrroles show interesting biological properties. From a pharmacological point of view, the drug AWD 140-190 19 proved to reveal a potent anticonvulsant activity, indicating that this substance has a potential for an antiepileptic therapy.21 The natural alkaloid rhazinilam 20 is interesting because of its ability to mimic the cellular effects of the anticancer drug paclitaxel.22 Atorvastatin 21 is used for its lipid lowering effect and for treating vascular disorders.23 Many other 3-arylpyrroles exhibit anti-inflammatory, analgesic, antiallergic and anti-HIV activities.24

In another strategy to obtain azaheterocyclic compounds, the ring contraction of 2,2-dichlorocyclobutanones 12 towards cyclopropanecarbaldehydes 1625 will be used as a key step to synthesize trichlorinated butanals 17, which are good precursors for a variety of halogenated pyrrolines and pyrroles 18. 3-Halogenated pyrroles are of particular importance due to their interesting physiological properties and their difficult synthesis. Indeed, direct halogenation of pyrroles gives predominantly 2-halopyrroles in a mixture of halogenated pyrroles.26

Therefore, only limited entries towards the specific 3-halopyrroles are known. A wide diversity of 3-halogenated pyrroles has been isolated from nature which show various
biological activities, e.g. pyrrolnitrin \( \textbf{1a} \) (fungicide) and pyoluteorin \( \textbf{22} \) (antimicrobial, herbicidal).\(^{27}\) The synthetic 3-bromopyrrole \( \textbf{23} \) (Chlorfenapyr or Pirate®) is used as an insecticide.\(^{28}\)

Also 2-(hydroxymethyl)- and 2-(aminomethyl)pyrroles will be accessed via the above mentioned methodology of initial ring contraction of halogenated cyclobutanones and subsequent pyrrole synthesis. Pyrroles bearing aminomethyl (\( \textbf{24} \))\(^{29}\) or hydroxymethyl (\( \textbf{25} \))\(^{30}\) substituents at the 2-position are of current interest due to their specific affinity for dopamine receptors and \( \alpha \)-chymotrypsine inhibition, respectively.

The second part of this work deals with a reactivity study of \( N \)-(cyclobutylidene)alkylamines, a barely studied class of compounds. Among others, the reactivity of polychlorinated imines \( \textbf{26} \) will be evaluated in order to verify whether nucleophiles induce ring opening, ring contraction or substitution. Ring contraction would lead to halogenated cyclopropanes \( \textbf{27} \), which are good precursors for the intriguing cyclopropenones \( \textbf{28} \). Cyclopropenones have attracted considerable attention during the last decades because of their high ring strain and physiological activities.\(^{31}\) Penitricin \( \textbf{29} \) is an antibiotic isolated from \textit{Penicillium aculeatum} and various synthetic analogues also display antibacterial properties.\(^{32,33}\) In that respect, attempts will also be made to construct new cyclopropane derivatives via dimethoxy- or dihalocarbene additions to olefins and by ring closure of \( \alpha,\alpha' \)-dihaloketones as precursors for new cyclopropenones.
If substitution of the halogens occurs when treating \( N\)-(cyclobutylidene)amines 26 with nucleophiles, a new route could be established towards cyclobutenediones 31. These compounds are derivatives of the naturally occurring moniliformin 32, a mycotoxin isolated from *Fusarium moniliforme* and *Gibberella fujikuroi*.\(^{34}\) Dibutoxycyclobutenedione 35 is used for the treatment of hair loss and as a therapy for warts.\(^{35,36}\) Pibutidine 36 is a potent histamine H2-receptor antagonist and can be used to treat stomach ulcers.\(^{37}\) A large number of different vinylogous amide analogues, or squaramides, were recently patented for a wide range of activities, such as smooth muscle relaxation (37)\(^{38}\) and antimigraine activity (38).\(^{39}\) In addition, cyclobutenediones have attracted much attention as versatile building blocks for a variety of quinones, cyclopentenones and furanones.\(^{40}\)

A third reaction possibility when treating 26 with nucleophiles consists of the ring opening of 26 leading to polychlorinated compounds 33. In turn, these compounds might be used in nucleophile induced ring closing reactions to yield halogenated azaheterocyclic compounds 34. Every new compound will be subjected to a diversity of reactions in order to develop new synthetic pathways for physiologically interesting compounds.

In the last part of this work, 2-substituted cyclobutanones 41-43 will be synthesized. These specific cyclobutanones are formed in lipid-containing foodstuffs by \( \gamma \)-irradiation and can be used as markers for irradiated foods.\(^{41}\) \( \gamma \)-Irradiation of food for preservation and disinfection is not generally accepted and allowed. For that reason, it is of importance to rely on techniques that can detect whether food is \( \gamma \)-irradiated or not. One of these methodologies, which is approved by the European Committee for Standardization, is the detection of 2-substituted cyclobutanones 41-43, formed from the \( \gamma \)-irradiation induced cyclization of the parent triglycerides or fatty acids.\(^{42}\) It is obvious that for the further development of this technique, standard material, *i.e.* 2-substituted cyclobutanones, should be readily accessible. However, the currently available synthetic pathways to these cyclobutanones are either not efficient and easy to perform or lack the formation of the olefinic substituents in a stereospecific way.\(^{43}\) Earlier research at the Department of Organic Chemistry, Faculty of
Agricultural and Applied Biological Sciences, Ghent University, already gave rise to a preliminary synthetic pathway to obtain cyclobutanones 41b,d,e and 42.  

It is the purpose of this work to develop a high yielding and efficient stereospecific synthesis of 2-alkylcyclobutanones 41a,c and (5Z,8Z)-2-(5,8-tetradecadien-1-yl)cyclobutanone 43 via monoalkylation of \( N \)-(cyclobutylidene)isopropylamine 44. Alkylation of imines generally proceeds with less side-reactions as compared to ketones, where aldolcondensation and polyalkylation occur easier and cause problems in the specific case of cyclobutanone (see II.4.2.3).

The synthesis of the tetradecadienyl substituent will be accomplished by a partial reduction of the corresponding diyne 48 using hydrogen in the presence of poisoned Pd (Lindlar catalyst). This pathway should provide stereochemically pure (5Z,8Z)-alkadiene 50, which can be used in the alkylation protocol of \( N \)-(cyclobutylidene)isopropylamine 44.
Introduction and Goal

Cu(I) cross coupling

H₂ (Lindlar cat.)

Br

HO

8

46 + 47

48

49

50
II LITERATURE OVERVIEW

II.1 Cyclobutanones in nature

In contrast to numerous small ring compounds isolated from natural sources, e.g. cyclopropanes, cyclobutanes and β-lactams (penicillins, cephalosporins), carbocyclic four-membered ring ketones are not so widespread in nature. Until today, only 8 naturally occurring cyclobutanones are known. The simple 2-methylcyclobutanone 51 and 2-hydroxy-2-methylcyclobutanone 52 were found in the latex fraction of the rubber tree *Hevea brasiliensis*.\(^{44}\) Tsugicoline A 53 is a sesquiterpene produced by the Basidiomycetes *Laurillia tsugicola*.\(^{45}\) This compound showed no antibacterial or antifungal properties, but inhibits the germination of the water cress *Lepidium sativum*. The structure of coriolin, an antibiotic from *Coriolus concors* was first reported as a tsugicolin-like cyclobutanone,\(^{46}\) but later studies revealed that in fact no cyclobutanone moiety was present.\(^{47}\)

![Structures](image)

An investigation of an isolate from *Trichoderma viride*, which shows strong antifungal activity without phytopathogenic effects, led to the identification of the active metabolite isoharziandione 54. This polycyclic cyclobutanone is a growth inhibitor of soil-borne plant pathogenic fungi and has potential use as an agent for biocontrol in agriculture.\(^{48}\) Solanoeclepin A 55, excreted by the potato root, has a fascinating architecture made up of all ring sizes from three to seven, which is an unprecedented structural feature in natural products. This compound is the most active agent that promotes the growth of the potato cyst nematodes *Globodera rostochiensis* and *G. pallida*, causing severe crop losses in potato production.\(^{49}\)
In the steam distillate of the Arizonian sand sage or Artemisia filifolia (Torrey), which has been used by Hopi Indians as a medicinal plant, various terpenes were detected, a. o. (-)-filifolone (-)-56. The other isomer, (+)-56, was isolated from an Australian plant Ziera smithii. The structurally related chrysantenone 57 was found in the flowers of Chrysanthemum sinense. A more recent study reports the coexistence of filifolones 56 and racemic chrysanthenone 57, both as enantiomeric mixtures, in various plants. A careful analysis of the various constituents of the steam distillates and comparison with the compounds obtained by cold extractions of the plant material revealed that filifolones are most probably artefacts, originating from the thermo- and photolabile chrysanthenone 57. The paper indicates very clearly that results obtained from steam distillation of plant essential oils must be evaluated with great care, especially when labile compounds are involved.

II.2 Structure and properties of cyclobutanones

In 1874, van ‘t Hoff and Le Bel proposed that four-coordinate carbon has a tetrahedral geometry. Ten years later, Aldolf von Baeyer proposed his strain theory, where he stated that three- and four-membered rings would be less stable because of the deviation in bond angles from the tetrahedral values. Four-membered rings were extensively studied in the 1960s and 1970s, which resulted in a more thorough understanding of the structure and properties of small ring compounds. The most important factors attributing to the strain energy of cyclobutanes are the ring strain and the torsional strain, the latter originating from the eclipsation of the hydrogen atoms. To minimize the total strain, cyclobutane is not planar but puckered (folded) resulting in a small increase of the ring strain, but a considerable decrease of the torsional strain (58). The angle \( \theta \) between the planes C1-C2-C4 and C2-C3-C4 in cyclobutanes is about 35° and the rings were found to undergo an anharmonic “butterfly-like” inversion motion.
In addition, the maximum electron densities of the C-C bonds are not located along the C-C axis, but are bent away from the ring by $\alpha = 7^\circ$ (59). These bent bonds are often referred to as “banana-bonds”.

The cyclobutane C-atoms are not really sp$^3$-hybridized, but resemble more to p-orbitals, whose preferred bond angles are 90° instead of 109.5°. This hybridization is, besides the ring puckering, a compensating factor for the ring strain. As a consequence of this hybridization, the C-H orbitals have more s-character, which has an influence on the chemical reactivity of these compounds (see below). All these factors make the puckered conformation 6.3 kJ/mol (1.5 kcal/mol) lower in energy as compared to the planar conformation.

Surprisingly, extensive spectroscopic studies and molecular calculations proved that cyclobutanone (60) is planar, in contrast to cyclobutane (58,59). This is rationalized by the fact that cyclobutanone contains only three CH$_2$-moieties and thus, the torsional strain is less as compared to cyclobutane. Moreover, the sp$^2$-carbon introduces additional ring strain. Therefore there is no reason to fold the molecule. Ring puckering is a delicate balance between ring strain and torsion strain. Whereas ring strain is a planar driving force, the ring torsion favours non-planarity. Molecules with high ring strain and lower torsion strain, e.g. cyclobutanone, are best depicted as planar.

A minor substituent on the cyclobutanone can alter the relative importance of the two types of strain, resulting in a puckered conformation of the cyclobutanone ring, e.g. 2-bromocyclobutanone (61, R = Br). Thus, cyclobutanones can either adopt a planar or folded conformation, depending on the substituents. Another structural feature of cyclobutanones, which is rather unexpected, is the fact that the carbonyl double bond is tilted ($\beta = 1^\circ$ to $14^\circ$) towards the endo-face of the ring resulting in a “Concorde-nose” (61). This deviation allows the p-orbitals at C1 and O to take a perpendicular position to the tangential plane (at C1) formed by the bent bonds enabling a perfect sp$^2$-hybridization of the C1. A minor structural property of cyclobutanone is the tilt of the hydrogen atoms at $\alpha$-position towards the carbonyl moiety (60) with about 5° ($\delta$). This is in accordance with other structural determinations in which hydrogens are observed to tilt towards electronegative groups.

The specific structural characteristics of cyclobutanones have a profound influence on the chemical properties of these small rings. The lowered pK$_a$ of the hydrogens in $\alpha$-position, due to the increased s-character of the C-H bonds, gives rise to a faster base-catalyzed enolization (Et$_3$N-DMF) as compared to less strained cycloalkanones. It is interesting to note that the reactivity for acid-catalyzed enolization of cycloalkanones as a function of ring
size is $6>5>7>4$ (in HOAc/HCl), whereas for base-catalyzed enolization the order is $4>5>6>7$ (in DMF-Et$_3$N). A recent study of base-catalyzed enolization in D$_2$O with 3-quinuclidinone as a base catalyst revealed that there was no striking difference in enolization rate of cyclobutanone and acetone, indicating that the C-H hybridization, entropy (free rotation of bonds) and the destabilizing effect of a strained transition state (internal double bond) can compensate each other in varying reaction conditions.

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Introduction of a carbonyl moiety in a cyclobutane increases ring strain ($120^\circ \rightarrow 90^\circ$ versus $109.5^\circ \rightarrow 90^\circ$). Therefore, conversion of the carbonyl carbon into a tetrahedral carbon should relieve this additional strain, facilitating nucleophilic additions to the carbonyl group. This ring size effect was demonstrated by the accelerated rate of reaction of cyclobutanone with sodium borohydride as compared to other cycloalkanones.

The effect of ring strain on the spectral properties of cyclobutanone is recognized in the increased C=$\varepsilon$O stretching vibration frequency in IR ($\nu_{C=O, \text{cyclobutanone}} = 1780$ cm$^{-1}$, $\nu_{C=O, \text{cyclohexanone}} = 1720$ cm$^{-1}$) and in the downfield shift of the CH$_2$-$\alpha$ in $^1$H and $^{13}$C NMR (resp. 3.00 and 47.59 ppm, versus 2.25-2.40 (m) and 38.31 ppm in cyclohexanone). The major fragmentation of cyclobutanone (m/z 70, M$^+$) in mass spectrometry at 70 eV involves the elimination of ethene (m/z 28) leaving a ketene moiety (m/z 42).

**II.3 Synthesis of cyclobutanones**

The first synthesis of cyclobutanone dates from the beginning of the previous century. In this synthesis, cyclobutanone was obtained from $\alpha$-bromocyclobutanecarboxamide by reaction with bromine and KOH. Various syntheses of cyclobutanones starting from cyclobutane derivatives followed, the most important being the oxidation of substituted cyclobutanes, e.g. the oxidation of cyclobutylamines and methylenecyclobutane. Since then, numerous methods have been developed which are more general and easier to perform.

Instead of giving a complete coverage of the literature, the following literature overview gives a survey of today’s most important routes to cyclobutanones, which are suitable for preparative organic synthesis.
II.3.1 [2+2]-Cycloadditions

One of the most general and cheapest methods to construct cyclobutanones is the [2+2]-cycloaddition reaction of ketenes or ketene derivatives with olefins. Depending on the electronic and steric characteristics of the olefin, the reaction is carried out using ketenes, ketene acetals or keteniminium salts.

II.3.1.1 Reaction of olefins with ketenes

Alkyl- or arylketenes react with olefins following a thermally allowed [2+2]-cycloaddition reaction to give cyclobutanones. However, this approach often suffers from severe drawbacks due to the instability of the ketenes, the formation of ketene dimers and the inertness of these ketenes towards unactivated alkenes. With electron rich olefins such as styrenes, reactive dienes (e.g. cyclopentadiene), enol ethers (e.g. 64) and enamines, numerous reactions have been reported with diarylketenes, dialkylketenes and even ketene itself yielding cyclobutanones in good yields. Also, reaction of dimethylketene with allene 66 results in 2-methylenecyclobutanone 67 in a fair yield.

Halogenated ketenes are expected to be more electrophilic due to the electronegativity of the halogen substituents. Furthermore, the ability of halogens to stabilize a negative charge at the $\alpha$-carbon increases the tendency of these ketenes to undergo nucleophilic additions. In contrast to alkyl- and arylketenes, dihaloketenes react under mild conditions in high yields, also with unactivated olefins. Dichloro- and dibromoketenes are generally prepared in situ.
by dehydrohalogenation of dihaloacetyl halides or dehalogenation of trihaloacetyl halides by activated zinc. Both methods have disadvantages, e.g. decomposition of the ketene by ammonium salts or polymerization of reactive olefins by zinc salts, so, exact reaction conditions should be evaluated at all times. This methodology has been expanded to the synthesis of monohalocyclobutanones, using alkyl- or arylchloroketenes and to intramolecular cycloadditions where ketene and olefin are part of the same molecule. As an example, the syntheses of cyclobutanones and are given.

The mechanism of the thermally allowed [2+2]-cycloaddition of olefins to ketenes is described in the literature as a \([2\pi_s+2\pi_a]\)-process where, according to the theory of Woodward and Hoffmann, the olefinic reactant participates in a suprafacial way and the ketene in an antarafacial way (see 77). This pericyclic reaction proceeds via a concerted non-synchronous mechanism involving a transition state with some degree of charge separation, although some ketene additions to electron rich olefins such as enamines are known to proceed by a zwitterionic, two-step mechanism. Nowadays, the proposal of Woodward and Hoffmann seems not to be the only possible reaction mechanism and recent studies indicate that another pericyclic mechanism is involved, confirmed by recent theoretical calculations. While there still is some speculation on the exact geometry of the transition state, the reaction is believed to follow a \([2\pi_s+(2\pi_s+2\pi_s)]\)-process instead of a \([2\pi_s+2\pi_a]\)-mechanism. As can be seen in the schematic representation 78, the first process is a nucleophilic attack of the \(\pi_y(C3,C4)\) bond orbital to C1 of the ketene. The \(\pi_y(C3,C4)\) bond is delocalized between C3-C4-C1 and simultaneously, the \(\pi_y(C1,O)\) bond is converted to a \(\pi\)-lone pair on oxygen (78, step 2). The second process is an attack of the \(\pi_y(C1,C2)\) bond to the electron deficient C3. The electron deficiency is therefore shifted to C1 which is compensated by the transformation
of the $\pi$-lone pair on oxygen into a $\pi_{\ell}$(C1,O) bond orbital. The stereochemical outcome of this reaction is in agreement with experimental data, where e.g. monosubstituted ketenes react with olefins to form a contra-thermodynamic cis-2,3-substituted cyclobutanone 79. This appears to result from the electronic preference to form 3-substituted cyclobutanones and the steric preference to form the transition state with the lowest steric hindrance.

II.3.1.2 Ketene acetals

When electron poor olefins are used as a starting material to synthesize cyclobutanones, the reaction with ketenes often results in poor yields. The use of ketene equivalents, such as ketene acetals (e.g. 81) or thioacetals extended the scope of this reaction, but their use is restricted to very electron poor olefins, like acrylates or acrylonitrile 82.

II.3.1.3 Keteniminium salts

A third important group of ketene derivatives to synthesize cyclobutanones are keteniminium salts, which are usually synthesized by the dehydration of amides with triflic anhydride and substituted pyridines as a base. Keteniminium cations are more electrophilic as compared to other ketenes and, as a consequence, are more reactive to a broader range of olefinic substrates. A second advantage of the use of keteniminium species is the fact that they do not dimerize or polymerize and can be stored in solution for some time. In addition, they form an easy entry to chiral cyclobutanones since chiral substituents can be readily introduced on the nitrogen as shown in the synthesis of bicycloheptanone 86.
**II.3.2 Ring expansion of cyclopropanes**

A second important and widely used method to synthesize cyclobutanones is the ring expansion of cyclopropanes. This route is of particular importance in the asymmetric synthesis of substituted cyclobutanones, which are interesting building blocks for further organic synthesis. Several methodologies have been developed, each having its pros and cons. The general mechanism of the ring expansion can be schematically given as a pinacolic rearrangement of 87 or 88 to yield cyclobutanones 89. Using this strategy, a substantial number of enantioselective syntheses have been reported.

**II.3.2.1 Ring expansion of cyclopropanols and derivatives**

Methylene cyclopropane 91 (b.p. 11°C), which is available from 3-chloro-2-methylpropene 90 in good yield, can be used as a universal starting material to synthesize cyclopropanol 92. Reaction of 91 with NBS in aqueous DMSO yields the unstable 1-(bromomethyl)cyclopropanol 92 which rearranges towards cyclobutane 93 in rather low yield. A better yield can be obtained by tosylation of 1-(hydroxymethyl)cyclopropanols 97, which are unstable compounds that can be synthesized by dihydroxylation of methylene cyclopropanes 96.
An asymmetric version of this reaction has been performed by initial Sharpless asymmetric dihydroxylation of methylenecyclopropanes $^{99}$ and subsequent rearrangement of cyclopropanols $^{100}$ towards optically active cyclobutanones $^{101}$. $^{43}$. The rather low enantiomeric excesses are due to the initial dihydroxylation, which is not completely stereoselective. In contrast, the ring expansion occurs with complete retention of stereochemistry towards cyclobutanones. Also, no epimerization of the end products under the given reaction conditions was detected.

A second, comparable method which has been developed for construction of cyclobutanones $^{108}$, comprehends the addition of 1-ethoxycyclopropyllithium $^{105}$ to aldehydes and ketones $^{106}$. $^{96,97}$ The resulting cyclopropylcarbinols $^{107}$ rearrange after treatment with HBF$_4$. Usually, high yields and clean reaction mixtures are obtained, but, a drawback of this synthesis is the preparation of the starting material ($^{102}$ → $^{105}$), using the pyrophoric tert-butyllithium.
A third important synthetic method that is related to the cyclopropane ring expansion described above, is the use of phenylthiocyclopropane 111 as a valuable precursor of several substituted cyclopropane derivatives.\textsuperscript{98,99} Deprotonation of 111 with butyllithium and subsequent addition of the cyclopropyllithium species to aldehydes and ketones 106 provides 1-phenylthio-1-(hydroxymethyl)cyclopropanes 113. These substances react readily with acids in the presence of water to yield cyclobutanones 108 in good yields. To inhibit side reactions due to thiophenol, HgCl\textsubscript{2} is often added to trap this nucleophile.\textsuperscript{100}

Vinylcyclopropanols (115, 118) are often used as substrates for electrophile induced ring expansions to cyclobutanones.\textsuperscript{101,102} In some cases, the hydroxyl moiety of 115 or 118 serves as a proton source for activation of the double bond resulting in cyclobutanones (51, 119) after heating. In other cases, electrophiles are used to induce the ring expansion.\textsuperscript{92,103,104}
II.3.2.2 Ring expansion of 1-oxaspiro[2.2]pentanes

The highly strained heterocyclic title compounds have been studied in detail, particularly because of their synthetic potential as intermediates in the cyclobutanone synthesis.\textsuperscript{105} Unsubstituted oxaspiropentane \textsuperscript{122} (R = H) is stable in solution at room temperature, but the intermediacy of analogous substituted spiroannelated compounds can often not be detected in ring expansion reactions towards cyclobutanones. OXaspiropentanes \textsuperscript{122} are usually prepared by reacting cyclopropyldiphenylsulfonyl ylids \textsuperscript{120} or 1-bromocyclopropyllithium \textsuperscript{121} with aldehydes or ketones \textsuperscript{106}, or by epoxidation of methylenecyclopropanes \textsuperscript{123}.\textsuperscript{108} The latter methodology provides a suitable pathway to reach chiral cyclobutanones \textsuperscript{125} using an enantioselective Sharpless epoxidation.\textsuperscript{93}
II.3.3 Synthesis of cyclobutanones from 1,3-dihalopropanes and derivatives

Cyclobutanones have been prepared from 1,3-dihalopropanes 126, 129 and 134 by double nucleophilic substitution of the dihalide. Deprotonation of malonic esters,\textsuperscript{109} tosylmethlisocyanide\textsuperscript{110} or methyl methylthiomethylsulfoxide\textsuperscript{111} with a base and subsequent reaction with substituted 1,3-dibromopropanes 126 or 129 yields the corresponding cyclobutanes 127, 130 and 132 respectively. A final hydrolysis of the intermediate cyclobutanes yields cyclobutanones in good yields. A convenient synthesis of unsubstituted cyclobutanone 94 consists of the generation of a dianion 135 from 1,3-dibromopropane 134 by reaction with magnesium.\textsuperscript{112} This dianion readily attacks carbon dioxide to form cyclobutanone in 13\% total yield from 134. Although the yield is low, this method is competitive with other laboratory preparations of cyclobutanone due to the inexpensive starting materials.

\begin{align*}
\text{MeO} & \text{O} \\
\text{Br} & \text{Br} \\
\text{126} & \text{CH}_2(\text{COO-Pr})_2 \\
\text{NaH, DMF} & \rightarrow \\
\text{MeO} & \text{O} \\
\text{COO-Pr} & \text{COO-Pr} \\
\text{127 (56\%)} & \text{H}_2\text{O}^+ \\
\text{128 (97\%)} & \\
\text{Br} & \text{Br} \\
\text{R} & \text{TosMIC, NaH} \\
\text{DMSO} & \rightarrow \\
\text{Tos} & \text{NC} \\
\text{130 R = Me (74\%)} & \text{H}_3\text{O}^+ \\
\text{Me} & \text{Me} \\
\text{131 (90\%)} & \\
\text{MeS} & \text{SMe} \\
\text{132 R = benzyl (77\%)} & \text{KH} \\
\text{S(O)Me} & \rightarrow \\
\text{133 (89\%)} & \text{H}_3\text{O}^+ \\
\text{Br} & \rightarrow \\
\text{Bn} & \\
\text{134} & \text{Mg} \\
\text{ether} & \rightarrow \\
\text{BrMg} & \text{MgBr} \\
\text{135} & \text{CO}_2 \\
\text{94 (13\%)} & \\
\end{align*}
II.3.4 Rearrangements of γ-oxoalkyl toluenesulfonates

This section deals with base-induced conversions of γ-oxoalkyl toluenesulfonates (e.g. compound 136). Two types of rearrangements can occur when treating the title compounds with base. At first, one can imagine a homoallylic rearrangement from 138 to the bicyclic cyclobutanone 139. However, after careful analysis of all reaction products formed by reacting substrate 136 with base at different reaction conditions, another major reaction product 141 came to light.\(^\text{113,114}\) This cyclobutanone is formed by what is called a 1234-1243 rearrangement.\(^\text{115}\) In general, the outcome of the reaction of γ-oxoalkyl toluenesulfonates with base cannot be predicted for now and has to be determined experimentally.

![Diagram showing the reaction of 136 with aq. NaOH to form 139 and 141.]

II.3.5 Synthesis of cyclobutanones from bicyclobutanes

In a fashion similar to many other highly strained systems, bicyclobutanes undergo a facile reaction with electrophiles.\(^\text{116}\) In this respect, a novel route to cyclobutanone 94 was developed by the acid-catalyzed rearrangement of 1-bromobicyclo[1.1.0]butane 144. Treatment of bicyclobutane 144 with aqueous sulfuric acid yielded cyclobutanone 94 in 28% yield after distillation.\(^\text{117}\)
II.3.6 Synthesis of cyclobutanones from cyclobutenes

In cases where ketene cycloadditions to olefins do not result in cyclobutanones in good yields, it can be expedient to construct the four-membered rings via the intermediacy of cyclobutenes. For instance, cyclobutene 147 can be synthesized in large scale from 1,4-bis(diphenylthio)butane 146.\textsuperscript{118}

Hydrolysis of cyclobutene 147 results in 2-(phenylthio)cyclobutanone 148. α-Alkylation and subsequent desulfurization via reductive lithiation with lithium 1-dimethylaminonaphthalenide yielded mono-substituted cyclobutanones (e.g. 150) in good yield. Another possibility for constructing a cyclobutene precursor for cyclobutanones is the use of an acyloin condensation of diesterified starting products.\textsuperscript{119} Treatment of 151 with sodium in the presence of trimethylsilyl chloride gives rise to cyclobutenes 152, which can be
hydrolyzed towards α-hydroxycyclobutanones. To remove the hydroxyl moiety, a simple acetylation and subsequent reduction with zinc can be used.119

II.3.7 Miscellaneous

Cyclobutanones have emerged from reactivity studies of a wide variety of starting materials. Unfortunately, a lot of pathways are of no preparative use, e.g. the diazomethane ring expansion of the labile cyclopropanone 155120 or the photochemical cyclization of α-halo-α-diketones 156.121 In what follows, recent synthetic pathways are described which use transition metal complexes to form four-membered rings. A one-pot procedure has been developed to synthesize trans-1,2-disubstituted cyclobutanones (e.g. 161) via the carbonylation of titanacyclobutane complexes 160.122
The latter were generated from allylic Grignard reagents with titanocene derivatives resulting in a \( \eta^3 \)-allyltitanium(III) complex which can be reductively alkylated with alkyl iodides and samarium iodide. Another pathway, using titanium intermediates to construct cyclobutanones, consist of the reaction of dimetalated iminiumspecies with benzophenone. In the last decade, a more general approach towards the synthesis of chiral cyclobutanones has been developed by the photolytic reaction of chromium alkoxycarbene complexes with olefins (e.g. 166) in the presence of carbon monoxide.

II.4 Reactivity of cyclobutanones

The specific reactivity of cyclobutanones is as a matter of course related to their structural features, the ring strain in particular. Reactions which relieve this ring strain are promoted and can be of concern when handling these compounds. For instance, treating \( \alpha \)-halocyclobutanones with nucleophiles can induce, among others, a nucleophilic addition to the carbonyl group, ring opening, substitution of the halogen atom, semi-benzilic Favorskii rearrangement, dehydrohalogenation or a combination of these. In general, the steric and electronic effects of the starting cyclobutanones and reagents as well as reaction conditions have to be evaluated carefully in order to promote one reaction at the expense of the other.

II.4.1 Reactions involving nucleophilic additions to the carbonyl group

II.4.1.1 Synthesis of cyclobutane derivatives

As explained in section II.2, reduction of the carbonyl group of cyclobutanone is faster as compared to less strained molecules. The reduction of cyclobutanones with a wide variety of reducing agents to cyclobutanols is well documented in the literature; however the reaction often proceeds with lack of stereoselectivity. Reduction of 3-phenylcyclobutanone 174 with lithiumtri-tert-butoxyaluminumhydride yielded cis-cyclobutanol 175 in high yield, whereas
the same reaction with diisobutylaluminumhydride yielded a mixture of *cis*- and *trans-*
cyclobutanones 175 and 176. An enantioselective reduction of bicyclic cyclobutanone 177
has been performed with baker’s yeast resulting in a reduction from the exo face and leaving
the other isomer unaffected.

Additions of carbon nucleophiles to the carbonyl function of cyclobutanones (e.g. 180)
have resulted in the synthesis of alkenylcyclobutanols, which are of importance for the
synthesis of cyclopentenones (*vide infra*).

Transformations of cyclobutanones towards the corresponding acetals, imines
(oximes) or alkylidencyclobutanes proceeds normally without difficulty when no
reactive substituents are present (e.g. 183, 185). *N*-((Cyclobutylidene)amines have not been
intensively studied until now and could provide a plethora of possibilities for further organic
synthesis.

\[
\begin{align*}
\text{LiAlH(Ot-Bu)}_3 & (89\%, 175/176 = 97/3) \\
\text{DIBALH} & (74\%, 175/176 = 53/47)
\end{align*}
\]

\[
\begin{align*}
\text{Bakers’ yeast} & \\
\text{177} & \rightarrow \text{178 (19%, ee 88%)}, \text{179 (27%, ee >99%)}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \rightarrow \text{181 (87%)} \\
\text{180} & \rightarrow \text{181 (87%)} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_{3}\text{P} & \rightarrow \text{182 (90%)} \\
\text{183} & \rightarrow \text{183 (90%)} \\
\text{Cl} & \rightarrow \text{184} \\
\text{184} & \rightarrow \text{185 R = alkyl (70-80%)}
\end{align*}
\]
II.4.1.2 Ring opening reactions

The ring opening of cyclobutanones can be of importance for the vicinal difunctionalization of olefins and has been used to construct suitable substrates for further transformations.\(^\text{62}\)

A smooth cleavage of the cyclobutanone ring can be expected if the latter bears anion-stabilizing groups in \(\alpha\)-position. The role of the anion-stabilizing groups has been demonstrated using \(186\) and \(188\) as substrates.\(^\text{132}\) As shown in the scheme below, with cyclobutanone \(186\) considerably harsher reaction conditions are necessary to induce ring opening. Reaction of dihaloketenes with alkenes provides cyclobutanones which cleave upon reaction with alkoxides or amines. Whereas the ring opening of \(\alpha,\alpha\)-dihalocyclobutanones with sodium methoxide is generally applied to form e.g. \(190\),\(^\text{133}\) only four publications are known concerning an amine-induced ring opening (e.g. \(192 \rightarrow 193\)).\(^\text{134}\) Until now, no monocyclic cyclobutanones have been ring opened with amines.

\[
\begin{align*}
186 & \xrightarrow{2M \text{NaOH}} 187 & 188 & \xleftarrow{1) \text{0.5% aq. NaOH} \quad 2) \text{PBr}_3} & \to 193
\end{align*}
\]

\[
\begin{align*}
189 & \xrightarrow{\text{NaOMe}} 190 (52\%) & 191 (65\%)
\end{align*}
\]

\[
\begin{align*}
192 & \xrightarrow{\text{piperidine}} 193 (78\%)
\end{align*}
\]
II.4.1.3 Ring expansions of cyclobutanones

Various γ-butyrolactones and to a smaller extent some γ-lactams were synthesized via ring expansion of cyclobutanones via Baeyer-Villiger (194 → 195\textsuperscript{43d,135}) and Beckmann rearrangements (196 → 197) or Schmidt reactions (174 → 199),\textsuperscript{136-138} respectively.

Reaction of cyclobutanones with azides,\textsuperscript{136} Tamura’s reagent \(O\)-(methanesulfonyl)-hydroxylamine\textsuperscript{137} or its \(N\)-alkylated analogue\textsuperscript{138} resulted already in various pyrrolidinones.

Rearrangements of cyclobutanones to cyclopentanones are usually performed with diazomethane or derivatives. Whereas the reaction of alkyl substituted cyclobutanones with diazomethane is not regioselective, treatment of the 2,2-dichlorinated analogues (e.g. 200) results in a methylene insertion on the non-halogenated side (200 → 201).\textsuperscript{139} Next to the diazomethane ring expansion, the conversion of the keto function of cyclobutanones into oxiranes provides also a useful route to cyclopentanones.\textsuperscript{140} This is exemplified in the synthesis of the spirooxirane 203 and subsequent treatment with lithium iodide to yield the bicyclic cyclopentanone 204. Via the same principle, a Tiffenau-Demyanov reaction on cyclobutaneone cyanohydrin 205 results in cyclopentanones, albeit as an isomeric mixture of 207 and 208.\textsuperscript{141}
1-Alkenyl substituted cyclobutanols can expand when treated with electrophiles. 1-Alkenyl-1-cyclobutanols 181 can either yield cyclopentenones (e.g. 210) or cyclopentanones depending whether a $\beta$-H elimination is possible or not.\textsuperscript{128,142}

II.4.1.4 Ring contractions of halogenated cyclobutanones

One of the most intensively studied reactions of halogenated cyclobutanones is the ring contraction to cyclopropane derivatives. As stated in the introduction, these reactions are of paramount importance for the synthesis of cyclopropane skeletons, e.g. the insecticidal pyrethroids.\textsuperscript{143} Considerable efforts have been expended in elucidating the mechanism and reaction conditions which favour ring contraction above other side reactions. The fact that there seems to be no straightforward answer whether contraction or substitution occurs in reactions of $\alpha$-halogenated cyclobutanones with nucleophiles is demonstrated by the following examples. Reaction of 2,4-dibromocyclobutanone 211 with aqueous sodium
carbonate results in ring contraction whereas 2,2-dibromocyclobutanone 213 is ring opened under the same conditions.\textsuperscript{144} In contrast to 213, 2,2-dichlorocyclobutanone 200 undergoes ring contraction to 217 when treated with sodium methoxide.\textsuperscript{145,146}

Another example is the difference in reactivity of the bicyclic cyclobutanones 215 and 218. Reaction of 218 with sodium methoxide in refluxing methanol results in ring contraction, whereas 215 results in the substituted cyclobutanone 216 under the same conditions.\textsuperscript{147} The latter can be explained by the retarded enolization (for the role of the enol form in substitutions, see section II.4.2.1) of 218 as compared to 215, which promotes ring contraction. In addition, the kind of leaving group, the solvent and the temperature can have huge effects on the stereoselectivity of the ring contraction.\textsuperscript{148} The mechanism of this ring contraction is believed to proceed via a semi-benzilic Favorskii rearrangement, although it is quite different from a Favorskii-rearrangement \textit{sensu strictu}. There are four possible mechanisms to end up with cyclopropanes from the corresponding cyclobutanones, as shown in the scheme below (pathways \textit{a-d}).\textsuperscript{145} Pathway \textit{a}, in which a bicyclobutanone 221 is formed, can be excluded since the reaction of 2-bromocyclobutanone 220 with NaOD in D\textsubscript{2}O resulted in no incorporation of any deuterium in the cyclopropane ring of 223 (confirmed by \textit{\textsuperscript{1}H NMR}) and since ring contraction also occurs when no \textit{\alpha}-hydrogen atom is present.
The latter experimental observation also excludes the possibility of the formation of an intermediate ketene 230, as proposed in pathway c. Pathway b, which involves the formation of an epoxide 225, has been discarded since no by-products such as 227 or 228 are formed. The only possibility left is a semi-benzilic Favorskii rearrangement (pathway d). This mechanism is consistent with the observed stereochemistry of this ring contraction (233 → 234) and has also been confirmed by numerous mechanistic studies. Because the semi-benzilic ring contraction can be seen as a kind of a concerted internal S_{N,2} reaction, the leaving group has to adapt a pseudo-equatorial position (233) in order to obtain an efficient orbital overlap. When the leaving group is forced into a pseudo-axial position, no ring contraction can take place. Instead, other reactions or hydride shifts are observed.

\[ \text{pathway a} \]
\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{Br} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{OD} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{D} \\
\text{O} \\
\end{array}
\]

\[ \text{but: } ^1\text{H-NMR: } H_\alpha/H_\beta = 1/4 \]

\[ \text{pathway b} \]
\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{OD} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{OD} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{COOD} \\
\text{OD} \\
\end{array}
\]

\[ \text{not observed} \]

\[ \text{pathway c} \]
\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{O} \\
\text{O} \\
\end{array}
\to
\begin{array}{c}
\text{COOH} \\
\text{OD} \\
\end{array}
\]

\[ \text{pathway d} \]
\[
\begin{array}{c}
\text{Br} \\
\text{H} \\
\end{array}
\to
\begin{array}{c}
\text{Br} \\
\text{H} \\
\end{array}
\to
\begin{array}{c}
\text{H} \\
\text{H} \\
\end{array}
\]

\[ \text{not observed} \]
II.4.2 Reactions at the α-carbon of cyclobutanones

II.4.2.1 The cine-substitution and cine-rearrangement

The term cine-substitution is used for the nucleophilic substitution of halogens at the α-position in four-membered ring ketones where the nucleophile is introduced at the opposite carbon atom (α'-position). The mechanism proceeds via an initial enolization of the ketone 235 and subsequent attack of the nucleophile at the α'-position (236) with expulsion of the halide in α-position. The resulting enol 237 is tautomerized towards the ketone 238. This reaction has first been reported some decades ago in the synthesis of tropolones (e.g. 7), a class of compounds with renewed interest as interesting physiologically active compounds (see Introduction). When halogenated cyclobutanones are treated with catalytic amounts of amines or ammonium salts, one halogen is expelled and attacks the opposite carbon atom. This process

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{X} \\
\text{R} 
\end{array} \\
\text{235} & \quad \xrightarrow{\text{Nu}^-} \\
\text{Nu} & \quad \begin{array}{c}
\text{OH} \\
\text{R} 
\end{array} \\
\text{236} & \quad \xrightarrow{\text{Nu}^-} \\
\text{Nu} & \quad \begin{array}{c}
\text{OH} \\
\text{R} 
\end{array} \\
\text{237} & \quad \xrightarrow{\text{Nu}^-} \\
\text{Nu} & \quad \begin{array}{c}
\text{O} \\
\text{R} 
\end{array} \\
\text{238} & \\
\end{align*}
\]
is called a cine-rearrangement (243 → 244). This rearrangement is often observed when treating 2-halo-2-substituted cyclobutanones which bear bulky groups at C-2, e.g. 243. The cine-substitution has been studied and explored at Ciba-Geigy as a key step in the synthesis of dimethylcyclopropanes as insecticidal pyrethroid precursors.\(^\text{14}\)

II.4.2.2 Halogenation, dehalogenation and dehydrohalogenation of cyclobutanones

Cyclobutanones can be mono- or dibrominated using standard procedures with bromine or NBS. This reaction is often not specific and the different mono-, di- and other polybrominated cyclobutanones have to be separated.\(^\text{144}\) Monochlorination can be carried out by reaction of cyclobutanones with sulfuryl chloride. Unfortunately, this reaction also results in dichlorinated cyclobutanones, which have to be separated from the reaction mixture.\(^\text{144}\) In general, dihalogenated cyclobutanones are obtained in much higher yield by applying the dihaloketene-method to synthesize the cyclobutanones. The corresponding monohalogenated cyclobutanones can be obtained by treatment of the dihalogenated cyclobutanones with one equivalent of activated zinc (e.g. synthesis of 247),\(^\text{155}\) or by reaction with tributyltinhydride.\(^\text{79}\) A complete dehalogenation is readily carried out using a zinc-copper couple (2 equivalents),\(^\text{156}\) chromium chloride\(^\text{157}\) or with tributyltinhydride.\(^\text{158}\)

Dehydrohalogenations can be performed with regular bases such as pyridine. Both syn- as well as anti-elimination is possible in the case of cyclobutane 248, which is illustrated in the formation of 249 and 250.\(^\text{159}\)
II.4.2.3 \( \alpha \)-Alkylation and \( \alpha \)-acylation of cyclobutanones

Condensation of cyclobutanones by deprotonation and reaction with alkyl halides, aldehydes and ketones or acyl halides generally results in complex reaction mixtures and self-condensation products.\(^{62}\) So far, no general method has been developed for the monoalkylation of cyclobutanones. In cases where monochlorocyclobutanones can be synthesized, the reaction with dimethylcopperlithium results in the corresponding enolate which can be trapped with electrophiles.\(^{160}\) Alternative procedures make use of zirconium or boron enolates.\(^{62}\) With specific cyclobutanones (e.g. 174), trapping of the corresponding lithium enolate with triethylsilyl chloride yields a stable silyl enol ether 251 that can be treated with aldehydes and TBAF to yield \( \alpha \)-alkylated products 252.\(^{16}\) In contrast, reaction of enolate 251 with alkyl halides did not result in the alkylated product 253. Also, the corresponding trimethylsilyl enol ethers were not stable and could not be used.\(^{16}\)
III Results and Discussion

III.1 Synthesis of azaheterocyclic compounds from cyclobutanones

III.1.1 Ring expansion of 3-aryl-2,2-dichlorocyclobutanones

III.1.1.1 Introduction

Cyclobutanones reveal interesting characteristics such as a high electrophilicity and ring tension which make them good substrates for ring transformation reactions.\(^{52,93}\) Functionalized cyclobutanones have indeed been the subject of numerous studies which describe their reactivity with nucleophiles to induce ring opening, ring contraction and ring expansion (see literature overview).\(^{125b,133,145,161}\) Various \(\gamma\)-butyrolactones and to a smaller extent some \(\gamma\)-lactams were synthesized via ring expansion of dihalocyclobutanones via Baeyer-Villiger\(^ {43c,135}\) and Beckmann rearrangements or Schmidt reactions,\(^ {136-138}\) respectively. Reaction of dichlorocyclobutanones with azides,\(^ {136}\) Tamura’s reagent \([O-(methanesulfonyl)hydroxylamine]\)\(^ {137}\) or its \(N\)-alkylated analogue\(^ {138}\) resulted in various pyrrolidinones. Cyclobutanones bearing functional groups which can be eliminated could give rise to interesting pyrrolinones. However, no ring expansion was reported leading to the unsaturated 3-pyrrolin-2-ones, a class of compounds of particular importance as physiologically active compounds and as synthons for further transformation into various azaheterocycles. 3,4-Diarylpyrrolinones \(9\) were recently patented and show anti-inflammatory (\(R = \text{alkyl}\)) and cyclooxygenase-2 inhibitor (\(R = \text{aryl}\)) activities.\(^ {18}\) \(N\)-unsubstituted pyrrolinones \(10\) are blood pressure reducing agents,\(^ {19}\) while 4-[4-(1H-imidazol-1-yl)phenyl]pyrrolinones \(11\) possess selective positive inotropic properties.\(^ {20}\)
Earlier experiments at the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, regarding the potentiality of 2,2-dihalocyclobutanones resulted already in the preliminary synthesis of pyrrolinones. This reaction pathway was evaluated and optimized towards various substituted pyrrolinones which are suitable synthons for further organic synthesis.

III.1.1.2 Results and discussion

2,2-Dichlorocyclobutanones 12 were synthesized via a [2+2]-cycloaddition of \textit{in situ} generated dichloroketene to substituted styrenes. In contrast to the synthesis of 2,2-dibromo-3-phenylcyclobutanone, which is a more laborious and low yielding procedure, 2,2-dichlorocyclobutanones are readily obtained from commercially available starting products.

\[
\begin{array}{c}
\text{R}^1
\end{array}
\begin{array}{c}
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{R}^1
\end{array}
\]

The resulting 2,2-dichlorocyclobutanones were treated with 2 equivalents of alkylamines to induce a ring opening towards \textit{N}-alkyl-3-aryl-4,4-dichlorobutanamides 13. When fewer equivalents of amine were used, longer reaction times were required and, as a consequence, more side products were formed which hamper the recrystallization of the butanamides 13. In that way, new 3-aryl-4,4-dichlorobutanamides 13a-c were synthesized from the corresponding cyclobutanones 12 in fair to good yield. It must be emphasized that the ring opening of dihalocyclobutanones with amines has previously been described only with fused cyclobutanones like bicycloheptanones, -heptenones and benzocyclobutanones. No monocyclic 2,2-dichlorocyclobutanones were ever ring opened by amines before.
Attempts to cyclize the dichlorobutanamides 13 directly to pyrrolinones by heating in toluene or DMSO yielded only traces of pyrrolinone 257 after reflux for 15 hours. Also heating in aqueous 2M HCl did not improve the yield. When t-BuOK was used as a base no cyclization occurred, probably because the CH of the CHCl₂-moiety is more acidic than the NH of the amide, resulting in side reactions. Also, attempts to reduce the amide moiety towards an amine to produce valuable starting materials (255) for pyrroline syntheses did not work out.

Reaction of dichlorobutanamides 13 with sodium methoxide resulted in enol ethers 258 which were thought to be good substrates for ring closure towards 3-pyrrolin-2-ones 257. The obtained crystalline N-alkyl-4-methoxy-3-phenyl-3-butenamides 258 occurred in both the E- and Z-isomers in ratios varying from 74:26 to 88:12. The major isomer could be separated from the mixture by column chromatography, while the minor isomer could not be obtained as a pure compound. DIFNOE experiments on both isomers were inconclusive concerning the stereochemistry of the double bond. However, after a detailed ¹H and ¹³C NMR study and comparison of the NMR-data with literature data of analogous compounds, it became quite certain that the major compound of 258a was the E-isomer (see scheme below)²⁶²-²⁶⁴. The hydrogen at C-4 in isomer (E)-258a resonates at lower field as compared to the Z-isomer, and the ¹H NMR signal of the aromatic protons of (E)-258a consists of a small multiplet from
Results and Discussion

7.26 to 7.32 ppm, while the Z-isomer has a multiplet from 7.18 to 7.23 and 7.53 to 7.56 ppm. Both results are in strong accordance with NMR studies of analogous (2-methoxyethenyl)benzenes and (2-methoxy-1-methylethenyl)benzenes.\textsuperscript{162} Also, the chemical shifts of the hydrogen at C-4 were predicted via additive increment calculations for olefinic protons\textsuperscript{163} and compared with the experimental data (CDCl\textsubscript{3}) (E-isomer, calc.: 6.77, found: 6.59; Z-isomer, calc.: 6.32, found: 6.27). In \textsuperscript{13}C NMR, the CH\textsubscript{2} of the E-isomer resonates at higher field than the CH\textsubscript{2} of the Z-isomer, due to the shielding effect of the OMe group,\textsuperscript{164} which is again in line with the literature and a sign that the proposed stereochemical assignments are correct.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textsuperscript{1}H NMR: 3.18 ppm \textsuperscript{13}C NMR: 40.9 ppm \textsuperscript{1}H NMR: 6.27 ppm \textsuperscript{13}C NMR: 148.5 ppm \textsuperscript{13}C NMR: 109.9 ppm};
\node (B) at (2,0) {\textsuperscript{1}H NMR: 3.38 ppm \textsuperscript{13}C NMR: 36.2 ppm \textsuperscript{1}H NMR: 6.59 ppm \textsuperscript{13}C NMR: 147.3 ppm \textsuperscript{13}C NMR: 113.9 ppm};
\node (C) at (0,-.5) {\textsuperscript{13}C NMR: 258a (minor)};
\node (D) at (2,-.5) {\textsuperscript{13}C NMR: 258a (major)};
\end{tikzpicture}
\end{center}

\textsuperscript{1}H NMR: 3.18 ppm
\textsuperscript{13}C NMR: 40.9 ppm
\textsuperscript{1}H NMR: 6.27 ppm
\textsuperscript{13}C NMR: 148.5 ppm
\textsuperscript{13}C NMR: 109.9 ppm

\textsuperscript{1}H NMR: 3.38 ppm
\textsuperscript{13}C NMR: 36.2 ppm
\textsuperscript{1}H NMR: 6.59 ppm
\textsuperscript{13}C NMR: 147.3 ppm
\textsuperscript{13}C NMR: 113.9 ppm

(\textit{d}-values were obtained at 300 MHz, CDCl\textsubscript{3})

To accomplish a ring closure of 4-methoxy-3-butenamides 258, the mixture of both stereoisomers of the enol ethers 258 was treated with an excess of aqueous 2M HCl. After protonation of the enol ether moiety, a nucleophilic attack of the amide and subsequent elimination of methoxide resulted in 4-pyrrolin-2-ones 259, which isomerized spontaneously to the thermodynamically more stable 3-pyrrolin-2-ones 257. The value of this reaction pathway is reflected in the fact that both previous steps (13 $\rightarrow$ 258 and 258 $\rightarrow$ 257) proceed in high yield and that in fact no purification is needed before the ring closure reaction. As stated in the introduction, this is the first ring expansion of cyclobutanones towards 3-pyrrolin-2-ones. Attempts were performed to introduce a chlorine atom at C-3 of pyrrolinone 257a by deprotonation and subsequent trapping of the anion with NCS, hexachloroacetone or CCl\textsubscript{4}. In neither case, a chlorinated pyrrolinone could be isolated.
Deprotonation of pyrroline 257a resulted in the formation of an anion where the negative charge can be delocalized towards the oxygen atom. It is known that the trapping of such anions with electrophiles rather proceeds at the 2-position instead of the 4-position of the anion system. The reaction of deprotonated 257 with alkyl halides as electrophiles yielded a mixture of alkylated and double alkylated pyrrolinones 14 and 260, respectively. Various reaction conditions were evaluated, but the formation of double alkylated pyrrolinones 260 could not be suppressed completely. In conclusion, a synthetic pathway was developed to prepare substituted pyrrolinones 257 and 14 from 2,2-dichlorocyclobutanones in an efficient way.

III.1.2 Reduction of pyrrolinones towards 3-arylpurroles

III.1.2.1 Introduction

Functionalized 3-arylpurroles exhibit a wide range of agrochemical and pharmacological properties. Pyrroline 1a is used in agriculture as a crop protection agent because of its antifungal activity. Its derivatives fenpiclonil 1b (Beret®) and fludioxonil 1c (Celeste®), active against fungi on seeds and seedlings, have already established their
Pyrrolnitrin, isolated from the bacteria *Pseudomonas pyrrocinia, P. cepacia* and *P. fluorescens* also revealed a promising activity against *Mycobacterium avium* and *M. tuberculosis*, strains which acquired considerable resistance towards conventional antibiotics and cause problems in the chemotherapy of numerous diseases (tuberculosis, AIDS, ...). Recently, some halogenated 3-arylpyrroles were patented as herbicidal agents. From a pharmacological point of view, the drug AWD 140-190 (19), proved to display potent anticonvulsant activity, indicating that this substance has a potential for an antiepileptic therapy. The natural alkaloid rhazinilam 20 is interesting because of its ability to mimic the cellular effects of the anticancer drug paclitaxel. Many other 3-arylpyrroles exhibit anti-inflammatory, analgesic, antiallergic and anti-HIV activities.

According to the physiological importance of these pyrroles, substantial attention has been paid to develop efficient synthetic approaches. One of the synthetic pathways consists of the use of 3- and 4-pyrrolin-2-ones to obtain 2-oxygenated or 2-halogenated pyrroles. Until now, only one article has been published using a reductant (DIBALH) to synthesize 3-substituted pyroles without the introduction of an additional functionality at the 2-position. That publication deals only with 4-methoxy-3-pyrrolin-2-ones, which can be viewed as enol ethers and, as a consequence, reveal different electronic properties as compared to 4-arylpyrrolinones 14 and 257. In addition, it is of synthetic utility to have at one’s disposal various reagents for the conversion of pyrrolinones to pyrroles. Therefore, a number of reducing agents were evaluated in order to accomplish an efficient and general method to synthesize pyrroles from 3-pyrrolin-2-ones.
III.1.2.2 Results and discussion

1-Isopropyl-4-phenyl-3-pyrrolin-2-one 257a was used as a model compound and treated with NaBH₄, LiAlH₄ and BH₃ in diethyl ether, THF or toluene from 0°C to reflux temperatures. No pyrroles were formed in the case of NaBH₄ and LiAlH₄ reduction of pyrrolinone 257a. Only the reaction of pyrrolinone 257a with 3 equivalents of borane in THF at reflux for 15 hours resulted in a small amount of pyrrole 15a which could barely be detected in the complex reaction mixture (not isolable, yield < 2%, calculated from ¹H NMR). With this result in mind, another borane derivative, 9-borabicyclo[3.3.1]nonane 261 was used to reduce pyrrolinone 257a. Fortunately, this reaction gave better results, and numerous reaction conditions were evaluated in order to optimize this reaction. The best yields were obtained using 3 equivalents of 9-BBN in refluxing toluene for 15h, under N₂-atmosphere using dry glassware. When more equivalents of 9-BBN were used, the yield did not increase and residual hydride was recovered (¹¹B NMR: δ 27 ppm (R₂B-H)).¹⁷⁴ A decrease in yield was observed when less equivalents of 9-BBN were used, even when the hydride was added in portions (5 × 0.2 equiv.) to the refluxing mixture with time intervals of 1.5h to minimize the thermal decomposition of 9-BBN.

With this procedure physiologically interesting 3-aryl and 3,4-disubstituted pyrroles 15 could be synthesized in fair yields from the corresponding 3-pyrrolinones.

To evaluate the generality of the 9-BBN reduction of pyrrolinones to pyrroles, efforts were done to develop a convenient route to other substituted starting materials. 5-Methyl-4-phenyl-4-pyrroline 264a was synthesized by reacting phenylacetone 262 with t-BuOK and chloroacetamide 263 (R = H) in DMSO.¹⁷⁵ Deprotonation of phenylacetone 262 at C-1 and subsequent reaction with chloroacetamide yields 4-oxo-3-phenylpentanamide via a nucleophilic substitution. At the reaction temperature (80°C) this intermediate cyclizes.
spontaneously and results in pyrrolinone 264a after elimination of water. The same literature procedure was used to synthesize the N-propyl derivative 264b, a new 4-pyrrolinone, which isomerized towards the more stable 3-pyrrolin-2-one 265 within three days at room temperature.

With N-isopropyl-2-chloroacetamide 267 as a reactant to obtain 1-isopropylpyrrolinones 271, no ring closure occurred, probably due to the steric hindrance of the isopropyl moiety, resulting in 3-aryl-N-isopropyl-4-oxopentanamides 268. To induce cyclization, the γ-ketoamides were treated with or without acid at various reaction conditions (some of these conditions are listed in Table 1). Upon heating of N-isopropyl-4-oxo-3-phenylpentanamide 268a in DMSO at 100°C for 1 hour, cyclization took place, but the formed 4-pyrrolinone 270a was not stable under these conditions and partially isomerized to the thermodynamically more stable 3-pyrrolinone 271a. In refluxing dichloromethane containing a trace of sulfuric acid, 3-pyrrolinone 271a was formed exclusively out of 268a, while the use of toluene yielded a mixture of the two isomers. The less stable 4-pyrrolinone 270a was easily separated from the mixture by column chromatography. After standing at room temperature for 4 hours, the pure 4-pyrrolinone 270a isomerized towards 3-pyrrolinone 271a and after one day the process of isomerization was completed. When treating 1-isopropyl-4-phenyl-5-methyl-4-pyrrolin-2-one 270a with a catalytic amount of sulfuric acid in refluxing dichloromethane, a complete isomerization occurred towards 3-pyrrolinone 271a. Analogous results were observed in the synthesis of pyrrolinone 271b. However, during the cyclization process of 4-oxopentanamide 268b, the intermediate hemiaminal 269b could be isolated as a crystalline compound. When the former γ-ketoamide 268b was allowed to stand at room temperature for 2 days, ca. 10% cyclization was observed towards the hemiaminal 269b, which could be easily filtered off and washed with dry diethyl ether.
In addition to the synthesis of pyrrolinones outlined above, some more derivatives were synthesized in order to have in hands a variety of substrates for the conversion into pyrroles. 1,3-Dimethylsuccinimide 273a and 1-methyl-3-phenylsuccinimide 273b, obtained from succinic acids 272 and methylamine, were reduced with NaBH₄ in acidic ethanol and
subsequently treated with acetic acid or aq. 2M HCl to induce dehydroethoxylation.\textsuperscript{176,177}

Both mixtures of isomers were chromatographed yielding pure isomers of 1-methyl-3-pyrrolinones 274 and 275 (in the literature, these compounds were not separated and were characterized as mixtures).\textsuperscript{176,177}

\[
\begin{align*}
\text{272} & \quad \text{aq. CH}_3\text{NH}_2 40\% \quad \text{fractional dest.} \\
\text{273a} & \quad R = \text{CH}_3 (84\%) \text{ ref 176,177} \\
\text{273b} & \quad R = \text{Ph} (79\%) \text{ ref 176,177} \\
\end{align*}
\]

The above synthesized pyrrolinones 264, 265, 270, 271, 274 and 275 were used as starting material to obtain various substituted pyroles (see Table 2). Using the optimized reduction conditions with 9-BBN, pyroles 278 could be synthesized in rather good yields. Only in the case of 1,3-dimethylpyrrole 278a the yields were very low, probably due to the volatility of the final product.

\[
\begin{align*}
\text{264 and 270} & \quad \text{3 equiv. 9-BBN} \quad \text{toluene, A, 15h} \\
\text{265, 271, 274 and 275} & \quad \text{276} \\
\end{align*}
\]

These results encouraged us to verify whether succinimides could be transformed directly to pyroles by reduction with 9-BBN. \textit{N}-Methyl-3-phenylsuccinimide 273b was dissolved in toluene and treated with 4 equivalents of 9-BBN at reflux for 15h. The reaction indeed yielded 1-methyl-3-phenylpyrrole 278b, however, in rather low yield.
Table 2. Synthesis of pyrroles 278 from pyrrolin-2-ones 264, 265, 270, 271, 274 and 275

<table>
<thead>
<tr>
<th>Pyrrole</th>
<th>Starting material</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>278a</td>
<td>274a</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>15%²</td>
</tr>
<tr>
<td>278a</td>
<td>275a</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>12%²</td>
</tr>
<tr>
<td>278b</td>
<td>274b</td>
<td>CH₃</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>48%</td>
</tr>
<tr>
<td>278b</td>
<td>275b</td>
<td>CH₃</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>55%</td>
</tr>
<tr>
<td>278c</td>
<td>264a</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>CH₃</td>
<td>21%</td>
</tr>
<tr>
<td>278d</td>
<td>270a or 270b</td>
<td>i-Pr</td>
<td>H</td>
<td>Ph</td>
<td>CH₃</td>
<td>53%</td>
</tr>
<tr>
<td>278e</td>
<td>264b or 265</td>
<td>n-Pr</td>
<td>H</td>
<td>Ph</td>
<td>CH₃</td>
<td>50%</td>
</tr>
<tr>
<td>278f</td>
<td>270b or 271b</td>
<td>i-Pr</td>
<td>H</td>
<td>4-CH₃OC₆H₄</td>
<td>CH₃</td>
<td>58%</td>
</tr>
</tbody>
</table>

² low yields probably due to volatility

In conclusion, various 4-aryl-3-pyrrolin-2-ones, 4-aryl-4-pyrrolin-2-ones and succinimides were synthesized and reduced with 9-borabicyclo[3.3.1]nonane towards 3-arylpyrroles 15 and 278b-f, an interesting class of compounds with broad physiological importance.

### III.1.3 Ring contraction of 3-aryl-2,2-dichlorocyclobutanones as a key step towards new 3-chloropyrroles

#### III.1.3.1 Introduction

As stated in the Literature Overview, the semi-benzilic Favorskii rearrangement has proven to be a valuable tool to construct cyclopropanes from the corresponding halogenated cyclobutanones. Whereas numerous reports describe the synthesis of cyclopropanecarbaldehydes from 2-halocyclobutanones, it is surprising to notice that only very few publications are found regarding the stereoselective synthesis of cis-1-
halocyclopropane-1-carbaldehydes. In most cases the synthetic pathways have no stereochemical impact, thus chromatographic separation of the formed isomers is required. Only two publications were found concerning a ring contraction of 2,2-dichlorocyclobutanones towards 1-chlorocyclopropanecarbaldehydes. One article describes the semi-benzilic Favorskii rearrangement after chromatographic separation of a diastereomeric mixture of steroidal spirocyclobutanones towards the corresponding spirocyclopropane steroids\textsuperscript{178d} and a second publication deals with the ring contraction of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (the dichloroketene adduct of cyclopentadiene).\textsuperscript{178b}

Up to now, \(\alpha\)-halogenated cyclopropanecarbaldehydes were (less efficiently) obtained via a dihalocarbene addition to \(O\)-protected 2-halopropen-1-ols\textsuperscript{179} or via a lithium-halogen exchange of geminal dihalocyclopropanes (synthesized via dihalocarbene additions to olefins) and subsequent reaction with formates or formamides.\textsuperscript{180} Also, oxidation of mixtures of stereoisomers of 1-halocyclopropylmethanol derivatives leads to the corresponding \(\alpha\)-halogenated aldehydes.\textsuperscript{181} Another approach consists of a carbene addition to \(\alpha\)-haloacrylates or derivatives.\textsuperscript{182} With the latter method, 5-(1-halocyclopropyl)-2,4-dienamides\textsuperscript{279} were synthesized and are patented as acaricidal and insecticidal compounds, e.g. against \textit{Musca domestica}, the common housefly.\textsuperscript{183}

Many other cyclopropane derivatives bearing carbonyl moieties or 1-alkenyl substituents show interesting physiological activities.\textsuperscript{184} Dictyopterene A\textsuperscript{280}, isolated from brown seaweeds in Hawaiian waters, is a constituent of a hydrocarbon mix excreted by these seaweeds that acts as a sperm attractant pheromone for the gametes of these seaweeds, and in certain cases deters feeding by herbivorous amphipods.\textsuperscript{185} Anthoplalone\textsuperscript{281} was isolated from the Okinawan actinia \textit{Anthopleura pacifica} and exhibits cytotoxicity against melanoma cells.\textsuperscript{186}
III.1.3.2 Results and discussion

3-Arylcyclobutanones 12 were reduced with sodium borohydride towards intermediate cyclobutylborates 282. Reaction of the latter with aqueous NaOH resulted in a semi-benzilic Favorskii rearrangement, yielding cyclopropanes 16. The stereoselectivity of the reaction is not due to an \textit{exo}-attack of the hydride, but due to steric hindrance of the aryl-substituent in the 3-position. An \textit{exo}-attack yielding \textit{cis}-substituted cyclobutanols is only possible when the substituent adapts a thermodynamically less favoured axial position. Having in hands an efficient procedure to synthesize \textit{cis}-2-aryl-1-chlorocyclopropanecarbaldehydes 16 from the corresponding 3-aryl-2,2-dichlorocyclobutanones 12,\textsuperscript{25} attempts were performed to explore the reactivity of these small rings in the light of the synthesis of new substituted cyclopropanes.

![Chemical structures and reaction schemes](attachment:image.png)

The obtained cyclopropanecarbaldehydes 16 were used as starting material for Wittig and Knoevenagel reactions yielding 1-alkenyl-1-chlorocyclopropanes 283-285, a class of compounds with pharmacological and agrochemical interest (see above). Attempts to use 284 or 285 for Michael induced ring closure (MIRC) reactions failed when treating these substrates with NaOEt. Also, dehydrochlorination reactions of 16a with various bases did not result in the formation of cyclopropenes, even when using the corresponding acetal 286. The
reaction of aldehyde 16a or acetal 286, with NBS/AIBN to induce a benzylic bromination did not work out, but instead an oxidation took place to the reactive acid bromide 288 and methyl cyclopropanecarboxylate 290, respectively. The latter substrate was also submitted to various dehydrohalogenation reactions, but no cyclopropene 291 was formed. In order to eliminate the possibility that the formed cyclopropenes decompose in situ and are not stable during workup, diphenylbenzofuran was used to trap any possible cyclopropene via a cycloaddition reaction. Also these reactions proved to be unsuccessful.

In the following reactivity study, the obtained 1-chlorocyclopropanecarbaldehydes 16 were used as precursors to synthesize new azaheterocyclic compounds. Especially 3-halogenated pyrroles are of particular agrochemical and pharmacological interest.

III.1.3.3 Literature of halogenated pyrroles

In the unabated search for new physiologically active compounds, the study of substituted pyrroles still remains a subject of considerable importance. Halogenated pyrroles isolated from nature, associated with diverse physiological activities, have served as lead structures to synthesize pyrroles with current use in agrochemistry (e.g. the antifungal pyrrolnitrin 1a)\textsuperscript{4-6} and medicine (3-chloropyrrole 292, fibrosis inhibitor).\textsuperscript{187,188}
Pentabromopseudilin $^{293}$ was first isolated from the marine bacterium *Alteromonas luteoviolaceus* and shows antitumor, antibacterial and antifungal activities and inhibits various enzyme systems in the cholesterol biosynthesis.$^{189}$ The alkaloids manzacidin A ($R = H$) and B ($R = OH$) $^{294}$ were isolated from the Okinawan sponge *Hymeniacidon species.*$^{190}$ Roseophilin $^{295}$ is a 3-chloropyrrole found in *Streptomyces griseoviridis* and has antibiotic and anti-leukaemic properties.$^{191}$ More than 20 compounds of the ‘oroidin’ ($^{296}$) family of $\beta$-brominated pyrroles (*i.e.* 4-bromo- and 4,5-dibromopyrrole-2-carbamides) have been isolated from nature and tested for physiological activities.$^{192}$ For instance, clathramides, isolated from *Agelas clathrodes*, have antifungal properties,$^{193}$ while other oroidins show antiserotonergic (keramadine), cytotoxic (agelastatin), antiviral (sceptrin), antihistaminergic (dispacamide) or antifouling (mauritiamine) activities.$^{192,194,195}$ With respect to this diversity of activities related to halogenated pyrroles, various synthetic methods to produce these compounds are already developed, where each method displays its own advantages to access pyrroles with specific substitution patterns.$^{26,196}$

Pentabromopseudilin $^{293}$  
*Alteromonas luteoviolaceus*

Pentabromopseudilin $^{293}$  
*Hymeniacidon species*

Pentabromopseudilin $^{293}$  
*Streptomyces griseoviridis*

Pentabromopseudilin $^{293}$  
*Agelas clathrodes*
Of current interest is the synthesis of 3-halogenated pyrroles bearing electron withdrawing groups (e.g. COOR, CN or CF$_3$). Structure-activity relationship studies revealed that also the presence of an aryl moiety at the pyrrole $\alpha$-carbon is often responsible for specific biological activities, e.g. 2-arylpyrrole 297 and derivatives are insecticidal compounds (100% mortality at 10 mg 297/l against Spodoptera eridania). Related pyrroles 298 were recently patented for the protection of wood from termites. In addition, substituted pyrroles with cyano- or carboxylic acid moieties at the $\alpha$-carbon are important intermediates in the synthesis of porphyrins and other ‘pigments of life’.

### III.1.3.4 Synthesis of halogenated pyrroles

In this section, an efficient synthesis is disclosed of halogenated 2-arylpyrroles from 3-aryl-2,2-dichlorocyclobutanones 12 via the intermediacy of 1-chlorocyclopropane-1-carbaldehydes 16. Only a few publications report the use of cyclopropanecarbaldehydes as building blocks for pyrrole syntheses by acid or thermal rearrangement of the corresponding imines. In the present strategy, cyclopropanecarbaldehydes 16 were ring opened and the resulting $\gamma$-haloaldehydes were iminated and treated with cyanide to induce a ring closure. In this way, another substituent could be introduced at the pyrrole ring.

2-Aryl-1-chlorocyclopropane-1-carbaldehydes 16 were treated with DMF-HCl to induce a ring opening towards 4-aryl-2,4-dichlorobutanals which were in situ chlorinated with Cl$_2$-gas towards the corresponding $\alpha$,$\alpha$-dichloroaldehydes 17 in high yields. After distillation, the obtained aldehydes 17 were converted to imines 303 by reaction with amines and titanium(IV) chloride, which serves as an activator and dehydrating agent. The obtained imines were unstable at room temperature, especially the $n$-propyl derivative, which decomposed within 2 hours at room temperature. The reaction of trichlorinated $N$-(butylidene)amines 303 with potassium cyanide in refluxing methanol resulted in a nucleophile induced cyclization towards 2-pyrrolines 304. Also with this type of compounds,
the $n$-propyl derivative proved to be unstable at room temperature. The obtained compounds 304 were used as starting material for the further synthesis of azaheterocyclic compounds. Deprotonation of pyrrolines 304 with sodium methoxide in methanol as a base yielded the isomeric 3-pyrrolines 305, which could not be isolated from the reaction mixture. Instead, the cyanide moiety was expelled and the resulting [2H]-pyrroles 306 isomerized towards 3-chloropyrroles 307 in good overall yield. Applying this procedure, interesting 3-chloropyrroles 307 could be synthesized in an efficient and straightforward manner.
In order to synthesize pyrroles still bearing the cyanide functionality, which is an important substituent contributing for specific physiological activities, the pyrrolines 304 were oxidized towards the corresponding pyrroles 308 using DDQ in toluene. This pathway towards 5-aryl-3-chloro-2-cyanopyrroles 308 with a specific substitution pattern is of importance because it introduces specific substituents in a rather short and efficient synthetic route.

![Chemical Structure](image)

In addition, the cyano functionality leaves opportunities for functional group transformation to various other physiologically interesting pyrroles, e.g. 2-(aminomethyl)pyrroles and pyrrole-2-carboxylates. Attempts to hydrolyse the cyano function of 308a with aqueous base or acid did not result in pyrrole-2-carboxylate 309. Starting material accompanied with decomposition products were recovered after treatment of 308a with aq. 6M HCl or 48% aq. HBr at reflux overnight. Alkaline treatment with a 50% aq. KOH solution did not result in hydrolysis, but at reflux temperatures in glycol, a decarboxylation occurred towards pyrrole 307a.

![Chemical Structure](image)

Attempts to hydrolyse the cyano function of pyrroline 304a, resulted in pyrrolidinone 315 as a single isomer. When the same reaction was performed at reflux temperatures, a mixture of cis- and trans-pyrrolidinones 315 and 316 was obtained, due to the isomerization of the initially formed cis-isomer to the thermodynamically more stable trans-pyrrolidinone 316. The stereochemical assignment of the two isomers was possible via analysis of $^1$H NMR.
The easy reaction of pyrroline 304a with electrophiles and the subsequent hydrolysis towards pyrrolidinones is also demonstrated in the formation of dichloropyrrolidinone 312 by reaction of pyrroline 304a with trichloroisocyanuric acid (TCIA).

2-Cyanopyrrole 308a was easily brominated using bromine in acetic acid towards polyfunctionalized pyrrole 319. This procedure can thus be used to synthesize 3,4-dihalogenated pyrroles bearing different halogens.

To arrive at 2-acylpyrroles, pyrrole 308a was treated with methyl lithium, resulting in the imine 317, which was hydrolyzed to 318 by reaction with aq. 6M HCl at room temperature. Attempts to make pyrrole-2-carbaldehydes via DIBALH reduction of the cyano group of 308a and subsequent hydrolysis did not yield the expected products. Alternatively, pyrrole-2-carbaldehyde 320a and pyrrole-2-carboxylate 321a could be synthesized by electrophilic substitution of 2-unsubstituted pyrrole 307a. A Vilsmeier-Haack reaction of pyrrole 307a with DMF-POCl3 yielded pyrrolecarbaldehydes 320a and 320b which could easily be separated by column chromatography (ratio 320a/320b 65:35). Due to the fact that the electrophilic substitution of pyrroles is kinetically driven to take place at the α-position, the major compound was the 2-formylated pyrrole 320a, as expected.
Analogous reactions were evaluated to synthesize pyrrole-2-carboxylates. Reaction of pyrrole 307a with trichloroacetyl chloride/AlCl₃ in dry THF and subsequent quenching with NaOMe did not result in pyrrole 321a. Friedel-Crafts acylation using methyl chloroformate and aluminum(III) chloride in carbon disulfide yielded a mixture of carboxylated pyrroles 321, consisting predominantly of pyrrole 321b. Substitution at β-position of pyrroles has been observed when the nitrogen bears bulky groups. Indeed, the carboxylation of pyrrole 307a could be seen to be a little more sterically demanding as compared to the formylation, which shifts the ratio towards the 3-substituted pyrrole 321b (ratio 321a/321b 1:4). Also, under the used reaction conditions, rearrangements of pyrrole substituents are known to result in the thermodynamically most stable compounds (in this case pyrrole 321b).²⁰³ The HSAB-theory as a rationale for selective acylation has only been demonstrated for pyrroles bearing electron withdrawing groups at nitrogen. With these substrates the hard Lewis acid AlCl₃ promotes C-3 substitution via a charge controlled mechanism instead of a frontier orbital controlled mechanism (driving the substitution towards the C-2).²⁰⁴ However, N-alkyl- or N-unsubstituted pyrroles are generally acylated at C-2. To accomplish a carboxylation at C-2, deprotonation of the most acidic hydrogen of pyrrole 307a, i.e. the hydrogen at α-position, and subsequent reaction with methyl chloroformate yielded exclusively methyl pyrrole-2-carboxylate 321a in acceptable yield. With the procedures outlined above, various interesting halogenated pyrroles could be synthesized in a straightforward manner.
III.1.4 Synthesis of 2-(hydroxymethyl)- and 2-(aminomethyl)pyrroles

III.1.4.1 Introduction

The obtained 3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole \(308a\) and 3-chloro-2-formyl-1-isopropyl-5-phenylpyrrole \(320a\) are good substrates to synthesize 2-(aminomethyl)- and 2-(hydroxymethyl)pyrroles, which are members of an interesting class of physiologically active compounds. 2-Methylene-spaced substituted pyrroles are versatile intermediates in the synthesis of natural products, especially porphyrins and related pyrrole oligomers. \(^{205}\)
Porphobilinogen (PBG 322) is the central building block for the biosynthesis of haemoglobin, chlorophyll and many other brightly-colored pigments of life 323. This cyclotetramerization of PBG can also be mimicked by the acid-catalyzed reaction of 2-(hydroxymethyl)pyrroles.206

Recently, 2-(hydroxymethyl)pyrroles (e.g. 324) were discovered as a new class of inhibitors of α-chymotrypsin, a member of serine protease enzymes.207 Viminol 325 is a central analgesic and used for the treatment of drug dependency.208

Substituted 2-(aminomethyl)pyrroles have attracted renewed interest due to their specific binding properties to dopamine receptors. Pyrrole 326 (DU 122290) and 327 bind specifically at the dopamine D3 receptors and can be used for antipsychotic therapy,209 whereas pyrrole 328 (FAUC 356) is a selective dopamine D4 receptor partial agonist and might be of interest in the treatment of ADHD.210 2-(Aminomethyl)pyrrole derivatives were also patented as analgesics211 and used as building blocks for pyrrolo[2,1c][1,4]benzodiazepines, compounds with pronounced antitumor activities.212 Other 2-(aminomethyl)-5-arylpyrroles are mono-amine oxidase inhibitors and show antidepressant activities.213

III.1.4.2 Results and discussion

2-Formylpyrrole 320a and 2-cyanopyrrole 321a were reduced with NaBH₄ and LiAlH₄ respectively to yield the corresponding 2-(hydroxymethyl)- and 2-(aminomethyl)pyrroles 329 and 330. These pyrroles were purified by a fast flash
chromatography, because these compounds tended to polymerize on silica gel, forming a mixture of brightly colored (red-purple) compounds, which could not be characterized.

In order to establish a convenient method to synthesize 2-methylene-spaced functionalized pyrroles, cyclic imines 332 were evaluated as starting material. 1-Pyrrolines are known to serve as good substrates for the synthesis of halogenated pyrroles by dihalogenation and subsequent dehydrohalogenation. In this respect, the known cyclic imines 332 were prepared by a nucleophilic addition of 3-butenylmagnesium bromide to benzonitriles, followed by a cyclization of the intermediate γ,δ-unsaturated ketimine salt induced by N-bromosuccinimide.215

These pyrrolines 332a,b were treated with halogenating agents in order to obtain 3,3-dihalogenated-1-pyrrolines 335. Reactions with NBS resulted in tarry reaction mixtures. Analogous reactions with NCS in refluxing CCl$_4$ or CHCl$_3$/CH$_3$CN for 1 hour yielded mixtures of mono- and dichlorinated pyrrolines 334 and 335 (ratio 1:1, calculated from $^1$H NMR spectra, see Table 3). Prolongation of the reaction time shifted this reaction towards dichlorinated pyrrolines. However, the reaction mixture contained some decomposition material due to the inherent instability of the halogenated pyrrolines 335. A better result was obtained by the use of trichloroisocyanuric acid (TCIA) as the halogenating agent. The fact that this reagent is cheaper as compared to NCS and the fact that less reagent is necessary due to the presence of 3 chloro atoms per molecule, should re-establish its use in organic
synthesis. Treatment of pyrroline 332a with 0.7 equivalents of TCIA resulted in a clean reaction mixture consisting of almost exclusively dichlorinated pyrroline 335a. In the reaction mixture a second compound was formed and could be separated from the major compound 335a by flash chromatography. The compound was characterized as the N-chlorinated analogue 336. A complete conversion of dichloropyrroline 335a towards the overchlorinated product 336 could be established with an excess of TCIA in a refluxing mixture of CHCl₃/CH₃CN for 5 hours. An analogous reaction with NCS did not yield any 336 at all, even after reflux overnight. Treatment of 336 with a saturated aqueous NaHSO₃-solution at room temperature for 15 minutes yielded dichlorinated pyrroline 335a quantitatively.
Table 3. Chlorination of pyrroline 332a using NCS or TCIA

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Starting material 332a (%)a</th>
<th>334 (%)a</th>
<th>335a (%)a</th>
<th>336 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 equiv NCS, CCl₄, Δ, 1h</td>
<td>30</td>
<td>40</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>2.1 equiv NCS, CHCl₃/CH₃CN (9:1), Δ, 1h</td>
<td>20</td>
<td>40</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>2.1 equiv NCS, CHCl₃/CH₃CN (9:1), Δ, 15h</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>0.7 equiv. TCIA, CHCl₃/CH₃CN (9:1), Δ, 1.5h</td>
<td>0</td>
<td>0</td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td>1) 0.7 equiv. TCIA, CHCl₃/CH₃CN (9:1), Δ, 1.5h 2) aq. NaHSO₃, r.t., 15min.</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2 equiv. TCIA, CHCl₃/CH₃CN (9:1), Δ, 5h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

a ratios calculated from ¹H NMR spectra

The obtained 2-aryl-5-(bromomethyl)-3,3-dichloro-1-pyrrolines 335 were treated with triethylamine to induce a dehydrochlorination towards 2-(bromomethyl)pyrroles 337. However, despite the various attempts, no clean reaction towards pyrrole 337 could be accomplished. In contrast, a one-pot procedure using sodium hydroxide, methoxide or ethoxide resulted in a simultaneous nucleophilic substitution and dehydrohalogenation yielding the corresponding 2-(alkoxymethyl)pyrroles 338 in good yields.
Analogous reactions with amines in CH$_2$Cl$_2$ in the presence of potassium carbonate as a base also yielded pyrroles 339 in good yields. In addition, the reaction of pyrroline 335b with trimethyl phosphite in acetonitrile to accomplish a synthesis of dimethyl (4-chloro-5-(4-chlorophenyl)pyrrol-2-yl)methylphosphonate 340 via an Arbuzov-reaction proceeded in almost quantitative yield.

![Chemical structures showing reaction pathways and yields](image)

In conclusion, it can be stated that a generally applicable synthesis is developed to access 2-(hydroxymethyl)-, 2-(alkoxymethyl)- and 2-(aminomethyl)pyrroles, a class of compounds with currently renewed interest as physiologically active heterocycles.

### III.2 Reactivity of N-(cyclobutylidene)amines

#### III.2.1 Introduction

The conversion of ketones towards the corresponding imines alters the reactivity profoundly and extends the scope of reactions that can be used to transform or functionalize the parent ketones. In that respect, the reactivity of N-(cyclobutylidene)amines will be evaluated to provide new synthetic pathways leading to physiologically active compounds. It is surprising that no N-(3-arylcyclobutylidene)alkylamines have been described so far, which makes the study of these compounds worthwhile. In addition, halogenated N-(cyclobutylidene)amines in general have barely been studied. Besides theoretical calculations, only one article was found concerning halogenated N-(cyclobutylidene)amines. This article deals with the synthesis of the N-t-butylimine of a
III.2.2 Synthesis and reactivity of \( N \)-(cyclobutylidene)amines

III.2.2.1 Synthesis of \( N \)-(3-arylcyclobutylidene)alkylamines

The readily available 3-aryl-2,2-dichlorocyclobutanones \( 12 \)\(^{76,77} \) were dehalogenated with zinc in acetic acid prior to the conversion to imines \( 342 \), because a direct imination of dichlorinated cyclobutanones \( 12 \) was not successful and resulted in complex reaction mixtures. In contrast, dehalogenated cyclobutanones \( 174 \) were easily iminated using titanium(IV) tetrachloride as a catalyst and dehydrating agent, resulting in imines \( 342 \), which were stable at -20°C for several days. These new compounds served as starting products for further transformations.

III.2.2.2 Reduction of \( N \)-(cyclobutylidene)amines

Having in hands new \( N \)-(3-arylcyclobutylidene)alkylamines \( 342 \), efforts were performed to prepare the corresponding cyclobutylamines \( 346 \). Synthetic methods to synthesize cyclobutylamines are not widespread, despite the fact that cyclobutylamines are an important group of compounds with current interest in the development of anti-HIV
therapy. Indeed, since the discovery that oxetanocin (343) possessed potent anti-HIV properties, the study towards carbocyclic analogues has been increased the last years. The remarkable antiviral activities of Cyclobut-A (344a) and -G (344b) justify the development of stereoselective synthetic pathways to form new cyclobutylamines.

3-Arylcyclobutylamines 346 were synthesized in good yields by reduction of imines 342. Only one stereo-isomer was formed and the configuration was determined on the \(N\)-\(t\)-butyl-\(N\)-(3-phenylcyclobutyl)amine by DIFNOE experiments, which revealed that the substituents adapted a cis-configuration. This result is due to the steric hindrance of the aryl moiety, driving the attack of the hydride to the imine to the least hindered side of the cyclobutane ring and is analogous to the result obtained by reduction of 3-phenylcyclobutanone 174 towards cis-3-phenylcyclobutanol 282 (see Section III.1.3.2).

III.2.2.3 Synthesis and reactivity of halogenated imines

As stated above, a synthetic detour had to be made to end up with chlorinated \(N\)-cyclobutylidene)amines from 2,2-dichlorocyclobutanones 12 via initial dechlorination and subsequent imination. Imines 342 were treated with \(\text{NCS}\) in \(\text{CCl}_4\) to synthesize the crystalline tetrachlorinated imines 347, which could be stored even at room temperature for several days. When large amounts of imines 347 were synthesized, the reaction was carried out using dried \(\text{CCl}_4\) (technical \(\text{CCl}_4\) was washed with \(\text{H}_2\text{SO}_4\) and distilled over \((\text{MgCO}_3)_4\cdot\text{Mg(OH)}_2\)). These
new compounds were reacted with nucleophiles to evaluate whether ring opening, ring contraction or ring substitution occurs.

To accomplish a ring contraction towards polychlorinated cyclopropanes (analogous to the synthesis of cis-2-aryl-1-chlorocyclopropanecarbaldehydes 16, see Section III.1.3.2), attempts were made to reduce 3-phenyl-N-(2,2,4,4-tetrachlorocyclobutylidene)amine 347a. Reactions with LiAlH₄ or NaBH₄ under various reaction conditions yielded complex reaction mixtures, in which the dehydrochlorinated product 348 could be determined. Surprisingly, the reaction of imine 347a with borane yielded the reduced compound 350 in high yield. Also in this case, the cis-stereochemistry was confirmed by DIFNOE-experiments.
Treatment of tetrachlorocyclobutylamine 350 with base, in casu sodium methoxide in methanol did not result in a ring contraction (as compared to the ring contraction of 2,2-dichlorocyclobutanol 282 in methanol, Section III.1.3). Attempts to obtain cyclopropanes as intermediates for new cyclopropenones via other methodologies will be discussed in Section III.3.

The reaction of N-(cyclobutylidene)amine 347a with an excess of 4M sodium methoxide in methanol resulted in a compound which could be N-(cyclobutenylidene)amine 353 or cyclopropene 359, based on the spectroscopic data. Also from a mechanistic point of view both end products are possible. In pathway A (see Scheme below) an initial dehydrohalogenation takes place followed by substitution of the remaining chloro atoms by methoxide. In pathway B, a nucleophilic attack to the imine results in a semi-benzilic Favorskii rearrangement, analogous to the ring contraction of 2,2-dichlorocyclobutanones (see section III.1.3), followed by dehydrohalogenation and substitution of the chloro atoms by methoxide. No such cyclopropanes are known today, so spectroscopic data could not be compared. Also, trimethoxycyclobutenimines are not described before. After hydrolysis of the compound, only aromatic protons were visible in the $^1$H NMR spectra. Other spectroscopic data ($^{13}$C NMR, IR or MS) also could not discriminate between structures 360 and 361. Fortunately, cyclobutenedione 360 is a known compound and the melting point and all spectra of compound 360 corresponded to those reported for this structure. In the following chapters, this reaction pathway will be further studied and evaluated.
In order to develop a short synthetic pathway towards hydroxycyclobutenedione 360, attempts were made to chlorinate 2,2-dichlorocyclobutanone 12a with NCS. Under various reaction conditions, always a complex reaction mixture was obtained in which starting
material could still be determined. A better result was obtained by chlorination of 12a with chlorine gas in DMF/chloroform, yielding 2,4,4-trichloro-3-phenylcyclobutene 362 in high yield. Hydrolysis under very harsh conditions, i.e. 90% sulfuric acid at 80°C overnight, afforded cyclobutenedione 360 in high yield. This procedure is cheaper, more efficient and easier to perform as compared to other literature procedures (see Section III.2.3.3).

III.2.3 A concise literature overview of cyclobutenediones

III.2.3.1 General aspects

Cyclobutenediones have interested organic chemists since long time due to the intriguing molecular skeleton of this compound, suggesting specific properties and reactivities. Indeed, since the first synthesis of cyclobutenedione 360,224 also called a cyclobutadienoquinone in analogy with benzoquinones, in 1955 via a cycloaddition of phenylacetylene with trifluorochloroethene and subsequent hydrolysis, numerous studies have been performed on this type of compounds.225 Hydroxylated cyclobutenediones 364a (squaric acid) and 364b (semisquaric acid) are members of the homologous series shown below.

\[
\begin{align*}
363a & \quad R = \text{OH deltalic acid} \\
363b & \quad R = \text{H semideltalic acid} \\
364a & \quad R = \text{OH squaric acid} \\
364b & \quad R = \text{H semisquaric acid} \\
365a & \quad R = \text{OH croconic acid} \\
365b & \quad R = \text{H semicroconic acid} \\
366a & \quad R = \text{OH rhodizonic acid} \\
366b & \quad R = \text{H semirhodizonic acid}
\end{align*}
\]
3-Hydroxycyclobutenediones display remarkable acidic properties (e.g. 4-phenylsemisquaric acid $\text{360}$) probably because of the possibility to form aromatically stabilized mesomeric forms $\text{368}$ and $\text{369}$. However, a recent study revealed that cyclobutenediones $\text{367}$ show only a moderate degree of aromaticity.\textsuperscript{226}

\[
\begin{align*}
\text{360, pKa} &= -0.2 \\
\text{367} &\quad \text{368} &\quad \text{369}
\end{align*}
\]

III.2.3.2 Natural occurrence and uses of 3-hydroxy-, 3-alkoxy- and 3-aminocyclobutenediones

Semisquaric acid or 3-hydroxy-3-cyclobutene-1,2-dione $\text{364b}$ has been isolated from the maize molds \textit{Fusarium moniliforme} and \textit{Gibberella fujikuroi} as a sodium and potassium salt (pK\textsubscript{a} = 0.88).\textsuperscript{227} These salts were named Moniliformin (32) and are toxic for mammals and possess plant growth regulating and phytotoxic effects.\textsuperscript{228,229} Since the discovery of Moniliformin, it served as a “lead” compound to synthesize numerous analogues which showed interesting physiological properties. Squaric acid derivatives were patented for their application in the treatment of chronic inflammatory diseases such as asthma, multiple sclerosis and rheumatoid arthritis.\textsuperscript{230} The vinylogous dibutylester 35 can be used as a therapy for \textit{alopecia areata}, a kind of hair loss.\textsuperscript{35,36} More general, positive results have been obtained in medicinal chemistry by the use of the squaryl group as an isosteric group to enhance biological activity.\textsuperscript{231} Squarates possess also a strong chelating ability to metal ions.\textsuperscript{232}

\[
\begin{align*}
\text{32 Moniliformin} \\
(M = \text{K}^+, \text{Na}^+) \\
\text{35} \\
\text{370} \\
R^1 = \text{NHR}^2, \text{H, aryl, alkyl} \\
R^2 = \text{H, aryl, alkyl} \\
\text{371}
\end{align*}
\]
More recently, significant research is focussed to mono- and diamino substituted cyclobutenediones, or (semi)squaramides 370 which is reflected in the large amounts of patents concerning this topic. For instance, semisquaramide 371 and derivatives showed neuroexcitatory activity in mammalian central nervous systems and showed a potent paralytic activity. 233 Other semisquaramides display smooth muscle relaxation (37) 38 and antimigraine activities (38 and BMS-181885 372). 39,234 Also diaminocyclobutenediones were the subject of considerable research and resulted in pharmacologically interesting compounds, such as Pibutidine 36, a histamine H2 receptor antagonist, 37 squaramide 373 (antiatherosclerotic agent) 235 and EAA-090 374 (neuroprotectant with potential as a treatment for brain damage resulting from stroke). 236 Besides the above mentioned physiological properties of cyclobutenediones, these compounds also proved to be powerful synthetic building blocks for the synthesis of a variety of carbo- and heterocycles, such as quinones, furanones, xanthones, cyclopentenediones, phenols and 2-pyridones. 40,237

III.2.3.3 Synthesis of 4-unsubstituted and 4-arylsemisquarates and -squaramides

a) Via [2+2]-cycloaddition reactions

Thermal and photochemical [2+2]-cycloadditions of ketenes or ketene analogues to alkoxyalted or perhalogenated alkenes and alkynes have resulted in the formation of a variety of substituted cyclobutenes, which yielded cyclobutenediones after acidic hydrolysis. 225 As examples, the syntheses of 4-aryl-3-hydroxy-3-cyclobutene-1,2-diones 378 238 and
Results and Discussion

Semisquaric acid $364b^{239,240}$ are given in the scheme below. Often, difficult procedures or not readily available starting materials are used to get to these compounds. $^{225}$

\[
\begin{align*}
\text{RO}_2\text{OR} & \quad + \quad \text{Ar}-\text{COCl} \quad \xrightarrow{\text{Et}_3\text{N}} \quad \text{hexane, 20°C} \quad \text{RO}_2\text{Ar} \quad \xrightarrow{\text{H}_3\text{O}^+} \quad \text{HO}_2\text{Ar} \\
\text{375} & \quad 376 \quad \text{377} (60-70\%) \quad \text{378} (65-85\%)
\end{align*}
\]

\[
\begin{align*}
\text{F} \quad \text{Cl} & \quad + \quad \text{Cl} \quad \text{Cl} \quad \xrightarrow{180\,°C, \ 10\,h} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \xrightarrow{\text{Et}_3\text{N}} \quad \text{Cl} \quad \text{Cl} \quad \xrightarrow{\text{aq. H}_2\text{SO}_4} \quad \text{Cl} \quad \text{Cl} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \\
\text{379} & \quad 380 \quad \text{381} (48\%) \quad \text{382} (88\%) \quad \text{364b} (95\%)
\end{align*}
\]

b) Via bromination of cyclobutanone

3-Hydroxycyclobutenedione $364b$ was also synthesized via bromination of cyclobutanone $94^{240}$. Subsequent dehydrobromination by triethylamine yielded the unstable cyclobutenone $384$, which was hydrolyzed towards $364b$. Although the starting cyclobutanone is commercially available, the very low overall yield makes this procedure of no preparative use.

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{Br}_2, \text{CHCl}_3} \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \xrightarrow{\text{Et}_3\text{N}, \text{Et}_2\text{O}} \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \xrightarrow{\text{conc. HCl}, \ 55\,°C, \ 16\,h} \quad \text{Br} \quad \text{Br} \quad \text{F} \quad \text{F} \quad \text{O} \\
\text{94} & \quad 383 (90\%) \quad \text{384} \quad \text{364b} (11\%)
\end{align*}
\]

c) Via functionalization of cyclobutenediones

A number of methods have been developed to synthesize cyclobutenediones via functionalization of the parent (semi)squaric acids. For instance, 3-hydroxycyclobutenedione $364b$ can be synthesized by reduction of 3,4-dihydroxycyclobutenedione $364a$ via the intermediacy of the corresponding chlorides $385$ and $386^{241}$. 
Semisquaric esters can be obtained by azeotropic esterification with alcohols in refluxing benzene or by reaction with diazomethane.\textsuperscript{225c} The corresponding amides are readily obtained by reaction of semisquarates with amines. To synthesize 4-aryl substituted cyclobutenediones 378, semisquaric acid was treated with aryldiazonium salts in the presence of copper(II) chloride.\textsuperscript{242} Also the reaction of Grignard or aryllithium reagents with squarates 388 yielded arylated cyclobutenediones 391 in varying yields.\textsuperscript{225}

\section*{III.2.4 Reactivity of \textit{N}-(cyclobutenyldiene)amines}

The reaction of \textit{N}-(3-aryl-2,2,4,4-tetrachlorocyclobutylidene)isopropylamines 347 with an excess of sodium methoxide yielded \textit{N}-(trimethoxycyclobutenyldiene)amines 353, as
discussed in Section III.2.2.3. In a more controlled way, the intermediate imine 348 could be isolated by treatment of 347a with 1 equivalent of 4M sodium methoxide in methanol at 0°C or with 1 equivalent of triethylamine in diethyl ether. Subsequent treatment of 348 with 3 equivalents of 4M sodium methoxide in methanol resulted, as expected, in N-(cyclobutenylidene)amine 353a via substitution of the chloro atoms. Attempts to reduce this compound towards the corresponding amine 392 were unsuccessful. In contrast to experiments with other nucleophiles, such as sodium ethoxide or sodium isopropoxide, the reaction of imine 348 with n-propylamine did not lead to the substituted imine 393a.

![Chemical structures and reaction schemes](image)

To accomplish a synthetic pathway to hydroxylated cyclobutenylamine 396, the corresponding imine 353a was treated with various reducing agents. These reactions only resulted in complex reaction mixtures, which often still contained starting material. Also the reaction of 353a with methyllithium was unsuccessful.

A partial hydrolysis of cyclobutenimine 353a could result in new α-imino cyclobutenones (e.g. 394), which are interesting building blocks for further reactions. Unfortunately, it proved to be impossible to synthesize these compounds via hydrolysis of
In this respect, it was thought that a non-acidic hydrolysis of thioacetals (e.g. 393b) could provide α-imino ketone 394. However, the reaction of N-(trichlorocyclobutenylidene)amine 348 with 4M sodium ethanethiolate in ethanethiol did not result in the substituted product 393b.

III.2.5 Synthesis and reactivity of cyclobutenediones

Cyclobutenediones possess interesting properties both from a pharmaceutical and synthetic point of view (see Section III.2.3). Therefore, different cyclobutenediones were synthesized from N-(cyclobutenylidene)amines 353 in order to develop a new route to produce these compounds. N-(Cyclobutenylidene)amines 353 were hydrolyzed with an excess of aqueous 2M HCl in refluxing dichloromethane (biphasic system) towards 397 in high yields. When harsher conditions were used, a complete hydrolysis towards 4-phenylsemisquaric acid 360 took place. Also the reaction of methyl 4-phenylsemisquarate 397a with isopropylamine at room temperature for 10 minutes yielded the corresponding squaramide 398 in quantitative yield. Attempts to synthesize iminocyclobutenones 399 via imination of diones 397a or 398 did not work out.
Having in mind the renewed interest of squaramides as potent physiologically active compounds, the reaction pathway described above was evaluated in order to verify whether this route is also applicable to unsubstituted cyclobutane 94. Commercially available cyclobutane was used to synthesize the corresponding N-alkylimines 44.

The obtained imines have to be handled with care in order to reach optimal yields (low boiling points!). Their heat and moist sensitivity are responsible for the relative instability of these compounds. Especially the n-propyl derivative 44b, could not be stored even at low
temperature (-20°C). Nevertheless, when the obtained imines were used directly for further synthesis, no special precautions had to be taken. \(N\)-(Cyclobutylidene)amines 44 were reacted with 5 equivalents of NCS in dry tetrachloromethane resulting in new \(N\)-(2,2,4,4-tetrachlorocyclobutylidene)alkylamines 400, which were more stable as compared to the non-chlorinated imines. A direct chlorination of cyclobutanone with NCS or chlorine gas did not result in tetrachlorocyclobutanone 401, but yielded a mixture of compounds which could not be separated by distillation or chromatography. Treatment of the chlorinated imines 400 with an excess of 4M sodium methoxide in methanol yielded not the expected \(N\)-(2,4,4-trimethoxy-2-cyclobutenylidene)alkylamines, but compounds 408.

\[
\begin{align*}
\text{400} & \xrightarrow{10 \text{ equiv. } 4\text{M NaOMe}} \text{MeOH, } \Delta, \text{ 1h} \quad \text{402} \\
\text{402} & \xrightarrow{-\text{HCl}} \text{403} \\
\text{403} & \xrightarrow{\text{excess aq. } 2\text{M HCl}} \text{CH}_2\text{Cl}_2, \Delta, \text{ 1h} \quad \text{409a} \text{ R} = \text{i-Pr} (75\%) \\
& \quad \text{409b} \text{ R} = \text{n-Pr} (25\%, \text{ from 94}) \\
& \quad \text{409c} \text{ R} = \text{i-Bu} (34\%, \text{ from 94}) \\
& \quad \text{409d} \text{ R} = \text{s-Bu} (81\%) \\
& \quad \text{409e} \text{ R} = \text{t-Bu} (80\%)
\end{align*}
\]

The formation of these compounds can be rationalized by a Michael-addition of methoxide to the intermediate \(N\)-(trichlorocyclobutenylidene)amine 402 and subsequent dehydrochlorination and substitution of the remaining chloro atoms by methoxide. The intermediates 403, 404 and the resulting imines 407 could not be isolated, but instead the
hydrolyzed cyclobutenones 408 were obtained after aqueous workup. After hydrolysis of the vinylogous amides 408 with aqueous HCl, crystalline semisquaramides 409 were isolated and purified by chromatography in good yields. Due to the low stability of n-propyl and isobutylamino intermediates, a rapid synthesis of 409b and 409c was necessary, without purification of the intermediates. In that way, an overall yield of about 30% for squaramides 409b,c and ca. 40-45% for derivatives 409a,d,e could be accomplished from commercially available cyclobutanone.

Because cyclobutenones 408 are vinylogous amides, the free electron pair at the nitrogen atom of 408 is delocalized as depicted in the scheme below (mesomeric forms 408 ↔ 408bis). It is not surprising that compounds 408 occur as mixtures of E- and Z-isomers with respect to the iminium bond due to the hindered rotation of the C-N bond as a consequence of its high double bond character. These isomers (ratio major/minor 92:8 to 100:0) have slightly different chemical shifts in 1H NMR and 13C NMR. In the case of the t-butyl derivative 408e (R = t-Bu), only one isomer was detected. An analogous hindered rotation was observed with cyclobutenediones 409.

To establish a synthesis of semisquaric acid 364b, squaramide 409a was treated with numerous acids in varying concentration, but no hydrolysis product could be determined, even when treating 409a with 95% sulfuric acid at 80°C overnight. Also an alkaline hydrolysis was not successful, yielding reaction mixtures probably by ring opening of the cyclobutenedione ring. A clean ring opening of 409a could be established by the reaction with n-propylamine, resulting in α-ketoamide 411. Because the above mentioned attempts to synthesize semisquaric acid did not work out, hydrolysis reactions were performed on the parent tetrachlorinated imine 400a and N-(2,4,4-trichloro-2-cyclobutenylidene)-isopropylamine 402a, which could be synthesized from 400a by reaction with triethylamine. In no cases, semisquaric acid was found. Instead, the reaction of imine 402a with 3M NaOH in refluxing dioxane yielded the ring opened product 410.
Results and Discussion

III.2.6 Synthesis and reactivity of hydroxycyclobutenones

III.2.6.1 Reduction of cyclobutenediones

In the present literature only a few publications describe the synthesis of 2-hydroxycyclobutenones from (semi)squarates or (semi)squaramides. In one publication, sodium borohydride was used to reduce 4-phenylsemisquaramides,\(^{243}\) while other publications make use of DIBALH or LiAlH\(_{(t-BuO)}\).\(^{244}\) In an evaluation of different reducing agents to synthesize hydroxycyclobutenones from 397, it was found that an efficient reduction could be established using zinc in acetic acid at room temperature. This procedure provides a new, easy to perform and cheap method to synthesize 4-hydroxy-2-cyclobuten-1-ones 412 from 397. When higher temperatures were used, a substantial amount of O-acetylated product was formed, lowering the yield of 412. Therefore, the temperature of the reduction reaction was kept under 25°C at all times. In that way various new hydroxycyclobutenones 412 were synthesized. Derivatives 413, 414 and 416 were synthesized from 412a by reaction with
sodium hydroxide, isopropylamine and methyllithium, respectively. In the latter case, methyllithium added only once to the cyclobutene moiety, probably due to the formation of a stabilized enolate. New O-acyl derivatives were synthesized in high yield by the treatment of hydroxycyclobuteneones with acid chlorides or anhydrides.

III.2.6.2 Attempts to synthesize 4-aminocyclobutenones

In a second part of this research, efforts were performed to substitute the hydroxyl moiety of 412a with N-nucleophiles. In order to do so, several reactions were carried out to transform the hydroxy functionality into a better leaving group. The reaction of 412a with thionyl chloride and pyridine did not result in the transformation into 420 (X = Cl).
standard procedures to convert 412\textsuperscript{a} to the corresponding mesylate, tosylate or triflate were unsuccessful (see Table 4). Surprisingly, the reaction of hydroxycyclobutenone 412\textsuperscript{a} with 1.5 equivalents of tosyl chloride in the presence of silver(I) oxide and potassium iodide yielded the tosylate 418. Via this procedure\textsuperscript{245} an intermediate tosyl iodide is formed \textit{in situ} which reacts readily with the hydroxyl function of 412\textsuperscript{a}, whereas the reaction with tosyl chloride gave no satisfactory results.

When the tosylate 418 was treated with isopropylamine to realize a nucleophilic substitution, complex reaction mixtures were obtained. Instead, the reaction in DMF with potassium phthalimide, which is less nucleophilic and does not react with the vinylogous ester moiety, gave the substituted product 421\textsuperscript{a}. An analogous reaction with sodium azide, also resulted in a substitution of the tosyl group to 421\textsuperscript{b}. In order to evaluate the possibility for substitution of the tosyl group with other nucleophiles, also the reaction with adenine/K\textsubscript{2}CO\textsubscript{3}/18-crown-6-ether, KCN and diethyl phosphite/NaH were carried out, however without results.
Table 4. Attempts to synthesize 418, 420 from 4-hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a (see previous Scheme)

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 1.5 equiv. mesyl chloride, 0.1 equiv. DMAP, pyridine, 0°C to r.t., 1h</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>2. 1 equiv. triflic anhydride, 1 equiv. Et₃N, CH₂Cl₂, 0°C, 30min.</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>3. 1) see 2. 2) 1 equiv. K-phthalimide, 0°C to r.t., 30min</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>4. 1.1 equiv. SOCl₂, 1 equiv. pyridine, CH₂Cl₂, 0°C, 1h</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>5. 1.05 equiv. tosyl chloride, pyridine, 0°C, 4h</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>6. 1.05 equiv. tosylation chloride, 1.05 equiv. Et₃N, CH₂Cl₂, 0°C to r.t., 30min</td>
<td>complex reaction mixture</td>
</tr>
<tr>
<td>7. 1.5 equiv. tosyl chloride, 2 equiv. Ag₂O, 2 equiv. KI, CH₂Cl₂, 40°C, 45min</td>
<td>418 (66%, crude)</td>
</tr>
</tbody>
</table>

Due to hydrolysis on silicagel, the resulting tosylate 418 could not be purified and in order to achieve a maximum yield of the substituted product, the tosylate 418 was reacted with nucleophiles immediately after isolation.

Having in hands the substituted compounds 421, a simple N-deprotection could provide new 4-aminocyclobutenones (e.g. 422). Unfortunately, the deprotection of the phthalimido group of 421a by standard procedures such as reaction with hydrazine in ethanol, treatment with sodium hydroxide or reduction with sodium borohydride, only resulted in complex reaction mixtures. A clean reaction mixture was obtained by acidic hydrolysis of compound 421a. However, after spectroscopic analysis the reaction product proved to be a ring opened compound 428 (spectroscopic analysis: ¹H and ¹³C NMR, H-C COSY, DEPT, IR and MS). A possible reaction mechanism could proceed via a nucleophilic attack of water to the hydrolyzed product 423 and subsequent ring opening. After decarboxylation of 426, the end product 428 is produced.

It is known that tetrachlorophthalimides hydrolyze more easily as compared to the non chlorinated analogues upon treatment with aqueous sodium hydroxide, but the tetrachlorophthalimido substituted cyclobutenone could not be synthesized probably due to the decreased nucleophilicity of K-tetrachlorophthalimide.
4-Azido-3-methoxy-2-phenyl-2-cyclobutenone 421b was treated with trimethylphosphine to synthesize the free amine 422. However, after reaction for 2 hours in toluene at -78°C to room temperature a complex reaction mixture was obtained which still contained starting material. Following another procedure, the azide 421b was treated with iron(III) chloride and sodium iodide in acetonitrile at room temperature. The reaction mechanism of this azide reduction is not known, but has been used with success previously. In the case of 421b, a compound could be isolated with a molecular weight corresponding to 421b - N₂ (confirmed by MS), albeit in low yield. Other spectroscopic data (¹H and ¹³C NMR and IR) do not correspond with the structure of 4-aminocyclobutenone 422, but suggest a rearranged product. The structure of this compound could not be elucidated until now.
In a study towards the reactivity of imines with hydroxycyclobutenones, 412a was reacted with N-(diphenylmethylene)amine and K$_2$CO$_3$ in DMF at 70°C for 3 hours. Via $^1$H NMR, $^{13}$C NMR, IR, MS and 2D NMR spectra, the structure of the obtained compound was assigned to be pyrrolinone 433. The reaction mechanism can be explained by an initial nucleophilic attack of N-(diphenylmethylene)amine to the vinylogous ester (analogous to O-nucleophiles) and subsequent thermal ring opening of the cyclobutene ring. After ring closure, pyrrolinone 433 can be formed.

III.2.6.3 Ring expansion of 4-hydroxycyclobutenones towards furanones

III.2.6.3.1 Introduction

2(5H)-Furanones are of particular importance as physiologically active compounds, which resulted already in numerous patents.$^{253,254}$ For instance, 3-phenylfuranones 434 and 435 were patented as herbicides, plant protection agents and pesticides,$^{247}$ whereas 5-...
alkoxyfuranones \( \textbf{436} \) in general were patented for their potential in the treatment of osteoporosis.\(^{248}\) Losigamone \( \textbf{437} \) is a well-studied furanone and is used as an antiepilepticum.\(^{249}\) Also spirodiclofen (\( \textbf{438}, \text{Envidor}\)) and spiromesifen \( \textbf{439} \) are furanones with pronounced insecticidal and acaricidal activities.\(^{250}\)

![Chemical structures of Losigamone, Spirodiclofen, and Spiromesifen](image)

Although numerous ring expansions of hydroxycyclobutenones towards furanones are known, these reactions generally proceed via thermal,\(^{251}\) photochemical\(^{252}\) or via radical processes.\(^{237a,253}\) In the study towards the latter reaction mechanisms, hydroxycyclobutenone \( \textbf{440} \) was treated with iodine/HgO and irradiated with a sunlamp or heated.\(^{253a}\) The generated radical triggered the ring opening of cyclobutenone \( \textbf{441} \) giving rise to 5-butylidene-2(5\(H\))-furanone \( \textbf{445} \).

In contrast, an analogous reaction of \( \text{I}_2/\text{HgO}, \text{NIS} \) or \( \text{PhI(OAc)}_2 \) with alkynyl substituted cyclobutenones \( \textbf{446} \) at room temperature resulted in cyclopentenediones \( \textbf{448} \) via an ionic mechanism.\(^{254}\) Further research resulted in the synthesis of different furanones via carbocation intermediates \( \textbf{451} \) created by the reaction of hydroxycyclobutanones \( \textbf{449} \) with \( \text{PhI(OAc)}_2 \).\(^{255}\)
The present reactivity study of 4-hydroxycyclobutenones 412 deals with the reaction of these compounds with chlorinating or brominating agents. The synthesis of new furanones via an ionic rearrangement of 4-hydroxycyclobutenones bearing no additional substituents at 4-position eliminates further dehalogenation reactions towards 5-alkylidene-2(5$H$)-furanones (e.g. 445). In addition, the presence of a halogen at this position could expand the synthetic potential of these derivatives, because both nucleophiles (454 → 455) and electrophiles (454 → 456, after halogen-metal exchange) can be attached to the furanone ring.
III.2.6.3.2 Results and discussion

In a preliminary experiment, 4-hydroxy-3-methoxy-2-phenyl-2-cyclobutenone 412a was treated with 1 equivalent of bromine in dichloromethane at 0°C for 3 hours. Two major compounds were observed in the $^1$H NMR spectrum, namely starting material 412a and the oxidized product 397a. Besides these compounds, also a third minor compound was detected. After chromatography, this compound could be isolated in 5% yield and proved to be 2(5H)-furanone 457.256

The mechanism of this ring expansion can be rationalized by a 1,2-acyl shift ($\text{460} \rightarrow \text{457}$) of the intermediate hypobromite 458, and subsequent attack of the expelled bromide to the generated positive charge. A radical mechanism is not likely because the reaction proceeds at low temperature and the same results are obtained when performing the reaction in the dark. It is not surprising that next to this acyl shift, also dehydrobromination of the intermediate hypobromite 458 occurs towards the oxidized compound 397a.
Because the reaction of hydroxycyclobutenone with bromine produced only small amounts of ring expanded product 457, also reactions with other electrophiles were evaluated (see Table 5). Treatment of 412a with NBS gave rise to an increased amount of 2(5H)-furanone, which was accompanied by an equal amount of oxidation product. Better results were obtained with the use of t-butyl hypochlorite in dichloromethane. After 15 hours reaction at room temperature, a ratio 397a/462a of 23:77 was obtained (calculated from 1H NMR spectra). Performing the same reaction at reflux temperatures shifted the ratio towards 16:84. The best results were obtained by reaction of hydroxycyclobutenones with 1.05 equivalents of NCS in CCl4 at reflux temperature for 2 hours. These reaction conditions directed the transformation predominantly to 2(5H)-furanone 462a, while only a slight amount of cyclobutenedione (4%) was produced.

Using the optimized reaction conditions, a simple and efficient route was established towards various new furanones bearing a halogen at 5-position. It should be emphasized that this synthetic pathway is performed only with low cost reagents (Zn in HOAc, NCS, etc.) and standard organic synthesis procedures. The presence of a halogen at 5-position makes these compounds of particular interest for further organic transformations to furanones bearing interesting substitution patterns. Indeed, the reaction of 4-alkoxy-3-aryl-5-chloro-2(5H)-furanones 462 with sodium alkoxides under mild conditions, resulted in 4,5-dialkoxyfuranones 464 in high yields. The use of more equivalents of alkoxide resulted in a nucleophilic addition to the vinylogous ester giving rise to “transesterified” compounds, e.g. the reaction of 462a with NaOEt in EtOH gave rise to 4,5-diethoxyfuranone 464b. In addition, the heating of dimethoxyfuranone 464a in refluxing isopropylamine resulted in 4-
isopropyl-5-methoxy-3-phenyl-2(5\textit{H})-furanone 467 in good yield. The reaction of furanone 462\textit{a} with an excess of isopropanol gave only a substitution of the chloro atom, affording furanone 466 in good yield.

**Table 5.** Optimalization of the rearrangement of cyclobutenone 412\textit{a} to 2(5\textit{H})-furanones 457 and 462\textit{a}

<table>
<thead>
<tr>
<th></th>
<th>Reaction conditions</th>
<th>Starting material 412\textit{a} (%)\textsuperscript{a}</th>
<th>Cyclobutenedione 397\textit{a} (%)\textsuperscript{a}</th>
<th>2(5\textit{H})-Furanone 457, 462\textit{a} (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.1 equiv. NBS, CCl\textsubscript{4}, Δ, 1h</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2.</td>
<td>1.1 equiv. t-BuOCl, CH\textsubscript{2}Cl\textsubscript{2}, 0°C, 1h</td>
<td>13</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>3.</td>
<td>1.1 equiv. t-BuOCl, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 15h</td>
<td>0</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>4.</td>
<td>1.1 equiv. t-BuOCl, CH\textsubscript{2}Cl\textsubscript{2}, Δ, 4h</td>
<td>0</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>5.</td>
<td>1.05 equiv. NCS, CCl\textsubscript{4}, Δ, 2h</td>
<td>0</td>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

\textsuperscript{a} calculated from \textsuperscript{1}H NMR spectra

Chlorinated furanones 462 were reacted with zinc in acetic acid to yield dechlorinated products 463, which in turn were reduced with hydrogen in the presence of a catalytic amount of Pd/C to substituted γ-lactones 465. The stereochemistry is most probably \textit{cis} (as is generally the case with Pd/H\textsubscript{2} reductions), although isomerization could take place during reaction towards the \textit{trans}-isomer. Because during the reaction no other isomer could be determined one could state that no such isomerization occurs (ester groups do not enolize fast in the absence of base or acid). Neither DIFNOE-experiments were inconclusive to consolidate this hypothesis, nor did an analysis of the coupling constants and comparison of literature data of other furanone derivatives.

In conclusion, a new and efficient pathway was developed towards interesting furanones with a remarkable substitution pattern, which renders these compounds suitable for conversion to polysubstituted physiologically interesting 2(5\textit{H})-furanones and γ-lactones.
Results and Discussion

1.05 equiv. NCS, CCl₄, Δ, 2h

462a R¹ = H, R² = Me (81%)
462b R¹ = H, R² = Et (62%)
462c R¹ = H, R² = i-Pr (65%)
462d R¹ = Cl, R² = Me (78%)

1 equiv. NaOR²

463a R¹ = H, R² = Me (89%)
463b R¹ = H, R² = Et (80%)
463c R¹ = H, R² = i-Pr (73%)
463d R¹ = Cl, R² = Me (81%)

1.5 equiv. Zn/Cu

464a R¹ = H, R² = Me (87%)
464b R¹ = H, R² = Et (80%)
464c R¹ = H, R² = i-Pr (51%)
464d R¹ = Cl, R² = Me (86%)

H₂-atmosphere (4 bar)
cat. Pd/C, THF, r.t., 15h

465a R¹ = H, R² = Me (68%)
465b R¹ = H, R² = Et (76%)
465c R¹ = H, R² = i-Pr (59%)

excess NaOEt in EtOH, r.t., 15h

466 (72%)

excess i-PrOH, Δ, 15h

464b (69%)

excess i-PrNH₂, Δ, 12h

467 (69%)
III.3 Evaluation of entries to new cyclopropenones

III.3.1 Introduction

In the previous chapter, attempts were performed to accomplish a semi-benzilic ring contraction of halogenated cyclobutanones towards the corresponding cyclopropanes (see Section III.2.2.3). Whereas the ring contraction of 2,2-dichlorocyclobutanones $^{12}$ proceeded smoothly towards 1-chlorocyclopropanecarbaldehydes $^{16}$ (which could be converted to different cyclopropanes $^{468}$), analogous reactions of 2,2,4,4-tetrahalogenated imines $^{347}$ did not yield cyclopropanes $^{469}$ at all. These halogenated cyclopropanes could however give rise to cyclopropenones $^{470}$, substituted with acyl moieties. Such compounds are barely studied and form a new class of intriguing compounds. $^{31}$ For that reason, reactions will be performed to arrive at these new compounds $^{472}$ and to synthesize physiologically interesting cyclopropenones.

Cyclopropenones have attracted considerable attention the last decades because of their high ring strain and physiological properties. Until now, only five cyclopropenones have been isolated from natural sources. Among them, penitricin $^{29}$ shows antibiotic activity$^{32,33}$
and the recently discovered alutacenoic acids A and B are potent inhibitors of factor VIIIa, an enzyme which acts at the final step in the blood-coagulation cascade. Since the first synthesis of diphenylcyclopropenone in 1959, a substantial amount of synthetic pathways has been developed towards these three-membered rings. However, no study has been performed towards cyclopropenones substituted with electron withdrawing groups. In this part of the research, entries towards the yet unknown cyclopropenones via carbene additions to suitable olefins and via ring closure of substituted α,α'-dihalo ketones will be evaluated. Finally, reactions will be evaluated to acylate phenylcyclopropenone acetals in order to form new cyclopropenones.

III.3.2 Results and discussion

III.3.2.1 Evaluation of carbene additions to olefins as a key step for cyclopropenone synthesis

In a first evaluation study of entries leading to new cyclopropenones and derivatives, the reactivity of dihalocarbenes and dimethoxycarbene towards halogenated alkenes and alkynes was investigated. Carbenes were generated from:
- bromoform and t-BuOK
- bromoform and NaOH (with phase transfer catalysts TEBACl, triethylbenzylammonium chloride or TMAB, tetramethylammonium bromide)
- Cl₃CCOOH and Et₃N
- 2,2-dimethyl-5,5-dimethoxyoxadiazoline.

The latter oxadiazoline was synthesized following literature procedures from acetone methylcarbazone and lead(IV) acetate. For the synthesis of α-chlorocinnamaldehyde, a new synthetic pathway was developed starting from 3-phenylpropanol. Reaction of 476 with chlorine gas in DMF-HCl resulted in the corresponding α,α'-dichloroaldehyde, which was purified by distillation and subsequently
Results and Discussion

treated with α-picoline-HCl at 120°C for 48 hours. In that way, α-chlorocinnamaldehyde 477 was synthesized on a multigram scale to be used as starting material. Numerous reactions of this aldehyde with different carbene precursors under varying reaction conditions often resulted in a nucleophilic attack of the trihalomethyl anion to the aldehyde moiety, affording compounds 478 and 479. When carbenes were generated using NaOH under phase transfer conditions, a Cannizzaro reaction was observed resulting in the formation of α-chlorocinnamic acid 481 and the corresponding alcohol 480.

To avoid the above mentioned problems, analogous experiments were performed with the dimethyl acetal of α-chlorocinnamaldehyde (482), which was prepared from the latter by treatment with trimethyl orthoformate under acidic catalysis. Dimethyl acetal 482 did not react when applying the same reaction conditions as used for the aldehyde 477 (analogous to reactions 1 to 5, Table 6) and when harsher reaction conditions were used, decomposition took place resulting in brown, tarry mixtures. Also attempts to add a dimethoxycarbene 475 to the double bond of 482 were not successful.
Table 6. Reactions of different carbene precursors with α-chlorocinnamaldehyde 477 or the corresponding dimethyl acetal 482

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>477 3 equiv. CHBr₃, 3 equiv. NaOH, 20mol% TEBACl, -15°C, 1h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2.</td>
<td>477 3 equiv. CHBr₃, 3 equiv. NaOH, 20mol% TEBACl, 0°C, 4h</td>
<td>480 + 481 (1:1)</td>
</tr>
<tr>
<td>3.</td>
<td>477 3 equiv. CHBr₃, 3 equiv. NaOH, 20mol% TMAB, 0°C, 4h</td>
<td>480 + 481 (1:1)</td>
</tr>
<tr>
<td>4.</td>
<td>477 3 equiv. CHBr₃, 3 equiv. t-BuOK in hexane, -78°C, 4h</td>
<td>479</td>
</tr>
<tr>
<td>5.</td>
<td>477 3 equiv. Cl₃CCOOH, 3 equiv. Et₃N, Δ, 24h</td>
<td>478</td>
</tr>
<tr>
<td>6.</td>
<td>482 1 equiv. oxadiazoline 474, toluene, Δ, 5h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7.</td>
<td>482 1 equiv. oxadiazoline 474, benzene, 100°C, 24h</td>
<td>no reaction</td>
</tr>
<tr>
<td>8.</td>
<td>482 1 equiv. oxadiazoline 474, benzene, 135°C, 24h a</td>
<td>decomposition b</td>
</tr>
</tbody>
</table>

a the reaction was carried out in a sealed pyrex glass tube.
b the reaction mixture still contained starting material

In a second strategy, β-chlorocinnamaldehyde 484 was chosen as starting material to accomplish a carbene addition as a key step for the synthesis of cyclopropenones. Unfortunately, also in this case the aldehyde functionality was attacked by the formed trihalomethyl anions to form adducts 485 and 486. Therefore, the corresponding dimethyl acetal 487 was synthesized and subjected to the same set of carbene addition reactions as listed in Table 6. Under no circumstances cyclopropanes could be detected in the reaction mixtures.
In a third strategy, methyl propiolate 489 and the corresponding acetal 490 were treated again with the same set of carbene precursors as listed in Table 6, but also in this case, no positive results were obtained. Because the above mentioned reactions gave no satisfactory results, no further experiments were done concerning carbene additions to substituted olefins.

III.3.2.2 Evaluation of $\alpha,\alpha'$-dihaloketones and derivatives as precursors for cyclopropenones

Dihaloketones and acetals of dichloroacetone were already used for the synthesis of unsubstituted cyclopropenones. Subsequent palladium($0$) catalyzed coupling with aryl halides yields arylcyclopropenones. However, no literature data exist to prepare aryl substituted cyclopropenones or alkoxycarbonylcyclopropenones directly via ring closure of suitable dihaloketones or -acetals. For the synthesis of these cyclopropenones the following strategies were put forward:

- initial $\alpha,\alpha'$-dihalogenation of suitable ketones and subsequent acetalization
- initial $\alpha$-monohalogenation, subsequent acetalization followed by a second halogenation
- initial acetalization and subsequent dihalogenation of the acetal
- analogous reactions with $\beta$-keto esters to synthesize alkoxycarbonylcyclopropenones

Bromination of phenylacetone 262 with bromine in acetic acid yielded $\alpha,\alpha'$-dibromoketone 492. $\alpha,\alpha'$-Dibromoketones are thermodynamically less stable and are transformed to the corresponding $\alpha,\alpha'$-dibromoketones under the used reaction conditions. This isomerization is not possible with analogous dichloroketones, which makes the selective synthesis of $\alpha,\alpha'$-dichloroketones 496 not so easy as compared to the corresponding dibrominated compounds. Fortunately, when the chlorination reaction is carefully controlled, $\alpha,\alpha'$-dichloroketone 496...
could be synthesized as the major compound in a mixture of di- and trichlorinated phenylacetones and could easily be separated from the mixture by distillation.

After dibromination of 492, various reactions were performed to establish an acetalization of the ketone moiety. In no case the desired acetal 493 was obtained, probably due to the low polarity of the carbonyl group induced by the electron withdrawing effect of the bromo atoms and due to the easy enolization of these compounds. These factors disfavour a nucleophilic attack on the carbonyl group by alcohols (and diols) to form the corresponding acetals 493. The tendency of dibromoketones 492 to enolize under the used reaction conditions resulted in a rapid loss of a bromine anion with benzylic stabilization of the generated positive charge. Present nucleophiles, in casu methanol, add to the positive carbocation resulting in bromomethoxyketone 494. An attempt to synthesize the dimethyl acetal of dibromoketone 492 by initial activation of the carbonyl group by reaction with dimethyl sulfate and subsequent addition of sodium methoxide resulted in the formation of (Z)-methyl cinnamate 495, what proved that the use of dimethyl sulfate had no effect. The formation of (Z)-methyl cinnamate 495 proceeds via the mechanism of a Favorskii rearrangement induced by methoxide.

Because dibromoketone 492 proved not to be a suitable substrate for acetalization reactions, the same experiments were performed with the dichlorinated ketone 496. Unfortunately this substrate also gave no rise to the corresponding acetals 497.
Just at the start of the evaluation of a second strategy involving a halogenation of phenylacetone 262, subsequent acetalization followed by a second halogenation, the same methodology was published by Jikihara and coworkers. In this publication, phenylcyclopropenone acetal 501 was synthesized by α-chlorination of phenylacetone 262, subsequent acetalization with 2,2-dimethylpropane-1,3-diol, followed by bromination of 499 at the α’-position using pyridinium perbromide. At least, it proved that the chosen reaction pathway indeed would result in an efficient synthesis of phenylcyclopropenones 501. Of course, this part of the research was stopped and further evaluation studies were performed using β-keto esters as starting materials for the synthesis of new cyclopropenones.

β-Keto ester 502 was first acetalized with 2,2-dimethylpropane-1,3-diol towards acetal 503. Bromination in α-position of an ester is normally possible by reaction with LDA and subsequent trapping with electrophilic halogenated compounds or with CBr₄, but in the present case, deprotonation of the ester 503 resulted in a ring opening of the acetal moiety, yielding compound 507. Also, attempts to brominate the acetal 503 following a recently reported procedure (see above) only resulted in complex reaction mixtures. Alternatively, compound 503 was brominated at the benzylic position using NBS in refluxing CCl₄ in the presence of a catalytic amount of AIBN. The obtained crystalline compound 504 was treated with pyridinium perbromide or with LDA/CBr₄, but in both cases only starting material was detected in the complex ¹H NMR spectra of the reaction mixture.
III.3.2.3 Attempts to acylate phenylcyclopropenone acetal 501

Phenylcyclopropenone acetal 501 was synthesized following literature procedures.\textsuperscript{259c} The procedure comprises the acetalization of dichloroacetone 508, ring closure by double dehydrochlorination and subsequent palladium catalyzed coupling with iodobenzene. This substrate (501) was reacted with BuLi and treated with various electrophiles, such as dimethyl carbonate, methyl chloroformate and propylisocyanate, but in no cases alkoxycarbonylcyclopropenone acetals 511 ($Z = $ OMe) or $N$-propylcarbamoylcyclopropenone acetals 511 ($Z = $ NHPr) were formed.

Because all experiments described above did not result in the synthesis of alkoxycarbonyl-substituted cyclopropenones or derivatives, no further actions were undertaken to get to these compounds.
III.4 Synthesis of 2-substituted cyclobutanones as markers for γ-irradiated foodstuffs

III.4.1 Introduction

Ionizing radiation, e.g. γ-irradiation, for the preservation of foods is not generally accepted and allowed. The development of tests for the detection of irradiated foods is of importance in this matter. Together with a good management at the irradiation facility, such tests would facilitate international trade and increase consumer confidence in the existing control procedures. At present, reliable detection methods for irradiated foods include electron spin resonance to monitor long-lived radicals, thermoluminiscence, detection of ortho-tyrosine formed in meat, and the detection of volatile compounds from irradiated fats. The detection of 2-substituted cyclobutanones as markers for γ-irradiated foods proved to be very successful for chicken, peanuts, papaya, liquid whole egg, pork, lamb, beef and fish. These 2-substituted cyclobutanones are formed from the γ-irradiation induced cyclization of triglycerides or fatty acids, and were shown to contain the same number of carbon atoms as the parent fatty acids. The mechanism is believed to proceed via a radical induced ring closure of intermediates, which are generated by γ-irradiation. Expulsion of the residual diglyceride radical gives rise to cyclobutanones. As palmitic acid, stearic acid, oleic acid and linoleic acid are the four major fatty acids found in most foods, the presence of 2-dodecylcyclobutanone and 2-tetradecylcyclobutanone...
2-(tetradec-5-enyl)cyclobutanone 42 and 2-(tetradeca-5,8-dienyl)cyclobutanone 43 was proven in foods following irradiation. Methods using GC-MS have been developed for the detection of such 2-substituted cyclobutanones 41-43 in foods (containing minimum 1% of fat) irradiated with 500Gy or even less. One of these cyclobutanone detection methodologies has been selected by the European Committee for Standardization to prove food irradiation. The success of the detection of 2-substituted cyclobutanones is dependant upon the ready availability of the standard compounds by chemical synthesis. In recent years, efforts have been performed to make such cyclobutanones 41-43 accessible, but most of the synthetic pathways are too long, using reagents which are difficult to handle e.g. sensitive cyclopropanes and the pyrophoric tert-butyllithium.

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{O} & \quad \text{R}^2 \\
\text{O} & \quad \text{R}^3 \\
\gamma\text{-irradiation} & \\
\text{R}^1, \text{R}^2, \text{R}^3 & = \text{fatty acid chains (e.g. palmitic, stearic, oleic, linoleic acid)} \\
\text{41a} & (n = 1) \\
\text{41b} & (n = 3) \\
\text{41c} & (n = 5) \\
\text{41d} & (n = 7) \\
\text{41e} & (n = 9)
\end{align*}
\]
III.4.2 Results and discussion

Commercially available cyclobutanone 94 was converted into \( N \)-(cyclobutylidene)isopropylamine 44 by reaction with isopropylamine (3.5 equiv.) in diethyl ether in the presence of stoichiometric amounts of titanium(IV) chloride which acts as an activator and chemical dehydrating agent. Without purification, the cyclobutanone imine 44a was deprotonated with LDA in THF at -78°C and the resulting 1-azaallylic anion intermediate was reacted with hexyl- and decyl bromide to afford the corresponding \( N \)-(2-alkyl-1-cyclobutylidene)isopropylamines 45. The latter crude imines 45 were hydrolyzed with aqueous HCl in a two-phase system under reflux resulting in 2-substituted cyclobutanones 41a and 41c in 75 and 80% yield, respectively. Besides 2-octyl- (41b), 2-dodecyl- (41d), 2-
tetradecyl- (41e) and 2-(5-tetradecen-1-yl)cyclobutanone 42, which are common in irradiated foodstuffs and which were synthesized earlier at the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University.\(^{17e}\) this procedure also provided the less ubiquitous but more specific hexyl- (41a), and decylcyclobutanone (41c) in good yields. Further purification of cyclobutanones 41a and 41c was performed by flash chromatography giving rise to the pure standards, useful for the detection of markers for irradiated foodstuffs.

To synthesize the unsaturated cyclobutanone derivative 43, the corresponding olefinic bromide 50 was synthesized in order to use this substrate in the alkylation step. Of prime importance is the fact that the final alkadienylcyclobutanone 43 is obtained stereochemically pure. For the synthesis of 1-bromo-5,8-tetradecadiene 50, a copper(I) catalyzed cross-coupling of 5-hexynol 46 and 1-bromo-2-octyn 47 was used,\(^ {277}\) followed by partial reduction of 48. To transform the obtained 5,8-tetradecadienol into the 1-bromodiene 50, the unsaturated alcohol 49 was reacted with triphenylphosphine and tetrabromomethane in dichloromethane at 0°C and afforded 1-bromodiene 50 in high yield.

Finally, the obtained bromoalkene 50 was used for the alkylation of cyclobutanone. The same procedure was followed as for the synthesis of the saturated derivatives 41. In this way, a new efficient route is established towards 2-(5,8-tetradecadien-1-yl)cyclobutanone 43, which can be used as a marker for irradiated foodstuffs.
Results and Discussion

\[
\begin{align*}
\text{46} & \quad + \quad \text{Br} \quad \text{47} \\
\downarrow & \quad 2 \text{ equiv. Cul, 2 equiv. NaI, 1.5 equiv. K}_2\text{CO}_3, \quad \text{DMF, r.t., 15h, N}_2\text{-atmosphere} \\
\text{48 (87\%)} & \quad \downarrow & \quad 20 \text{ mol\% Pd (Lindlar cat., H}_2\text{-saturated) } \\
& \quad 3.5 \text{ equiv. quinoline, benzene, 10\degree C to r.t., } \\
& \quad 15\text{h, H}_2\text{-atmosphere (atmospheric pressure)} \\
\text{49 (94\%)} & \quad \downarrow & \quad 1.5 \text{ equiv. PPh}_3, 1.5 \text{ equiv. CBr}_4, \\
& \quad \text{CH}_2\text{Cl}_2, 0\degree \text{C to r.t., 8h} \\
\text{50 (90\%)} & \\
\end{align*}
\]

\[
\begin{align*}
\text{44a} & \quad \rightarrow \\
& \quad 1) 1.05 \text{ equiv. LDA, THF, } -78\degree \text{C, 30 min} \\
& \quad 2) 1 \text{ equiv. } R\text{Br 50, THF, } -78\degree \text{C to r.t., 15h} \\
& \quad 3) \text{ excess aq. 1M HCl, r.t., 2h} \\
\text{43 (69\%)} & \\
\end{align*}
\]
IV EXPERIMENTAL PART

IV.1 Materials and methods

IV.1.1 Solvents and reagents

Commercially available solvents and reagents were used without further purification, unless stated otherwise. Diethyl ether, toluene and tetrahydrofuran were distilled from sodium and sodium benzophenone ketyl. Dichloromethane was distilled over calcium hydride. Benzene, petroleum ether and chloroform were dried and purified by washing with concentrated sulfuric acid and subsequent treatment with magnesium carbonate hydroxide ((MgCO₃)₄·Mg(OH)₂).

IV.1.2 Chromatographical methods

IV.1.2.1 Flash chromatography

The purification of reaction mixtures was performed by flash chromatography using a glass column filled with silica gel (Across, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis (Merck Kieselgel 60F₂₅₄, precoated 0.25 mm). As detection methods, UV light, coloring with iodine vapours, basic KMnO₄-solution or a 50% aq. sulfuric acid solution was used.

IV.1.2.2 Gas chromatography

The purity of the synthesized compounds or reaction mixtures was analyzed by gas chromatography, using a Delsi DI 200 (fused silica, AT-1, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm, N₂ as carrier gas, FID, H₂ gas).
IV.1.3 Spectroscopic methods

IV.1.3.1 NMR-spectroscopy

$^1$H NMR (270 MHz or 300 MHz), $^{13}$C NMR (68 MHz or 75 MHz), $^{31}$P NMR (109.4 MHz) and $^{11}$B NMR (96.2 MHz) spectra were run with a Jeol JNM-EX 270 NMR spectrometer or with a Jeol Eclipse FT 300 NMR spectrometer. Peak assignments were done with the aid of DEPT, 2D-HETCOR, 2D-COSY NMR techniques. The compounds were diluted in deuterated solvents (CDCl$_3$, D$_2$O, acetone-d$_6$ or DMSO-d$_6$) with tetramethylsilane (TMS) as reference ($\delta=0$ ppm).

IV.1.3.2 Infrared spectroscopy

IR spectra were obtained from a Perkin Elmer Spectrum One infrared spectrometer. For liquid samples, the spectra were collected by preparing a thin film of compound between two sodium chloride plates. Solid compounds were mixed with potassium bromide and pressed until a transparent plate was obtained.

IV.1.3.3 Mass spectrometry

Mass spectra were recorded on a Varian MAT 112 spectrometer (70eV), using either GC-MS coupling or a direct inlet system. Some volatile compounds were recorded on a HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector). LC-MS was performed with an Agilent 1100 Series VS (ES, 4000V) mass spectrometer.

IV.1.4 Melting point

Melting points of crystalline compounds were measured with a Büchi 540 apparatus.

IV.1.5 Elemental Analysis

The elemental analysis of several new compounds was performed on a Perkin Elmer 2400 Elemental Analyser.
IV.2 Synthesis of alkyl and aryl substituted pyrrolinones and pyrroles

IV.2.1 Synthesis of 3-pyrrolin-2-ones from 2,2-dichlorocyclobutanones

IV.2.1.1 Synthesis of \(N\)-alkyl-3-aryl-4,4-dichlorobutanamides 13

3-Aryl-2,2-dichlorocyclobutanones 12 were prepared according to literature procedures from substituted styrenes and dichloroketene, and were used as starting materials for the synthesis of \(N\)-alkyl-3-aryl-4,4-dichlorobutanamides 13.

To a solution of 5.00 g (23.25 mmol) 2,2-dichloro-3-phenylcyclobutanone 12a in 50 ml of \(\text{Et}_2\text{O}\) was added a solution of 2.74 g (46.51 mmol, 2 equiv.) isopropylamine in 50 ml of \(\text{Et}_2\text{O}\) at 0°C during 15 minutes. After addition, cooling was stopped and the reaction mixture was stirred at r.t. for 8 h. The resulting mixture was poured into 100 ml of aq. 0.5 M NaOH and extracted with \(\text{Et}_2\text{O}\) (3 x 100 ml). The organic phase was dried (\(\text{MgSO}_4\)), filtered and evaporated in vacuo yielding 4,4-dichloro-\(N\)-isopropyl-3-phenylbutanamide 13a as a brown solid. Other derivatives were prepared following an analogous procedure.

4,4-Dichloro-\(N\)-isopropyl-3-phenylbutanamide 13a

Crude yield 87%. Recrystallization (\(\text{Et}_2\text{O}/\text{hexane}/\text{CH}_2\text{Cl}_2\) 5:1:5); yield 70%, mp 97-98°C. \(^1\text{H NMR (CDCl}_3\)): \(\delta\) 0.91 and 1.07 (6H, 2 \(\times\) d, \(J=6.6\text{Hz}\)), 2.65 and 2.93 (2H, 2 \(\times\) dd, \(J=14.5\text{Hz}, 8.6\text{Hz}, 5.9\text{Hz}, \text{CH}_2\)), 3.85-3.94 (1H, m, \text{CHCH}_2\)), 3.94 (1H, sept, \(J=6.6\text{Hz}\)), \(\text{CH(CH}_3)_2\)), 5.25 (1H, s(b), NH), 6.07 (1H, d, \(J=4.6\text{Hz}, \text{CHCl}_2\)), 7.27-7.38 (5H, m, \(\text{C}_6\text{H}_5\)). \(^1\text{C NMR (CDCl}_3\)): \(\delta\) 2 \(\times\) 22.5 (2 \(\times\) \(\text{CH}_3\)), 38.4 (\(\text{CH}_2\)), 41.4 (\(\text{CHCH}_2\)), 52.2 (\(\text{CH(CH}_3)_2\)), 76.3 (\(\text{CHCl}_2\)), 128.0 (\(\text{CH}_\text{ar}\)), 2 \(\times\) 128.4 (2 \(\times\) \(\text{CH}_\text{ar}\)), 2 \(\times\) 129.0 (2 \(\times\) \(\text{CH}_\text{ar}\)), 137.6 (\(\text{C}_\text{quat}\)), 169.0 (C=O). \(\text{IR (KBr)}\): \(\nu_{\text{max}}\) 3342, 1647, 1535 cm\(^{-1}\). \(\text{MS m/z (\%)}\): no \(\text{M}^+\), 238/40 (\(\text{M}^+-\text{Cl}\), 12), 202 (100), 115 (15), 101 (18), 86 (48), 69 (42). \(\text{Anal. Calcd. for } \text{C}_{13}\text{H}_{17}\text{NOCl}_2\): C, 54.95; H, 6.25; N, 5.11. Found: C, 54.80; H, 6.38; N, 5.19.

3-(4-Chlorophenyl)-4,4-dichloro-\(N\)-isopropylbutanamide 13b

Crude yield 76%. Flash chromatography (hexane/EtOAc 3:7, \(R_f = 0.37\)); yield 56%, mp 84°C. \(^1\text{H NMR (CDCl}_3\)): \(\delta\) 0.98 and 1.10 (6H, 2 \(\times\) d, \(J=6.6\text{Hz}\)), 2.62 and 2.90 (2H, 2 \(\times\) dd, \(J=14.9\text{Hz}, 8.3\text{Hz}, 6.1\text{Hz}, \text{CH}_2\)), 3.86-3.94 (1H, m, \text{CHCH}_2\)), 3.98 (1H, sept, \(J=
6.6Hz, CH(CH$_3$)$_2$), 5.22 (1H, s(b), NH), 6.06 (1H, d, J= 4.3Hz, CHCl$_2$), 7.25-7.34 (4H, m, C$_6$H$_4$). $^{13}$C NMR (CDCl$_3$): δ 2 × 22.5 (2 × CH$_3$), 38.2 (CH$_2$), 41.5 (CHCH$_2$), 51.3 (CH(CH$_3$)$_2$), 75.8 (CHCl$_2$), 2 × 128.6 (2 × CH$_{ar}$), 2 × 130.4 (2 × CH$_{ar}$), 134.0 (C$_{quat}$), 136.0 (C$_{quat}$), 168.6 (C=O). IR (KBr): $\nu_{max}$ 3398, 1638, 1553 cm$^{-1}$. MS m/z (%): no M$^+$, 111 (2), 91 (12), 85 (3), 58 (37), 43 (100). Anal. Calcd. for C$_{13}$H$_{16}$NOCl$_3$: C, 50.59; H, 5.23; N, 4.54. Found: C, 50.65; H, 6.36; N, 4.65.

N-Benzyl-4,4-dichloro-3-phenylbutanamide 13c Crude yield 75%. Recrystallization (hexane/Et$_2$O 10:1); yield 58%, mp 117°C. $^1$H NMR (CDCl$_3$): δ 2.75 (1H, dd, J= 14.8Hz, 8.9Hz, CH$_a$H$_b$CO), 3.03 (1H, dd, J= 14.8Hz, 5.3Hz, CH$_a$H$_b$CO), 3.91-3.98 (1H, m, CHCH$_2$), 4.24 and 4.39 (2H, 2 × dd, J= 14.9Hz, 6.3Hz, 5.3Hz, NHCH$_2$), 5.82 (1H, s(b), NH), 6.05 (1H, d, J= 4.6Hz, CHCl$_2$), 6.95-6.99 (2H, m, 2 × CH$_{ar}$), 7.21-7.28 (3H, m, 3 × CH$_{ar}$), 7.33 (5H, s, 5 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): δ 38.1 (CH$_2$CO), 43.5 (CHCH$_2$), 52.1 (NHCH$_2$), 76.3 (CHCl$_2$), 127.1 (CH$_{ar}$), 2 × 127.5 (2 × CH$_{ar}$), 128.1 (CH$_{ar}$), 2 × 128.5 (2 × CH$_{ar}$), 128.6 (2 × CH$_{ar}$), 2 × 129.0 (2 × CH$_{ar}$), 137.4 (C$_{quat}$), 137.8 (C$_{quat}$), 169.7 (C=O). IR (KBr): $\nu_{max}$ 3260, 1630, 1565 cm$^{-1}$. MS m/z (%): 321/3/5 (M$^+$-1, 8), 250 (30), 148 (22), 107 (61), 106 (81), 91 (100), 77 (27). Anal. Calcd. for C$_{17}$H$_{17}$NOCl$_2$: C, 63.37; H, 5.32; N, 4.35. Found: C, 63.52; H, 5.38; N, 4.22.

IV.2.1.2 Synthesis of N-alkyl-3-aryl-4-methoxy-3-butenamides 258

To 1.10 g (4.01 mmol) of dichlorobutanamide 13a was added 4.0 ml (16.04 mmol, 4 equiv.) of 4M NaOMe in methanol. After 2 hours of reflux, the mixture was poured in 10 ml water and extracted three times with dichloromethane (3 × 20 ml). Drying of the extracts with MgSO$_4$, filtration and evaporation of the solvent resulted in butenamide 258a as a dark brown solid (E/Z 88:12, yield 91%), which could be easily recrystallized from EtOAc or chromatographed on column to yield the pure E-isomer. The Z-isomer could not be obtained in a pure form by flash chromatography.
(E)-N-Isopropyl-4-methoxy-3-phenyl-3-butenamide 258a

Crude yield 91%. Flash chromatography (hexane/EtOAc 1:1, Rf = 0.35); yield: 60%, mp 106-108°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.04 (6H, d, J= 6.6Hz, 2 $\times$ CH$_3$), 3.38 (2H, s, CH$_2$), 3.78 (3H, s, OCH$_3$), 4.02 (1H, sept, J= 6.6Hz, CH(CH$_3$)$_2$), 5.70 (1H, s(b), NH), 6.59 (1H, s, CH=C), 7.26-7.32 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 $\times$ 22.6 (2 $\times$ CH$_3$), 36.2 (CH$_2$), 41.2 (C$_H$(CH$_3$)$_2$), 60.2 (OCH$_3$), 113.9 (C=CH), 2 $\times$ 125.2 (2 $\times$ CH$_{ar}$), 126.5 (CH$_{ar}$), 2 $\times$ 128.7 (2 $\times$ CH$_{ar}$), 138.4 (C$_{quat}$C=C), 147.3 (CHOCH$_3$), 170.1 (C=O). IR (KBr): $\nu_{max}$ 3380, 1675, 1520 cm$^{-1}$. MS m/z (%): 233 (M$^+$, 62), 148 (100), 147 (35), 117 (35), 43 (60). Anal. Calcd. for C$_{14}$H$_{19}$NO$_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.19; H, 8.36; N, 6.14.

(E)-3-(4-Chlorophenyl)-N-isopropyl-4-methoxy-3-butenamide 258b

Crude yield 97%. Recrystallization (EtOAc); yield 63%, mp 148°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.06 (6H, d, J= 6.6Hz, 2 $\times$ CH$_3$), 3.34 (2H, s, CH$_2$), 3.79 (3H, s, OCH$_3$), 4.01 (1H, sept, J= 6.6Hz, C$_H$(CH$_3$)$_2$), 5.66 (1H, s(b), NH), 6.58 (1H, s, CHOCH$_3$), 7.26 (4H, s, C$_6$H$_4$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 $\times$ 22.6 (2 $\times$ CH$_3$), 36.0 (CH$_2$), 41.2 (C$_H$(CH$_3$)$_2$), 60.3 (OCH$_3$), 113.0 (C=CH), 2 $\times$ 126.4 (2 $\times$ CH$_{ar}$), 2 $\times$ 128.7 (2 $\times$ CH$_{ar}$), 132.1 (C$_{quat}$), 136.9 (C$_{quat}$), 147.4 (CHOCH$_3$), 169.9 (C=O). IR (KBr): $\nu_{max}$ 3283, 1651, 1551 cm$^{-1}$. MS m/z (%): 267/69 (M$^+$, 22), 182/84 (37), 99 (47), 91 (33), 71 (42), 43 (100). Anal. Calcd. for C$_{14}$H$_{18}$NO$_2$Cl: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.68; H, 6.94; N, 5.10.

(E)-N-Benzyl-4-methoxy-3-phenyl-3-butenamide 258c

Crude Yield 82%. Flash chromatography (hexane/EtOAc 1:1, Rf = 0.25); yield 56%, mp 97°C. $^1$H NMR (CDCl$_3$): $\delta$ 3.51 (2H, s, CH$_2$C=O), 3.73 (3H, s, OCH$_3$), 4.42 (2H, s, CH$_2$), 6.20 (1H, s(b), NH), 6.60 (1H, s, CH), 7.09-7.12 (2H, m, 2 $\times$ CH$_{ar}$), 7.17-7.36 (8H, m, 8 $\times$ CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 35.8 (C$_H$(CH$_3$)$_2$), 43.3 (CH$_2$), 60.3 (OCH$_3$), 113.5 (C=CH), 2 $\times$ 125.1 (2 $\times$ CH$_{ar}$), 126.6 (CH$_{ar}$), 127.2 (CH$_{ar}$), 2 $\times$ 127.3 (2 $\times$ CH$_{ar}$), 2 $\times$ 128.5 (2 $\times$ CH$_{ar}$), 2 $\times$ 128.7 (2 $\times$ CH$_{ar}$), 138.1 and 138.4 (C$_{quat}$CH$_2$ and C$_{quat}$C=C), 147.5 (CHOCH$_3$), 170.9 (C=O). IR (KBr): $\nu_{max}$ 3270, 1633, 1525 cm$^{-1}$. MS m/z (%): 281 (M$^+$, 47), 149 (21), 148 (87), 147 (70), 117 (48), 91 (100), 43 (39). Anal. Calcd. for C$_{18}$H$_{19}$NO$_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.89; H, 6.88; N, 5.10.
IV.2.1.3 Synthesis of 1-alkyl-4-aryl-3-pyrrolin-2-ones 257

To 2.00 g (8.58 mmol) of 258a was added an excess (25 ml) of an aqueous 2M HCl solution. The suspension was refluxed for 2h. After cooling, the acidic mixture was extracted three times with 20 ml of dichloromethane. Drying of the extract over MgSO₄ and evaporation of the solvent resulted in crystalline 3-pyrrolin-2-one 257a. Purification was performed by flash chromatography.

1-Isopropyl-4-phenyl-3-pyrrolin-2-one 257a

Flash chromatography (EtOAc/hexane 1:1, Rf = 0.17); yield 69%, mp 76°C (no literature data). All spectroscopic data were in accordance with literature data.²⁷⁸

4-(4-Chlorophenyl)-1-isopropyl-3-pyrrolin-2-one 257b

Flash chromatography (3% MeOH in CH₂Cl₂, Rf = 0.32); yield 57%, mp 92°C. ¹H NMR (CDCl₃): δ 1.27 (6H, d, J= 6.9Hz, 2 × CH₃), 4.27 (2H, d, J= 1.4Hz, CH₂), 4.52 (1H, sept, J= 6.9Hz, CH(CH₃)₂), 6.41 (1H, t, J= 1.4Hz, C=CH), 7.40 and 7.44 (4H, 2 × d, J= 8.6Hz, C₆H₄). ¹³C NMR (CDCl₃): δ 2 × 21.0 (2 × CH₃), 42.5 (CH(CH₃)₂), 47.6 (CH₂), 121.3 (C=CH), 2 × 127.0 (2 × CH₉), 2 × 129.3 (2 × CH₉), 130.5 (C₉H₈), 136.0 (C₉H₈), 152.7 (C=CH), 170.8 (C=O). IR (KBr): v max 1669, 1654, 1493, 1461 cm⁻¹. MS m/z (%): 235/7 (M⁺, 4), 115 (17), 86 (30), 84 (59), 58 (63), 49 (100), 43 (78). Anal. Calcd. for C₁₃H₁₄NOCl: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.10; H, 6.14; N, 5.90.

1-Benzyl-4-phenyl-3-pyrrolin-2-one 257c

Flash chromatography (EtOAc/hexane 1:1, Rf = 0.18); yield 64%, mp 156°C (lit.,²⁷⁹a 158°C; lit.,²⁷⁹c 162°C). All spectroscopic data were in accordance with literature data.²⁷⁹a,c
IV.2.1.4 Alkylation of 3-pyrrolin-2-ones 257

A solution of 5.22 mmol (1.05 equiv.) of LDA in 20 ml of dry THF, prepared by adding 2.10 ml of a 2.5M solution of BuLi in hexane to a solution of 0.53 g (5.22 mmol) of diisopropylamine in dry THF, was cooled to -78°C under N₂-atmosphere. To the cooled solution was added 1.00 g (4.98 mmol) of pyrrolinone 257a in portions and the mixture was allowed to reach 0°C during 45 minutes. Afterwards, the mixture was cooled again to -78°C and a solution of 0.85 g (4.98 mmol, 1 equiv.) 1-iodopropane in 5 ml of dry THF was added dropwise. Cooling was stopped and the resulting reaction mixture was stirred for 6 hours. Afterwards, the mixture was poured into 50 ml water and extracted with diethyl ether (3 × 50 ml). The organic phase was dried over MgSO₄, filtered and evaporated in vacuo. The crude mixture existed predominantly of 3-propyl-3-pyrrolinone 14a and contained traces of dipropylated pyrrolinone 260a and starting material 257a. The mixture could easily be separated in the different compounds by flash chromatography.

1-Isopropyl-4-phenyl-3-propyl-3-pyrrolin-2-one 14a

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.08); yield 46%, mp 46-48°C. ¹H NMR (CDCl₃): δ 0.96 (3H, t, J= 7.6Hz, CH₃CH₂), 1.25 (6H, d, J= 6.8Hz, 2 × CH₃), 1.61 (2H, sext, J= 7.6Hz, CH₂CH₃), 2.47 (2H, t, J= 7.6Hz, CH₃CH₂CH₂), 4.10 (2H, s, NCH₂), 4.52 (1H, sept, J= 6.8Hz, CH(CH₃)₂), 7.36-7.46 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 14.4 (CH₃), 2 × 21.1 (2 × CH₃), 21.8 (CH₃CH₂), 26.8 (CH₂), 42.6 (NCH), 47.9 (CH₂N), 2 × 127.3 (2 × CH₃), 128.6 (CH₃), 2 × 128.9 (2 × CH₃), 134.2 (C₆H₅), 134.7 (C₆H₅), 146.0 (C=CCO), 171.5 (C=O). IR (KBr): νmax 1676, 1453 cm⁻¹. MS (ES+) m/z (%): 244 (M+H⁺, 100). Anal. Calcd. for C₁₆H₂₁NO: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.08; H, 8.82; N, 5.84.

1-Isopropyl-4-phenyl-3,3-dipropyl-4-pyrrolin-2-one 260a

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.30); yield 12%. ¹H NMR (CDCl₃): δ 0.78 (6H, t, J= 7.3Hz, 2 × CH₃), 0.88-1.17 (4H, m, 2 × CH₂CH₃), 1.26 (6H, d, J= 6.8Hz, CH(CH₃)₂), 1.79-1.87 (4H, m, 2 × CH₂), 4.45 (1H, sept, J= 6.8Hz, CH(CH₃)₂), 6.89 (1H, s, C=CH), 7.30-7.39 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 2 × 14.3 (2 × CH₂CH₃), 2 × 17.6 (2 × CH₂CH₃), 2 × 21.7 (CH(CH₃)₂), 2 × 39.7 (2 × CH₂), 42.7 (CH(CH₃)₂), 57.9 (C₆H₅), 123.9 (C=CHN), 124.6 (C=CHN), 2 × 124.9 (2 × CH₃), 126.5 (CH₃), 2 × 128.8 (2 × CH₃), 134.5
3-Ethyl-1-isopropyl-4-phenyl-3-pyrrolin-2-one 14b

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.09); yield 50%. 

$^1$H NMR (CDCl$_3$): $\delta$ 1.19 (3H, t, J = 7.5Hz, CH$_3$CH$_2$), 1.25 (6H, d, J = 6.8Hz, 2 × CH$_3$), 2.52 (2H, q, J = 7.5Hz, CH$_3$CH$_2$), 4.10 (2H, s, CH$_2$N), 4.53 (1H, sept, J = 6.8Hz, CH), 7.29-7.43 (5H, m, C$_6$H$_5$). 

$^{13}$C NMR (CDCl$_3$): $\delta$ 12.8 (CH$_3$(CH$_3$)$_2$), 17.5 (CH$_3$C CH$_2$), 2 × 21.1 (CH(C$_3$H$_3$)$_2$), 42.3 (CH(CH$_3$)$_2$), 47.4 (CH$_2$N), 2 × 127.0 (2 × CH$_{ar}$), 2 × 128.4 (2 × CH$_{ar}$), 128.6 (CH$_{ar}$), 133.6 (C$_{quat}$), 135.4 (C$_{quat}$), 145.3 (C=C=CO), 171.1 (C=O). 

IR (NaCl): $\nu_{max}$ 1674, 1497, 1455 cm$^{-1}$. 

MS m/z (%): 229 (M$^+$, 72), 214 (100), 186 (17), 172 (14), 158 (15), 128 (13). 

Anal. Calcd. for C$_{15}$H$_{19}$NO: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.71; H, 8.48; N, 6.01.

3,3-Diethyl-1-isopropyl-4-phenyl-4-pyrrolin-2-one 260b

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.21); yield 9%, mp 47°C. 

$^1$H NMR (CDCl$_3$): $\delta$ 0.64 (6H, t, J = 7.4Hz, (CH$_3$CH$_2$)$_2$), 1.27 (6H, d, J = 6.9Hz, CH(CH$_3$)$_2$), 1.88 (2H, q, J = 7.4Hz, CH$_2$), 1.89 (2H, q, J = 7.4Hz, CH$_2$), 4.47 (1H, sept, J = 6.9Hz, CH(CH$_3$)$_2$), 6.93 (1H, s, C=CH), 7.19-7.43 (5H, m, C$_6$H$_5$). 

$^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 8.7 (2 × C$_3$H$_3$CH$_2$) 2 × 21.7 (CH(CH$_3$)$_2$), 2 × 30.0 (2 × CH$_2$), 42.8 (CH(CH$_3$)$_2$), 59.1 (C$_{quat}$), 123.7 (C=CHN), 124.5 (C=CHN), 2 × 125.0 (2 × CH$_{ar}$), 126.6 (CH$_2$), 2 × 128.8 (2 × CH$_{ar}$), 134.4 (C$_{quat}$), 180.8 (C=O). 

IR (KBr): $\nu_{max}$ 1695, 1612, 1457 cm$^{-1}$. MS m/z (%): 258 (M$^+$, 100). 

Anal. Calcd. for C$_{17}$H$_{23}$NO: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.61; H, 9.12; N, 5.33.

1-Benzyl-3-ethyl-4-phenyl-3-pyrrolin-2-one 14c

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.11); yield 53%, mp 68-69°C. 

$^1$H NMR (CDCl$_3$): $\delta$ 1.23 (3H, t, J = 7.5Hz, CH$_3$), 2.58 (2H, q, J = 7.5Hz, CH$_2$), 4.02 (2H, s, NCH$_2$), 4.70 (2H, s, NCH$_2$C$_{ar}$), 7.24-7.42 (10H, m, 2 × C$_6$H$_5$). 

$^{13}$C NMR (CDCl$_3$): $\delta$ 13.1 (CH$_3$), 18.3 (CH$_2$), 46.3 (CH$_2$C$_{ar}$), 52.0 (NCH$_2$), 2 × 127.3 (2 × CH$_{ar}$), 127.7 (CH$_{ar}$), 3 × 128.2 (3 × CH$_{ar}$), 4 × 128.9 (4 × CH$_{ar}$), 133.8 (C$_{quat}$), 135.3 (C$_{quat}$), 137.5 (C$_{quat}$),
146.1 (C=\text{-}C=\text{-}C), 172.1 (C=O). \textbf{IR} (KBr): \nu_{\text{max}} 1678, 1452 \text{ cm}^{-1}. \textbf{MS} (ES+) \text{ m/z} (%) : 278 (M+H\textsuperscript{+}, 100). \textbf{Anal. Caled.} for \text{C}_{19}\text{H}_{19}\text{NO}: \text{C}, 82.28; \text{H}, 6.90; \text{N}, 5.05. \text{Found: \text{C}, 82.08; \text{H}, 7.11; \text{N}, 4.89.}

1-Benzyl-3,3-diethyl-4-phenyl-4-pyrrolin-2-one 260c

Flash chromatography (hexane/EtOAc 9:1, \text{Rf} = 0.29); yield 8%. \textbf{1H NMR (CDCl\textsubscript{3})}: \delta 0.67 (6H, t, J= 7.2Hz, 2 \times \text{CH}_3), 1.90 (2H, q, J= 7.2Hz, \text{CH}_2\text{CH}_3), 1.97 (2H, q, J= 7.2Hz, \text{CH}_2\text{CH}_3), 4.71 (2H, s, N\text{CH}_2), 6.76 (1H, s, N\text{CH}), 7.24-7.40 (10H, m, 2 \times \text{C}_6\text{H}_5). \textbf{13C NMR (CDCl\textsubscript{3})}: \delta 2 \times 9.0 (2 \times \text{CH}_3), 2 \times 30.2 (2 \times \text{CH}_2), 45.8 (N\text{CH}_2), 58.9 (\text{C}_{\text{quat}}), 123.9 (\text{C}=\text{CN}), 2 \times 125.2 (2 \times \text{CH}_{\text{ar}}), 126.8 (\text{CH}_{\text{ar}}), 127.5 (\text{C}=\text{CHN}), 127.9 (\text{CH}_{\text{ar}}), 2 \times 128.1 (2 \times \text{CH}_{\text{ar}}), 2 \times 128.8 (2 \times \text{CH}_{\text{ar}}), 2 \times 128.9 (2 \times \text{CH}_{\text{ar}}), 134.1 (\text{C}_{\text{quat}}), 136.9 (\text{C}_{\text{quat}}), 181.5 (\text{C}=\text{O}). \textbf{IR (NaCl)}: \nu_{\text{max}} 1701, 1631, 1497, 1455 \text{ cm}^{-1}. \textbf{MS} (ES+) \text{ m/z} (%) : 306 (M+H\textsuperscript{+}, 100). \textbf{Anal. Caled.} for \text{C}_{21}\text{H}_{23}\text{NO}: \text{C}, 82.58; \text{H}, 7.59; \text{N}, 4.59. \text{Found: \text{C}, 82.79; \text{H}, 7.76; \text{N}, 4.65.}

3-Benzyl-4-(4-chlorophenyl)-1-isopropyl-3-pyrrolin-2-one 14d

Flash chromatography (hexane/EtOAc 85:15, \text{Rf} = 0.09); yield 57%, mp 122-123°C. \textbf{1H NMR (CDCl\textsubscript{3})}: \delta 1.27 (6H, d, J= 6.8Hz, \text{CH}(\text{CH}_3)_2), 3.84 (2H, s, \text{CH}_2\text{C}_{\text{ar}}), 4.16 (2H, s, N\text{CH}_2), 4.55 (1H, sept, J= 6.8Hz, \text{CH}(\text{CH}_3)_2), 7.18-7.37 (9H, m, \text{C}_6\text{H}_4 and \text{C}_6\text{H}_5). \textbf{13C NMR (CDCl\textsubscript{3})}: \delta 2 \times 21.1 (2 \times \text{CH}_3), 30.4 (\text{CH}_2\text{C}_{\text{ar}}), 42.9 (\text{CH}(\text{CH}_3)_2), 47.9 (\text{NCH}_2), 126.3 (\text{CH}_{\text{ar}}), 2 \times 128.5 (2 \times \text{CH}_{\text{ar}}), 2 \times 128.6 (2 \times \text{CH}_{\text{ar}}), 2 \times 128.7 (2 \times \text{CH}_{\text{ar}}), 2 \times 129.1 (2 \times \text{CH}_{\text{ar}}), 132.1 (\text{C}_{\text{quat}}), 133.4 (\text{C}_{\text{quat}}), 135.0 (\text{C}_{\text{quat}}), 139.0 (\text{C}_{\text{quat}}), 146.4 (\text{C}=\text{C}-\text{C}=\text{O}), 171.1 (\text{C}=\text{O}). \textbf{IR (KBr)}: \nu_{\text{max}} 1672, 1494 \text{ cm}^{-1}. \textbf{MS} (ES+) \text{ m/z} (%) : 326/28 (M+H\textsuperscript{+}, 100). \textbf{Anal. Caled.} for \text{C}_{20}\text{H}_{20}\text{NOCl}: \text{C}, 73.72; \text{H}, 6.19; \text{N}, 4.30. \text{Found: \text{C}, 73.79; \text{H}, 6.28; \text{N}, 4.41.}

4-(4-Chlorophenyl)-3,3-dibenzyl-1-isopropyl-4-pyrrolin-2-one 260d

Flash chromatography (hexane/EtOAc 85:15, \text{Rf} = 0.36); yield 18%, mp 156-157°C. \textbf{1H NMR (CDCl\textsubscript{3})}: \delta 0.69 (6H, d, J= 6.8Hz, \text{CH}(\text{CH}_3)_2), 3.35 (4H, s, 2 \times \text{CH}_2), 4.07 (1H, sept, J= 6.8Hz, \text{CH}(\text{CH}_3)_2), 6.33 (1H, s, N\text{CH}), 6.90-7.01 (4H, m, 4 \times \text{CH}_{\text{ar}}), 7.02-7.09 (6H, m, 6 \times \text{CH}_{\text{ar}}), 7.34-7.44 (4H, m, \text{C}_6\text{H}_5). \textbf{13C NMR (CDCl\textsubscript{3})}:...
1-Isopropyl-3-phenylpyrrole 15a

Flash chromatography (EtOAc/hexane 95:5, Rf = 0.25); yield 40%. $^1$H NMR (CDCl$_3$): $\delta$ 1.47 (6H, d, J= 6.6Hz, CH(CH$_3$)$_2$), 4.23 (1H, sept, J= 6.6Hz, CH(CH$_3$)$_2$), 6.44 (1H, dd, J= 2.8Hz, 2.0Hz, CH=CHN), 6.73 (1H, dd, J= 2.8Hz, 2.3Hz, CHN), 7.02 (1H, dd, J= 2.3Hz, 2.0Hz, CHN), 7.10-7.16 (1H, m, CH$_{ar}$), 7.28-7.33 (2H, m, 2 × CH$_{ar}$), 7.49-7.52 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 23.9 (2 × CH$_3$), 51.0 (CH(CH$_3$)$_2$), 105.7 (NC=CH), 115.1 (NCH), 119.2 (NCH), 124.0 (NCH=CH), 2 × 124.9 (2 × CH$_{ar}$), 125.1 (CH$_{ar}$), 2 × 128.5 (2 × CH$_{ar}$), 136.1 (C$_{quat}$). IR (NaCl): $\nu_{\text{max}}$ 1602, 1545, 1483 cm$^{-1}$. MS m/z (%): 185 (M$^+$, 100), 170 (84), 143 (81), 115 (46), 105 (32), 43 (21). Anal. Calcld. for C$_{13}$H$_{15}$N: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.42; H, 8.29; N, 7.31.

1-Isopropyl-3-phenyl-4-propylpyrrole 15b

Flash chromatography (hexane/EtOAc 85:15, Rf = 0.62); yield 47%. $^1$H NMR (CDCl$_3$): $\delta$ 0.95 (3H, t, J= 7.5Hz, CH$_3$CH$_2$), 1.46 (6H, d, J= 6.7Hz, 2 × CH$_3$), 1.59 (2H, sext, J= 7.5Hz, CH$_3$CH$_3$), 2.59 (2H, t, J= 7.5Hz, CH$_3$CH$_2$CH$_2$), 4.18 (1H, sept, J= 6.7Hz, CH(CH$_3$)$_2$), 6.55 (1H, d,
J = 2.5 Hz, CHN), 6.77 (1H, d, J = 2.5 Hz, CHN), 7.15-7.21 (1H, m, CH$_2$), 7.30-7.40 (2H, m, 2 × CH$_{ar}$), 7.42-7.69 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): δ 14.5 (CH$_3$CH$_2$), 2 × 23.8 (CH(=CH$_3$)$_2$), 24.0 (CH$_2$CH$_3$), 28.6 (CH$_2$CH$_2$CH$_2$), 50.8 (CH(=CH$_3$)$_2$), 116.6 (NCH), 116.9 (NCH), 121.8 (C=CHN), 123.5 (C=CHN), 125.2 (CH$_{ar}$), 2 × 127.8 (2 × CH$_{ar}$), 2 × 128.4 (2 × CH$_{ar}$), 137.2 (C$_{quat}$). IR (NaCl): ν$_{max}$ 1602, 1532, 1455 cm$^{-1}$. MS m/z (%): 227 (M$^+$, 78), 198 (100), 156 (65). Anal. Calcd. for C$_{16}$H$_{21}$N: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.38; H, 9.53; N, 5.94.

4-Ethyl-1-isopropyl-3-phenylpyrrole 15c

Flash chromatography (EtOAc/hexane 1:1, R$_f$ = 0.83); yield 43%. No spectroscopic data reported.$^{280}$ $^1$H NMR (CDCl$_3$): δ 1.19 (3H, t, J = 7.5 Hz, CH$_3$CH$_2$), 2.66 (2H, q, J = 7.5 Hz, CH$_3$CH$_2$), 4.16 (1H, sept, J = 6.6 Hz, CH$_3$(CH$_3$)$_2$), 6.56 (1H, d, J = 2.3 Hz, CHN), 6.77 (1H, d, J = 2.3 Hz, CHN), 7.13-7.43 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 14.7 (C$_3$H$_3$CH$_2$), 19.4 (CH$_3$C$_2$H$_2$), 2 × 23.8 (CH(=CH$_3$)$_2$), 50.6 (CH(=CH$_3$)$_2$), 116.2 (CHN), 116.5 (CHN), 123.2 (C=CHN), 123.3 (C=CHN), 125.1 (CH$_{ar}$), 2 × 127.6 (2 × CH$_{ar}$), 2 × 128.2 (2 × CH$_{ar}$), 136.9 (C$_{quat}$). IR (NaCl): ν$_{max}$ 1602, 1494, 1451 cm$^{-1}$. MS (ES$^+$) m/z (%): 214 (M$^+$+1, 100).

1-Benzyl-4-ethyl-3-phenylpyrrole 15d

Flash chromatography (EtOAc/hexane 95:5, R$_f$ = 0.40); yield 52%.

$^1$H NMR (CDCl$_3$): δ 1.18 (3H, t, J = 7.5 Hz, CH$_3$CH$_2$), 2.66 (2H, qd, J = 7.5 Hz, 1.0 Hz, CH$_2$CH$_3$), 5.03 (2H, s, NCH$_2$), 6.53 (1H, dt, J = 2.5 Hz, 1.0 Hz, NCH=CCH$_2$), 6.75 (1H, d, J = 2.5 Hz, NCH), 7.15-7.46 (10H, m, 2 × C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 14.8 (CH$_3$CH$_2$), 19.5 (CH$_3$CH$_2$), 53.5 (NCH$_2$), 119.2 (NCH=CCH$_2$), 119.5 (NCH), 124.2 (NCH=C), 124.5 (NCH=C), 125.4 (CH$_{ar}$), 2 × 127.3 (2 × CH$_{ar}$), 3 × 127.8 (3 × CH$_{ar}$), 2 × 128.4 (2 × CH$_{ar}$), 2 × 128.8 (2 × CH$_{ar}$), 136.7 (C$_{quat}$), 138.0 (C$_{quat}$). IR (NaCl): ν$_{max}$ 1602, 1534 cm$^{-1}$. MS m/z (%): 261 (M$^+$, 100), 246 (80), 91 (79). Anal. Calcd. for C$_{19}$H$_{19}$N: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.10; H, 7.44; N, 5.30.
4-Benzyl-3-(4-chlorophenyl)-1-isopropylpyrrole 15e

Flash chromatography (hexane/EtOAc 4:1, Rf = 0.46); yield 57%. \(^1H\) NMR (CDCl\(_3\)): \(\delta\) 1.43 (6H, d, J= 6.7Hz, CH(CH\(_3\))\(_2\)), 3.91 (2H, s, CH\(_2\)), 4.16 (1H, sept, J= 6.7Hz, CH(CH\(_3\))\(_2\)), 6.37 (1H, d, J= 2.5Hz, NCH), 6.81 (1H, d, J= 2.5Hz, NCH), 7.17-7.35 (9H, m, C\(_6\)H\(_4\) and C\(_6\)H\(_5\)). \(^{13}C\) NMR (CDCl\(_3\)): \(\delta\) 2 \times 23.8 (2 \times CH\(_3\)), 32.3 (CH\(_2\)), 50.8 (CH(CH\(_3\))\(_2\)), 116.6 (NCH), 118.6 (NCH), 120.0 (NCH=\(-\)), 122.5 (NCH=\(-\)), 125.7 (CH\(_{ar}\)), 2 \times 128.2 (2 \times CH\(_{ar}\)), 2 \times 128.4 (2 \times CH\(_{ar}\)), 2 \times 128.7 (2 \times CH\(_{ar}\)), 2 \times 128.9 (2 \times CH\(_{ar}\)), 130.9 (C\(_{quat}\)), 135.0 (C\(_{quat}\)), 141.8 (C\(_{quat}\)). IR (NaCl): \(\nu_{\text{max}}\) 1592, 1532, 1452 cm\(^{-1}\). MS (ES+) m/z (%): 310/12 (M+H\(^+\), 100). Anal. Calcd. for C\(_{20}\)H\(_{20}\)NCl: C, 77.53; H, 6.51; N, 4.52. Found: C, 77.73; H, 6.74; N, 4.33.

IV.2.3 Synthesis of 2,3-disubstituted pyrroles from pyrrolinones 264, 265, 270 and 271

IV.2.3.1 Synthesis of 4- and 3-pyrrrol-2-ones 264, 265, 270 and 271

For the synthesis of 5-methyl-4-phenyl-4-pyrrolin-2-one 264a, the procedure was followed as found in the literature.\(^{175}\) Analogous to this procedure, 5-methyl-4-phenyl-1-propyl-4-pyrrolin-2-one 264b was synthesized, which isomerized towards the corresponding 3-pyrrolinone 265 at room temperature. The synthesis of pyrrolinones 270 and 271 was accomplished using the following adapted literature procedure.

To a solution of potassium \(t\)-butoxide (14.98 g, 133.48 mmol, 1.1 equiv.) in 100 ml of DMSO was added slowly phenylacetone 262 (16.26 g, 121.34 mmol) at room temperature. Subsequently 18.09 g (133.48 mmol, 1.1 equiv.) of \(N\)-isopropyl-2-chloroacetamide was added portionwise, which was prepared from chloroacetyl chloride and isopropylamine using a Schotten-Baumann procedure. The reaction mixture was stirred at 80°C during three hours. After cooling, the mixture was poured in ice water and the resulting suspension was extracted with chloroform (3 x 100 ml). The combined extracts were washed with water and after drying (MgSO\(_4\)) and evaporation of the solvent, 4-oxo-pentanamide 268a was obtained, which was purified by flash chromatography. One drop of concentrated sulfuric acid was added to a solution of 2.00 g (8.58 mmol) of 4-oxo-pentanamide 268a in 10 ml of toluene and the mixture was refluxed for 1.5 hours. The resulting mixture of 3-pyrrolinone 271a and 4-pyrrolinone 270a was column chromatographed. To synthesize only 3-pyrrolinone 271a, the
mixture of 4- and 3-pyrrolinones was refluxed for 2 hours in dichloromethane containing a catalytic amount of sulfuric acid.

### 5-Methyl-4-phenyl-1-propyl-4-pyrrolin-2-one 264b

Flash chromatography (EtOAc/hexane 3:7; \( R_f = 0.27 \)); yield 63%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 0.96 (3H, t, J = 7.5Hz, CH\(_3\)CH\(_2\)), 1.63 (2H, sext, J = 7.5Hz, CH\(_3\)CH\(_2\)), 2.19 (3H, t, J = 2.3Hz, C=CH\(_3\)), 3.36 (2H, q, J = 2.3Hz, CH\(_2\)=O), 3.49 (2H, t, J = 7.5Hz, NCH\(_2\)), 7.18-7.45 (5H, m, C\(_6\)H\(_5\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 10.4 (CH\(_3\)), 10.8 (CH\(_3\)), 21.9 (CH\(_2\)), 38.1 (C\(_H_2\)CO), 40.6 (NCH\(_2\)), 111.6 (CH\(_2\)=C\(_H_2\)), 124.9 (CH\(_a\)), 2 \times 126.0 (2 \times CH\(_a\)), 127.4 (2 \times CH\(_a\)), 134.0 (C\(_{quat}\)), 135.0 (C=CH\(_3\)), 174.9 (C=O). IR (NaCl): \( \nu_{\text{max}} \) 1703, 1641, 1597, 1497 cm\(^{-1}\). MS (ES+) \( m/z \) (%): 238 (M+Na\(^+\), 100), 216 (M+H\(^+\), 10), 175 (75).

### 5-Methyl-4-phenyl-1-propyl-3-pyrrolin-2-one 265

Flash chromatography (EtOAc/hexane 3:7; \( R_f = 0.08 \)); yield 86%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 0.96 (3H, t, J = 7.4Hz, CH\(_3\)CH\(_2\)), 1.32 (3H, d, J = 6.7Hz, CHCH\(_3\)), 1.53-1.76 (2H, m, CH\(_3\)CH\(_2\)CH\(_2\)), 3.11 (1H, ddd, J = 13.9Hz, 8.6Hz, 5.3Hz, CH\(_a\)H\(_b\)CH\(_2\)CH\(_3\)), 3.80 (1H, ddd, J = 13.9Hz, 8.7Hz, 7.4Hz, CH\(_a\)H\(_b\)CH\(_2\)CH\(_3\)), 4.60 (1H, qd, J = 6.7Hz, 1.0Hz, CH\(_3\)CH\(_2\)CH\(_3\)), 6.32 (1H, d, J = 1.0Hz, C=CH), 7.36-7.47 (5H, m, C\(_6\)H\(_5\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 11.6 (CH\(_3\)), 17.8 (CH\(_2\)), 22.2 (CH\(_3\)), 41.6 (NCH\(_2\)), 57.5 (CHCH\(_3\)), 120.7 (C=CH-C=O), 2 \times 127.0 (2 \times CH\(_a\)), 2 \times 129.2 (2 \times CH\(_a\)), 130.0 (CH\(_a\)), 132.0 (C\(_{quat}\)), 160.5 (C=CH-C=O), 171.2 (C=O). IR (NaCl): \( \nu_{\text{max}} \) 1682, 1447, 1412, 1242 cm\(^{-1}\). MS (ES+) \( m/z \) (%): 216 (M+H\(^+\), 100).

### N-Isopropyl-4-oxo-3-phenylpentanamide 268a

Flash chromatography (hexane/EtOAc/Et\(_3\)N 13:7:1; \( R_f = 0.17 \)); yield 69%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.02 (3H, d, J = 6.6Hz, CHCH\(_3\)=CH\(_3\)), 1.10 (3H, d, J = 6.6Hz, CHCH\(_3\)=CH\(_3\)), 2.11 (3H, s, CH\(_3\)C=O), 2.34 (1H, dd, J = 14.7Hz, 5.4Hz, CH\(_3\)H\(_b\)), 2.95 (1H, dd, J = 14.7Hz, 9.3Hz, CH\(_3\)H\(_b\)), 3.94-4.02 (1H, m, CH(CH\(_3\))\(_2\)), 4.28 (1H, dd, J = 5.4Hz, 9.3Hz, CHCH\(_2\)), 5.41 (1H, d(br), J = 6.3Hz, NH), 7.19-7.36 (5H, m, C\(_6\)H\(_5\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 2 \times 22.6 (CH(CH\(_3\))\(_2\)), 29.1 (CH\(_3\)C=O), 39.5 (CH\(_2\)), 41.3 (CH(CH\(_3\))\(_2\)), 55.2 (CHCH\(_2\)), 127.6 (CH\(_a\)), 2 \times
113                                              Experimental Part

128.2 (2 × CH₃), 2 × 129.1 (2 × CH₃), 137.8 (Cₗₗₗ), 170.1 (CONH), 207.7 (CH₃=O). IR (NaCl): \( \nu_{\text{max}} \) 3300, 1714, 1644, 1548 cm\(^{-1}\). MS (ES+) \( m/z \) (%): 216 (M-H₂O+H\(^+\), 100).

N-Isopropyl-3-(4-methoxyphenyl)-4-oxopentanamide 268b

Flash chromatography (hexane/EtOAc/Et\(_3\)N 7:3:1, \( R_f = 0.07 \)); yield 72%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.02 (3H, d, J= 6.4Hz, CH\(_3\)CH\(_3\)CH\(_3\)b), 1.09 (3H, d, 6.4Hz, CH\(_3\)CH\(_3\)CH\(_3\)b), 2.09 (3H, s, CH₃CO), 2.35 (1H, dd, J= 14.9Hz, 5.5Hz, CH\(_a\)H\(_b\)), 2.94 (1H, dd, 14.9Hz, 9.2Hz, CH\(_a\)H\(_b\)), 3.77 (3H, s, CH\(_3\)O), 3.90-4.03 (1H, m, CH(CH\(_3\))\(_2\)), 4.22 (1H, dd, J= 9.2Hz, 5.5Hz, CHCH\(_2\)), 6.84 and 7.11 (2 × 2H, 2 × d, J= 8.7Hz, C\(_6\)H\(_4\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 2 × 22.9 (CHC\(_H\)\(_3\)_a), 21.2 (CHC\(_H\)\(_3\)_b), 22.3 (CH\(_3\)_CH\(_3\)), 35.6 (CH\(_2\)), 44.2 (CH(CH\(_3\))\(_2\)), 51.9 (CH\(_2\)), 55.3 (CH\(_3\)), 93.5 (COH), 113.9 (2 × CH\(_a\)), 2 × 128.7 (2 × CH\(_a\)), 139.4 (C\(_\text{quat}\)), 158.4 (C\(_\text{quat}\)), 169.7 (CONH), 207.2 (C=O). IR (NaCl): \( \nu_{\text{max}} \) 3300, 1711, 1643, 1511, 1547, 1250 cm\(^{-1}\). MS (ES+) \( m/z \) (%): 264 (M+H\(^+\), 100), 205 (M\(^+\)-NH\(_i\)-Pr, 65).

5-Hydroxy-1-isopropyl-4-(4-methoxyphenyl)-5-methylpyrrolidin-2-one 269b

This compound was isolated from the reaction mixture as an intermediate. Recrystallization (Et\(_2\)O); yield 10%, mp 139°-140°C. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.03 (3H, s, CH\(_3\)), 1.43 (3H, d, J= 6.9Hz, CH\(_3\)CH\(_3\)CH\(_3\)b), 1.46 (3H, d, J= 6.9Hz, CH\(_3\)CH\(_3\)CH\(_3\)b), 2.61 (1H, dd, J= 16.4Hz, 9.7Hz, CH\(_a\)H\(_b\)), 2.71 (1H, dd, J= 16.4Hz, 8.6Hz, CH\(_a\)H\(_b\)), 2.91 (1H, s(b), OH), 3.36 (1H, “t”, J= 9.1Hz, CH\(_2\)), 3.68 (1H, sept, J= 6.9Hz, CH(CH\(_3\))\(_2\)), 3.81 (3H, s, CH\(_3\)O), 6.89 and 7.19 (4H, 2 × d, J= 8.7Hz, C\(_6\)H\(_4\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 20.1 (CHC\(_H\)\(_3\)_a), 21.2 (CHC\(_H\)\(_3\)_b), 22.3 (CH\(_3\)_CH\(_3\)), 35.6 (CH\(_2\)), 44.2 (CH(CH\(_3\))\(_2\)), 51.9 (CH\(_2\)), 55.3 (CH\(_3\)), 93.5 (COH), 113.9 (2 × CH\(_a\)), 2 × 128.4 (2 × CH\(_a\)), 129.8 (C\(_\text{quat}\)), 158.9 (C\(_\text{quat}\)), 172.3 (C=O). IR (KBr): \( \nu_{\text{max}} \) 3183, 1644, 1610, 1515, 1353, 1257 cm\(^{-1}\). MS (ES+) \( m/z \) (%): 264 (M+H\(^+\), 100), 246 (M\(^+\)-H₂O, 52), 315 (M\(^+\)-H₂O-H\(^+\), 100).

1-Isopropyl-5-methyl-4-phenyl-4-pyrrolin-2-one 270a

Flash chromatography (hexane/ethyl acetate 4:1, \( R_f = 0.25 \)); yield 13%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.47 (6H, d, J= 7.0Hz, CH(CH\(_3\))\(_2\)), 2.18 (3H, t, J= 2.4Hz, CH\(_2\)), 3.30 (2H, q, J= 2.4Hz, CH\(_2\)), 4.19 (1H, sept, J= 7.0Hz, CH(CH\(_3\))\(_2\)), 7.17-7.40 (5H, m, C\(_6\)H\(_5\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 11.9 (CH\(_3\)), 2
Experimental Part

× 19.8 (2 x CH₃), 39.1 (CH₂), 44.2 (NCH), 112.5 (CH₂=C=C), 125.3 (CH₂), 2 x 126.7 (2 x CH₃), 2 x 127.7 (2 x CH₃), 134.5 (C=CH), 135.8 (C=CH), 175.5 (C=O). IR (NaCl): νₘₐₓ 1698, 1496, 1405, 1355 cm⁻¹. MS m/z (%): 216 (M+H⁺, 100).

1-Isopropyl-5-methyl-4-phenyl-3-pyrrolin-2-one 271a

Flash chromatography (hexane/ethyl acetate 4:1, Rf = 0.07); yield 75%, mp 76°C. ¹H NMR (CDCl₃): δ 1.37 (6H, d, J= 6.9Hz, CH(CH₃)₂), 1.42 (3H, d, J= 6.8Hz, CHCH₂), 4.29 (1H, sept, J= 6.9Hz, CH(CH₃)₂), 4.65 (1H, qd, J= 6.8Hz, 0.9Hz, CHCH₃), 6.28 (1H, d, J= 0.9Hz, CHC=O), 7.37-7.46 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 18.8 and 19.6 (CH(C₃H₃)₂), 21.0 (CHCH₃), 43.6 (CH(CH₃)₂), 56.5 (CHCH₃), 119.9 (C=CH-C=O), 2 x 126.1 (2 x CH₃), 2 x 128.1 (2 x CH₃), 128.8 (CH₃), 130.9 (C=CH), 134.5 (C=CH), 159.6 (C=CH-C=O), 169.4 (C=O). IR (KBr): νₘₐₓ 1671 cm⁻¹. MS m/z (%): 216 (M+H⁺, 100).

1-Isopropyl-4-(4-methoxyphenyl)-5-methyl-4-pyrrolin-2-one 270b

Flash chromatography (hexane/ethyl acetate 4:1, Rf = 0.25); yield 8%. ¹H NMR (CDCl₃): δ 1.46 (6H, d, J= 6.9Hz, CH(CH₃)₂), 2.15 (3H, t, J= 2.4Hz, =CCH₃), 3.26 (2H, q, J= 2.4Hz, CH₂), 3.81 (3H, s, OCH₃), 4.28 (1H, sept, J= 6.9Hz, CH(CH₃)₂), 7.14 and 6.89 (4H, 2 x d, J= 8.9Hz, C₆H₄). ¹³C NMR (CDCl₃): δ 12.6 (CH₃), 2 x 20.6 (2 x CH₃), 40.2 (CH₂), 44.7 (NCH), 55.3 (CH₃O), 113.1 (CH₂=C=C), 2 x 113.9 (2 x CH₃), 127.7 (C=CH), 2 x 128.5 (2 x CH₃), 135.2 (C=CH₂), 157.9 (C=CH), 176.4 (C=O). IR (NaCl): νₘₐₓ 1697, 1513, 1246 cm⁻¹. MS m/z (%): 246 (M+H⁺, 100).

1-Isopropyl-4-(4-methoxyphenyl)-5-methyl-3-pyrrolin-2-one 271b

Flash chromatography (hexane/ethyl acetate 1:3, Rf = 0.25); yield 75%, mp 87-88°C. ¹H NMR (CDCl₃): δ 1.37 (6H, d, J= 6.9Hz, CH(CH₃)₂), 1.40 (3H, d, J= 7.1Hz, CHCH₂), 1.40 (3H, d, J= 7.1Hz, CHCH₂), 3.85 (3H, s, CH₃O), 4.28 (1H, sept, J= 6.9Hz, CH(CH₃)₂), 4.61 (1H, q, J= 7.1Hz, CHCH₃), 6.18 (1H, s, CHC=O), 6.95 and 7.37 (4H, 2 x d, J= 8.9Hz, C₆H₄). ¹³C NMR (CDCl₃): δ 19.7 and 20.1 (CH(CH₃)₂), 21.7 (CHCH₃), 43.9 (CH(CH₃)₂), 55.0 (CH₃O), 56.8 (CHCH₃), 2 x 114.0 (2 x CH₃), 118.5 (C=CH-C=O), 124.0
(C_{quat}), 2 \times 128.0 (2 \times CH_{ar}), 159.6 and 160.4 (C_{quat} and C=C-C=O), 170.3 (C=O). IR (KBr): v_{max} 1658, 1602, 1511, 1400, 1260, 1178 cm^{-1}. MS m/z (%): 246 (M+H^+, 100).

IV.2.3.2 Synthesis of 3-aryl-2-methylpyrroles 278c-f

To a solution of 1-isopropyl-5-methyl-4-phenyl-3-pyrrolin-2-one 271a (0.88 g, 4.08 mmol) in 5 ml of dry toluene, was added 1.49 g (12.24 mmol, 3 equiv.) 9-borabicyclo[3.3.1]nonane as a solid dimer. The mixture was allowed to reflux overnight (15 h) and was subsequently poured in 25 ml water. Extraction with ether (3 x 25 ml), drying (MgSO_4) and evaporation of the solvents in vacuo afforded pyrrole 278d, which was purified by flash chromatography.

2-Methyl-3-phenylpyrrole 278c

Flash chromatography (hexane/EtOAc 9:1, R_f = 0.19); yield 21%. Spectroscopic data were in accordance with literature data.

1-Isopropyl-2-methyl-3-phenylpyrrole 278d

Flash chromatography (hexane/EtOAc 9:1, R_f = 0.47); yield 53%, mp 81°C (no lit. data). Spectroscopic data were in accordance with literature data.

2-Methyl-3-phenyl-1-propylpyrrole 278e

Flash chromatography (hexane/EtOAc 95:5, R_f = 0.41); yield 50%. Spectroscopic data were in accordance with literature data.

1-Isopropyl-3-(4-methoxyphenyl)-2-methylpyrrole 278f

Flash chromatography (hexane/EtOAc 95:5, R_f = 0.25); yield 58%. 

^{1}H NMR (CDCl_3): \delta 1.41 (6H, d, J= 6.7Hz, CH(CH_3)_2), 2.30 (3H, s, CH_3), 3.78 (3H, s, CH_3O), 4.28 (1H, sept, J= 6.7Hz, CH(CH_3)_2), 6.22 (1H, d, J= 3.0Hz, NCHCH), 6.70 (1H, d, J= 3.0Hz, NCHCH), 7.10 (2H, d, J= 8.7Hz, 2 \times CH_{ar}), 7.30 (2H, d, J= 8.7Hz, 2 \times CH_{ar}). ^{13}C NMR (CDCl_3): \delta 10.3
116  Experimental Part

(CH₃), 2 × 23.2 (2 × CH₃), 46.7 (CH(CH₃)₂), 54.8 (CH₃O), 107.2 (NCHCH), 2 × 113.4 (2 × CH₂), 114.3 (NCHCH), 121.1 (Cquat), 123.3 (Cquat), 2 × 128.9 (2 × CH₂), 130.1 (Cquat), 157.1 (Cquat). IR (NaCl): vₘₐₓ 1612, 1559, 1508, 1459 (C=C), 1243 cm⁻¹. MS (ES⁺) m/z (%): 230 (M+H⁺, 100).

IV.2.4  Synthesis of 3-substituted 1-methylpyrroles from 1-methylpyrrolinones 274 and 275

IV.2.4.1  Reduction of succinimides 273

1-Methylpyrrolinones 274 and 275 were prepared following literature procedures. In the literature, a mixture of 3- and 4-substituted 1-methyl-3-pyrrolin-2-ones was obtained which was not separated. The obtained compounds could however easily be separated by flash chromatography.

1,3-Dimethyl-3-pyrrolin-2-one 274a

Flash chromatography (hexane/acetone 3:1, Rₕ = 0.16); yield 32%. Spectroscopic data were in accordance with literature data.

1,4-Dimethyl-3-pyrrolin-2-one 275a

Flash chromatography (hexane/acetone 3:1, Rₕ = 0.07); yield 39%. Spectroscopic data were in accordance with literature data.

1-Methyl-3-phenyl-3-pyrrolin-2-one 274b

Flash chromatography (hexane/acetone 7:3, Rₕ = 0.25); yield 29%, mp 138-139°C (no lit. data). Spectroscopic data were in accordance with literature data.
1-Methyl-4-phenyl-3-pyrrolin-2-one 275b \(^{176,177}\)

\[
\begin{array}{c}
\text{O} \\
\text{N-CH}_3 \\
\text{C}
\end{array}
\]

Flash chromatography (hexane/acetone 7:3, \(R_f = 0.14\)); yield 41\%, mp 111-112\(^\circ\)C (no lit. data). \(^{176,177}\) Spectroscopic data were in accordance with literature data.\(^{176,177}\)

IV.2.4.2 Synthesis of 1-methylpyrroles 278a,b

An analogous procedure was followed as used for the synthesis of pyrroles 15 and 278c-f via reduction with 3 equivalents 9-BBN in refluxing toluene for 15 hours.

1,3-Dimethylpyrrole 278a \(^{284}\)

\[
\text{H}_3\text{C} \\
\text{N-CH}_3
\]

Flash chromatography (hexane/EtOAc 1:1, \(R_f = 0.60\)); yield 15\%. Spectroscopic data were in accordance with literature data.\(^{284}\)

1-Methyl-3-phenylpyrrole 278b \(^{285}\)

\[
\text{N-CH}_3 \\
\text{C}
\]

Flash chromatography (hexane/EtOAc 95:5, \(R_f = 0.26\)); yield 55\%. Spectroscopic data were in accordance with literature data.\(^{285}\)

IV.3 Ringcontraction of 2,2-dichlorocyclobutanones towards cyclopropanes

IV.3.1 Synthesis of cis-2-aryl-1-chlorocyclopropanecarbaldehydes 16

To a cooled solution of 1.00 g (4.65 mmol) 2,2-dichloro-3-phenylcyclobutanone 12a in 10 ml of methanol, was added in portions 0.18 g (4.65 mmol, 1 equiv.) sodium borohydride at 0\(^\circ\)C. After stirring for 2 hours at 0\(^\circ\)C, 30 ml of aqueous 1M NaOH was added and stirring was continued for 15 minutes at room temperature. After extraction with chloroform (3 \(\times\) 20 ml), drying of the extracts (MgSO\(_4\)) and evaporation of the solvents, a colorless oil was obtained which could be purified by distillation.

Cis-1-chloro-2-phenylcyclopropanecarbaldehyde 16a

Distillation (58\(^\circ\)-60\(^\circ\)C, 0.01 mmHg); yield 78\%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.87 (1H, dd, \(J_1 = 8.6\)Hz, 6.3Hz, CH\(_2\)H\(_3\)), 2.17 (1H, dd, \(J_2 = 10.2\)Hz, 6.3Hz, CH\(_2\)H\(_3\)), 3.00 (1H, “t”, \(J_3 = 9.4\)Hz, CH), 7.20-7.38 (5H, m, C\(_6\)H\(_5\)), 9.61 (1H,
s, CHO). $^{13}$C NMR (CDCl$_3$): $\delta$ 23.4 (CH$_2$), 34.9 (CH), 53.2 (C$_{quat}$), 127.9 (CH$_{ar}$), 2 $\times$ 128.3 (2 $\times$ CH$_{ar}$), 2 $\times$ 129.3 (2 $\times$ CH$_{ar}$), 133.6 (C$_{quat}$), 197.1 (C=O). IR (NaCl): $\nu_{max}$ 2837, 1717 cm$^{-1}$. MS m/z (%): 180/182 (M$^+$, 33), 145 (100), 127 (29), 117 (33), 116 (25), 115 (83), 91 (32).

Cis-1-chloro-2-(4-chlorophenyl)cyclopropanecarbaldehyde 16b

Distillation (100$^\circ$-105$^\circ$, 0.03 mmHg); yield 84%. $^1$H NMR (CDCl$_3$): $\delta$ 1.84 (1H, dd, J= 9.8Hz, 6.2Hz, CH$_a$H$_b$), 2.19 (1H, dd, J= 8.9Hz, 6.2Hz, CH$_a$H$_b$), 2.97 (1H, “t”, J= 9.4Hz, CH), 7.14-7.35 (4H, m, C$_6$H$_4$), 9.63 (1H, s, CHO). $^{13}$C NMR (CDCl$_3$): $\delta$ 23.4 (CH$_2$), 33.9 (CH), 52.9 (C$_{quat}$), 2 $\times$ 128.4 (2 $\times$ CH$_{ar}$), 2 $\times$ 130.6 (2 $\times$ CH$_{ar}$), 132.2 (C$_{quat}$), 133.7 (C$_{quat}$), 196.7 (C=O). IR (NaCl): $\nu_{max}$ 1716 cm$^{-1}$. MS m/z (%): 214/16/18 (M$^+$, 28), 179/81 (66), 144 (57), 115 (100).

IV.3.2 Functionalization of cyclopropanecarbaldehydes 16

IV.3.2.1 Synthesis of 1-chloro-1-alkylidenecyclopropanes 283-285

Cis-1-Chloro-1-(2,2-dibromovinyl)-2-phenylcyclopropane 283

To 0.50 g (2.77 mmol) of cyclopropanecarbaldehyde 16a in 25 ml of dichloromethane was added 4.35 g (16.62 mmol, 6 equiv.) of triphenylphosphine at 0$^\circ$C under N$_2$-atmosphere. When the triphenylphosphine was completely dissolved in the solvent, 2.76 g (8.31 mmol, 3 equiv.) of tetrabromomethane was added in portions, cooling was stopped and the mixture was stirred for 4 hours. After reaction, 25 ml of pentane was added and the resulting solids were filtered. After washing of the filtrate with sodium bicarbonate and drying of the organic phase (MgSO$_4$), the solvent was removed in vacuo, yielding cyclopropane 283, which could be purified by flash chromatography.

Flash chromatography (hexane/EtOAc 3:1, $R_f$ = 0.71); yield 69%. $^1$H NMR (CDCl$_3$): $\delta$ 1.68 (2H, d, J= 9.1Hz, CH$_2$), 2.56 (1H, t, J= 9.1Hz, CH), 6.97 (1H, s, C=CH), 7.22-7.37 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): $\delta$ 21.8 (CH$_2$), 31.1 (CH), 46.5 (C$_{quat}$), 99.2 (CBr$_2$), 127.3 (CH$_{ar}$), 2 $\times$ 128.2 (2 $\times$ CH$_{ar}$), 2 $\times$ 129.3 (2 $\times$ CH$_{ar}$), 135.7 (C$_{quat}$), 137.8 (CH=CBr$_2$). IR (NaCl): $\nu_{max}$ 1603, 1588, 1497, 1453 cm$^{-1}$. MS m/z (%): 334/36/38/40 (M$^+$, 1), 255/57/59 (11), 176/78 (100), 141 (47).
**Ethyl (2E)-(cis-1-chloro-2-phenylcyclopropyl)-2-propenoate 284**

For the synthesis of 284, the following procedure was applied. Cyclopropanecarbaldehyde 16a (1.00 g, 5.54 mmol) was dissolved in 10 ml of dry diethyl ether and added dropwise to a solution of 1.93 g (5.54 mmol, 1 equiv.) ethyl (triphenylphosphoranylidene)acetate in 20 ml of dry diethyl ether at room temperature and under N₂-atmosphere. After stirring for 6 hours, the reaction mixture was diluted with 25 ml of pentane and the formed solids (triphenylphosphinoxide) were filtered. After drying (MgSO₄) and evaporation of the solvents, (E)- and (Z)-cyclopropylpropenoate 284 were obtained (ratio E/Z 96:4, calculated from ¹H NMR spectra). After flash chromatography only the major (E)-isomer was obtained in a pure form.

Flash chromatography (hexane/EtOAc 95:5, Rₜ = 0,23); yield 68%, mp 49-50°C. ¹H NMR (CDCl₃): δ 1.29 (3H, t, J= 7.2Hz, CH₃), 1.78 (1H, dd, J= 9.9Hz, 6.6Hz, CHₐHₗ), 1.90 (1H, dd, J= 8.2Hz, 6.6Hz, CHₗHₐ), 2.66 (1H, “t”, J= 9.2Hz, CHCH₃), 4.20 (2H, q, J= 7.2Hz, CH₂CH₃), 6.18 (1H, d, J= 14.8Hz, CH=CH-C=O), 6.70 (1H, d, 14.8Hz, CH=CH-C=O), 7.26-7.36 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 19.6 (CH₃), 23.2 (CH₂), 33.8 (CH), 47.5 (Cₜₙ), 60.4 (CH₂O), 120.0 (CH=C=CH-C=O), 127.5 (CH₉), 2 × 128.4 (2 × CH₉), 2 × 129.2 (2 × CH₈), 134.8 (Cₜₙ), 150.2 (CH=CH-C=O), 166.2 (C=O). IR (KBr): vₑₓₜ 1712, 1645, 1311, 1182 cm⁻¹. MS m/z (%): 250/52 (M⁺, 2), 218 (92), 176 (100).

**Dimethyl 2-[(cis-1-chloro-2-phenylcyclopropyl)methylene]malonate 285**

A mixture of 3.00 g (16.62 mmol) cyclopropanecarbaldehyde 16a, 2.20 g (16.62 mmol, 1 equiv.) dimethyl malonate, 0.07 g (0.83 mmol, 0.05 equiv.) piperidine and 0.03 g (0.49 mmol, 0.03 equiv.) acetic acid in 50 ml of benzene was refluxed overnight using a Dean Stark apparatus to remove the formed water by azeotropic distillation. After 20 hours, the mixture was diluted with 50 ml water. After separation of the organic layer, the aqueous phase was extracted with diethyl ether (3 × 25 ml). Drying (MgSO₄) and evaporation of the solvents in vacuo afforded the Knoevenagel adduct 285.

Distillation (130-134°C, 0.01 mmHg) or flash chromatography (hexane/EtOAc 3:1, Rₜ = 0.35); yield 54%. ¹H NMR (CDCl₃): δ 1.82-1.92 (2H, m, CH₂), 2.74 (1H, “t”, J= 9.2Hz, CHCH₂), 3.80 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 6.81 (1H, s, C=CH), 7.23-7.38 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 24.2 (CH₂), 34.1 (CH), 44.7 (Cₜₙ), 52.6 (CH₃O), 52.9
(CH₃O), 127.3 (CH=𝐶), 127.7 (CH₂), 2 × 128.3 (2 × CH₂), 2 × 129.5 (2 × CH₂), 134.6 (Cquat), 147.4 (CH=𝐶), 164.1 (C=O), 165.9 (C=O). **IR (NaCl):** νmax 1728, 1643, 1436, 1270 cm⁻¹. **MS m/z (%):** 294/96 (M⁺, 17), 262/64 (M⁺−MeOH, 25), 234/36 (100), 175 (55), 141 (38), 91 (5).

**IV.3.2.2 Synthesis of cis-1-chloro-1-(dimethoxymethyl)-2-phenylcyclopropane 286**

To a solution of 2.00 g (11.08 mmol) cyclopropanecarbaldehyde 16a in 20 ml of trimethyl orthoformate was added a catalytic amount of p-toluene sulfonic acid and the mixture was refluxed overnight. After reaction, the mixture was poured in 50 ml of a saturated aqueous solution of sodium bicarbonate and subsequently extracted with 3 × 50 ml of diethyl ether. The extracts were dried over a mixture of MgSO₄ and K₂CO₃, filtered and the solvents evaporated *in vacuo*. The resulting oil was distilled to afford pure dimethyl acetal 286.

**Cis-1-chloro-1-dimethoxymethyl-2-phenylcyclopropane 286**

Distillation (62-70°C, 0.1 mmHg); yield 90%. **¹H NMR (CDCl₃):** δ 1.40 (1H, dd, J= 6.3Hz, 7.8Hz, CH₆H₅b), 1.62 (1H, dd, J= 6.3Hz, 10.1Hz, CH₆H₅b), 2.59 (1H, dd, J= 7.8Hz, 10.1Hz, CCH₂), 3.45 (3H, s, OCH₃), 3.46 (3H, s, OCH₃), 4.66 (1H, s, CH(OCH₃)₂), 7.22-7.36 (5H, m, C₆H₅). **¹³C NMR (CDCl₃):** δ 16.8 (CH₂), 25.7 (CH), 48.5 (Cquat), 54.3 (CH₃O), 54.8 (CH₃O), 104.1 (CH(OCH₃)₂), 126.9 (CH₂), 2 × 128.1 (2 × CH₂), 2 × 129.2 (2 × CH₂), 136.2 (Cquat). **IR (NaCl):** νmax 1605, 1499, 1454, 1115, 1069 cm⁻¹. **MS m/z (%):** 226/28 (M⁺, 1), 194/96 (M⁺−MeOH, 17), 121 (100), 115 (42), 91 (13), 77 (14).

**IV.3.2.3 Reaction of cyclopropanecarbaldehyde 16a with NBS**

1-Chloro-2-phenylcyclopropanecarbaldehyde 16a (1.30 g, 7.20 mmol) was dissolved in 25 ml of dry CCl₄. To the solution was added 1.28 g (7.92 mmol, 1.1 equiv.) NBS and 0.06 g (0.36 mmol, 0.05 equiv.) AIBN and the resulting mixture was refluxed for 15 hours. After reaction, the solvent was evaporated *in vacuo* and the resulting reaction mixture was distilled (without aqueous workup) to recover 1-chloro-2-phenylcyclopropanecarbonyl bromide 288. Using the same procedure, but with standard aqueous work up, the corresponding carboxylic acid 289 was obtained.
Cis-1-chloro-2-phenylcyclopropanecarbonyl bromide 288

Distillation (74-76°C, 0.01 mmHg); yield 64%. $^1$H NMR (CDCl$_3$): $\delta$ 1.96 (1H, dd, J= 6.8Hz, 9.1Hz, CH$_6$H$_3$), 2.50 (1H, dd, J= 6.8Hz, 10.5Hz, CH$_6$H$_3$), 3.41 (1H, “t”, J= 9.9Hz, CHCH$_2$), 7.21-7.24 (2H, m, 2 × CH$_{ar}$), 7.30-7.45 (3H, m, 3 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 25.6 (CH$_2$), 36.5 (CH), 53.5 (C$_{quat}$), 128.2 (CH$_{ar}$), 2 × 128.3 (2 × CH$_{ar}$), 2 × 129.4 (2 × CH$_{ar}$), 132.5 (C$_{quat}$), 169.3 (C=O). IR (NaCl): $\nu_{max}$ 1779, 1499, 1453 cm$^{-1}$. MS m/z (%): 258/60/62 (M$^+$, 2), 179/81 (M$^+$-Br, 37), 143 (30), 115 (100), 91 (20).

Cis-1-chloro-2-phenylcyclopropanecarboxylic acid 289

Recrystallization (pentane); yield 52%, mp 76-77°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.84 (1H, dd, J= 5.9Hz, 9.5Hz, CH$_6$H$_3$), 2.23 (1H, dd, J= 5.9Hz, 9.5Hz, CH$_6$H$_3$), 3.17 (1H, t, J= 9.5Hz, CHCH$_2$), 7.21-7.39 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): $\delta$ 24.0 (CH$_2$), 34.7 (CH), 44.2 (C$_{quat}$), 127.8 (CH$_{ar}$), 2 × 128.2 (2 × CH$_{ar}$), 2 × 129.4 (2 × CH$_{ar}$), 133.8 (C$_{quat}$), 177.0 (C=O). IR (KBr): $\nu_{max}$ 3414, 1693, 1617, 1498 cm$^{-1}$. MS m/z (%): 196/98 (M$^+$, 20), 115 (100), 91 (14).

IV.3.2.4 Reaction of dimethoxymethylcyclopropane 286 with NBS

1-Chloro-1-dimethoxymethyl-2-phenylcyclopropane 286 (0.20 g, 0.88 mmol) and 0.16 g (0.88 mmol, 1 equiv.) NBS were dissolved in 25 ml of CCl$_4$ and irradiated with an UV-lamp at room temperature for 12 hours. After cooling to 0°C, the mixture was filtered and the filtrate cooled again at -20°C and filtered another time to remove most of the formed succinimide. In the reaction mixture, methyl cyclopropanecarboxylate 290 was detected which could be separated from the mixture by flash chromatography.

Cis-methyl 1-chloro-2-phenylcyclopropanecarboxylate 290

Flash chromatography (hexane/EtOAc 9:1, R$_f$ = 0.38); yield 29%. $^1$H NMR (CDCl$_3$): $\delta$ 1.78 (1H, dd, J= 5.9Hz, 9.4Hz, CH$_6$H$_3$), 2.16 (1H, dd, J= 5.9Hz, 9.4Hz, CH$_6$H$_3$), 3.09 (1H, t, J= 9.4Hz, CHCH$_2$), 3.84 (3H, s, OCH$_3$), 7.21-7.39 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): $\delta$ 22.8
(CH₂), 33.2 (CH), 44.2 (C₉H₅), 52.1 (OCH₃), 127.1 (CH₆H₅), 2 × 127.7 (2 × CH₆H₅), 2 × 128.9 (2 × CH₆H₅), 133.9 (C₉H₅), 170.0 (C=O). IR (NaCl): vₘₐₓ 1724, 1606, 1500, 1437 cm⁻¹. MS m/z (%): 210/12 (M⁺, 33), 178 (17), 174 (17), 131 (25), 115 (100), 91 (9).

IV.4 Ring expansion of cyclopropanes towards halogenated pyrroles

IV.4.1 Synthesis of 4-aryl-2,2,4-trichlorobutanals 17

A solution of 4.56 g (25.26 mmol) cis-1-chloro-2-phenylcyclopropanecarbaldehyde 16a and 5.53 g (50.52 mmol, 2 equiv.) of DMF-HCl in 5.00 g of DMF was heated to 40°-60°C. After reaction for 20 minutes, 10 ml of dry chloroform was added and chlorine gas was bubbled through the solution. During chlorination, the temperature was allowed to reach 65-70°C. After 15 minutes, when no temperature increase by addition of chlorine was observed, the reaction was stopped and cooled down to room temperature. The reaction mixture was poured in 25 ml of concentrated HCl and extracted with chloroform (3 × 20 ml). The combined organic extracts were washed with an aqueous solution of sodium bisulfite and concentrated HCl (20 ml) and subsequently dried over MgSO₄. Filtration and evaporation of the solvent yielded butanal 17a, which could be purified by distillation.

2,2,4-Trichloro-4-phenylbutanal 17a

Distillation (80°-85°C, 0.05 mmHg); yield 81%. ¹H NMR (CDCl₃): δ 3.11 (1H, dd, J= 15.5Hz, 5.6Hz, CH₆H₅b), 3.32 (1H, dd, J= 15.5Hz, 7.9Hz, CH₆H₅b), 5.22 (1H, dd, J= 7.9Hz, 5.6Hz, CH), 7.29-7.45 (5H, m, C₆H₅), 9.14 (1H, s, CHO). ¹³C NMR (CDCl₃): δ 51.3 (CH₂), 58.0 (CH), 85.9 (CCl₂), 2 × 127.0 (2 × CH₆H₅), 2 × 128.8 (2 × CH₆H₅), 129.0 (CH₆H₅), 139.3 (C₉H₅), 183.5 (C=O). IR (NaCl): vₘₐₓ 1738 cm⁻¹. MS m/z (%): 250/52/54/56 (M⁺, 10), 151/53 (31), 138/40 (97), 125/27 (100), 115 (70), 91 (46), 77 (10).

2,2,4-Trichloro-4-(4-chlorophenyl)butanal 17b

Distillation (105°-109°C, 0.05 mmHg); yield 76%. ¹H NMR (CDCl₃): δ 3.07 (1H, dd, J= 15.2Hz, 5.7Hz, CH₆H₅b), 3.28 (1H, dd, J= 15.2Hz, 7.8Hz, CH₆H₅b), 5.20 (1H, dd, J= 7.8Hz, 5.7Hz, CH), 7.26-7.36 (4H, m, C₆H₅), 9.17 (1H, s, CHO). ¹³C NMR (CDCl₃): δ 50.9 (CH₂), 57.3 (CH), 85.6 (CCl₂), 2 × 128.6 (2 × CH₆H₅), 2 × 129.2 (2 × CH₆H₅), 135.0 (C₉H₅),
138.1 (C\textsubscript{quat}), 183.6 (C\textsubscript{=O}). \textbf{IR (NaCl)}: \(\nu\text{max} 1742 \text{ cm}^{-1}\). \textbf{MS m/z (%):} no M+, 214/16/18 (M\textsuperscript{+}-2\text{Cl}, 44), 173 (100), 150 (95), 126 (36).

**IV.4.2 Synthesis of 5-aryl-3-chloro-2-cyano-2-pyrrolines 304**

To a solution of 1.00 g (3.98 mmol) trichlorobutanal 17a in 10 ml of dry diethyl ether was added 0.45 g (2.38 mmol, 0.6 equiv.) titanium(IV) chloride in 5 ml of dry pentane at 0°C. After addition, the mixture was stirred for 15 minutes at 0°C, followed by addition of 0.94 g (15.92 mmol, 4 equiv.) isopropylamine in 10 ml of diethyl ether. Cooling was stopped and the mixture was stirred for 15 hours. Subsequently, the mixture was poured in 25 ml of 1M NaOH and rapidly extracted with diethyl ether (3 \times 25 ml). The extract was dried (K\textsubscript{2}CO\textsubscript{3}/MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo} at 0-10°C. The resulting imine 303a was used as such (without purification), to minimize decomposition. Especially the \textit{n}-propylderivative was extremely unstable (complete decomposition after 2 hours at -20°C).

To 1.00 g (3.42 mmol) of \(N\)-(2,2,4-trichloro-4-phenylbutylidene)isopropylamine 303a in 20 ml of methanol was added 0.24 g (3.76 mmol, 1.1 equiv.) potassium cyanide and the mixture was heated under reflux during 4 hours. After reaction, the mixture was poured in 20 ml 0.5M NaOH and extracted with dichloromethane (3 \times 20 ml). After drying (MgSO\textsubscript{4}) and evaporation of the solvent, pyrroline 304a was obtained which could be purified by flash chromatography.

\textbf{3-Chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline 304a}

Flash chromatography (hexane/EtOAc 4:1, \(R_f = 0.60\)); yield 58\%. \textbf{\textsuperscript{1}H NMR (CDCl\textsubscript{3})}: \(\delta 0.98 \text{ (3H, d, J= 6.9Hz, CH}_3\text{)}, 1.23 \text{ (3H, d, J= 6.9Hz, CH}_3\text{)}, 2.63 \text{ (1H, dd, J= 17.3Hz, 11.5Hz, CH}_2\text{H}_5\text{)}, 3.21 \text{ (1H, dd, J= 17.3Hz, 11.2Hz, CH}_2\text{H}_5\text{)}, 3.33 \text{ (1H, sept, J= 6.9Hz, CH(C(CH}_3\text{))}_2\text{)}, 4.48 \text{ (1H, dd, J= 11.2Hz, 11.5Hz, CH)}, 7.25-7.50 \text{ (5H, m, C\textsubscript{6}H\textsubscript{5})}. \textbf{\textsuperscript{13}C NMR (CDCl\textsubscript{3})}: \(\delta 2 \times 19.3 \text{ (2 x CH}_3\text{)}, 45.1 \text{ (CH}_2\text{)}, 50.8 \text{ (CH(CH}_3\text{))}_2\text{), 63.0 \text{ (CH)}, 112.1 \text{ (CN), 120.8 (C\textsubscript{quat}), 121.4 (C\textsubscript{quat}), 2 x 126.7 (2 x CH}_ar\text{), 127.7 (CH}_ar\text{), 2 x 128.7 (2 x CH}_ar\text{), 142.9 (C\textsubscript{quat}). IR (NaCl): \(\nu\text{max} 2227 \text{ cm}^{-1}\). \textbf{MS m/z (%):} 246/48 (M\textsuperscript{+}, 55), 231/33 (98), 169 (46), 142 (25), 91 (100), 77 (17).
3-Chloro-2-cyano-5-phenyl-1-propyl-2-pyrroline 304b

This compound was unstable and could not be completely purified by flash chromatography. The spectra still contained impurities (ca. 10%); crude yield 79%. $^1$H NMR (CDCl$_3$): $\delta$ 0.80 (3H, t, J= 7.3Hz, CH$_3$), 1.30-7.54 (2H, m, CH$_2$CH$_3$), 2.72 (1H, dd, J= 12.7Hz, 17.1Hz, NCHCH$_2$H$_3$), 2.83 (1H, t, J= 6.6Hz, NCH$_3$H$_5$), 2.85 (1H, t, J= 6.6Hz, NCH$_3$H$_5$), 3.15 (1H, dd, J= 11.0Hz, 17.1Hz, NCHCH$_2$H$_3$), 4.39 (1H, dd, J= 12.7Hz, 11.0Hz, NCH$_2$H$_5$), 7.31-7.65 (5H, m, C$_6$H$_5$).

$^{13}$C NMR (CDCl$_3$): $\delta$ 11.5 (CH$_3$), 20.3 (CH$_2$), 45.2 (CH$_2$), 52.7 (NCH$_2$H$_5$), 67.8 (NCH), 111.8 (CN), 120.0 (C$_{quad}$), 2 × 127.3 (2 × CH$_{ar}$), 127.8 (C$_{quad}$), 128.3 (CH$_{ar}$), 2 × 128.9 (2 × CH$_{ar}$), 141.1 (C$_{quad}$). IR (NaCl): $\nu_{max}$ 2229 cm$^{-1}$. MS (ES+) m/z (%): 238/40 (M$^+$-CN+H$_2$O, 100).

3-Chloro-5-(4-chlorophenyl)-2-cyano-1-isopropyl-2-pyrroline 304c

Flash chromatography (hexane/EtOAc 4:1, R$_f$ = 0.60); yield 52%.

$^1$H NMR (CDCl$_3$): $\delta$ 0.98 (3H, d, J= 6.9Hz, CH$_3$), 1.22 (3H, d, J= 6.9Hz, CH$_3$), 2.59 (1H, dd, J= 17.5Hz, 11.1Hz, CH$_3$H$_5$), 3.23 (1H, dd, J= 17.5Hz, 11.4Hz, CH$_2$H$_5$), 3.35 (1H, sept, J= 6.9Hz, CH(CH$_3$)$_2$), 4.49 (1H, dd, J= 11.1Hz, 11.4Hz, CH), 7.26-7.38 (4H, m, C$_6$H$_4$). $^{13}$C NMR (CDCl$_3$): $\delta$ 19.3 (CH$_3$), 19.6 (CH$_3$), 45.2 (CH$_2$), 51.1 (CH(CH$_3$)$_2$), 62.2 (NCH), 112.1 (CN), 121.6 (C$_{quad}$), 2 × 128.3 (2 × CH$_{ar}$), 128.5 (C$_{quad}$), 2 × 129.0 (2 × CH$_{ar}$), 133.5 (C$_{quad}$), 141.8 (C$_{quad}$). IR (NaCl): $\nu_{max}$ 2213, 1453 cm$^{-1}$. MS m/z (%): 280/82/84 (M$^+$, 68), 265/67/69 (100), 238 (34), 203 (34), 125 (57).

IV.4.3 Synthesis of 5-phenyl-2-pyrrolidinones 312, 315 and 316

3-Chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline 304a (0.50 g, 2.03 mmol) was dissolved in 10 ml of a 1:1 mixture of acetic acid and aq. 2M HCl. The solution was stirred at room temperature in a well vented fume hood (formation of HCN!) for 2 hours and subsequently poured in 25 ml water and extracted with dichloromethane (3 × 25 ml). After drying (MgSO$_4$) and evaporation of the solvent in vacuo in a fume hood, cis-substituted pyrrolidinone 315 was obtained. When the reaction temperature was raised to reflux temperatures (reflux, 15 hours) a mixture of cis- and trans-substituted pyrrolidinones 315 and
316 was obtained in a ratio 1:3, calculated from $^1$H NMR spectra. The 2 isomers could easily be separated by flash chromatography. Treatment of 304a with 1.1 equiv. of trichloroisocyanuric acid in CHCl$_3$/CH$_3$CN 1:1 at reflux temperature for 4 hours, resulted in the corresponding dichloropyrrolidinone 312, after standard workup and subsequent flash chromatography.

**Cis-3-chloro-1-isopropyl-5-phenyl-2-pyrrolidinone 315**

Flash chromatography (hexane/EtOAc 4:1, $R_f = 0.31$); yield 57%, mp 110-112°C. $^1$H NMR (CDCl$_3$): δ 0.99 (3H, d, J= 6.9Hz, CH$_3$), 1.25 (3H, d, J= 6.9Hz, CH$_3$), 2.20 (1H, dt, J= 14.3Hz, 6.3Hz, CH$_a$H$_b$), 3.06 (1H, ddd, J= 14.3Hz, 9.1Hz, 7.8Hz, CH$_a$H$_b$), 3.85 (1H, sept, J= 6.9Hz, CH(CH$_3$)$_2$), 4.45 (1H, dd, J= 9.1Hz, 6.3Hz, CH), 4.62 (1H, dd, J= 7.8Hz, 6.3Hz, CH), 7.32-7.42 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 19.6 (CH$_3$), 20.3 (CH$_3$), 39.5 (CH$_2$), 46.8 (CH(CH$_3$)$_2$), 54.3 (NCH), 60.3 (CHCl), 2 × 127.5 (2 × CH$_a$), 128.6 (CH$_a$), 2 × 129.0 (2 × CH$_a$), 141.2 (C$_{quat}$), 170.6 (C=O). IR (KBr): $\nu_{max}$ 1677, 1419 cm$^{-1}$. MS m/z (%): 237/39 (M$^+$, 9), 222/24 (30), 202 (100), 117(84).

**Trans-3-chloro-1-isopropyl-5-phenyl-2-pyrrolidinone 316**

Flash chromatography (hexane/EtOAc 4:1, $R_f = 0.06$); yield 32%. $^1$H NMR (CDCl$_3$): δ 0.99 (3H, d, J= 6.8Hz, CH$_3$), 1.27 (3H, d, J= 6.8Hz, CH$_3$), 2.44 (1H, ddd, J= 14.0Hz, 7.4Hz, 5.3Hz, CH$_a$H$_b$), 2.60 (1H, ddd, J= 14.0Hz, 7.4Hz, 5.3Hz, CH$_a$H$_b$), 3.89 (1H, sept, J= 6.8Hz, CH(CH$_3$)$_2$), 4.60 (1H, dd, J= 7.4Hz, 5.3Hz, CH), 4.79 (1H, dd, J= 7.4Hz, 5.3Hz, CH), 7.33-7.42 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 19.7 (CH$_3$), 20.0 (CH$_3$), 40.7 (CH$_2$), 46.4 (CH(CH$_3$)$_2$), 55.1 (NCH), 59.7 (CHCl), 2 × 126.8 (2 × CH$_a$), 128.5 (CH$_a$), 2 × 129.1 (2 × CH$_a$), 140.8 (C$_{quat}$), 170.6 (C=O). IR (NaCl): $\nu_{max}$ 1699, 1495, 1456, 1222 cm$^{-1}$. MS m/z (%): 237/39 (M$^+$, 13), 222/24 (30), 202 (100), 117(88).

**3,3-Dichloro-1-isopropyl-5-phenyl-2-pyrrolidinone 312**

Flash chromatography (hexane/EtOAc 85:15, $R_f = 0.26$); yield 75%, mp 86-87°C. $^1$H NMR (CDCl$_3$): δ 1.11 (3H, d, J= 6.8Hz, CH$_3$), 1.32 (3H, d, J= 6.8Hz, CH$_3$), 2.71 (1H, dd, J= 14.4Hz, 8.0Hz, CH$_a$H$_b$), 3.28 (1H, dd, J= 14.4Hz, 6.1Hz, CH$_a$H$_b$), 3.60 (1H, sept, J= 6.8Hz, CH(CH$_3$)$_2$), 4.66 (1H,
dd, J = 8.0 Hz, 6.1 Hz, CH3, 7.31-7.45 (5H, m, C6H5). 13C NMR (CDCl3): δ 18.9 (CH3), 19.7 (CH3), 47.8 (CH2), 51.7 (NCH), 59.6 (NCH), 81.6 (CCl2), 2 × 127.6 (2 × CHar), 129.2 (CHar), 2 × 129.3 (2 × CHar), 138.4 (Cquat), 167.3 (C=O). IR (KBr): νmax 1710, 1605, 1496 cm⁻¹. MS m/z (%): 271/73/75 (M⁺+ 5), 236/38 (87), 151/53 (100), 115 (56).

**IV.4.4 Synthesis of 2aryl-4-chloropyrroles 307**

To 5.00 g (20.28 mmol) 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline 304a was added 41 ml (81.13 mmol, 4 equiv.) of 2M NaOMe in methanol at room temperature. The mixture was refluxed for 2 hours, cooled and poured in 100 ml water. After extraction with dichloromethane (3 × 50 ml), the extract was dried (MgSO4) and the solvents evaporated in vacuo. The resulting pyrrole 307a was purified by flash chromatography.

**4-Chloro-1-isopropyl-2-phenylpyrrole 307a**

Flash chromatography (hexane/EtOAc 95:5, Rf = 0.50); yield 83%, mp 42°C. 1H NMR (CDCl3): δ 1.35 (6H, d, J = 6.6 Hz, CH(CH3)2), 4.40 (1H, sept, J = 6.6 Hz, CH(CH3)2), 6.05 (1H, d, J = 1.9 Hz, NC=CH), 6.78 (1H, d, J = 1.9 Hz, NCH=C), 7.30-7.43 (5H, m, C6H5). 13C NMR (CDCl3): δ 2 × 23.9 (2 × CH3), 47.7 (CH), 108.2 (NC=CH), 111.8 (Cquat), 114.3 (NCH=CH), 127.6 (CHar), 2 × 128.5 (2 × CHar), 2 × 129.3 (2 × CHar), 132.7 (Cquat), 133.8 (Cquat). IR (KBr): νmax 1497, 1463, 1394 cm⁻¹. MS m/z (%): 219/21 (M⁺ 53), 178/80 (12), 177/79 (100), 115 (21).

**4-Chloro-2-phenyl-1-propylpyrrole 307b**

Flash chromatography (hexane/EtOAc 98:2, Rf = 0.35); yield 59%. 1H NMR (CDCl3): δ 0.79 (3H, t, J = 7.4 Hz, CH3), 1.64 (2H, sext, J = 7.4 Hz, CH2CH3), 3.80 (3H, t, J = 7.4 Hz, NCH2), 6.10 (1H, d, J = 1.9 Hz, NC=CH), 6.69 (1H, d, J = 1.9 Hz, NCH=CH), 7.30-7.42 (5H, m, C6H5). 13C NMR (CDCl3): δ 11.3 (CH3), 24.9 (CH2), 49.2 (NCH2), 108.8 (NC=CH), 111.7 (Cquat), 118.9 (NCH), 127.7 (CHar), 2 × 128.8 (2 × CHar), 2 × 129.3 (2 × CHar), 132.8 (Cquat), 134.5 (Cquat). IR (NaCl): νmax 1603, 1500, 1475, 1324 cm⁻¹. MS m/z (%): 219/21 (M⁺ 100), 190/92 (84), 177/79 (39), 155 (37), 142 (15), 115 (20).
**4-Chloro-2-(4-chlorophenyl)-1-isopropylpyrrole 307c**

Flash chromatography (hexane/EtOAc 97:3, Rf = 0.42); yield 77%, mp 61°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.34 (6H, d, J= 6.7Hz, CH(CH$_3$)$_2$), 4.34 (1H, sept, J= 6.7Hz, CH(CH$_3$)$_2$), 6.04 (1H, d, J= 1.9Hz, NC=CH), 6.78 (1H, d, J= 1.9Hz, NCH=C), 7.21-7.26 (2H, m, 2 × CH$_{ar}$), 7.34-7.39 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 24.0 (2 × CH$_3$), 47.9 (CH), 108.6 (NC=CH), 112.1 (C$_{quat}$), 114.8 (NCH=C), 2 × 128.9 (2 × CH$_{ar}$), 2 × 130.6 (2 × CH$_{ar}$), 131.1 (C$_{quat}$), 132.6 (C$_{quat}$), 133.7 (C$_{quat}$). IR (KBr): $\nu_{max}$ 1495, 1415, 1288 cm$^{-1}$. MS m/z (%): 253/55/57 (M$^+$, 76), 211/13/15 (100), 176 (27), 149 (19).

**IV.4.5 Synthesis of 3-chloro-2-cyanopyrroles 308**

To a solution of 0.54 g (2.19 mmol) of 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline 304a in 20 ml of dry toluene was added 0.55 g (2.41 mmol, 1.1 equiv.) DDQ and the resulting mixture was refluxed for 6 hours. After reaction, the mixture was diluted with 20 ml pentane and subsequently filtered over Celite®. The filtrate was diluted with 50 ml water and extracted with pentane (3 × 50 ml). The extracts were dried (MgSO$_4$) and purified by flash chromatography (short column). In general, the pyrroles synthesized in this PhD-work are not very stable on silicagel, so efforts have to be done to perform the purification step by chromatography as rapid as possible.

**3-Chloro-2-cyano-1-isopropyl-5-phenylpyrrole 308a**

Flash chromatography (hexane/EtOAc 95:5, Rf = 0.25); yield 43%, mp 68-71°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.58 (6H, d, J= 6.9Hz, CH(CH$_3$)$_2$), 4.52 (1H, sept, J= 6.9Hz, CH(CH$_3$)$_2$), 6.11 (1H, s, NC=CH), 7.28-7.34 (2H, m, 2 × CH$_{ar}$), 7.43-7.49 (3H, m, 3 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 22.5 (2 × CH$_3$), 50.3 (NCH), 100.0 (CN), 109.6 (NC=CH), 113.2 (C$_{quat}$), 124.9 (C$_{quat}$), 2 × 128.8 (2 × CH$_{ar}$), 129.2 (CH$_{ar}$), 2 × 129.6 (2 × CH$_{ar}$), 130.7 (C$_{quat}$), 139.4 (C$_{quat}$). IR (KBr): $\nu_{max}$ 2211, 1454 cm$^{-1}$. MS m/z (%): 244/46 (M$^+$, 38), 202/4 (100), 166 (9), 140 (16).
3-Chloro-2-cyano-5-phenyl-1-propylpyrrole 308b

Flash chromatography (hexane/EtOAc 9:1, \( R_f = 0.35 \)); yield 43%.

\[ ^1H \text{NMR (CDCl}_3\text{)}: \delta 0.79 (3H, t, J= 7.5Hz, \text{CH}_3), 1.70 (2H, sext, J= 7.5Hz, \text{CH}_2), 3.98 (2H, t, J= 7.5Hz, \text{NCH}_2), 6.18 (1H, s, \text{NC}=\text{CH}), 7.32-7.49 (5H, m, \text{C}_6\text{H}_5). \]

\[ ^13C \text{NMR (CDCl}_3\text{)}: \delta 10.9 (\text{CH}_3), 24.5 (\text{CH}_2), 48.7 (\text{NCH}_2), 103.5 (\text{CN}), 110.1 (\text{NC}=\text{CH}), 112.4 (\text{C}_\text{quat}), 123.1 (\text{C}_\text{quat}), 2 \times 129.0 (2 \times \text{CH}_\text{ar}), 3 \times 129.2 (2 \times \text{CH}_\text{ar} \text{ and C}_\text{quat}), 130.6 (\text{CH}_\text{ar}), 139.7 (\text{C}_\text{quat}). \]

\[ \text{IR (NaCl)}: \nu_{\text{max}} 2217, 1460, 1337 \text{ cm}^{-1}. \]

\[ \text{MS m/z (%): 244/46 (M}^+\text{, 83), 202/4 (100), 190 (23), 180 (24), 166 (13), 140 (20).} \]

3-Chloro-5-(4-chlorophenyl)-2-cyano-1-isopropylpyrrole 308c

Flash chromatography (hexane/EtOAc 97:3, \( R_f = 0.19 \)); yield 50%, mp 101-104°C.

\[ ^1H \text{NMR (CDCl}_3\text{)}: \delta 1.59 (6H, d, J= 6.9Hz, \text{CH(CH}_3)_2), 4.46 (1H, sept, J= 6.9Hz, \text{CH(CH}_3)_2), 6.11 (1H, s, \text{NC}=\text{CH}), 7.22-7.28 (2H, m, 2 \times \text{CH}_\text{ar}), 7.40-7.48 (2H, m, 2 \times \text{CH}_\text{ar}). \]

\[ ^13C \text{NMR (CDCl}_3\text{)}: \delta 2 \times 22.5 (2 \times \text{CH}_3), 50.5 (\text{CH}), 100.4 (\text{CN}), 109.8 (\text{NC}=\text{CH}), 113.0 (\text{C}_\text{quat}), 124.9 (\text{C}_\text{quat}), 129.0 (\text{C}_\text{quat}), 2 \times 129.3 (2 \times \text{CH}_\text{ar}), 2 \times 130.8 (2 \times \text{CH}_\text{ar}), 135.5 (\text{C}_\text{quat}), 138.1 (\text{C}_\text{quat}). \]

\[ \text{IR (KBr)}: \nu_{\text{max}} 2215, 1449, 1337 \text{ cm}^{-1}. \]

\[ \text{MS m/z (%): 278/80/82 (M}^+\text{, 54), 236/38/40 (100), 201/3 (16), 174 (21).} \]

IV.4.6 Functionalization of pyrroles 307 and 308

IV.4.6.1 Synthesis of 3-chloro-2-acetyl-1-isopropyl-5-phenylpyrrole 318

A solution of 1.6 M MeLi in diethyl ether (2.60 ml, 4.09 mmol, 1 equiv.) was added to a solution of 1.00 g (4.09 mmol) 3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole 308a in 50 ml of dry THF under N₂-atmosphere. After stirring for 2 hours at room temperature, the reaction mixture was diluted with 50 ml of water and subsequently extracted with diethyl ether (3 \( \times \) 25 ml). Drying of the solvents (MgSO₄/K₂CO₃), filtration and evaporation of the solvents \textit{in vacuo} yielded a mixture of 2-acetylpyrrole and the corresponding imine 317. Separation of these two products was not possible, because the imine 317 hydrolyzed towards 318 during chromatography. The mixture was dissolved in 25 ml dichloromethane to which 10 ml of aq. 6M HCl was added. The resulting biphasic solution was stirred at room temperature for 2
hours and extracted with dichloromethane afterwards. Standard workup yielded 2-acetylpyrrole 318, which could be purified by flash chromatography.

**2-Acetyl-3-chloro-1-isopropyl-5-phenylpyrrole 318**

Flash chromatography (hexane/EtOAc 97:3, Rf = 0.20); yield 58%, mp 41-43°C. $^1$H NMR (CDCl$_3$): δ 1.42 (6H, d, J= 7.0Hz, CH(CH$_3$)$_2$), 2.67 (3H, s, CH$_3$CO), 4.73 (1H, sept, J= 7.0Hz, CH(CH$_3$)$_2$), 6.12 (1H, s, NC=CH), 7.34-7.38 (2H, m, 2 × CH$_{ar}$), 7.41-7.47 (3H, m, 3 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): δ 2 × 22.4 (2 × CH$_3$), 31.7 (CH$_3$), 51.8 (CH), 111.9 (NC=CH), 121.5 (C$_{quat}$), 2 × 128.5 (2 × CH$_{ar}$), 2 × 128.9 (C$_{quat}$ and CH$_{ar}$), 2 × 129.9 (2 × CH$_{ar}$), 132.7 (C$_{quat}$), 141.4 (C$_{quat}$), 189.0 (C=O). IR (NaCl): $\nu$$_{max}$ 1651, 1445 cm$^{-1}$. MS m/z (%): 261/63 (M$^+$, 58), 219/21 (100), 204/6 (50), 191/1 (25).

IV.4.6.2 Formylation of pyrrole 307a

To a solution of 1.00 g (4.56 mmol) 3-chloro-1-isopropyl-5-phenylpyrrole 307a in 20 ml of DMF and 20 ml of dry dichloromethane was added a solution of 0.84 g (5.47 mmol, 1.2 equiv.) of POCl$_3$ in 5 ml of dry dichloromethane at 0°C under N$_2$-atmosphere. After stirring for 5 hours, the reaction mixture was diluted with 25 ml of aq. 1M NaOH at 0°C and stirred for 15 minutes at the same temperature. The mixture was poured in 25 ml water and extracted with dichloromethane (3 × 30 ml). The extracts were dried over MgSO$_4$ and after filtration, the solvent was removed in vacuo. To remove residual DMF, additional evaporation at high vacuum (0.01 mmHg) was applied. This procedure yielded a mixture of formylated pyroles 320a and 320b (ratio 65:35, calculated from $^1$H NMR spectra) which could easily be separated by flash chromatography.

**3-Chloro-2-formyl-1-isopropyl-5-phenylpyrrole 320a**

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.54); yield 53%, mp 53°C. $^1$H NMR (CDCl$_3$): δ 1.49 (6H, d, J= 6.9Hz, CH(CH$_3$)$_2$), 4.64 (1H, sept, J= 6.9Hz, CH(CH$_3$)$_2$), 6.18 (1H, s, NC=CH), 7.33-7.37 (2H, m, 2 × CH$_{ar}$), 7.43-7.50 (3H, m, 3 × CH$_{ar}$), 9.80 (1H, s, CHO). $^{13}$C NMR (CDCl$_3$): δ 2 × 21.4 (2 × CH$_3$), 50.9 (CH), 111.1 (NC=CH), 126.1 (C$_{quat}$), 2 × 128.8 (2 × CH$_{ar}$), 129.2 (C$_{quat}$), 129.3 (CH$_{ar}$), 2 × 129.5 (2 × CH$_{ar}$), 131.6 (C$_{quat}$), 142.8 (C$_{quat}$), 176.7
Experimental Part

(C=O). IR (KBr): $\nu_{\text{max}}$ 2845, 2806, 1655, 1450, 1207 cm$^{-1}$. MS m/z (%): 247/49 (M$^+$, 83), 205 (100), 149 (31), 140 (18), 115 (16).

**4-Chloro-3-formyl-1-isopropyl-2-phenylpyrrole 320b**

Flash chromatography (hexane/EtOAc 9:1, $R_f = 0.13$); yield 21%, mp 97-98°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.36 (6H, d, J= 6.7Hz, CH(CH$_3$)$_2$), 4.25 (1H, sept, J= 6.7Hz, CH(CH$_3$)$_2$), 6.81 (1H, s, NCH=C), 7.32-7.37 (2H, m, 2 × CH$_{ar}$), 7.45-7.52 (3H, m, 3 × CH$_{ar}$), 9.53 (1H, s, CHO). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 23.6 (2 × CH$_3$), 48.3 (CH), 112.9 ($C_{quat}$), 116.3 (NCH=C), 118.8 ($C_{quat}$), 128.7 ($C_{quat}$), 2 × 128.8 (2 × CH$_{ar}$), 129.6 (CH$_{ar}$), 2 × 130.9 (2 × CH$_{ar}$), 141.8 ($C_{quat}$), 185.2 (C=O). IR (KBr): $\nu_{\text{max}}$ 2739, 1672, 1434 cm$^{-1}$. MS m/z (%): 247/49 (M$^+$, 78), 204/6 (100), 169 (7), 141 (10), 115 (7).

**IV.4.6.3 Methoxycarbonylation of pyrrole 307a**

3-Chloro-1-isopropyl-5-phenylpyrrole 307a (0.10 g, 0.45 mmol) was dissolved in 10 ml of carbon disulfide and cooled to 0°C. To the cold solution, 45 mg (0.48 mmol, 1.05 equiv.) methyl chloroformate and 64 mg (0.48 mmol, 1.05 equiv.) AlCl$_3$ were added under N$_2$-atmosphere and the mixture was allowed to reach room temperature. After stirring for 4 hours, the mixture was diluted with 20 ml of water and extracted with dichloromethane (3 × 25 ml). After drying (MgSO$_4$), the solvents were removed in vacuo, in a fume hood (CS$_2$!) yielding a mixture of methoxycarbonylated pyroles 321a and 321b (ratio 1:4, calculated from $^1$H NMR spectra), which could easily be separated by flash chromatography.

In order to obtain only 2-methoxycarbonyl pyrrole 321a, the following procedure was applied.

3-Chloro-1-isopropyl-5-phenylpyrrole 307a (0.50 g, 2.28 mmol) was dissolved in 25 ml of dry THF and cooled to -78°C. Under N$_2$-atmosphere, 0.92 ml (2.28 mmol, 1 equiv.) of a 2.5 M BuLi solution in hexane was added and stirred for 30 min at 0°C. After deprotonation, 0.21 g (2.28 mmol, 1 equiv.) methyl chloroformate in 5 ml of dry THF was added via a syringe and the mixture was stirred for 2 hours at 0°C. After reaction, 25 ml water was added, the organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 25 ml). After drying (MgSO$_4$) and evaporation of the solvents, a crystalline compound was obtained which could be purified by recrystallization.
3-Chloro-1-isopropyl-2-methoxycarbonyl-5-phenylpyrrole 321a

Recrystallization (pentane); yield 77%, mp 66°C.  

$^1$H NMR (CDCl$_3$): $\delta$ 1.47 (6H, d, J= 7.0Hz, CH(CH$_3$)$_2$), 3.90 (3H, s, OCH$_3$), 4.71 (1H, sept, J= 7.0Hz, CH(CH$_3$)$_2$), 6.11 (1H, s, NC=CH), 7.33-7.38 (2H, m, 2 × CH$_{ar}$), 7.40-7.47 (3H, m, 3 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 22.4 (2 × CH$_3$), 51.4 and 51.5 (NCH and OCH$_3$), 111.5 (NC=CH), 119.3 (C$_{quat}$), 120.9 (C$_{quat}$), 2 × 128.5 (2 × CH$_{ar}$), 128.8 (CH$_{ar}$), 2 × 129.9 (2 × CH$_{ar}$), 132.7 (C$_{quat}$), 140.1 (C$_{quat}$), 161.5 (C=O). IR (KBr): $\nu_{max}$ 1697, 1454, 1223 cm$^{-1}$. MS m/z (%): 277/79 (M$^+$, 100), 246/48 (36), 235/37 (47), 204/6 (96).

4-Chloro-1-isopropyl-3-methoxycarbonyl-2-phenylpyrrole 321b

Flash chromatography (hexane/EtOAc 9:1, $R_f$ = 0.23); yield 63%, mp 109°C.  

$^1$H NMR (CDCl$_3$): $\delta$ 1.30 (6H, d, J= 6.7Hz, CH(CH$_3$)$_2$), 3.60 (3H, s, OCH$_3$), 4.10 (1H, sept, J= 6.7Hz, CH(CH$_3$)$_2$), 6.79 (1H, s, NCH=C), 7.26-7.30 (2H, m, 2 × CH$_{ar}$), 7.42-7.46 (3H, m, 3 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 23.7 (2 × CH$_3$), 48.2 (OCH$_3$), 50.9 (CH), 110.4 (C$_{quat}$), 113.2 (C$_{quat}$), 115.3 (NCH=C), 2 × 128.2 (2 × CH$_{ar}$), 128.7 (CH$_{ar}$), 2 × 130.5 (2 × CH$_{ar}$), 131.7 (C$_{quat}$), 138.1 (C$_{quat}$), 164.1 (C=O). IR (KBr): $\nu_{max}$ 1695, 1543, 1478, 1256 cm$^{-1}$. MS m/z (%): 277/79 (M$^+$, 68), 246/48 (13), 235/37 (45), 203/5 (100), 140 (64).

IV.4.6.4 Synthesis of 4-bromo-3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole 319

3-Chloro-2-cyano-1-isopropyl-5-phenylpyrrole 308a (0.25 g, 1.02 mmol) was dissolved in 10 ml of acetic acid containing 0.17 g (2.04, 2 equiv.) NaOAc. At room temperature, a solution of 0.17 g (1.07 mmol, 1.05 equiv.) bromine in 2 ml acetic acid was added dropwise. The mixture was refluxed for 5 hours and filtered after cooling. The filtrate was poured in 50 ml water and subsequently extracted with dichloromethane (3 × 30 ml). The extracts were neutralized with sodium bicarbonate and were dried over MgSO$_4$ afterwards. Filtration and evaporation of the solvent yielded almost pure brominated pyrrole 319. Some minor impurities were removed by recrystallization.
4-Bromo-3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole 319

Recrystallization (hexane/EtOAc 97:3); yield 87%, mp 110-113°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.55 (6H, d, J= 6.9Hz, CH(CH\(_3\))\(_2\)), 4.41 (1H, sept, J= 6.9Hz, CH(CH\(_3\))\(_2\)), 7.26-7.34 (2H, m, 2 × CH\(_{ar}\)), 7.46-7.55 (3H, m, 3 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 22.5 (2 × CH\(_3\)), 51.9 (CH), 97.4 (C\(_{quat}\)), 99.9 (CN), 112.4 (C\(_{quat}\)), 125.4 (C\(_{quat}\)), 2 × 129.0 (2 × CH\(_{ar}\)), 129.1 (C\(_{quat}\)), 129.9 (CH\(_{ar}\)), 2 × 130.4 (2 × CH\(_{ar}\)), 137.2 (C\(_{quat}\)). IR (KBr): \(\nu_{\text{max}}\) 2212, 1453, 1334 cm\(^{-1}\). MS \(m/z\) (%): 322/24/26 (M\(^+\), 29), 280/82/84 (100).

IV.5 Synthesis of 2-(hydroxymethyl)-, 2-(alkoxymethyl)- and 2-(aminomethyl)pyrroles

IV.5.1 Reduction of 2-formyl- and 2-cyanopyrroles 320a and 308a

IV.5.1.1 Synthesis of 2-(hydroxymethyl)pyrrole 329

To a solution of 3-chloro-2-formyl-1-isopropyl-5-phenylpyrrole 320a (0.50 g, 2.02 mmol) in 10 ml of dry THF was added 0.08 g (2.02 mmol, 1 equiv.) sodium borohydride at room temperature and under N\(_2\)-atmosphere. The mixture was stirred overnight (20 hours) and subsequently poured in 25 ml water. Extraction was performed with diethyl ether (3 × 25 ml) and the combined extracts were dried over MgSO\(_4\). After removal of the solvents in vacuo, a clean reaction mixture was obtained containing only traces of impurities. To remove the latter, pyrrole 329 was chromatographed over a small column (3 cm) of silica gel.

3-Chloro-2-(hydroxymethyl)-1-isopropyl-5-phenylpyrrole 329

Flash chromatography (hexane/EtOAc 9:1, \(R_f\) = 0.35); yield 56%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.42 (6H, d, J= 7.1Hz, CH(CH\(_3\))\(_2\)), 4.54 (1H, sept, J= 7.1Hz, CH(CH\(_3\))\(_2\)), 4.70 (2H, s, CH\(_2\)O), 6.04 (1H, s, NC=CH), 7.29-7.42 (5H, m, C\(_6\)H\(_5\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 23.3 (2 × CH\(_3\)), 49.4 (CH), 61.0 (OCH\(_2\)), 108.6 (NC=CH), 114.4 (C\(_{quat}\)), 124.5 (C\(_{quat}\)), 127.9 (CH\(_{ar}\)), 2 × 128.3 (2 × CH\(_{ar}\)), 2 × 130.1 (2 × CH\(_{ar}\)), 133.8 (C\(_{quat}\)), 134.9 (C\(_{quat}\)). IR (NaCl): \(\nu_{\text{max}}\) 3396, 1603, 1552, 1468, 1333 cm\(^{-1}\). MS \(m/z\) (%): 232/34 (M\(^+\)-OH, 88), 190 (100).
IV.5.1.2 Synthesis of 2-(aminomethyl)pyrrole 330

To a solution of 3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole 308a (1.00 g, 4.09 mmol) in 25 ml of dry THF was added 0.16 g (4.09 mmol, 1 equiv.) of LiAlH₄. The mixture was refluxed for 4 hours and after cooling to room temperature, the reaction was stopped by adding slowly (dropwise) 5 ml of ice water. The reaction mixture was subsequently poured in 25 ml water and extracted with 3 × 25 ml of diethyl ether. The solvents were evaporated in vacuo after drying over MgSO₄. To remove minor impurities a flash chromatography over a small column was applied.

2-(Aminomethyl)-3-chloro-1-isopropyl-5-phenylpyrrole 330

Flash chromatography (hexane/EtOAc/Et₃N 48:50:2, R₁ = 0.50); yield 49%. ¹H NMR (CDCl₃): δ 1.45 (6H, d, J= 7.0Hz, CH(CH₃)₂), 3.99 (2H, s, CH₂), 4.54 (1H, sept, J= 7.0Hz, CH(CH₃)₂), 6.02 (1H, s, NC=CH), 7.29-7.44 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 2 × 23.5 (2 × CH₃), 36.4 (CH₂NH₂), 48.8 (NCH), 108.4 (NC=CH), 111.4 (C₉), 127.7 (C₆H₅), 2 × 128.4 (2 × CH₆H₅), 129.9 (C₉), 2 × 130.0 (2 × CH₆H₅), 133.4 (C₉), 133.7 (C₉). IR (NaCl): ν_max 3374, 1602, 1470, 1332 cm⁻¹. MS m/z (%): 248/50 (M⁺, 69), 232/34 (55), 190/92 (100).

IV.5.2 Substitution and aromatization of 5-(bromomethyl)pyrrolines 335

IV.5.2.1 Synthesis of 2-aryl-5-(bromomethyl)-3,3-dichloro-1-pyrrolines 335

To a solution of 1.00 g (4.20 mmol) of 5-(bromomethyl)-2-phenyl-1-pyrroline 332a in 25 ml of CHCl₃/CH₃CN (9:1) was added 0.68 g (2.94 mmol, 0.7 equiv.) of trichloroisocyanuric acid. The mixture was refluxed for 1.5 hours and was poured in 25 ml water after cooling to room temperature. The dichlorinated pyrroline 335a was extracted from the mixture with chloroform (3 × 20 ml). After drying (MgSO₄) and evaporation of the solvent, a mixture of dichlorinated product 335a and N-chlorinated pyrroline 336 (ratio 9:1) was obtained. The latter was converted to the desired 5-(bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline 335a by simple washing of the reaction mixture (dissolved in 25 ml of dichloromethane) with a saturated aqueous solution of NaHSO₃ during 15 minutes. Standard workup yielded almost pure product 335a. Flash chromatography was used to remove the last traces of impurities.
5-(Bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline 335a

Flash chromatography (hexane/EtOAc 95:5, R<sub>f</sub> = 0.19); yield 69%.<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.90 (1H, dd, J= 14.5Hz, 7.0Hz, CH<sub>a</sub>H<sub>b</sub>), 3.31 (1H, dd, J= 14.5Hz, 6.1Hz, CH<sub>a</sub>H<sub>b</sub>), 3.74 (1H, dd, J= 10.5Hz, 6.9Hz, BrCH<sub>a</sub>H<sub>b</sub>), 3.80 (1H, dd, J= 10.5Hz, 4.1Hz, BrCH<sub>a</sub>H<sub>b</sub>), 4.57-4.65 (1H, m, NCH), 7.44-7.57 (3H, m, 3 × CH<sub>ar</sub>), 8.17-8.21 (2H, m, 2 × CH<sub>ar</sub>).<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 34.9 (CH<sub>2</sub>), 53.2 (CH<sub>2</sub>Br), 68.5 (NCH), 86.8 (CCl<sub>2</sub>), 2 × 128.4 (2 × CH<sub>ar</sub>), 129.2 (2 × CH<sub>ar</sub>), 129.3 (C<sub>quat</sub>), 131.6 (CH<sub>ar</sub>), 170.1 (C=N). IR (NaCl): <em>v</em><sub>max</sub> 1693, 1597, 1250 cm<sup>-1</sup>. MS m/z (%): 305/7/9/11 (M<sup>+</sup>+, 13), 189 (18), 154 (21), 130 (100), 104 (45).

5-(Bromomethyl)-1,4,4-trichloro-2-phenyl-1-pyrrolium 336

Flash chromatography (hexane/EtOAc 95:5, R<sub>f</sub> = 0.23); yield 70%.<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.02 (1H, dd, J= 16.0Hz, 4.8Hz, CH<sub>a</sub>H<sub>b</sub>), 3.23 (1H, dd, J= 16.0Hz, 5.5Hz, CH<sub>a</sub>H<sub>b</sub>), 3.79 (1H, dd, J= 11.1Hz, 6.6Hz, BrCH<sub>a</sub>H<sub>b</sub>), 3.99 (1H, dd, J= 11.1Hz, 5.8Hz, BrCH<sub>a</sub>H<sub>b</sub>), 4.15-4.23 (1H, m, NCH), 7.46-7.52 (2H, m, 2 × CH<sub>ar</sub>), 7.54-7.64 (1H, m, CH<sub>ar</sub>), 8.22-8.33 (2H, m, 2 × CH<sub>ar</sub>).<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 31.1 (CH<sub>2</sub>), 45.0 (CH<sub>2</sub>Br), 77.0 (NCH), 84.3 (CCl<sub>2</sub>), 2 × 128.4 (2 × CH<sub>ar</sub>), 2 × 131.1 (2 × CH<sub>ar</sub>), 131.5 (C<sub>quat</sub>), 133.9 (CH<sub>ar</sub>), 187.7 (C=N). IR (NaCl): <em>v</em><sub>max</sub> 1606, 1574, 1297 cm<sup>-1</sup>. MS (ES+) m/z (%): 306/8/10 (M+H<sup>+</sup>-HCl, 100).

5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline 335b

Flash chromatography (hexane/EtOAc 9:1, R<sub>f</sub> = 0.20); yield 77%.<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.88 (1H, dd, J= 14.6Hz, 7.2Hz, CH<sub>a</sub>H<sub>b</sub>), 3.28 (1H, dd, J= 14.6Hz, 6.3Hz, CH<sub>a</sub>H<sub>b</sub>), 3.69 (1H, dd, J= 10.5Hz, 6.9Hz, BrCH<sub>a</sub>H<sub>b</sub>), 3.76 (1H, dd, J= 10.5Hz, 4.3Hz, BrCH<sub>a</sub>H<sub>b</sub>), 4.57 (1H, “dq”, J= 6.8Hz, 4.3Hz, NCH), 7.40-7.45 (2H, m, 2 × CH<sub>ar</sub>), 8.09-8.13 (2H, m, 2 × CH<sub>ar</sub>).<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 34.7 (CH<sub>2</sub>), 53.2 (CH<sub>2</sub>Br), 68.5 (NCH), 86.6 (CCl<sub>2</sub>), 127.7 (C<sub>quat</sub>), 2 × 128.8 (2 × CH<sub>ar</sub>), 2 × 130.6 (2 × CH<sub>ar</sub>), 137.9 (C<sub>quat</sub>) 169.0 (C=N). IR (NaCl): <em>v</em><sub>max</sub> 1607, 1492, 1093 cm<sup>-1</sup>. MS m/z (%): 339/41/43/45 (M<sup>+</sup>, 8), 164/66 (100), 138 (35).
IV.5.2.2 Synthesis of 2-(hydroxymethyl)- and 2-(alkoxymethyl)pyrroles 338

5-(Bromomethyl)-3,3-dichloro-2-phenyl-1-pyrroline 335a (1.70 g, 5.54 mmol) was dissolved in 8 ml of 1,4-dioxane and 8.31 ml (16.61 mmol, 3 equiv.) of an aqueous 2M NaOH solution was added. The resulting homogeneous mixture was refluxed for 2 hours and subsequently acidified with aq. 2M HCl until neutral. Extraction was performed with dichloromethane (3 × 20 ml). After drying of the solvents (MgSO₄), 2-(hydroxymethyl)pyrrole 338a was obtained which could be purified by flash chromatography (short column). The synthesized 2-(hydroxymethyl)- and 2-(alkoxymethyl)pyrroles 338 were acid sensitive and decomposed on silica gel during flash chromatography, leaving an intensively colored red material on the silica. For that reason it is of importance to perform the purification step as fast as possible on a small silica column. For the synthesis of methoxy- and ethoxymethylpyrroles 338b,c, no dioxane was used as a solvent for the reaction, but the corresponding alcohols instead.

3-Chloro-5-(hydroxymethyl)-2-phenylpyrrole 338a

Flash chromatography (hexane/EtOAc 1:1, Rₙ = 0.30); yield 41%.

1H NMR (CDCl₃): δ 2.70 (1H, s(b), OH), 4.45 (2H, s, CH₂OH), 6.06 (1H, d, J= 3.0Hz, NC=CH), 7.20-7.36 (3H, m, 3 × CH₆), 7.53-7.57 (2H, m, 2 × CH₆), 8.95 (1H, s(b), NH).

13C NMR (CDCl₃): δ 57.8 (CH₂OH), 109.4 (C₆), 109.7 (NC=CH), 2 × 126.1 (2 × CH₆), 127.2 (CH₆), 127.5 (C₆), 2 × 128.9 (2 × CH₆), 130.3 (C₆), 131.1 (C₆). IR (NaCl): νₘₐₓ 3547, 3411, 1604, 1017 cm⁻¹. MS (ES⁺) m/z (%): 190/92 (M⁺H⁺-H₂O, 100).

3-Chloro-5-(methoxymethyl)-2-phenylpyrrole 338b

Flash chromatography (hexane/EtOAc 4:1, Rₙ = 0.21); yield 63%, mp 94-97°C.

1H NMR (CDCl₃): δ 3.32 (3H, s, OCH₃), 4.39 (2H, s, OCH₂), 6.17 (1H, d, J= 3.0Hz, NC=CH), 7.22-7.28 (1H, m, CH₆), 7.34-7.40 (2H, m, 2 × CH₆), 7.55-7.59 (2H, m, 2 × CH₆), 8.89 (1H, s(b), NH).

13C NMR (CDCl₃): δ 57.5 (CH₃O), 67.0 (CH₂O), 109.3 (C₆), 110.9 (NC=CH), 2 × 126.2 (2 × CH₆), 127.1 (CH₆), 2 × 127.7 (2 × C₆), 2 × 128.8 (2 × CH₆), 131.3 (C₆). IR (KBr): νₘₐₓ 3230, 1605, 1067 cm⁻¹. MS (ES⁺) m/z (%): 190/92 (M⁺H⁺-CH₃OH, 100).
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Experimental Part

3-Chloro-5-(ethoxymethyl)-2-phenylpyrrole 338c

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.11); yield 54%. $^1$H NMR (CDCl$_3$): δ 1.21 (3H, t, J = 7.0 Hz, CH$_3$), 3.53 (2H, q, J = 7.0 Hz, CH$_2$CH$_3$), 4.45 (2H, s, CH$_2$O), 6.15 (1H, d, J = 2.8 Hz, NC=CH), 7.24-7.30 (1H, m, CH$_{ar}$), 7.37-7.43 (2H, m, 2 × CH$_{ar}$), 7.59-7.63 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): δ 15.2 (CH$_3$), 65.2 (OCH$_2$), 65.6 (OCH$_2$), 109.4 (NC=CH), 110.3 (NC=CH), 2 × 126.1 (2 × CH$_{ar}$), 127.1 (CH$_{ar}$), 127.3 (C$_{quat}$), 128.3 (C$_{quat}$), 2 × 128.8 (2 × CH$_{ar}$), 131.3 (C$_{quat}$). IR (NaCl): $\nu_{\max}$ 3422, 3270, 1605, 1073 cm$^{-1}$. MS m/z (%): 235/37 (M$^+$), 190/92 (100), 154 (41).

IV.5.2.3 Synthesis of 2-(aminomethyl)pyrroles 339

5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline 335b (0.65 g, 1.90 mmol) was dissolved in 25 ml of dichloromethane containing 0.53 g (3.81 mmol, 2 equiv.) of potassium carbonate and 0.22 g (3.81 mmol, 2 equiv.) of isopropylamine. After heating the heterogeneous mixture at reflux temperature for 2 hours, the mixture was poured in 25 ml water and extracted with dichloromethane (3 × 25 ml). The extracts were dried over MgSO$_4$ and the solvent evaporated in vacuo. After a fast flash chromatography of the obtained reaction product, 2-(isopropylaminomethyl)pyrrole 339a was obtained. Analogous procedures were followed for the synthesis of 2-anilinomethyl- and 2-piperidinomethylpyrroles 339b and 339c.

3-Chloro-2-(4-chlorophenyl)-5-(isopropylaminomethyl)pyrrole 339a

Flash chromatography (hexane/EtOAc 3:1, Rf = 0.03); yield 59%, mp 73-74°C. $^1$H NMR (CDCl$_3$): δ 1.01 (6H, d, J = 6.3 Hz, CH(CH$_3$)$_2$), 1.33 (1H, s(b), NH), 2.84 (1H, sept, J = 6.3 Hz, CH(CH$_3$)$_2$), 3.73 (2H, s, NCH$_2$), 6.07 (1H, s, NC=CH), 7.19-7.28 (4H, m, C$_6$H$_4$), 10.40 (1H, s(b), NH). $^{13}$C NMR (CDCl$_3$): δ 2 × 22.8 (2 × CH$_3$), 44.2 and 49.1 (CH$_2$N and CHN), 108.8 (NC=CH), 109.5 (C$_{quat}$), 125.8 (C$_{quat}$), 2 × 127.7 (2 × CH$_{ar}$), 128.8 (2 × CH$_{ar}$), 130.1 (C$_{quat}$), 130.5 (C$_{quat}$), 132.4 (C$_{quat}$). IR (KBr): $\nu_{\max}$ 3435, 1632, 1518, 1091 cm$^{-1}$. MS (ES$^+$) m/z (%): 224/26/28 (M+H$^+$-iPrNH, 100).
5-(Anilinomethyl)-3-chloro-2-(4-chlorophenyl)pyrrole 339b

Flash chromatography (hexane/EtOAc 3:2, $R_f = 0.63$); yield 61%. $^1$H NMR (CDCl$_3$): $\delta$ 3.89 (1H, s(b), NH), 4.19 (2H, s, NCH$_2$), 6.10 (1H, d, J= 2.8Hz, NC=CH), 6.57-6.65 (2H, m, 2 × CH$_{ar}$), 6.74-6.76 (1H, m, CH$_{ar}$), 7.14-7.22 (2H, m, 2 × CH$_{ar}$), 7.28 and 7.44 (2 × 2H, 2 × dt, J= 8.9Hz, 2.3Hz, C$_6$H$_4$), 8.39 (1H, s(b), NH).

$^{13}$C NMR (CDCl$_3$): $\delta$ 42.0 (NCH$_2$), 108.8 (NC=CH), 110.2 (C$_{quat}$), 2 × 113.6 (2 × CH$_{ar}$), 118.9 (CH$_{ar}$), 125.3 (C$_{quat}$), 2 × 127.1 (2 × CH$_{ar}$), 2 × 129.0 (2 × CH$_{ar}$), 2 × 129.6 (2 × CH$_{ar}$), 129.7 (C$_{quat}$), 130.0 (C$_{quat}$), 132.6 (C$_{quat}$), 147.9 (C$_{quat}$). IR (NaCl): $\nu_{max}$ 3419, 1603, 1504 cm$^{-1}$. MS (ES+) m/z (%): 317/19/21 (M+H$^+$, 24), 224/26/28 (M$^+$-aniline, 100).

3-Chloro-2-(4-chlorophenyl)-5-(piperidinomethyl)pyrrole 339c

Purified by washing with cold diethyl ether; yield 67%, mp 179°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.35 (6H, m, 3 × CH$_2$), 2.36-2.48 (4H, m, 2 × NCH$_2$), 3.40 (2H, s, NCH$_2$), 6.09 (1H, d, J= 2.5Hz, NC=CH), 7.28 (4H, s, C$_6$H$_4$), 9.67 (1H, s(b), NH). $^{13}$C NMR (CDCl$_3$): $\delta$ 24.1 (CH$_2$), 2 × 25.5 (2 × CH$_2$), 2 × 55.0 (2 × NCH$_2$), 56.2 (NCH$_2$), 109.4 (C$_{quat}$), 110.6 (NC=CH), 126.0 (C$_{quat}$), 2 × 127.7 (2 × CH$_{ar}$), 128.5 (C$_{quat}$), 2 × 128.7 (2 × CH$_{ar}$), 130.0 (C$_{quat}$), 132.5 (C$_{quat}$). IR (KBr): $\nu_{max}$ 3436, 3091, 1586, 1516, 1471, 1339 cm$^{-1}$. MS (ES+) m/z (%): 224/26/28 (M$^+$-piperidine, 14), 86 (100).

IV.5.2.4 Synthesis of dimethyl (4-chloro-5-(4-chlorophenyl)pyrrol-2-yl)methylphosphonate 340

5-(Bromomethyl)-3,3-dichloro-2-(4-chlorophenyl)-1-pyrroline 335b (1.00 g, 2.93 mmol) was dissolved in 25 ml of acetonitrile containing 0.81 g (5.86 mmol, 2 equiv.) of potassium carbonate and 0.73 g (5.86 mmol, 2 equiv.) of trimethyl phosphite. After heating the heterogeneous mixture at reflux overnight (15 hours), the mixture was filtered and the filtrate was evaporated under a N$_2$-stream in a fume hood. The obtained crystalline compound was redissolved in 25 ml of dichloromethane and washed twice with 25 ml water. After drying of the organic phase and evaporation of the solvent in vacuo, the resulting pyrrolylmethylphosphonate 340 was washed with cold diethyl ether. Residual solvent was removed by evaporation at high vacuum (0.01 mmHg).
Dimethyl (4-chloro-5-(4-chlorophenyl)pyrrol-2-yl)methylphosphonate 340

Purified by washing with cold diethyl ether; yield 79%, mp 141°C. ¹H NMR (CDCl₃): δ 3.24 (2H, d, J= 20.4Hz, CH₂P), 3.75 (6H, d, J= 11.0Hz, P(OCH₃)₂), 6.05 (1H, “t”, J= 2.9Hz, NC=CH), 7.19-7.22 (2H, m, 2 × CH₂), 7.26-7.31 (2H, m, 2 × CH₃), 10.19 (1H, s(b), NH). ¹³C NMR (CDCl₃): δ 24.8 (d, J= 143.1Hz, CH₂P), 2 × 53.4 (d, J= 6.9Hz, P(OCH₃)₂), 109.8 (C quat), 110.4 (d, J= 8.1Hz, NC=CH), 120.3 (d, J= 10.4Hz, CH₂P), 126.0 (C quat), 2 × 126.8 (2 × CH₂), 2 × 128.4 (2 × CH₂), 129.7 (C quat), 131.9 (C quat). ³¹P NMR (CDCl₃): δ 28.13 (O=P(OCH₃)₂). IR (KBr): ν max 3436, 1585, 1512, 1227, 1059 cm⁻¹. MS (ES⁺) m/z (%): 334/36/38 (M+H⁺, 21), 224/26/28 (M+H⁺-O=P(OCH₃)₂, 100).

IV.6 Synthesis and reactivity of N-(cyclobutylidene)amines

IV.6.1 Synthesis of substituted cyclobutylamines

IV.6.1.1 Preparation of 3-arylcyclobutanones 174

3-Aryl-2,2-dichlorocyclobutanones 12 were prepared according to literature procedures from substituted styrenes and dichloroketene.⁷⁶,⁷⁷ Dehalogenation of these 2,2-dichlorocyclobutanones 12 was performed with zinc in acetic acid using the following standard procedure.²⁸⁶

2,2-Dichloro-3-phenylcyclobutanone 12a (40.00 g, 186.05 mmol) was dissolved in 250 ml of acetic acid. At room temperature, zinc powder (24.32 g, 372.09 mmol, 2 equiv.) was added in portions during 2 hours. The temperature was controlled by cooling the mixture with an ice bath when the temperature exceeded 30°C in order to avoid a too fast reaction. After reaction for two hours, an additional excess of zinc (24.32 g, 372.09 mmol, 2 equiv.) was added and the mixture was refluxed for 5 hours. After cooling, the mixture was filtered over Celite® (with washing of the solids with 2 × 100 ml of dichloromethane) and the filtrate was diluted with 250 ml of water. After extraction with dichloromethane and washing of the organic phase with saturated aqueous sodium bicarbonate until the acid was neutralized, the extract was dried (MgSO₄) and the solvent evaporated in vacuo. The resulting oily 3-phenylcyclobutanone 174a could be purified by distillation.
3-Phenylcyclobutanone 174a

Distillation (69-74°C, 0.2 mmHg); yield 84%. Spectroscopic data were in accordance with literature data.

3-(4-Chlorophenyl)cyclobutanone 174b

Distillation (93-98°C, 0.01 mmHg); yield 89%. Spectroscopic data were in accordance with literature data.

IV.6.1.2 Synthesis of N-(3-arylcyclobutylidene)alkylamines 342

To a solution of 30.00 g (205.48 mmol) 3-phenylcyclobutanone 174a in 200 ml of dry diethyl ether was added 48.50 g (821.92 mmol, 4 equiv.) isopropylamine. The mixture was cooled to 0°C and subsequently, 23.41 g (123.29 mmol, 0.6 equiv.) titanium(IV) chloride in 25 ml of dry petroleum ether was added dropwise during 30 minutes. After reaction at 0°C for 1 hour, the ice bath was removed and the mixture was allowed to reach room temperature and stirring was continued overnight. After reaction, the milky mixture was poured in 200 ml of 0.5M NaOH and rapidly extracted with diethyl ether (3 × 200 ml). The combined extracts were dried over a mixture of K$_2$CO$_3$ and MgSO$_4$ and the solvent evaporated at room temperature. The resulting cyclobutylimine 342a was purified by distillation and was used directly for further transformations or could be stored at -20°C for at least one week.

N-(3-Phenylcyclobutylidene)isopropylamine 342a

Distillation (68°-75°C, 0.2 mmHg); yield 81%. $^1$H NMR (CDCl$_3$): δ 1.14 (3H, d, J= 6.3Hz, CH$_3$), 1.15 (3H, d, J= 6.3Hz, CH$_3$), 2.89-3.11 (2H, m, 2 × CHCH$_{a}H_{b}$), 3.28-3.55 (4H, m, 2 × CHCH$_{a}H_{b}$ and NCH and CHCH$_2$), 7.17-7.34 (5H, m, C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 23.6 (CH$_3$), 23.7 (CH$_3$), 31.8 (CHCH$_2$), 41.8 (CH$_2$), 45.3 (CH$_2$), 52.0 (NCH), 126.3 (CH$_{ar}$), 2 × 126.4 (2 × CH$_{ar}$), 2 × 128.5 (2 × CH$_{ar}$), 144.7 (C$_{quat}$), 165.4 (C=N). IR (NaCl): $\nu_{\text{max}}$ 1710, 1603, 1495, 1455 cm$^{-1}$. MS $m/z$ (%): 187 (M$^+$, 14), 131 (10), 104 (20), 83 (100), 55 (27), 43 (48), 41 (92).
**N-(3-(4-Chlorophenyl)cyclobutylidene)isopropylamine 342b**

Distillation (93°-98°C, 0.01 mmHg); yield 82%. $^1$H NMR (CDCl$_3$): δ 1.14 (3H, d, J= 6.3Hz, CH$_3$), 1.15 (3H, d, J= 6.3Hz, CH$_3$), 2.85-3.07 (2H, m, 2 × CHCH$_a$H$_b$), 3.29-3.61 (4H, m, 2 × CHCH$_a$H$_b$ and NCH and CHCH$_2$), 7.20 (2H, d, J= 8.3Hz, 2 × CH$_ar$), 7.29 (2H, d, J= 8.3Hz, 2 × CH$_ar$). $^{13}$C NMR (CDCl$_3$): δ 23.0 (CH$_3$), 23.1 (CH$_3$), 30.7 (C$_H$CH$_2$), 41.3 (CH$_2$), 44.7 (CH$_2$), 51.4 (NCH), 2 × 127.2 (2 × CH$_ar$), 2 × 127.9 (2 × CH$_ar$), 131.3 (C$_{quat}$), 142.6 (C$_{quat}$), 164.3 (C=N). IR (NaCl): $\nu_{\text{max}}$ 1710, 1493 cm$^{-1}$. MS $m/z$ (%): 221/23 (M$^+$, 2), 138/40 (40), 83 (100).

**N-(3-Phenylcyclobutylidene)benzylamine 342c**

No purification (purity ca. 90%, calculated from $^1$H NMR); yield 74%. $^1$H NMR (CDCl$_3$): δ 2.98-3.20 (2H, m, 2 × CHCH$_a$H$_b$), 3.36-3.51 (2H, m, 2 × CHCH$_a$H$_b$), 3.53-3.68 (1H, m, CH), 4.47 (2H, s, NCH$_2$), 7.22-7.39 (10H, m, 2 × C$_6$H$_5$). $^{13}$C NMR (CDCl$_3$): δ 31.8 (CH), 42.6 (CH$_2$), 45.6 (CH$_2$), 56.4 (NCH$_2$), 126.5 (CH$_ar$), 2 × 126.6 (2 × CH$_ar$), 126.9 (CH$_ar$), 2 × 128.0 (2 × CH$_ar$), 2 × 128.6 (2 × CH$_ar$), 2 × 128.7 (2 × CH$_ar$), 129.8 (C$_{quat}$), 144.7 (C$_{quat}$), 169.7 (C=N). IR (NaCl): $\nu_{\text{max}}$ 1707, 1490 cm$^{-1}$. MS (ES+) $m/z$ (%): 236 (M+H$^+$, 100).

**IV.6.1.3 Synthesis of N-(3-aryl-2,2,4,4-tetrachlorocyclobutylidene)isopropylamines 347**

To a solution of 6.85 g (36.63 mmol) N-(3-phenycyclobutylidene)isopropylamine 342a in 250 ml of dry CCl$_4$ was added 22.01 g (164.84 mmol, 4.5 equiv.) of NCS and the mixture was refluxed for 30 min. When this reaction was performed on larger scale (e.g. 30 g, the NCS was added in portions during reflux over a period of 15 min (exothermic reaction!) and was subsequently refluxed for 30 min). After the reaction was complete, the mixture was cooled in an ice bath and filtered. To remove remaining succinimide, the filtrate was cooled again for 2 hours at -20°C and subsequently filtered. After evaporation of the CCl$_4$, a crystalline compound was obtained in high purity. The last impurities were removed via recrystallization.
N-(2,2,4,4-Tetrachloro-3-phenylcyclobutylidene)isopropylamine 347a

Crude yield 100%. Recrystallization (EtOAc/hexane 1:5); yield 70%, mp 83-84°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.35 (3H, d, J= 6.3Hz, CH$_3$), 1.38 (3H, d, J= 6.3Hz, CH$_3$), 4.66 (1H, sept, J= 6.3Hz, CH(CH$_3$)$_2$), 4.88 (1H, s, CH), 7.34-7.49 (3H, m, 3 × CH$_{ar}$), 7.57-7.64 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 22.7 (CH$_3$), 22.8 (CH$_3$), 52.2 (CH), 71.3 (CH), 78.1 (CCl$_2$), 81.4 (CCl$_2$), 2 × 128.4 (2 × CH$_{ar}$), 128.8 (CH$_{ar}$), 2 × 129.5 (2 × CH$_{ar}$), 130.2 (C$_{quat}$), 158.3 (C=N). IR (KBr): $\nu_{max}$ 1706, 1500 cm$^{-1}$. MS m/z (%): no M$^+$, 287/89/91/93 (M$^+$-HCl, 18), 245 (100), 183 (31), 43 (68), 41 (39). Anal. Calcd. for C$_{13}$H$_{13}$NCl$_4$: C, 48.03; H, 4.03; N, 4.31. Found: C, 48.26; H, 4.11; N, 4.24.

N-(2,2,4,4-Tetrachloro-3-(4-chlorophenyl)cyclobutylidene)isopropylamine 347b

Crude yield 98%. Recrystallization (EtOAc/hexane 1:5); yield 76%, mp 104-105°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.35 (3H, d, J= 6.2Hz, CH$_3$), 1.38 (3H, d, J= 6.2Hz, CH$_3$), 4.64 (1H, sept, J= 6.2Hz, CH(CH$_3$)$_2$), 4.83 (1H, s, CH), 7.52 (2H, d, J= 8.7Hz, 2 × CH$_{ar}$), 7.45 (2H, d, J= 8.7Hz, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 22.8 (CH$_3$), 22.9 (CH$_3$), 52.4 (CH), 70.8 (CH), 2 × 81.3 (2 × CCl$_2$), 128.6 (C$_{quat}$), 2 × 128.8 (2 × CH$_{ar}$), 130.9 (2 × CH$_{ar}$), 135.2 (C$_{quat}$), 158.0 (C=N). IR (KBr): $\nu_{max}$ 1708, 1495 cm$^{-1}$. MS m/z (%): no M$^+$, 321/23/25/27 (M$^+$-HCl, 24), 279/81/83/85/87 (M$^+$-i-Pr, 83), 244 (100), 217 (47). Anal. Calcd. for C$_{13}$H$_{12}$NCl$_5$: C, 43.43; H, 3.36; N, 3.90. Found: C, 43.59; H, 3.24; N, 4.08.

IV.6.1.4 Reduction of N-(cyclobutylidene)amines 342 and 347

To a solution of 0.94 g (4.24 mmol) N-(3-(4-chlorophenyl)cyclobutylidene)-isopropylamine 342b in 50 ml of dry diethyl ether was added 0.16 g (4.24 mmol, 1 equiv.) LiAlH$_4$ under N$_2$-atmosphere at room temperature. After stirring the heterogeneous mixture for 2 hours at the same temperature, ice water was added until no more hydrogen evolved from the reaction mixture. After stirring the mixture for 5 min, it was filtered over MgSO$_4$/Celite® and the solids were washed with 3 × 25 ml of diethyl ether. After evaporation of the solvent, almost pure cis-N-isopropyl-N-(3-(4-chlorophenylcyclobutyl)amine 346a was obtained, which could be purified by flash chromatography. The cis-stereochemistry was confirmed by DIFNOE-experiments.
To reduce tetrachlorinated imine 347a, borane was used as a reducing agent. To a solution of 1.00 g (3.06 mmol) imine 347a in 20 ml of dry THF was added 1.53 ml (3.06 mmol, 1 equiv.) of a 2M solution of a borane-dimethylsulfide complex via a syringe under N₂-atmosphere at 0°C. After addition, cooling was stopped and the reaction mixture was stirred for 3 hours. Standard workup by addition of water and extraction with diethyl ether yielded the reduced compound 350 after drying (MgSO₄) and evaporation of the solvents. Purification was performed by flash chromatography.

\textbf{N-(3-(4-Chlorophenylcyclobutyl)-N-isopropylamine 346a}

Flash chromatography (hexane/EtOAc/Et₃N 40:59:1, Rₗ = 0.05); yield 58%. \textbf{¹H NMR (CDCl₃)}: δ 1.05 (6H, d, J= 6.2Hz, CH(CH₃)₂), 1.67-1.78 (2H, m, 2 × CH₂H₃), 2.68-2.80 (2H, m, 2 × CH₃H₃), 2.86 (1H, sept, J= 6.2Hz, CH(CH₃)₂), 3.09 (1H, tt, J= 7.7Hz, 10.2Hz, CH), 3.31 (1H, tt, J= 6.9Hz, 8.8Hz, CH), 7.11-7.17 (2H, m, 2 × CHₜₐr), 7.23-7.32 (2H, m, 2 × CHₜₐr). \textbf{¹³C NMR (CDCl₃)}: δ 2 × 22.5 (2 × CH₃), 32.5 (CH), 2 × 39.8 (2 × CH₂), 46.8 (NCH), 48.0 (NCH), 2 × 127.9 (2 × CHₜₐr), 2 × 128.4 (2 × CHₜₐr), 131.5 (Cₜₐr), 143.8 (Cₜₐr). \textbf{IR (NaCl)}: \(\nu_{max}\) 3273, 1493 cm⁻¹. \textbf{MS m/z (%)}: no M⁺, 180/82 (M⁺-i-Pr, 1), 165 (4), 85 (100), 70 (98).

\textbf{N-Benzyl-N-(3-phenylcyclobutyl)amine 346b}

Flash chromatography (hexane/EtOAc/Et₃N 40:59:1, Rₗ = 0.14); yield 71%. \textbf{¹H NMR (CDCl₃)}: δ 1.75-1.85 (2H, m, 2 × CHCH₂H₃), 2.65-2.80 (2H, m, 2 × CHCH₂H₃), 3.06-3.29 (2H, m, 2 × CH), 3.75 (2H, s, NCH₂), 7.10-7.40 (10H, m, 2 × C₆H₅). \textbf{¹³C NMR (CDCl₃)}: δ 32.7 (CH), 2 × 38.7 (2 × CH₂), 49.5 and 51.2 (NCH and NCH₂), 125.8 (CHₜₐr), 2 × 126.4 (2 × CHₜₐr), 126.9 (CHₜₐr), 4 × 128.2 (4 × CHₜₐr), 2 × 128.4 (2 × CHₜₐr), 140.3 (Cₜₐr), 145.2 (Cₜₐr). \textbf{IR (NaCl)}: \(\nu_{max}\) 3303, 1602 cm⁻¹. \textbf{MS (ES⁺) m/z (%)}: 238 (M⁺+H⁺, 100).

\textbf{N-Isopropyl-N-(2,2,4,4-tetrachloro-3-phenylcyclobutyl)amine 350}

Flash chromatography (hexane/EtOAc 9:1, Rₗ = 0.55); yield 86%, mp 63°C. \textbf{¹H NMR (CDCl₃)}: δ 1.25 (6H, d, J= 6.3Hz, CH(CH₃)₂), 2.40 (1H, s(b), NH), 3.30 (1H, sept, J= 6.3Hz, CH(CH₃)₂), 4.50 (1H, s, CH), 4.73 (1H, s, CH), 7.34-7.46 (3H, m, 3 × CHₜₐr), 7.57-7.60 (2H, m, 2 × CHₜₐr).
**13C NMR (CDCl₃):** δ 2×23.6 (2×CH₃), 46.3 (CH(CH₃)₂), 67.2 (CH), 77.6 (CH), 2×86.2 (2×CCl₂), 2×128.2 (2×CH₉), 128.3 (CH₉), 2×128.5 (2×CH₉), 130.9 (C₉quat). **IR (KBr):** νₘₐₓ 3436, 1605, 1500 cm⁻¹. **MS m/z (%):** no M⁺, 153 (100), 138 (63), 111 (20).

**IV.6.2 Synthesis of cyclobutenediones**

**IV.6.2.1 Synthesis and hydrolysis of 2,4,4-trichloro-3-phenylcyclobutenone 362**

A solution of 10.00 g (46.51 mmol) 2,2-dichloro-3-phenylcyclobutanone 12a in 100 ml chloroform containing 25.19 g (0.23 mol, 5 equiv.) DMF-HCl and 25.19 g DMF was heated until 35°C (protected from light) and a stream of Cl₂-gas was bubbled through the solution under stirring. Cooling was applied when the reaction temperature exceeded 55°C. Chlorination was continued until no temperature raise was observed when adding chlorine. After reaction (ca. 20-30 minutes) the mixture was poured in 100 ml water and extracted with chloroform (4×50 ml). After washing of the extracts with sodium bisulfite, drying of the organic layer (MgSO₄) and evaporation of the solvent, trichlorocyclobutenone 362 was obtained which could be purified by flash chromatography over a short silica column.

To hydrolyze the obtained compound, an excess of 90% aqueous sulfuric acid (10 ml) was added to 2.00 g of trichlorocyclobutenone 362 and heated to 80º-90°C. After stirring for 15 hours, the acidic mixture was poured on crushed ice and extracted with chloroform (3×25 ml). The extracts were dried (MgSO₄) and the solvent evaporated, yielding almost pure 4-phenylessiquaric acid 360 as a crystalline compound.

**2,4,4-Trichloro-3-phenylcyclobutenone 362**

Flash chromatography (hexane/CHCl₃ 4:1, Rf = 0.31); yield 79%, mp: 125-126°C. **¹H NMR (CDCl₃):** δ 7.59-7.69 (3H, m, 3×CH₉), 8.16-8.20 (2H, m, 2×CH₉). **¹³C NMR (CDCl₃):** δ 87.9 (CCl₂), 125.4 (C₉quat), 127.6 (C₉quat), 2×129.6 (2×CH₉), 2×130.2 (2×CH₉), 134.4 (CH₉), 169.7 (C=CCl), 175.9 (C=O). **IR (KBr):** νₘₐₓ 1796, 1598, 1581, 1570 cm⁻¹. **MS m/z (%):** 246/48/50/52 (M⁺, 34), 184/86/88 (15), 183/85/87 (100), 113 (33), 105 (32), 91 (16), 77 (51). **Anal. Calcd.** for C₁₀H₅OCl₃: C, 48.53; H, 2.04. Found: C, 48.71; H, 2.19.
3-Hydroxy-4-phenyl-3-cyclobutene-1,2-dione 360

Purified by washing with cold diethyl ether; yield 91%, mp: 210°C (decomp.). Spectroscopic data were in accordance with literature data, but are given for the sake of completeness. 

$^1$H NMR (CDCl$_3$): $\delta$ 7.56-7.60 (3H, m, 3 × CH$_{ar}$), 8.06-8.11 (2H, m, 2 × CH$_{ar}$), 11.00 (1H, s(b), OH).

$^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 127.2 (2 × CH$_{ar}$), 128.6 (C$_{quat}$), 2 × 129.3 (2 × CH$_{ar}$), 132.1 (CH$_{ar}$), 172.4 (C$_{quat}$), 2 × 194.1 (C=O and C$_{quat}$-OH), 194.7 (C=O).

IR (KBr): $\nu_{\text{max}}$ 3000, 1784, 1726, 1586 cm$^{-1}$.

MS (ES$-$) $m/z$ (%): 173 (M-H$^+$, 100).

IV.6.2.2 Synthesis of $N$-(2,4,4-trichloro-3-phenyl-2-cyclobutenylidene)isopropylamine 348

$N$-(2,2,4,4-Tetrachloro-3-phenylcyclobutylidene)isopropylamine 347a (1.00 g, 3.08 mmol) was dissolved in 25 ml of dry diethyl ether. To the solution was added 0.34 g of Et$_3$N (3.38 mmol, 1.1 equiv.) and the solution was stirred at room temperature. After 30 min, the formed ammonium salts were filtered and the filtrate was washed with water (2 × 10 ml). After drying (MgSO$_4$) and evaporation of the solvent, imine 348 was obtained and was purified by flash chromatography.

$N$-(2,4,4-Trichloro-3-phenyl-2-cyclobutenylidene)isopropylamine 348

Crude yield 100%. Flash chromatography (hexane/EtOAc 9:1, R$_f$ = 0.50); yield 70%, mp 89-91°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.34 (6H, d, J= 6.3Hz, CH(CH$_3$)$_2$), 4.54 (1H, sept, J= 6.3Hz, CH(CH$_3$)$_2$), 7.52-7.55 (3H, m, 3 × CH$_{ar}$), 8.01-8.05 (2H, m, 2 × CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 23.6 (2 × CH$_3$), 51.6 (CH), 81.7 (CCl$_2$), 126.8 (C$_{quat}$), 2 × 128.5 (2 × CH$_{ar}$), 128.8 (C$_{quat}$), 2 × 129.3 (2 × CH$_{ar}$), 131.9 (CH$_{ar}$), 154.3 (C=C-C=N), 156.0 (C=N). IR (KBr): $\nu_{\text{max}}$ 1722, 1585 cm$^{-1}$. MS (ES+) $m/z$ (%): 288/90/92/94 (M+H$^+$, 100).

IV.6.2.3 Synthesis of $N$-(2,4,4-trialkoxy-3-aryl-2-cyclobutenylidene)isopropylamines 353

To 0.32 g (0.98 mmol) of $N$-(2,2,4,4-tetrachloro-3-phenylcyclobutylidene)-isopropylamine 347a was added dropwise 0.99 ml (3.94 mmol, 4 equiv.) of 4M NaOMe in methanol at 0°C (When working on big scale, e.g. 10 g, it is appropriate to dissolve the tetrachlorinated imine 347a in a minimal amount of methanol, prior to the addition of sodium methoxide to control the reaction speed (exothermic reaction!)). After reflux for 1 hour, the
mixture was diluted with 25 ml of water and extracted with dichloromethane (4 × 20 ml). The extracts were dried over a mixture of K₂CO₃ and MgSO₄ and after filtration, the solvents were evaporated yielding cyclobutenimine 353a, which could be purified by flash chromatography or by recrystallization in hexane/ethyl acetate (1:1).

**N-(2,4,4-Trimethoxy-3-phenyl-2-cyclobutenylidene)isopropylamine 353a**

Flash chromatography (hexane/EtOAc 9:1, Rᵣ = 0.19); yield 88%, mp 77-78°C. \(^1\)H NMR (CDCl₃): δ 1.19 (6H, d, J = 6.3 Hz, CH(CH₃)₂), 3.32 (6H, s, C(OCH₃)₂), 3.97 (1H, sept, J = 6.3 Hz, CH(CH₃)₂), 4.32 (3H, s, C=C-OCH₃), 7.27-7.41 (3H, m, 3 × CHₐr), 7.62-7.66 (2H, m, 2 × CHₐr). \(^13\)C NMR (CDCl₃): δ 2 × 24.0 (2 × CH₃), 2 × 52.5 (C(OC₂H₅)₂), 52.6 (NCH), 59.3 (OCH₃), 112.2 (C(OCH₃)₂), 2 × 126.4 (2 × CHₐr), 128.4 (CHₐr), 2 × 128.7 (2 × CHₐr), 131.0 (Cₐqua), 134.1 (Cₐquat), 156.0 (Cₐquat), 162.2 (C=N). IR (KBr): ν max 1688, 1612, 1450 cm⁻¹. MS m/z (%): 275 (M⁺, 11), 232 (100), 186 (62), 144 (72), 128 (54), 115 (48), 89 (65), 77 (37). Anal. Calcd. for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.92; H, 7.82; N, 4.95.

**N-(2,4,4-Triethoxy-3-phenyl-2-cyclobutenylidene)isopropylamine 353b**

Flash chromatography (hexane/EtOAc 9:1, Rᵣ = 0.35); yield 66%, mp 71-73°C. \(^1\)H NMR (CDCl₃): δ 1.17 (6H, d, J = 6.3 Hz, CH(CH₃)₂), 1.20 (6H, t, J = 6.9 Hz, C(OCH₂CH₃)₂), 1.39 (3H, t, J = 7.1 Hz, C=C-OCH₂CH₃), 3.45 and 3.46 (2 × 2H, 2 × q, J = 6.9 Hz, C(OCH₂CH₃)₂), 4.05 (1H, sept, J = 6.3 Hz, CH(CH₃)₂), 4.70 (2H, q, J=7.1 Hz, C=C-OCH₂CH₃), 7.25-7.40 (3H, m, 3 × CHₐr), 7.66-7.69 (2H, m, 2 × CHₐr). \(^13\)C NMR (CDCl₃): δ 2 × 15.3 (C(OCH₂CH₃)₂), 15.9 (OCH₂CH₃), 2 × 24.0 (CH(CH₃)₂), 52.4 (CH(CH₃)₂), 2 × 60.1 (C(OCH₂CH₃)₂), 67.5 (OCH₂CH₃), 110.5 (C(OEt)₂), 2 × 126.3 (2 × CHₐr), 128.3 (CHₐr), 2 × 128.7 (2 × CHₐr), 131.3 (Cₐqua), 135.3 (Cₐquat), 155.1 (Cₐquat), 163.4 (C=N). IR (NaCl): ν max 1697, 1615, 1479 cm⁻¹. MS m/z (%): 317 (M⁺, 30), 274 (87), 246 (35), 218 (49), 200 (100), 190 (51), 172 (82), 145 (96), 117 (34). Anal. Calcd. for C₁₉H₂₇NO₃: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.74; H, 8.73; N, 4.30.
N-(2,4,4-Trisopropoxy-3-phenyl-2-cyclobutenyldiene)isopropylamine 353c

Flash chromatography (hexane/EtOAc 95:5, Rf = 0.25); yield 37%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.03 (6H, d, J = 6.0Hz, NCH(CH\(_3\))\(_2\)), 1.17 and 1.19 (2 × 6H, 2 × d, J = 6.2Hz, C(OCH(CH\(_3\))\(_2\))\(_2\)), 1.38 (6H, d, J = 6.2Hz, C=C-OCH(CH\(_3\))\(_2\))\(_2\)), 3.89 (2H, sept, J = 6.2Hz, C(OCH(CH\(_3\))\(_2\))\(_2\)), 4.08 (1H, sept, J = 6.0Hz, NCH), 5.57 (1H, sept, J = 6.2Hz, C=C-OCH), 7.22-7.38 (3H, m, 3 × CH\(_{ar}\)), 7.67-7.71 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 23.1 (2 × CH\(_3\)), 2 × 24.0 (2 × CH\(_3\)), 4 × 24.1 (4 × CH\(_3\)), 51.9 (NCH), 2 × 67.3 (C(OCH(CH\(_3\))\(_2\))\(_2\))\(_2\)), 73.8 (C=C-OCH), 110.5 (C(OCH(CH\(_3\))\(_2\))\(_2\)), 2 × 126.9 (2 × CH\(_{ar}\)), 128.4 (CH\(_{ar}\)), 2 × 128.6 (2 × CH\(_{ar}\)), 132.1 (C\(_{quat}\)), 137.1 (C\(_{quat}\)), 154.9 (C\(_{quat}\)), 164.9 (C=N). IR (NaCl) \(\nu_{max}\) 1696, 1612 cm\(^{-1}\). MS \(m/z\) (%): 359 (M\(^+\), 6), 316 (17), 274 (19), 232 (50), 190 (76), 172 (63), 163 (68), 145 (95), 43 (100). Anal. Calcd. for C\(_{22}\)H\(_{33}\)NO\(_3\): C, 73.50; H, 9.25; N, 3.90. Found: C, 73.69; H, 9.42; N, 3.75.

N-(3-(4-Chlorophenyl)-2,4,4-trimethoxy-2-cyclobutenyldiene)isopropylamine 353d

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.41); yield 79%, mp 108-110°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.19 (6H, d, J = 6.3Hz, CH(CH\(_3\))\(_2\)), 3.31 (6H, s, 2 × OCH\(_3\)), 3.95 (1H, sept, J = 6.3Hz, CH(CH\(_3\))\(_2\)), 4.32 (3H, s, OCH\(_3\)), 7.33 (2H, d, J = 8.6Hz, 2 × CH\(_{ar}\)), 7.57 (2H, d, J = 8.6Hz, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 24.1 (2 × CH\(_3\)), 2 × 52.6 (2 × OCH\(_3\)), 52.8 (NCH), 59.5 (OCH\(_3\)), 112.1 (C(OCH(CH\(_3\))\(_2\))\(_2\)), 2 × 127.7 (2 × CH\(_{ar}\)), 2 × 129.1 (2 × CH\(_{ar}\)), 129.4 (C\(_{quat}\)), 132.8 (C\(_{quat}\)), 134.2 (C\(_{quat}\)), 156.3 (C\(_{quat}\)), 162.0 (C=N). IR (KBr) \(\nu_{max}\) 1697, 1620, 1372 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 310 (M+H\(^+\), 100). Anal. Calcd. for C\(_{16}\)H\(_{20}\)NO\(_3\)Cl: C, 62.03; H, 6.51; N, 4.52. Found: C, 61.89; H, 6.70; N, 4.35.

IV.6.2.4 Synthesis of 3-alkoxy-4-aryl-3-cyclobutene-1,2-diones 397

N-(2,4,4-Trimethoxy-3-phenyl-2-cyclobutenyldiene)isopropylamine 353a (3.92 g, 14.26 mmol) was dissolved in 50 ml of dichloromethane and 50 ml of aqueous 2M HCl. The biphasic mixture was refluxed for 2 hours and subsequently, the organic layer was separated after cooling. The aqueous phase was extracted with dichloromethane (2 × 50 ml) and the combined extracts were dried over MgSO\(_4\). After filtration and evaporation of the solvent in
vacuo, 3-methoxy-4-phenylcyclobuten-1,2-dione 397a was obtained as a yellow solid which could be purified by recrystallization.

3-Methoxy-4-phenyl-3-cyclobutene-1,2-dione 397a

Recrystallization (diethyl ether/hexane 1:1); yield 72%, mp 152-153°C (Lit.\textsuperscript{288}: 150-151°C). Spectral data were in accordance with literature data,\textsuperscript{288} but are given for the sake of completeness. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 4.61 (3H, s, OCH\textsubscript{3}), 7.50-7.55 (3H, m, 3 × CH\textsubscript{ar}), 8.02-8.06 (2H, m, 2 × CH\textsubscript{ar}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 61.7 (OCH\textsubscript{3}), 127.6 (C\textsubscript{quat}), 2 × 127.8 (2 × CH\textsubscript{ar}), 2 × 129.1 (2 × CH\textsubscript{ar}), 132.8 (CH\textsubscript{ar}), 173.9 (C=C-OCH\textsubscript{3}), 192.4 and 192.7 (C=C-OCH\textsubscript{3} and C=O), 194.8 (C=O). IR (KBr): \textit{v}\textsubscript{max} 1779, 1734, 1585 cm\textsuperscript{-1}. MS m/z (%): 188 (M\textsuperscript{+}, 17), 160 (48), 145 (88), 117 (72), 89 (100).

3-Ethoxy-4-phenyl-3-cyclobutene-1,2-dione 397b

Flash chromatography (hexane/EtOAc 4:1, R\textsubscript{f} = 0.29); yield 73%, mp 133-134°C (no lit. data). Spectral data were in accordance with literature data,\textsuperscript{289} but are given for the sake of completeness. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 1.59 (3H, t, J= 7.1Hz, CH\textsubscript{2}CH\textsubscript{3}), 4.98 (2H, q, J= 7.1Hz, OCH\textsubscript{2}), 7.51-7.53 (3H, m, 3 × CH\textsubscript{ar}), 8.04-8.08 (2H, m, 2 × CH\textsubscript{ar}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 16.5 (CH\textsubscript{2}CH\textsubscript{3}), 72.1 (OCH\textsubscript{2}), 128.3 (C\textsubscript{quat}), 2 × 128.4 (2 × CH\textsubscript{ar}), 2 × 129.7 (2 × CH\textsubscript{ar}), 133.3 (CH\textsubscript{ar}), 174.4 (C=C-OCH\textsubscript{2}), 193.1 and 193.4 (C=C-OCH\textsubscript{2} and C=O), 195.2 (C=O). IR (KBr): \textit{v}\textsubscript{max} 1778, 1752, 1600, 1582 cm\textsuperscript{-1}. MS m/z (%): 202 (M\textsuperscript{+}, 26), 174 (15), 146 (12), 145 (100), 117 (40), 89 (69).

3-Isopropoxy-4-phenyl-3-cyclobutene-1,2-dione 397c

Flash chromatography (hexane/EtOAc 4:1, R\textsubscript{f} = 0.31); yield 60%, mp 106-107°C (no lit. data). Spectral data were in accordance with literature data,\textsuperscript{288} but are given for the sake of completeness. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 1.57 (6H, d, J= 6.3Hz, CH(CH\textsubscript{3})\textsubscript{2}), 5.63 (1H, sept, J= 6.3Hz, CH(CH\textsubscript{3})\textsubscript{2}), 7.48-7.54 (3H, m, 3 × CH\textsubscript{ar}), 8.04-8.08 (2H, m, 2 × CH\textsubscript{ar}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 2 × 23.0 (CH(CH\textsubscript{3})\textsubscript{2}), 80.2 (CH(CH\textsubscript{3})\textsubscript{2}), 2 × 127.6 (2 × CH\textsubscript{ar}), 127.9 (C\textsubscript{quat}), 2 × 129.1 (2 × CH\textsubscript{ar}), 132.6 (CH\textsubscript{ar}), 173.9 (C=C-OCH), 192.5 and 192.9 (C=C-OCH and C=O), 194.3 (C=O). IR (KBr): \textit{v}\textsubscript{max} 1770, 1748, 1582 cm\textsuperscript{-1}. MS m/z (%): 216 (M\textsuperscript{+}, 17), 188 (15), 146 (15), 145 (100), 118 (29), 117 (38), 89 (55).
4-(4-Chlorophenyl)-3-methoxy-3-cyclobuten-1,2-dione 397d

Flash chromatography (hexane/EtOAc 4:1, Rf = 0.20); yield 78%, mp 126°C (no lit. data). Spectral data were in accordance with literature data, but are given for the sake of completeness. **1H NMR (CDCl3):** δ 4.61 (3H, s, OCH3), 7.46-7.52 (2H, m, 2 × CHar), 7.95-8.00 (2H, m, 2 × CHar). **13C NMR (CDCl3):** δ 62.1 (OCH3), 126.0 (Cquat), 2 × 128.9 (2 × CHar), 129.6 (2 × CHar), 138.9 (Cquat), 172.1 (C=O-CH3), 191.8 and 192.0 (C=O), 194.9 (C=O). **IR (KBr):** νmax 1786, 1748, 1730, 1597, 1582 cm⁻¹. **MS m/z (%):** 222/24 (M⁺, 36), 179/81 (67), 166/68 (77), 151/53 (82), 123/25 (100).

3-Isopropylamino-4-phenyl-3-cyclobutene-1,2-dione 398

Cyclobutenedione 397a (0.50 g, 2.66 mmol) was dissolved in 5 ml of isopropylamine and stirred for 10 minutes at room temperature. The complete reaction mixture was evaporated in vacuo leaving pure 3-isopropylaminocyclobutenedione 398 in quantitative yield. Mp 189°C. **1H NMR (CDCl3):** δ 1.40 (6H, d, J= 6.6Hz, CH(CH3)2), 4.68 (1H, sept × d, J= 6.6Hz, 8.6Hz, NCH), 6.33 (1H, d(b), J= 8.6Hz, NH), 7.43-7.51 (3H, m, 3 × CHar), 7.81-7.85 (2H, m, 2 × CHar). **13C NMR (CDCl3):** δ 2 × 24.0 (CH(CH3)2), 48.1 (NCH), 2 × 126.1 (2 × CHar), 2 × 129.1 (2 × CHar), 129.3 (Cquat), 130.8 (CHar), 162.9 (C=N-H), 179.3 (C=C-NH), 189.6 (C=O), 191.8 (C=O). **IR (KBr):** νmax 3436, 3150, 1771, 1720, 1610, 1582 cm⁻¹. **MS (ES+) m/z (%):** 254 (M+K⁺, 21), 238 (M+Na⁺, 7), 216 (M+H⁺, 100). **Anal. Calcd.** for C13H13NO2: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.36; H, 6.18; N, 6.36.

IV.6.2.5 Synthesis and reactivity of semisquaramides 409

IV.6.2.5.1 Synthesis of N-(cyclobutylidene)alkylamines 44

To a solution of 2.50 g (35.71 mmol) cyclobutanone 94 in 50 ml of dry diethyl ether was added 8.26 g (0.14 mmol, 4 equiv.) isopropylamine. The solution was cooled to -20°C with the use of a mixture of NaCl/ice. To the cooled solution was added dropwise 4.07 g (21.43 mmol, 0.6 equiv.) titanium(IV) chloride in 10 ml of dry petroleum ether over a period of 15 minutes. After stirring the reaction mixture for 3 hours during which the temperature raised to 0°C, the reaction mixture was poured in 100 ml aq. 0.5M NaOH and was rapidly extracted with 4 × 50 ml of diethyl ether. After each extraction, the solvent was collected in
an erlenmeyer containing a mixture of MgSO₄ and K₂CO₃. After extraction the combined organic phases were filtered and dried again over MgSO₄/K₂CO₃. The extraction procedure was performed fast, to minimize the time that the formed imine 44a was in contact with water. After careful evaporation of the solvent at low vacuum (30 mmHg) at ca. 10°C, a pale yellow oil was obtained which was used as such, without further purification. In the case of the n-propyl and isobutyl derivatives 44b and 44c, no full spectroscopic characterization was possible due to the lability of the compounds. Other derivatives (44a, 44d and 44e) were more stable and could even be distilled (44d and 44e) prior to further transformations.

**N-(Cyclobutylidene)isopropylamine 44a**

No purification (thermolabile and sensitive to hydrolysis); yield 78%. ¹H NMR (CDCl₃): δ 1.11 (6H, d, J= 6.3Hz, CH(CH₃)₂), 1.89-2.04 (2H, m, CH₂CH₂C=N), 2.83-2.97 (4H, m, 2 × CH₂C≡N), 3.42 (1H, sept, J= 6.3Hz, CH(CH₃)₂). ¹³C NMR (CDCl₃): δ 13.0 (CH₂CH₂C≡N), 23.3 (CH₃), 23.4 (CH₃), 33.9 and 37.6 (2 × CH₂C≡N), 51.1 (NCH), 168.7 (C≡N). IR (NaCl): νₓₘₐₓ 1705 cm⁻¹. MS m/z (%): 111 (M⁺, 2), 84 (2), 83 (17), 43 (29), 41 (100).

**N-(Cyclobutylidene)-2-butanamine 44d**

Distillation (50-53°C, 10 mmHg); yield 73%. ¹H NMR (CDCl₃): δ 0.82 (3H, t, J= 7.4Hz, CH₂CH₃), 1.08 (3H, d, J= 6.4Hz, CHCH₃), 1.37-1.55 (2H, m, CH₂CH₃), 1.95 (2H, quint, J= 8.1 Hz, CH₂CH₂C≡N), 2.82-2.97 (4H, m, 2 × CH₂N), 3.12 (1H, sext, J= 6.4Hz, NCH). ¹³C NMR (CDCl₃): δ 10.7 and 10.9 (CH₂CH₂C≡N and CH₂CH₃), 21.2 (CH₂CH₃), 30.4 (CHCH₃), 34.3 (CH₂C≡N), 37.6 (CH₂C≡N), 57.4 (NCH), 168.5 (C≡N). IR (NaCl): νₓₘₐₓ 1714 cm⁻¹. MS m/z (%): 125 (M⁺, 6), 97 (85), 69 (21), 57 (75), 41 (100).

**N-(Cyclobutylidene)-2-methyl-2-propanamine 44e**

Distillation (64-65°C, 35 mmHg); yield 80%. ¹H NMR (CDCl₃): δ 1.22 (9H, s, C(CH₃)₃), 1.93 (2H, quint, J= 8.2Hz, CH₂CH₂C≡N), 2.88-2.69 (2H, m, CH₂C≡N), 3.00-3.08 (2H, m, CH₂C≡N), 3.00-3.08 (2H, m, CH₂C≡N), 3.00-3.08 (2H, m, CH₂C≡N), 3.00-3.08 (2H, m, CH₂C≡N), 3.00-3.08 (2H, m, CH₂C≡N). ¹³C NMR (CDCl₃): δ 13.5 (CH₂), 3 × 27.8 (3 × CH₃), 38.5 (CH₂C≡N), 39.7 (CH₂C≡N), 55.8 (Cₜₛ), 167.7 (C≡N). IR (NaCl): νₓₘₐₓ 1712 cm⁻¹. MS m/z (%): 125 (M⁺, 5), 110 (6), 97 (23), 57 (100).
IV.6.2.5.2 Tetrachlorination of N-(cyclobutylidene)alkylamines 44

To a solution of 1.00 g (9.01 mmol) N-(cyclobutylidene)isopropylamine 44a in 50 ml of dry CCl₄ was added 5.29 g (45.05 mmol, 5 equiv.) of NCS in one portion. The flask was immediately immersed in a preheated oil bath and the mixture was refluxed for 30 minutes. Attention must be drawn to the fact that when this procedure is applied on larger scales, the exothermicity of the reaction can cause a rapid refluxing of the CCl₄, so cooling can be necessary in some cases. After reaction, the mixture was cooled in an ice bath and subsequently filtered. The filtrate was cooled again at -20°C for 2 hours and some more succinimide was filtered. After filtration, the filtrate was dried over MgSO₄, filtered and the CCl₄ was evaporated in vacuo at ca. 10°C. Yellow crystals were obtained which could be recrystallized. Also in this case, derivatives 400b and 400c were too labile and could not be purified.

N-(2,2,4,4-Tetrachlorocyclobutylidene)isopropylamine 400a
Recrystallization (hexane/CHCl₃ 9:1); yield 88%, mp 75-77°C. 

\[ \text{H NMR (CDCl₃): } \delta \ 1.32 \ (6H, d, J= 5.9Hz, CH(CH₃)₂), 3.73 \ (2H, s, CH₂), 4.53 \ (1H, sept, J= 5.9Hz, CH(CH₃)₂). \]

\[ \text{C NMR (CDCl₃): } \delta \ 2 \times 22.6 \ (2 \times CH₃), 51.7 \ (CH), 64.8 \ (CH₂), 2 \times 74.0 \ (2 \times CCl₂), 159.2 \ (C=N). \]

IR (KBr): \( \nu_{\text{max}} \) 1690 cm\(^{-1}\). MS m/z (%): no M\(^+\), 151/53/55 (18), 109/11/13 (25), 43 (100). Anal. Calcd. for C₇H₉NCl₄: C, 33.77; H, 3.64; N, 5.63. Found: C, 33.65; H, 3.55; N, 5.49.

N-(2,2,4,4-Tetrachlorocyclobutylidene)-2-butanamine 400d
No purification; yield 94%. 

\[ \text{H NMR (CDCl₃): } \delta \ 0.93 \ (3H, t, J= 7.4Hz, CH₂CH₃), 1.30 \ (3H, d, 6.3Hz, CHCH₃), 1.65-1.75 \ (2H, m, CH₂CH₃), 3.74 \ (2H, s, CH₂CCl₂), 4.25 \ (1H, sext, J= 6.3Hz, CHCH₃). \]

\[ \text{C NMR (CDCl₃): } \delta \ 11.0 \ (CH₂CH₃), 20.6 \ (CH₂CH₃), 30.5 \ (CHCH₃), 57.4 \ (NCH), 64.9 \ (CH₂CCl₂), 2 \times 74.2 \ (2 \times CCl₂), 159.8 \ (C=N). \]

IR (NaCl): \( \nu_{\text{max}} \) 1709, 1451 cm\(^{-1}\). MS m/z (%): 261/63/65/67/69 (M\(^+\), 1), 226/28/30/32 (M\(^+\)-Cl, 3), 165 (39), 57 (100), 41 (31).

N-(2,2,4,4-Tetrachlorocyclobutylidene)-2-methyl-2-propanamine 400e
Recrystallization (pentane/Et₂O); yield 80%, mp 55°C. 

\[ \text{H NMR (CDCl₃): } \delta \ 1.51 \ (9H, s, C(CH₃)₃), 3.75 \ (2H, s, CH₂). \]

\[ \text{C NMR (CDCl₃): } \delta \ 3 \times 30.5 \ (3 \times CH₃), 59.6 \ (C_{\text{quat}}), 65.1 \ (CH₂), 2 \times 77.4 \ (2 \times CCl₂), 153.6 \ (C=N). \]

IR
(KBr): ν_{max} 1710 cm^{-1}. **MS m/z (%)**: 261/63/65/67/69 (M^+, 1), 246/48/50/52/54 (M^+-CH3, 5), 57 (100).

**IV.6.2.5.3 Synthesis of 3-alkylamino-4,4-dimethoxy-2-cyclobuten-1-ones 408**

To 1.54 g (6.18 mmol) N-(2,2,4,4-tetrachlorocyclobutylidene)isopropylamine 400a (without solvent) was added dropwise (slowly, exothermic reaction!) 15.46 ml (61.85 mmol, 10 equiv.) of 4M MeOH in methanol at 0°C. After reaction for 15 minutes at 0°C, the mixture was refluxed for 1 hour. Standard workup by pouring the reaction mixture in 50 ml water and extraction with dichloromethane, yielded dimethoxycyclobutenone 408a after drying (MgSO_4) and evaporation of the solvents *in vacuo*. The resulting crystalline 3-isopropylamino-4,4-dimethoxy-2-cyclobuten-1-one 408a occurred as a mixture of isomers due to the high double bond character of the C-N bond. Recrystallization or flash chromatography could be used as a purification step.

**3-Isopropylamino-4,4-dimethoxy-2-cyclobuten-1-one 408a**

Spectroscopic data of the major isomer are given (cf. mesomerism 408 ↔ 408bis, Section III.2.5, p.73). Ratio E/Z 95:5 (calculated from ^1H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, R_f = 0.11); yield 54%, mp 91°C. ^1H NMR (CDCl_3): δ 1.28 (6H, d, J= 6.6Hz, CH(CH_3)_2), 3.51 (6H, s, C(OCH_3)_2), 3.54 (1H, sept, J= 6.6Hz, CH(CH_3)_2), 5.20 (1H, s, NC=CH), 5.72 (1H, s(b), NH). ^13C NMR (CDCl_3): δ 2 × 21.5 (CH(CH_3)_2), 47.5 (NCH), 2 × 52.6 (C(OCH_3)_2), 106.9 (NC=CH), 112.9 (C(OCH_3)_2), 172.6 (NC=CH), 188.7 (C=O). **IR (KBr):** ν_{max} 3248, 1744 cm^{-1}. **MS m/z (%)**: 185 (M^+, 1), 170 (100), 154 (37), 128 (17), 100 (89). **Anal. Calcd.** for C_9H_{15}NO_3: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.21; H, 8.10; N, 7.66.

**3-(Sec-butylamino)-4,4-dimethoxy-2-cyclobuten-1-one 408d**

Spectroscopic data of the major isomer are given (cf. mesomerism 408 ↔ 408bis, Section III.2.5, p.73). Ratio E/Z 92:8 (calculated from ^1H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, R_f = 0.14); yield 61%. ^1H NMR (CDCl_3): δ 0.97 (3H, t, J= 7.4Hz, CH_2CH(CH_3)_2), 1.27 (3H, d, J= 6.6Hz, CHCH(CH_3)_2), 1.61 (2H, dq, J= 7.4Hz, 6.6Hz, CH(CH_3)_2), 3.26-3.41 (1H, m, NCH), 3.51 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 5.19 (1H, s, NC=CH), 5.80 (1H, s(b), NH).
$^{13}$C NMR (CDCl$_3$): $\delta$ 10.5 (CH$_2$CH$_3$), 19.7 (CH$_2$CH$_3$), 28.9 (CHCH$_3$), 2 $\times$ 52.8 (2 $\times$ OCH$_3$), 53.9 (NCH), 106.9 (C(OCH$_3$)$_2$), 113.2 (NC=CH), 173 (NC=CH), 188.1 (C=O). IR (NaCl): $\nu_{\text{max}}$ 3237, 1740, 1590 cm$^{-1}$. MS $m/z$ (%): 199 (M$^+$, 1), 184 (M$^+$-CH$_3$, 100), 100 (95). Anal. Calcd. for C$_{10}$H$_{17}$NO$_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.43; H, 8.79; N, 6.86.

3-(Tert-butylamino)-4,4-dimethoxy-2-cyclobuten-1-one 408

Only one isomer (cf. mesomerism 408 $\leftrightarrow$ 408bis, Section III.2.5, p.73).

Recrystallization (diethyl ether); yield 64%, mp 134-136°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.38 (9H, s, 3 $\times$ CH$_3$), 3.50 (6H, s, 2 $\times$ OCH$_3$), 5.26 (NC=CH), 6.04 (1H, s(b), NH). $^{13}$C NMR (CDCl$_3$): $\delta$ 3 $\times$ 28.6 (3 $\times$ CH$_3$), 2 $\times$ 53.5 (2 $\times$ OCH$_3$), 53.6 (C$_{\text{quat}}$), 109.6 (C(OCH$_3$)$_2$), 114.7 (CH=CN), 171.3 (CH=CN), 188.3 (C=O). IR (KBr): $\nu_{\text{max}}$ 3197, 1733, 1587 cm$^{-1}$. MS $m/z$ (%): no M$^+$, 184 (M$^+$-CH$_3$, 14), 168 (23), 128 (100). 100 (66). Anal. Calcd. for C$_{10}$H$_{17}$NO$_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.43; H, 8.77; N, 6.86.

IV.6.2.5.4 Hydrolysis of 3-alkylamino-4,4-dimethoxy-2-cyclobutenones 408

To hydrolyze 3-isopropylamino-4,4-dimethoxy-2-cyclobuten-1-one 408a, 0.50 g (2.70 mmol) was dissolved in 25 ml of dichloromethane and an excess of aq. 2M HCl was added (10 ml). The biphasic system was refluxed for 1 hour, cooled down and extracted with dichloromethane (3 $\times$ 20 ml). After drying of the organic phase over MgSO$_4$ and evaporation of the solvent, cyclobutenedione 409a was obtained as white-yellow crystals, which were purified by flash chromatography.

3-Isopropylamino-3-cyclobutene-1,2-dione 409a

Spectroscopic data of the major isomer are given (cf. mesomerism 408 $\leftrightarrow$ 408bis, Section III.2.5, p.73). Ratio $E/Z$ 9:1 (calculated from $^1$H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, $R_f$ = 0.19); yield 75%, mp 91°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.35 (6H, d, J= 6.6Hz, CH(CH$_3$)$_2$), 3.68 (1H, sept, J= 6.6Hz, CH$_3$CH$_2$), 6.51 (1H, s(b), NH), 8.00 (1H, s, NC=CH). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 $\times$ 22.0 (CH(CH$_3$)$_2$), 49.0 (CH(CH$_3$)$_2$), 151.6 (NC=CH), 183.6 (NC=CH), 190.8 (C=O), 195.9 (C=O). IR (KBr): $\nu_{\text{max}}$ 3223, 1776, 1740 cm$^{-1}$. MS $m/z$ (%): no M$^+$, 111 (M$^+$-CO, 75), 96 (3), 83
3-Propylamino-3-cyclobutene-1,2-dione 409b

Spectroscopic data of the major isomer are given (cf. mesomerism 408 ↔ 408bis, Section III.2.5, p.73). Ratio E/Z 85:15 (calculated from $^1$H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, $R_f = 0.12$); yield 25%, mp 81°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.01 (3H, t, $J = 7.4$Hz, CH$_3$), 1.68-1.80 (2H, m, CH$_2$CH$_3$), 3.34 (2H, q, $J = 6.7$Hz, CH$_2$CH$_2$CH$_3$), 7.47 (1H, s(b), NH), 8.01 (1H, s, NC=CH). $^{13}$C NMR (CDCl$_3$): $\delta$ 11.3 (CH$_3$), 22.3 (CH$_2$CH$_3$), 48.2 (NCH$_2$), 151.5 (NC=CH), 185.4 (NC=CH), 191.1 (C=O), 195.3 (C=O). IR (KBr): $\nu_{max}$ 3185, 3099, 1781, 1743, 1733, 1608 cm$^{-1}$. MS $m/z$ (%): no M$,^+$, 111 (M$^+$-CO, 22), 82 (40), 68 (77), 54 (100). Anal. Calcd. for C$_7$H$_9$NO$_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.68; N, 10.20.

3-Isobutylamino-3-cyclobutene-1,2-dione 409c

Spectroscopic data of the major isomer are given (cf. mesomerism 408 ↔ 408bis, Section III.2.5, p.73). Ratio E/Z 81:19 (calculated from $^1$H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, $R_f = 0.17$); yield 34%, mp 82-83°C. $^1$H NMR (CDCl$_3$): $\delta$ 1.00 (6H, d, $J = 6.9$Hz, CH(CH$_3$)$_2$), 1.85-2.05 (1H, m, CH(CH$_3$)$_2$), 3.18 (2H, t, $J = 6.5$Hz, NCH$_2$), 6.95 (1H, s(b), NH), 7.98 (1H, s, NC=CH). $^{13}$C NMR (CDCl$_3$): $\delta$ 2 × 20.0 (2 × CH$_3$), 28.7 (CH(CH$_3$)$_2$), 54.1 (NCH$_2$), 151.9 (NC=CH), 185.6 (NC=CH), 190.5 (C=O), 195.4 (C=O). IR (KBr): $\nu_{max}$ 3190, 1795, 1776, 1739, 1730, 1605 cm$^{-1}$. MS $m/z$ (%): no M$,^+$, 125 (M$^+$-CO, 5), 84 (23), 68 (41), 44 (100). Anal. Calcd. for C$_8$H$_{11}$NO$_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.66; H, 7.40; N, 9.01.

3-(Sec-butylamino)-3-cyclobuten-1,2-dione 409d

Spectroscopic data of the major isomer are given (cf. mesomerism 408 ↔ 408bis, Section III.2.5, p.73). Ratio E/Z 86:14 (calculated from $^1$H NMR spectra). Flash chromatography (hexane/EtOAc 1:1, $R_f = 0.19$); yield 81%, mp 65-66°C. $^1$H NMR (CDCl$_3$): $\delta$ 0.98 (3H, t, $J = 7.4$Hz, CH$_2$CH$_3$), 1.33 (3H, d, $J = 6.6$Hz, CHCH$_3$), 1.56-1.73 (2H, m, CH$_2$CH$_3$), 3.36-3.50 (1H, m, CHCH$_3$), 7.07 (1H, s(b), NH), 7.99 (1H, s, NC=CH). $^{13}$C NMR (CDCl$_3$): $\delta$ 10.5 (CH$_2$CH$_3$), 19.7 (CH$_2$CH$_3$),
29.2 (CH\(\text{CH}_3\)), 55.1 (NCH), 151.3 (NC=CH), 184.2 (NC=CH), 191.2 (C=O), 195.6 (C=O).

**IR (KBr):** \(\nu_{\text{max}}\) 3205, 1778, 1746, 1615 cm\(^{-1}\). **MS m/z (%):** 153 (M\(^+\), 1), 125 (M\(^+\)-CO, 10), 110 (12), 84 (19), 68 (100). **Anal. Calcd.** for C\(_8\)H\(_{11}\)NO\(_2\): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.43; N, 8.98.

3-(Tert-butylamino)-3-cyclobutene-1,2-dione 409e

Only one isomer (cf. mesomerism 408 \(\leftrightarrow\) 408bis, Section III.2.5, p.73).

Recrystallization (diethyl ether); yield 80%, mp 162-163°C (Lit.: 165-167°C). Spectral data were in accordance with literature data, but are given for the sake of completeness. **\(^1\)H NMR (CDCl\(_3\)):** \(\delta\) 1.43 (9H, s, C(CH\(_3\)_3)), 6.55 (1H, s(b), NH), 8.04 (1H, s, NC=CH). **\(^{13}\)C NMR (CDCl\(_3\)):** \(\delta\) 3 \(\times\) 28.7 (C(CH\(_3\)_3)), 54.4 (C\(_\text{quat}\)), 152.2 (NC=CH), 181.8 (NC=CH), 191.2 (C=O), 197.2 (C=O). **IR (KBr):** \(\nu_{\text{max}}\) 3196, 1794, 1767, 1729, 1618 cm\(^{-1}\). **MS m/z (%):** no M\(^+\), 125 (M\(^+\)-CO, 55), 68 (100), 57 (48).

**IV.6.2.5.5 Synthesis of N-(2,4,4-trichloro-2-cyclobutenylidene)isopropylamine 402a**

N-(2,2,4,4-tetrachlorocyclobutylidene)isopropylamine 400a (0.25 g, 1.01 mmol) was dissolved in 10 ml of dry THF to which 0.12 g (1.21 mmol, 1.2 equiv.) Et\(_3\)N was added. The mixture was stirred for 5 hours and subsequently filtered and washed with brine (10 ml). After drying over MgSO\(_4\) and evaporation of the solvent, N-(trichlorocyclobutenylidene)isopropylamine 402a was obtained as a brown liquid, which could be purified by distillation.

N-(2,4,4-trichloro-2-cyclobutenylidene)isopropylamine 402a

\(E/Z\) 89:11 (calculated from \(^1\)H NMR spectra). Distillation (40°C, 0.3 mmHg); yield 68%. The spectral data given below correspond to the major (E)-isomer. **\(^1\)H NMR (CDCl\(_3\)):** \(\delta\) 1.30 (6H, d, J=6.2Hz, CH(CH\(_3\)_2)), 4.43 (1H, sept, J=6.2Hz, CH(CH\(_3\)_2)), 7.36 (C=CH). **\(^{13}\)C NMR (CDCl\(_3\)):** \(\delta\) 2 \(\times\) 23.1 (CH(CH\(_3\)_2)), 51.2 (CH(CH\(_3\)_2)), 81.4 (CCl\(_2\)), 138.0 (CCl), 149.4 (ClC=CH), 154.8 (C=N). **IR (NaCl):** \(\nu_{\text{max}}\) 1724, 1543 cm\(^{-1}\). **MS m/z (%):** no M\(^+\), 169/71/73/75 (M\(^+\)-i-Pr+H, 100), 134 (25), 107 (32).
IV.6.2.5.6 Synthesis of (3E)-2,2,4-trichloro-N-isopropyl-3-butenamide 410

To a solution of 0.10 g (0.47 mmol) \(N\)-(2,4,4-trichloro-2-cyclobutenylidene)-isopropylamine 402a in 1 ml of 1,4-dioxane was added 1 ml (3 mmol, 6.37 equiv.) of aq. 3M NaOH. The mixture was refluxed for 2 hours. After cooling, the reaction was diluted with 10 ml water and extracted with dichloromethane (3 × 25 ml). After drying (MgSO\(_4\)) and evaporation of the solvents in vacuo, the obtained butenamide 410 was purified by flash chromatography.

(3E)-2,2,4-trichloro-N-isopropyl-3-butenamide 410

Flash chromatography (hexane/EtOAc 1:1, \(R_f = 0.39\)); yield 46%, mp 64-66°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.19 (6H, d, J= 6.6Hz, CH(CH\(_3\))\(_2\)), 4.14 (1H, sept × d, J= 6.6Hz, 7.8Hz, CH(CH\(_3\))\(_2\)), 5.43 (1H, s(b), NH), 6.18 (1H, d, J= 13.1Hz, CH=CHCl), 7.26 (1H, d, J= 13.1Hz, CH=CHCl). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 22.8 (CH(CH\(_3\))\(_2\)), 41.7 (CH(CH\(_3\))\(_2\)), 77.3 (CCl\(_2\)), 127.1 (CH=CHCl), 133.8 (CCl), 162.4 (C=O). \(\text{IR (KBr)}\): \(v_{\text{max}}\) 3307, 1645, 1606, 1547 cm\(^{-1}\). MS \(m/z\) (%): no M\(^+\), 132 (38), 112 (82), 89/91 (M\(^+\)+H-NH\(_2\)iPr-CHCl-Cl, 100).

IV.6.2.5.7 Synthesis of (3E)-2-oxo-N-propyl-4-propylamino-3-butenamide 411

3-Isopropylamino-3-cyclobuten-1,2-dione 409a (0.20 g, 1.44 mmol) was dissolved in 10 ml isopropylamine and was refluxed as such for 2 hours. After standard aqueous workup (extraction with diethyl ether), butenamide 411 was obtained in quantitative yield.

(3E)-2-Oxo-N-propyl-4-propylamino-3-butenamide 411

Crude yield 100%. Flash chromatography (hexane/EtOAc 1:1, \(R_f = 0.21\)); yield 69%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.94 (3H, t, J= 7.2Hz, CH\(_3\)), 0.97 (3H, t, J= 7.2Hz, CH\(_3\)), 1.57 (2H, sext, J= 7.2Hz, CH\(_2\)CH\(_3\)), 1.64 (2H, sext, J= 7.2Hz, CH\(_2\)CH\(_3\)), 3.24-3.32 (4H, m, 2 × NCH\(_2\)), 6.06 (1H, d, J= 7.2Hz, NCH=CH), 7.13 (1H, dd, J= 7.2Hz, 13.3Hz, NCH=CH\(^a\)), 7.45 (1H, s(b), NH), 10.36 (1H, s(b), NH). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 11.1 (CH\(_3\)), 11.5 (CH\(_3\)), 22.8 (CH\(_2\)CH\(_3\)), 24.1 (CH\(_2\)CH\(_3\)), 40.9 (NCH\(_2\)), 51.4 (NCH\(_2\)), 88.8 (NCH=CH), 157.4 (NCH=CH), 163.5 (CONH), 181.9 (C=O). \(\text{IR (NaCl)}\): \(v_{\text{max}}\) 3185, 3099, 1781, 1743, 1733, 1608 cm\(^{-1}\). MS \(m/z\) (%): no M\(^+\), 111 (22), 82 (40), 68 (77), 54 (100). \(^a\) The extra coupling disappeared when D\(_2\)O was used.
IV.6.3 Synthesis and derivatization of 4-hydroxycyclobutenones 412

IV.6.3.1 Reduction of cyclobutenediones 397

To a solution of 1.00 g (5.32 mmol) 3-methoxy-4-phenyl-3-cyclobuten-1,2-dione 397a in 25 ml of acetic acid at room temperature was added 1.74 g (26.60 mmol, 5 equiv.) zinc powder in portions during 10 minutes. Cooling with an ice bath was applied when the reaction temperature exceeded 30°C. After stirring for 4 hours, the heterogeneous mixture was filtered over Celite®, the solids were washed with dichloromethane (3 × 20 ml) and the filtrate was diluted with 50 ml water. The organic layer was separated and the aqueous layer was treated with sodium bicarbonate until the mixture was only slightly acidic (ca. pH 6-7) and extracted again with dichloromethane (3 × 50ml). After drying over MgSO₄ and cold (<25°C) evaporation of the solvent, the resulting oil was further evaporated at highvacuum (<25°C) to remove residual acetic acid. After evaporation, a white solid was obtained, which could be purified by washing with cold diethyl ether or by flash chromatography.

When during the procedure, including workup, the temperature exceeded 30°C a significant amount (ca. 10%) of O-acetylated product 417a was obtained.

Treatment of the obtained 4-hydroxy-3-methoxycyclobutenone 412a with 3 equiv. of aq. 2M NaOH in methanol at room temperature for 4 hours, yielded the hydrolyzed dihydroxycyclobutenone 413. An analogous result was obtained by reaction of 4-hydroxy-3-methoxycyclobutenone 412a with 2.1 equivalents of isopropylamine in dichloromethane at room temperature for 4 hours, resulting in 4-hydroxy-3-isopropylamino-2-phenyl-2-cyclobuten-1-one 414.

4-Hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a

Purification by washing with cold diethyl ether; yield: 84%, mp 122°C (decomposed at 135°C). ¹H NMR (CDCl₃): δ 4.31 (3H, s, OCH₃), 5.43 (1H, s, CHOH), 7.28-7.39 (3H, m, 3 × CH₆₉), 7.71-7.74 (2H, m, 2 × CH₆₉).

¹³C NMR (CDCl₃): δ 60.6 (OCH₃), 82.2 (CHOH), 124.2 (C_quat), 2 × 127.0 (2 × CH₆₉), 2 × 128.5 (2 × CH₆₉), 2 × 128.3 (CH₂ and C_quat), 180.1 (C=COCH₃), 188.1 (C=O).

IR (KBr): ν_max 3303, 1735, 1589 cm⁻¹. MS m/z (%): 190 (M⁺, 100), 162 (31), 131 (29), 130 (37), 1239 (35), 119 (51), 102 (67), 91 (51), 77 (20).
3-Ethoxy-4-hydroxy-2-phenyl-2-cyclobuten-1-one 412b

Flash chromatography (hexane/ EtOAc 1:1; Rf = 0.23); yield: 61%, mp 113°C. \(^1\)H NMR (acetone-d6): \(\delta\) 1.52 (3H, t, J= 7.0 Hz, CH\(_3\)), 4.57-4.79 (2H, s(b), CHOH and OH), 7.25-7.42 (3H, m, 3 × CH\(_{ar}\)), 7.70-7.74 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (acetone-d6): \(\delta\) 15.7 (CH\(_3\)), 70.5 (CH\(_2\)), 83.9 (CHOH), 123.4 (C\(_{quat}\)-C=O), 2 × 127.3 (2 × CH\(_{ar}\)), 128.5 (CH\(_{ar}\)), 2 × 129.3 (2 × CH\(_{ar}\)), 181.5 (C\(_{quat}\)-OEt), 187.3 (C=O). IR (KBr): \(n_{max}\) 3276, 1736, 1623, 1596 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 227 (M+Na\(^+\), 23), 205 (M+H\(^+\), 100).

4-Hydroxy-3-isopropoxy-2-phenyl-2-cyclobuten-1-one 412c

Flash chromatography (hexane/ EtOAc 85:15; Rf = 0.34); yield: 54%, mp 130°C (decomposed). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.90 (3H, d, J= 6.2 Hz, CH\(_3\)), 1.54 (3H, d, J= 6.2 Hz, CH\(_3\)), 5.14 (1H, sept, J= 6.2 Hz, CH\(_{(CH_3)}^2\)), 5.46 (1H, d, J= 4.1 Hz, CHOH), 5.56 (1H, d(b), J= 4.1 Hz, CHOH). \(^{13}\)C NMR (CDCl\(_3\), int.ref. 77.00 ppm): \(\delta\) 22.4 (CH\(_3\)), 23.2 (CH\(_3\)), 78.9 (C\(_{H(CH_3)}^2\)), 82.0 (CHOH), 123.4 (C\(_{quat}\)-C=O), 2 × 126.6 (2 × CH\(_{ar}\)), 127.7 (CH\(_{ar}\)), 128.2 (2 × CH\(_{ar}\)), 128.5 (C\(_{quat}\)), 180.2 (C\(_{quat}\)-Oi-Pr), 189.2 (C=O). IR (KBr): \(n_{max}\) 3349, 1740, 1626, 1595 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 459 (2M+Na\(^+\), 8), 241 (M+Na\(^+\), 27), 219 (M+H\(^+\), 13), 177 (100).

2-(4-Chlorophenyl)-4-hydroxy-3-methoxy-2-cyclobuten-1-one 412d

Purification by washing with cold diethyl ether; yield: 70%, mp 164-165°C. \(^1\)H NMR (DMSO-d6): \(\delta\) 4.23 (3H, s, OCH\(_3\)), 5.33 (1H, s, CHOH), 6.48 (1H, s(b), OH), 7.46 (2H, d, J= 6.9 Hz, 2 × CH\(_{ar}\)), 7.59 (2H, d, J= 6.9 Hz, CH\(_{aq}\)). \(^{13}\)C NMR (DMSO-d6): \(\delta\) 61.2 (OCH\(_3\)), 82.9 (CHOH), 120.8 (C\(_{quat}\)-C=O), 2 × 128.2 and 3 × 129.5 (4 × CH\(_{ar}\) and C\(_{quat}\)), 132.6 (C\(_{quat}\)), 183.0 (C- OCH\(_3\)), 187.7 (C=O). IR (KBr): \(n_{max}\) 3260, 1735, 1621, 1586 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 225 (M+H\(^+\), 100).

3,4-Dihydroxy-2-phenyl-2-cyclobuten-1-one 413

Purification by washing with cold diethyl ether; yield: 63%, mp 143°C (decomposed). \(^1\)H NMR (DMSO-d6): \(\delta\) 4.98 (1H, s, CHOH), 7.21-7.26 (1H, m, CH\(_{aq}\)), 7.35-7.40 (2H, m, 2 × CH\(_{ar}\)), 7.63-7.66 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (DMSO-d6): \(\delta\) 83.3 (CHOH), 120.1 (C\(_{quat}\)-C=O), 2 × 125.8 (2 ×
CH₃, 127.1 (CH₃), 2 × 128.7 (2 × CH₃), 130.0 (C quat), 2 × 185.8 (C=C–OH and C=O). **IR (KBr):** v max 3277 (broad), 1741, 1619, 1594, 1428 cm⁻¹. **MS (ES+) m/z (%):** 177 (M+H⁺, 28), 131 (M+H⁺–CO-H₂O, 100).

### 4-Hydroxy-3-isopropylamino-2-phenyl-2-cyclobuten-1-one 414

Purification by washing with cold diethyl ether; yield: 81%, mp 156°C.

**1H NMR (acetone-d₆):** δ 1.36 (3H, d, J= 6.5Hz, CH₃), 1.37 (3H, d, J= 6.5Hz, CH₃), 4.11-4.27 (1H, m, CH(CH₃)₂), 5.21 (1H, s, CHOH), 5.28 (1H, s(b), OH), 7.08-7.30 (3H, m, 3 × CH ar), 7.54 (1H, d(b), J= 6.3Hz, NH), 7.63-7.66 (2H, m, 2 × CH ar), **13C NMR (acetone-d₆):** δ 23.4 (CH₃), 24.3 (CH₃), 49.5 (CH(CH₃)₂), 82.5 (CHOH), 114.9 (C quat–C=O), 2 × 126.0 (2 × CH₃), 126.3 (CH₃), 2 × 129.0 (2 × CH₃), 132.7 (C quat), 168.4 (C quat–NH), 185.5 (C=O). **IR (KBr):** v max 3340, 1720, 1579, 1561 cm⁻¹. **MS (ES+) m/z (%):** 240 (M+Na⁺, 14), 218 (M+H⁺, 100).

### IV.6.3.2 Acylation of 4-hydroxy-2-cyclobuten-1-ones 412

To a cooled (0°C) solution of 1.00 g (5.26 mmol) 4-hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a in 25 ml of dry dichloromethane was added 0.53 g (5.26 mmol, 1 equiv.) triethylamine. Subsequently, 0.40 g (5.26 mmol, 1 equiv.) acetyl chloride dissolved in 10 ml of dry dichloromethane was added dropwise to the cooled mixture. After stirring for 2 hours, the mixture was poured in 20 ml water and extracted with dichloromethane (3 × 25 ml). After drying (MgSO₄) and evaporation of the solvent the corresponding O-acetylated cyclobutenone 417a was obtained as a pure oil.

**3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl acetate 417a**

Crude yield 100%. Flash chromatography (hexane/CH₂Cl₂ 4:1, R f = 0.16); yield 75%. **1H NMR (CDCl₃):** δ 2.18 (3H, s, CH₃), 4.15 (3H, s, OCH₃), 6.44 (1H, s, CH), 7.28-7.41 (3H, m, 3 × CH ar), 7.73-7.77 (2H, m, 2 × CH ar). **13C NMR (CDCl₃):** δ 20.9 (CH₃), 60.8 (OCH₃), 81.6 (CH), 2 × 127.2 (2 × CH₃), 127.7 (CH₃), 127.9 (C quat), 2 × 128.6 (2 × CH₃), 128.7 (C quat), 169.8 and 174.9 (C=C–OCH₃ and C=O), 180.5 (C=O). **IR (NaCl):** v max 1765, 1746, 1595 cm⁻¹. **MS m/z (%):** 232 (M⁺, 3), 190 (67), 130 (15), 119 (20), 86 (45), 84 (64), 49 (100).
3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl benzoate 417b

Flash chromatography (hexane/EtOAc 4:1, R$_f$ = 0.26); yield 71%.

$^1$H NMR (CDCl$_3$): $\delta$ 4.13 (3H, s, OCH$_3$), 6.66 (1H, s, CH), 7.29-7.45 (5H, m, C$_6$H$_5$), 7.46-7.56 (1H, m, CH$_{ar}$), 7.77-7.81 (2H, m, 2 $\times$ CH$_{ar}$), 8.05-8.09 (2H, m, 2 $\times$ CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 60.7 (OCH$_3$), 81.8 (CH), 2 $\times$ 126.9 (2 $\times$ CH$_{ar}$), 127.5 (C$_{quat}$), 127.8 (C$_{quat}$), 2 $\times$ 128.3 (2 $\times$ CH$_{ar}$), 2 $\times$ 128.4 (2 $\times$ CH$_{ar}$), 128.5 (CH$_{ar}$), 128.6 (C$_{quat}$), 2 $\times$ 128.8 (2 $\times$ CH$_{ar}$), 133.5 (CH$_{ar}$), 165.1 and 166.4 (C$_{quat}$-OCH$_3$ and C=O), 180.2 (C=O). IR (NaCl): $\nu_{\text{max}}$ 1733, 1581, 1405 cm$^{-1}$. MS (ES$^+$) m/z (%): 333 (M+K$^+$, 12), 317 (M+Na$^+$, 24), 295 (M+H$^+$, 9), 173 (100), 145 (40).

3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl 2,4-dichlorobenzoate 417c

Flash chromatography (hexane/EtOAc 4:1, R$_f$ = 0.36); yield 80%, mp 137°C.

$^1$H NMR (CDCl$_3$): $\delta$ 4.19 (3H, s, OCH$_3$), 6.64 (1H, s, CH), 7.20-7.40 (5H, m, C$_6$H$_5$), 7.45-7.46 (1H, m, CH$_{ar}$), 7.75-7.79 (1H, m, CH$_{ar}$), 7.86-7.89 (1H, m, CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 60.9 (OCH$_3$), 82.3 (CH), 126.8 (C$_{quat}$), 2 $\times$ 127.0 (2 $\times$ CH$_{ar}$), 127.1 (CH$_{ar}$), 127.6 (C$_{quat}$), 128.0 (C$_{quat}$), 2 $\times$ 128.5 (2 $\times$ CH$_{ar}$), 128.7 (CH$_{ar}$), 131.0 (CH$_{ar}$), 132.8 (CH$_{ar}$), 135.2 (C$_{quat}$), 139.1 (C$_{quat}$), 163.2 and 174.4 (C$_{quat}$-OCH$_3$ and C=O), 179.8 (C=O). IR (KBr): $\nu_{\text{max}}$ 1772, 1738, 1635 cm$^{-1}$. MS (ES$^-$) m/z (%): no M-H$^-$, 347 (M-CH$_3$), 41, 111 (100).

3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl phenylacetate 417d

Flash chromatography (hexane/EtOAc 3:1, R$_f$ = 0.36); yield 89%, mp 77-79°C. $^1$H NMR (CDCl$_3$): $\delta$ 3.72 (2H, s, CH$_2$), 3.85 (3H, s, OCH$_3$), 6.42 (1H, s, CH), 7.29-7.39 (8H, m, 8 $\times$ CH$_{ar}$), 7.72-7.75 (2H, m, CH$_{ar}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 41.2 (CH$_2$), 60.4 (OCH$_3$), 81.7 (CH), 2 $\times$ 127.0 (2 $\times$ CH$_{ar}$), 127.3 (CH$_{ar}$), 127.5 (C$_{quat}$), 127.8 (C$_{quat}$), 2 $\times$ 128.5 (2 $\times$ CH$_{ar}$), 3 $\times$ 128.6 (3 $\times$ CH$_{ar}$), 2 $\times$ 129.1 (2 $\times$ CH$_{ar}$), 133.0 (C$_{quat}$), 170.2 and 174.6 (C$_{quat}$-OCH$_3$ and C=O), 180.1 (C=O). IR (KBr): $\nu_{\text{max}}$ 1752, 1738, 1629 cm$^{-1}$. MS (ES$^+$) m/z (%): 309 (M+H$^+$, 3), 145 (100).
2-(4-Chlorophenyl)-3-methoxy-1-oxo-2-cyclobuten-4-yl acetate 417e

Flash chromatography (hexane/EtOAc 7:3, R_f = 0.24); yield 84%, mp 87°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.91 (3H, s, CH\(_3\)), 3.89 (3H, s, OCH\(_3\)), 6.15 (1H, s, CH), 7.06 (2H, d, J= 8.3Hz, 2 \times CH\(_{ar}\)), 7.38 (2H, d, J= 8.3Hz, 2 \times CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 20.7 (CH\(_3\)), 60.9 (OCH\(_3\)), 81.6 (CH), 125.7 (C\(_{quat}\)), 126.4 (C\(_{quat}\)), 2 \times 128.2 (2 \times CH\(_{ar}\)), 2 \times 128.7 (2 \times CH\(_{ar}\)), 134.0 (C\(_{quat}\)), 169.4 and 175.2 (C=COCH\(_3\) and C=O), 180.0 (C=O). IR (KBr): \(\nu_{max}\) 1768, 1741, 1636, 1593 cm\(^{-1}\). MS m/z (%): 266/68 (M\(^+\), 1), 224 (M\(^+\)-OAc, 100), 189 (36), 161 (17).

3-Ethoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl acetate 417f

Flash chromatography (hexane/EtOAc 4:1, R_f = 0.20); yield 87%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.50 (3H, t, J= 7.1Hz, CH\(_2\)CH\(_3\)), 2.16 (3H, s, CH\(_3\)C=O), 4.40 (2H, q, J= 7.1Hz, CH\(_2\)CH\(_3\)), 6.43 (1H, s, CH), 7.27-7.40 (3H, m, 3 \times CH\(_{ar}\)), 7.76-7.89 (2H, m, 2 \times CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 15.5 (CH\(_2\)CH\(_3\)), 21.0 (CH\(_3\)C=O), 70.7 (CH\(_2\)), 81.9 (CH), 2 \times 127.2 (2 \times CH\(_{ar}\)), 127.7 (C\(_{quat}\)), 128.2 (C\(_{quat}\)), 2 \times 128.6 (2 \times CH\(_{ar}\)), 128.7 (CH\(_{ar}\)), 169.9 and 174.6 (C=COEt and C=O), 180.8 (C=O). IR (NaCl): \(\nu_{max}\) 1766, 1760, 1634, 1599, 1415 cm\(^{-1}\). MS m/z (%): 246 (M\(^+\), 1), 204 (100), 176 (38), 119 (32).

IV.6.3.3 Synthesis of 4-hydroxy-3-methyl-2-phenyl-2-cyclobuten-1-one 416

4-Hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a (0.50 g, 2.63 mmol) was dissolved in 25 ml of dry THF and cooled to -78°C under N\(_2\)-atmosphere. To the cooled solution was added 4.93 ml (7.89 mmol, 3 equiv.) of a 1.6M solution of MeLi in diethyl ether via a syringe and the reaction mixture was stirred for 15 min at the same temperature. The reaction was stopped by adding dropwise 25 ml ice water to the reaction mixture. After the mixture had reached room temperature, extraction was performed with diethyl ether (3 × 25 ml). Drying (MgSO\(_4\)) and evaporation of the solvent in vacuo resulted in 4-hydroxy-3-methyl-2-phenyl-2-cyclobuten-1-one 416, which was purified by flash chromatography.
4-Hydroxy-3-methyl-2-phenyl-2-cyclobuten-1-one 4\textsuperscript{16b} \(416\)

Flash chromatography (hexane/EtOAc 7:3, \(R_f = 0.14\)); yield 48\%, mp 57-61°C (no lit. data). Spectroscopic data were in accordance with literature data\textsuperscript{244b} but are given for the sake of completeness. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta\) 2.53 (3H, d, \(J = 0.8\text{Hz}, \text{CH}_3\)), 3.51 (1H, s(b), OH), 5.23 (1H, d, \(J = 0.8\text{Hz}, \text{CH}\)), 7.30-7.44 (3H, m, 3 × \text{CH}_\text{ar}), 7.67-7.71 (2H, m, 2 × \text{CH}_\text{ar}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta\) 14.2 (\text{CH}_3), 85.7 (CH), 2 × 127.6 (2 × \text{CH}_\text{ar}), 2 × 128.9 (2 × \text{CH}_\text{ar}), 129.3 (C\text{quat}), 129.4 (CH\text{ar}), 146.4 (C\text{quat}), 174.2 (C=\text{C}-\text{C}=\text{O}), 192.4 (C=O). IR (KBr): \(\nu_{\text{max}}\) 3367, 1732, 1622 cm\textsuperscript{-1}. MS \textit{m/z} (%): 174 (M\textsuperscript{+}, 77), 145 (100), 117 (98), 115 (64).

IV.6.3.4 Tosylation of 4-hydroxycyclobutenone 4\textsuperscript{12a} and reaction of 4\textsuperscript{18} with nucleophiles

Silver(I) oxide (0.59 g, 2.63 mmol, 2 equiv.), which was freshly prepared from silver(I) nitrate and NaOH, was mixed with 0.38 g (2.00 mmol, 1.5 equiv.) tosyl chloride and 0.44 g (2.63 mmol, 2 equiv.) potassium iodide.\textsuperscript{245} Dry dichloromethane (20 ml) was added to the solids and the mixture was stirred at room temperature. After reaction for 10 min under N\textsubscript{2}-atmosphere, 0.25 g (1.31 mmol) 4-hydroxycyclobutenone 4\textsuperscript{12a} was added as a solid. The temperature was raised to 40°C and stirring was continued for 45 min. After reaction, the solids were filtered over Celite\textsuperscript{®}, washed with 2 × 10 ml of dichloromethane and the filtrate was evaporated \textit{in vacuo}. The obtained tosylate 4\textsuperscript{18} was not purified but used directly in the following reactions. The reported spectral data (\textsuperscript{1}H NMR) of 4\textsuperscript{18} are obtained from the impure reaction mixture. To substitute the tosyl group of 4\textsuperscript{18} with potassium phthalimide, the following procedure was applied. For the substitution with sodium azide, an analogous procedure was followed.

Crude 3-methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl tosylate 4\textsuperscript{18} (0.45 g, 1.31 mmol) obtained via the procedure described above, was immediately redissolved in 20 ml of dry DMF. To the solution was added 0.37 g (1.97 mmol, 1.5 equiv.) K-phthalimide and the resulting mixture was heated to 50-60°C. After 1 hour, the reaction mixture was poured in 25 ml water and extracted with dichloromethane (3 × 50 ml). The organic phase was dried (MgSO\textsubscript{4}) and the solvents evaporated \textit{in vacuo}. Residual DMF was removed by evaporation at high vacuum (0.01 mmHg). The obtained \textit{N}-(3-methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl)phthalimide 4\textsuperscript{21a} was purified by flash chromatography.
3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl toluenesulfonate 418

No purification; yield 66%. Spectral data from the reaction mixture. $^1$H NMR (CDCl$_3$): $\delta$ 2.47 (3H, s, CH$_3$), 4.30 (3H, s, OCH$_3$), 6.08 (1H, s, CHO$_{\text{Tos}}$), 7.31-7.42 (3H, m, 3 $\times$ CH$_{\text{ar}}$), 7.67-7.70 (2H, m, 2 $\times$ CH$_{\text{ar}}$), 7.87-7.94 (4H, m, C$_6$H$_4$).

\[
\text{N-(3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl)phthalimide 421a}
\]

Flash chromatography (hexane/EtOAc 7:3, $R_f = 0.21$); yield 37%, mp 167-168°C. $^1$H NMR (CDCl$_3$): $\delta$ 4.10 (3H, s, OCH$_3$), 5.92 (1H, s, NCH), 7.25-7.45 (3H, m, 3 $\times$ CH$_{\text{ar}}$), 7.70-7.80 (4H, m, 2 $\times$ CH$_{\text{ar}}$ and 2 $\times$ CH$_{\text{phthal}}$), 7.84-7.88 (2H, dd, J= 5.6Hz, 2.9Hz, 2 $\times$ CH$_{\text{phthal}}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 60.5 (OCH$_3$), 63.4 (CHN), 2 $\times$ 123.7 (2 $\times$ CH$_{\text{phthal}}$), 125.6 (C$_{\text{quat}}$), 2 $\times$ 127.1 (2 $\times$ CH$_{\text{ar}}$), 128.2 (CH$_{\text{ar}}$), 128.3 (C$_{\text{quat}}$), 2 $\times$ 128.5 (2 $\times$ CH$_{\text{ar}}$), 2 $\times$ 131.7 (2 $\times$ C$_{\text{quat}}$), 2 $\times$ 134.6 (2 $\times$ CH$_{\text{phthal}}$), 2 $\times$ 167.4 (2 $\times$ NC=O), 173.9 (C=C-CH$_3$), 179.6 (C=O). IR (KBr): $\nu_{\text{max}}$ 1766, 1717, 1640, 1373 cm$^{-1}$. MS (ES+) $m/z$ (%): 320 (M$^+$, 100).

4-Azido-3-methoxy-4-phenyl-2-cyclobuten-1-one 421b

Flash chromatography (hexane/EtOAc 4:1, $R_f = 0.19$); yield 26%. $^1$H NMR (CDCl$_3$): $\delta$ 4.23 (3H, s, OCH$_3$), 5.03 (1H, s, CHN$_3$), 7.26-7.40 (3H, m, 3 $\times$ CH$_{\text{ar}}$), 7.70-7.73 (2H, m, 2 $\times$ CH$_{\text{ar}}$). $^{13}$C NMR (CDCl$_3$): $\delta$ 60.8 (OCH$_3$), 72.8 (CHN$_3$), 125.3 (C$_{\text{quat}}$), 127.1 (2 $\times$ CH$_{\text{ar}}$), 127.8 (C$_{\text{quat}}$), 2 $\times$ 128.6 (2 $\times$ CH$_{\text{ar}}$), 128.7 (CH$_{\text{ar}}$), 174.1 (C=C-C=O), 179.6 (C=O). IR (NaCl): $\nu_{\text{max}}$ 2104, 1767, 1637, 1370 cm$^{-1}$. MS (ES+) $m/z$ (%): 173 (M+H$^+$-N$_2$-CH$_3$, 90), 145 (173-CO, 100).

IV.6.3.5 Hydrolysis of N-(3-methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl)phthalimide 421a

N-(3-Methoxy-1-oxo-2-phenyl-2-cyclobuten-4-yl)phthalimide 421a (0.10 g, 0.31 mmol) was dissolved in a mixture of 4 ml acetic acid and 6 ml aq. 6M HCl. The acidic mixture was refluxed for 4 hours. After cooling to room temperature, the mixture was evaporated in vacuo and further dried at high vacuum (0.01 mmHg).
**N-(2-oxo-3-phenylpropyl)phthalimide 428**

Flash chromatography (hexane/EtOAc 1:1, Rf = 0.75); yield 27%, mp 84°C. \[^{1}H\] NMR (CDCl\(_3\)): \(\delta\) 3.84 (2H, s, CH\(_2\)), 4.47 (2H, s, CH\(_2\)), 7.21-7.38 (5H, m, C\(_6\)H\(_5\)), 7.70-7.75 (2H, m, 2 \times CH\(_{phthal}\)), 7.83-7.89 (2H, m, 2 \times CH\(_{phthal}\)). \[^{13}C\] NMR (CDCl\(_3\)): \(\delta\) 46.3 (CH\(_2\)), 47.6 (CH\(_2\)), 2 \times 123.7 (2 \times CH\(_{phthal}\)), 127.7 (CH\(_{ar}\)), 2 \times 129.1 (2 \times CH\(_{ar}\)), 2 \times 129.7 (2 \times CH\(_{ar}\)), 132.2 (C\(_{quat}\)), 2 \times 133.0 (2 \times C\(_{quat}\)), 2 \times 134.4 (2 \times CH\(_{phthal}\)), 2 \times 167.8 (2 \times C=O), 200.1 (C=O). IR (KBr): \(\nu_{\text{max}}\) 1772, 1725, 1415 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 280 (M+H\(^+\), 100).

IV.6.3.6 Reaction of 4-hydroxycyclobutenone 412a with N-(diphenylmethylene)amine

To a solution of 0.10 g (0.53 mmol) 4-hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a in 5 ml of DMF was added 0.10 g (0.53 mmol, 1 equiv.) N-(diphenylmethylene)amine and 0.15 g (1.05 mmol, 2 equiv.) K\(_2\)CO\(_3\). The mixture was heated to 70°C and stirred for 3 hours. After reaction, the mixture was poured in 25 ml aq. 0.5M HCl and extracted with EtOAc (3 \times 25 ml). Drying of the solvents (MgSO\(_4\)) and evaporation \textit{in vacuo}, yielded a reaction mixture from which pyrrolinone 433 could be isolated by flash chromatography.

**3,5,5-Triphenyl-2-formyl-2-pyrrolin-4-one 433**

Flash chromatography (hexane/EtOAc 7:3, Rf = 0.20); yield 35%, mp 196-199°C. \[^{1}H\] NMR (CDCl\(_3\)): \(\delta\) 7.34 (10H, s, 2 \times C\(_6\)H\(_5\)), 7.74-7.58 (3H, m, 3 \times CH\(_{ar}\)), 7.61-7.67 (2H, m, 2 \times CH\(_{ar}\)), 9.96 (1H, s, CHO). \[^{13}C\] NMR (CDCl\(_3\)): \(\delta\) 70.8 (C\(_{quat}\)), 4 \times 127.9 (4 \times CH\(_{ar}\)), 128.1 (C\(_{quat}\)), 2 \times 128.3 (2 \times CH\(_{ar}\)), 4 \times 128.5 (4 \times CH\(_{ar}\)), 2 \times 128.6 (2 \times CH\(_{ar}\)), 2 \times 130.7 (2 \times CH\(_{ar}\)), 130.8 (CH\(_{ar}\)), 2 \times 139.7 (2 \times C\(_{quat}\)), 147.5 and 150.4 (C=C-C=C-O), 169.7 (C=O), 187.8 (HC=O). IR (KBr): \(\nu_{\text{max}}\) 3180, 2850, 1698, 1677 cm\(^{-1}\). MS (ES+) \(m/z\) (%): 340 (M+H\(^+\), 100), 312 (M+H\(^+\)-CO, 32).
IV.6.4 Ring expansion of 4-hydroxycyclobutenones 412 to 2(5H)-furanones

IV.6.4.1 Synthesis of 4-alkoxy-3-aryl-5-halo-2(5H)-furanones 457 and 462

To a solution of 1.50 g (7.89 mmol) 4-hydroxy-3-methoxy-2-phenyl-2-cyclobuten-1-one 412a in 50 ml of CCl₄ was added 1.11 g (8.29 mmol, 1.05 equiv.) NCS. The mixture was refluxed for 2 hours and after cooling to 0°C the supernatant succinimide was filtered. The filtrate was cooled again to -20°C (2 hours) and subsequently filtered. After evaporation of the solvent, furanone 462a was obtained in almost quantitative yield. To remove minor impurities the product was purified by flash chromatography.

5-Chloro-4-methoxy-3-phenyl-2(5H)-furanone 462a

Crude yield 97%. Flash chromatography (hexane/EtOAc 4/1, Rf = 0.27); yield 81%. ¹H NMR (CDCl₃): δ 4.04 (3H, s, OCH₃), 6.54 (1H, s, CHCl), 7.34-7.44 (3H, m, 3 × CH₄ar), 7.71-7.75 (2H, m, 2 × CH₄ar). ¹³C NMR (CDCl₃): δ 59.1 (OCH₃), 80.8 (CHCl), 103.3 (C quat-C=O), 127.7 (C quat), 2 × 128.0 (2 × CH₄ar), 2 × 128.1 (2 × CH₄ar), 128.2 (CH₄ar), 168.6 (Cquat-OCH₃), 170.6 (C=O). IR (NaCl): νmax 1782, 1655, 1372, 1065 cm⁻¹. MS m/z (%): 224/26 (M⁺, 100), 195/97 (93), 189 (97), 118 (63), 89 (70).

5-Bromo-4-methoxy-3-phenyl-2(5H)-furanone 457

Flash chromatography (hexane/EtOAc 85:15, Rf = 0.17); yield 42%. Spectral data were in accordance with literature data, but are given for the sake of completeness. ¹H NMR (CDCl₃): δ 4.03 (3H, s, OCH₃), 6.82 (1H, s, CHBr), 7.32-7.47 (3H, m, 3 × CH₄ar), 7.70-7.79 (2H, m, 2 × CH₄ar). ¹³C NMR (CDCl₃): δ 59.3 (OCH₃), 70.9 (CHBr), 104.3 (C quat-C=O), 128.1 (C quat), 2 × 128.5 (2 × CH₄ar), 2 × 128.7 (2 × CH₄ar), 128.8 (CH₄ar), 168.6 (Cquat-OCH₃), 171.7 (C=O). IR (NaCl): νmax 1777, 1642, 1372, 1062 cm⁻¹. MS m/z (%): 268/70 (M⁺, 8), 189 (M⁺-Br, 100).

5-Chloro-4-ethoxy-3-phenyl-2(5H)-furanone 462b

Flash chromatography (hexane/EtOAc 4:1, Rf = 0.36); yield 62%, mp 100-101°C. ¹H NMR (CDCl₃): δ 1.41 (3H, t, J= 6.7Hz, CH₃), 4.14-4.23 (1H, m, CH₂H₆O), 4.38-4.46 (1H, m, CH₂H₆O), 6.52 (1H, s, CHCl), 7.35-7.41 (3H, m, 3 × CH₄ar), 7.73-7.75 (2H, m, 2 × CH₄ar). ¹³C NMR (CDCl₃): δ 15.2 (CH₃), 68.8 (CH₂CH₃), 81.6 (CHCl), 104.0 (Cquat-C=O), 128.3 (C quat), 2 × 128.5 (2 ×
CH₃), 3 × 128.7 (3 × CH₉ri), 169.1 (C₉quat-OCH₂), 170.2 (C=O). IR (KBr): νmax 1765, 1643, 1386, 1060 cm⁻¹. MS m/z (%): 238/40 (M⁺, 74), 145/47 (100), 119 (36), 89(47).

**5-Chloro-4-isopropoxy-3-phenyl-2(5H)-furanone 462c**

Flash chromatography (hexane/EtOAc 4:1, Rf = 0.33); yield 65%, mp 103-104°C. ¹H NMR (CDCl₃): δ 1.32 (3H, d, J= 6.1Hz, CH₃), 1.41 (3H, d, J= 6.1Hz, CH₃), 4.82 (1H, sept, J= 6.1Hz, CH(CH₃)₂), 6.50 (1H, s, CHCl), 7.30-7.45 (3H, m, 3 × CH₉ri), 7.72-7.80 (2H, m, 2 × CH₉ri). ¹³C NMR (CDCl₃): δ 22.5 (CH₃), 22.8 (CH₃), 76.1 (CH), 81.8 (CHCl), 104.6 (C₉quat-C=O), 128.3 (C₉quat), 2 × 128.5 (2 × CH₉ri), 2 × 128.6 (2 × CH₉ri), 128.7 (CH₉ri), 169.1 (C₉quat-O(CH(CH₃)₂)-CH₉ri), 169.5 (C=O). IR (KBr): νmax 1779, 1645, 1388 cm⁻¹. MS m/z (%): 252/54 (M⁺, 9), 210/12 (80), 181 (24), 175 (43), 145 (M⁺-OCH(CH₃)₂-CH₉ri), 91 (10), 77 (44).

**5-Chloro-3-(4-chlorophenyl)-4-methoxy-2(5H)-furanone 462d**

Flash chromatography (hexane/EtOAc 65:35, Rf = 0.43); yield 78%. ¹H NMR (CDCl₃): δ 4.11 (3H, s, OCH₃), 6.58 (1H, s, CHCl), 7.37 (2H, d, J= 8.6Hz, 2 × CH₉ri), 7.76 (2H, d, J= 8.6Hz, 2 × CH₉ri). ¹³C NMR (CDCl₃): δ 59.2 (OCH₃), 80.8 (CHCl), 102.9 (C₉quat-C=O), 126.3 (C₉quat), 2 × 128.5 (2 × CH₉ri), 2 × 129.5 (2 × CH₉ri), 134.3 (C₉quat), 168.3 (C₉quat-OCH₃), 170.6 (C=O). IR (NaCl): νmax 1785, 1646, 1370 cm⁻¹. MS (ES⁺) m/z (%): 259/61/63 (M⁺H⁺, 100).

IV.6.4.2 Dehalogenation of 4-alkoxy-3-aryl-5-chloro-2(5H)-furanones 462

5-Chloro-4-methoxy-3-phenyl-2(5H)-furanone 462a (0.10 g, 0.45 mmol) was dissolved in 5 ml acetic acid containing 0.44 g (0.67 mmol, 1.5 equiv.) of activated zinc (Zn/Cu). The heterogeneous mixture was stirred for 2 hours at room temperature and subsequently filtered to remove the excess of zinc. The filtrate was poured in 10 ml water and extracted with dichloromethane (3 × 20 ml). After drying (MgSO₄) and evaporation of the solvent in vacuo, almost pure dehalogenated product 463a was obtained, which could be further purified by flash chromatography.
4-Methoxy-3-phenyl-2(5H)-furanone 463a\textsuperscript{256}

Flash chromatography (hexane/EtOAc 65:35, \( R_f = 0.12 \)); yield 89\%, mp 118°C. Spectral data were in accordance with literature data,\textsuperscript{256} but are given for the sake of completeness. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 3.96 (3H, s, OCH\(_3\)), 4.84 (2H, s, CH\(_2\)), 7.26-7.41 (3H, m, 3 × CH\(_{ar}\)), 7.82-7.85 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 59.2 (OCH\(_3\)), 65.7 (CH\(_2\)), 103.9 (C\(_{quat}\)-C=O), 128.8 (CH\(_{ar}\)), 2 × 128.9 (2 × CH\(_{ar}\)), 2 × 129.4 (2 × CH\(_{ar}\)), 130.5 (C\(_{quat}\)), 173.8 (C\(_{quat}\)-OCH\(_3\)), 174.2 (C=O). IR (KBr): \( \nu_{max} \) 1738, 1640, 1387 cm\(^{-1}\). MS (ES\(^+\)) \( m/z \) (%): 191 (M+H\(^+\), 100).

4-Ethoxy-3-phenyl-2(5H)-furanone 463b

Flash chromatography (hexane/EtOAc 1:1, \( R_f = 0.40 \)); yield 80\%, mp 91°C. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.46 (3H, t, J= 7.0Hz, CH\(_3\)), 4.18 (2H, q, J= 7.0Hz, CH\(_2\)CH\(_3\)), 4.84 (2H, s, CH\(_2\)), 7.26-7.42 (3H, m, 3 × CH\(_{ar}\)), 7.86-7.91 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 15.2 (CH\(_3\)), 64.8 (CH\(_2\)O), 67.3 (CH\(_2\)O), 102.2 (C\(_{quat}\)-C=O), 127.5 (CH\(_{ar}\)), 2 × 127.7 (2 × CH\(_{ar}\)), 2 × 128.3 (2 × CH\(_{ar}\)), 129.6 (C\(_{quat}\)), 172.9 (C\(_{quat}\)-OCH\(_2\)), 173.0 (C=O). IR (KBr): \( \nu_{max} \) 1730, 1641, 1390, 1061 cm\(^{-1}\). MS \( m/z \) (%): 204 (M\(^+\), 100), 176 (40), 147 (60), 119 (34).

4-Isoproxy-3-phenyl-2(5H)-furanone 463c

Flash chromatography (hexane/EtOAc 3:2, \( R_f = 0.27 \)); yield 73\%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.41 (6H, d, J= 6.1Hz, CH(CH\(_3\))\(_2\)), 4.50 (1H, sept, J= 6.1Hz, CH(CH\(_3\))\(_2\)), 4.84 (2H, s, CH\(_2\)), 7.26-7.42 (3H, m, 3 × CH\(_{ar}\)), 7.87-7.97 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 2 × 22.9 (2 × CH\(_3\)), 65.0 (CH\(_2\)), 75.3 (CH), 102.9 (C\(_{quat}\)-C=O), 127.5 (CH\(_{ar}\)), 2 × 127.7 (2 × CH\(_{ar}\)), 2 × 128.3 (2 × CH\(_{ar}\)), 129.6 (C\(_{quat}\)), 172.9 (C\(_{quat}\)-OCH\(_2\)), 173.0 (C=O). IR (NaCl): \( \nu_{max} \) 1747, 1640, 1399, 1312, 1172 cm\(^{-1}\). MS \( m/z \) (%): 218 (M\(^+\), 21), 176 (100), 147 (55), 119 (21).

3-(4-Chlorophenyl)-4-methoxy-2(5H)-furanone 463d\textsuperscript{256}

Flash chromatography (hexane/EtOAc 7:3, \( R_f = 0.09 \)); yield 81\%, mp 76°C. (no lit. data). No spectral data reported.\textsuperscript{256} \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 3.98 (3H, s, OCH\(_3\)), 4.84 (2H, s, CH\(_2\)), 7.33 (2H, dt, J= 8.8Hz, 2.2Hz, 2 × CH\(_{ar}\)), 7.85 (2H, dt, J= 8.8Hz, 2.2Hz, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 58.1 (OCH\(_3\)), 64.5 (CH\(_2\)O), 101.7 (C\(_{quat}\)-C=O), 127.8 (C\(_{quat}\)), 2 × 128.5 (2 × CH\(_{ar}\)), 2 × 128.8
IV.6.3 Reduction of 4-alkoxy-3-aryl-2(5H)-furanones 463

To a solution of 4-methoxy-3-phenyl-2(5H)-furanone 463a (0.10 g, 0.53 mmol) in dry THF was added a catalytic amount of palladium black. The mixture was stirred under H₂-atmosphere (4 bar) at room temperature overnight (15 hours). After reaction, the reaction mixture was filtered over Celite® and the filtrate was evaporated in vacuo, yielding 4-methoxy-3-phenyldihydro-2(3H)-furanone 465a, which was purified by flash chromatography.

4-Methoxy-3-phenyldihydro-2(3H)-furanone 465a
Flash chromatography (hexane/EtOAc 1:1, Rₚ = 0.32); yield 68%, mp 81°C. ¹H NMR (CDCl₃): δ 3.05 (3H, s, OCH₃), 3.90 (1H, d, J = 5.5Hz, CHC=O), 4.18 (1H, ddd, J = 5.5Hz, 3.6Hz, 0.8Hz, CHOCH₃), 4.36 (1H, dd, J = 3.6Hz, 10.5Hz, CH₂H₅O), 4.45 (1H, dd, J = 0.8Hz, 10.5Hz, CH₂H₅O), 7.29-7.38 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 51.0 (CHC=O), 57.6 (OCH₃), 70.7 (CH₂), 79.6 (CHOCH₃), 127.6 (CH₆), 2 × 128.2 (2 × CH₆), 2 × 130.3 (2 × CH₆), 131.7 (Cquat), 175.8 (C=O). IR (KBr): v_max 1773, 1154, 1114 cm⁻¹. MS (ES⁺) m/z (%): 193 (M+H⁺, 100).

4-Ethoxy-3-phenyldihydro-2(3H)-furanone 465b
Flash chromatography (hexane/EtOAc 7:3, Rₚ = 0.21); yield 76%. ¹H NMR (CDCl₃): δ 0.95 (3H, t, J = 7.0Hz, CH₃), 2.97 (1H, qd, J = 7.0Hz, 9.0Hz, CH₂H₅O₃), 3.34 (1H, qd, J = 7.0Hz, 9.0Hz, CH₂H₅O₃), 3.88 (1H, d, J = 5.5Hz, CHC=O), 4.27 (1H, ddd, J = 1.7Hz, 3.0Hz, 5.5Hz, CHOEt), 4.41-4.42 (2H, m, CH₂O), 7.29-7.39 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 14.9 (CH₃), 51.5 (CHC=O), 66.0 (OCH₂CH₃), 71.9 (CH₂), 78.2 (CHOEt), 127.8 (CH₆), 2 × 128.3 (2 × CH₆), 2 × 130.6 (2 × CH₆), 132.0 (Cquat), 176.1 (C=O). IR (NaCl): v_max 1773, 1151, 1112 cm⁻¹. MS m/z (%): 206 (M⁺, 55), 118 (100), 91 (21), 77 (6).
4-Isopropoxy-3-phenyldihydro-2(3H)-furanone 465c

Flash chromatography (hexane/EtOAc 3:2, Rf = 0.30); yield 59%. $^1$H NMR (CDCl$_3$): $\delta$ 0.74 (3H, d, J = 6.1Hz, CH$_3$), 1.03 (3H, d, J = 6.1Hz, CH$_3$), 3.20 (1H, sept, J = 6.1Hz, CH(CH$_3$_2)), 3.87 (1H, d, J = 5.2Hz, CHC=O), 4.34-4.37 (2H, m, CH$_a$H$_b$ and CHOiPr), 4.45 (1H, dd, J = 10.0Hz, 4.0Hz, CH$_a$), 7.29-7.38 (5H, m, C$_6$H$_5$).

$^{13}$C NMR (CDCl$_3$): $\delta$ 21.8 (CH$_3$), 22.0 (CH$_3$), 51.5 (CHC=O), 72.0 and 73.1 (CHO and CH$_2$O), 75.8 (CH(CH$_3$_2)), 127.7 (CH$_ar$), 128.0 (C$_{quat}$), 2 × 128.2 (2 × CH$_ar$), 2 × 130.6 (2 × CH$_ar$), 175.9 (C=O). IR (NaCl): $\nu_{max}$ 1772, 1150, 1108 cm$^{-1}$. MS m/z (%): 220 (M$^+$, 19), 118 (100).

IV.6.4.4 Synthesis of 4,5-dialkoxy-3-aryl-2(5H)-furanones 464

To a solution of 0.50 g (2.23 mmol) 5-chloro-4-methoxy-3-phenyl-2(5H)-furanone 462a in 5 ml of methanol was added 0.61 ml (2.45 mmol, 1.1 equiv.) of 4M sodium methoxide in methanol at room temperature. After stirring overnight (15 hours) the mixture was poured in water (20 ml) and extracted with dichloromethane (3 × 20 ml). Drying (MgSO$_4$) and removal of the solvents in vacuo yielded dimethoxyfuranone 464a. When the same procedure was followed in the reaction of 5-chloro-4-methoxy-3-phenyl-2(5H)-furanone with 2.2 equiv. of sodium ethoxide in ethanol, diethoxyfuranone 464b was obtained. When 5-chloro-4-methoxy-3-phenyl-2(5H)-furanone was heated in isopropanol only substitution of the chloro atom occurred towards 466.

4,5-Dimethoxy-3-phenyl-2(5H)-furanone 464a

Flash chromatography (hexane/EtOAc 65:35, Rf = 0.24); yield 87%. $^1$H NMR (CDCl$_3$): $\delta$ 3.59 (3H, s, OCH$_3$), 4.04 (3H, s, OCH$_3$), 5.82 (OCHO), 7.30-7.42 (3H, m, 3 × CH$_ar$), 7.78-7.82 (2H, m, 2 × CH$_ar$).

$^{13}$C NMR (CDCl$_3$): $\delta$ 55.4 (OCH$_3$), 58.6 (OCH$_3$), 96.4 (CH), 104.4 (C$_{quat}$-C=O), 127.7 (CH$_ar$), 2 × 127.8 (2 × CH$_ar$), 2 × 127.9 (2 × CH$_ar$), 128.4 (C$_{quat}$), 168.3 (C$_{quat}$-OCH$_3$), 169.7 (C=O). IR (NaCl): $\nu_{max}$ 1767, 1755, 1659, 1386 cm$^{-1}$. MS m/z (%): 220 (M$^+$, 100), 205 (10), 189 (24), 161 (59), 145 (42), 118 (79).
4,5-Diethoxy-3-phenyl-2(5H)-furanone 464b

Flash chromatography (hexane/EtOAc 4:1, \(R_f = 0.26\)); yield 80\%, mp 49°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.32 (3H, t, \(J= 7.2\)Hz, CH\(_3\)), 1.42 (3H, t, \(J= 7.2\)Hz, CH\(_3\)), 3.79 (1H, qd, \(J= 9.3\)Hz, 7.2Hz, CH\(_a\)H\(_b\)CH\(_3\)), 3.93 (1H, qd, \(J= 9.3\)Hz, 7.2Hz, CH\(_a\)H\(_b\)CH\(_3\)), 4.23 (1H, qd, \(J= 9.6\)Hz, 7.2Hz, CH\(_a\)H\(_b\)CH\(_3\)), 4.44 (1H, qd, \(J= 9.6\)Hz, 7.2Hz, CH\(_a\)H\(_b\)CH\(_3\)), 5.85 (1H, s, CHOEt), 7.26-7.41 (3H, m, 3 × CH\(_{ar}\)), 7.81-7.85 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 15.1 (CH\(_3\)), 15.4 (CH\(_3\)), 65.1 (OCH\(_2\)), 67.9 (OCH\(_2\)), 96.1 (CHOEt), 104.4 (C\(_{quat}\)-C=O), 127.9 (CH\(_{ar}\)), 4 × 128.2 (4 × CH\(_{ar}\)), 129.1 (C\(_{quat}\)), 168.5 (C\(_{quat}\)-OEt), 170.3 (C=O). IR (KBr): \(v_{max}\) 1759, 1651, 1361, 1112 cm\(^{-1}\). MS \(m/z\) (%): 248 (M\(^+\), 49), 175 (37), 145 (100).

4,5-Diisopropoxy-3-phenyl-2(5H)-furanone 464c

Flash chromatography (hexane/EtOAc 7:3, \(R_f = 0.45\)); yield 51\%. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.33 (3H, d, \(J= 6.2\)Hz, CH\(_3\)), 1.34 (3H, d, \(J= 6.2\)Hz, CH\(_3\)), 1.37 (3H, d, \(J= 6.2\)Hz, CH\(_3\)), 1.42 (3H, d, \(J= 6.2\)Hz, CH\(_3\)), 4.16 (1H, sept, \(J= 6.2\)Hz, CH\(_{3}\)(CH\(_3\))\(_2\)), 4.85 (1H, sept, \(J= 6.2\)Hz, CH\(_{3}\)(CH\(_3\))\(_2\)), 5.90 (1H, s, OCHO), 7.26-7.44 (3H, m, 3 × CH\(_{ar}\)), 7.85-7.87 (2H, m, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 2 × 22.1 (2 × CH\(_3\)), 2 × 23.3 (2 × CH\(_3\)), 58.7 (CH(CH\(_3\))\(_2\)), 73.5 (C=C-OCH(CH\(_3\))\(_2\)), 95.0 (OCHO), 104.9 (C\(_{quat}\)-C=O), 128.0 (CH\(_{ar}\)), 2 × 128.3 (2 × CH\(_{ar}\)), 128.4 (2 × CH\(_{ar}\)), 128.9 (C\(_{quat}\)), 168.8 (C\(_{quat}\)-O-i-Pr), 170.3 (C=O). IR (NaCl): \(v_{max}\) 1759, 1647, 1402, 1386, 1109 cm\(^{-1}\). MS \(m/z\) (%): 276 (M\(^+\), 12), 234 (12), 192 (25), 174 (70), 145 (100).

3-(4-Chlorophenyl)-4,5-dimethoxy-2(5H)-furanone 464d

Flash chromatography (hexane/EtOAc 7:3, \(R_f = 0.22\)); yield 86\%, mp 50°C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.60 (3H, s, OCH\(_3\)), 4.08 (3H, s, OCH\(_3\)), 5.83 (OCHO), 7.34 (2H, dt, \(J= 8.8\)Hz, 2.3Hz, 2 × CH\(_{ar}\)), 7.83 (2H, dt, \(J= 8.8\)Hz, 2.3Hz, 2 × CH\(_{ar}\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 55.9 (OCH\(_3\)), 58.9 (OCH\(_3\)), 96.6 (OCHO), 104.0 (C\(_{quat}\)-C=O), 127.2 (C\(_{quat}\)), 2 × 128.5 (2 × CH\(_{ar}\)), 2 × 129.4 (2 × CH\(_{ar}\)), 133.9 (C\(_{quat}\)), 168.6 (C\(_{quat}\)-OCH\(_3\)), 169.6 (C=O). IR (KBr): \(v_{max}\) 1758, 1652, 1384 cm\(^{-1}\). MS \(m/z\) (%): 254/56 (M\(^+\), 100), 226/28 (33), 195/97 (49), 152/54 (77), 123 (46), 75 (56).
5-Isopropoxy-4-methoxy-3-phenyl-2(5H)-furanone 466

Flash chromatography (hexane/EtOAc 7:3, Rf = 0.35); yield 72%.

\[ ^1\text{H NMR (CDCl}_3) \delta 1.33 (3\text{H, d, } J= 6.2\text{Hz, CH}_3), 1.35 (3\text{H, d, } J= 6.2\text{Hz, CH}_3), 4.04 (3\text{H, s, OCH}_3), 4.17 (1\text{H, sept, } J= 6.2\text{Hz, CH(CH}_3)_2), 5.92 (1\text{H, s, OCHO}), 7.30-7.43 (3\text{H, m, } 3 \times \text{CH}_\text{ar}), 7.78-7.85 (2\text{H, m, } 2 \times \text{CH}_\text{ar}). \]

\[ ^{13}\text{C NMR (CDCl}_3) \delta 22.1 (\text{CH}_3), 23.3 (\text{CH}_3), 58.7 (\text{OCH}_3), 73.5 (\text{CH(CH}_3)_2), 95.0 (\text{OCHO}), 104.3 (\text{C}_\text{quat-C}=\text{O}), 128.0 (\text{CH}_\text{ar}), 2 \times 128.3 (2 \times \text{CH}_\text{ar}), 2 \times 128.4 (2 \times \text{CH}_\text{ar}), 128.9 (\text{C}_\text{quat}), 168.9 (\text{C}_\text{quat-OCH}_3), 170.3 (\text{C}=\text{O}). \]

\[ \text{IR (NaCl): } \nu_{\text{max}} \text{ 1755, 1656, 1372, 1104 \text{ cm}^{-1}.} \]

\[ \text{MS m/z (\%): 248 (M}^+\text{, 100), 189 (55), 161 (68), 146 (94), 118 (65).} \]

IV.6.4.5 Synthesis of 4-isopropylamino-5-methoxy-3-phenyl-2(5H)-furanone 467

5-Chloro-4-methoxy-3-phenyl-2(5H)-furanone 462a (0.10 g, 0.44 mmol) was dissolved in 5 ml of isopropylamine and was refluxed overnight (12 hours). The reaction mixture was evaporated in vacuo without aqueous workup, yielding isopropylaminofuranone 467 in quantitative yield. To remove traces of impurities, the compound was chromatographed on a short column of silica gel.

4-Isopropylamino-5-methoxy-3-phenyl-2(5H)-furanone 467

Crude yield 100%. Flash chromatography (hexane/EtOAc 1:1, Rf = 0.36); yield 69%, mp 106-108°C. \[ ^1\text{H NMR (CDCl}_3) \delta 1.13 (3\text{H, d, } J= 6.4\text{Hz, CH}_3), 1.18 (3\text{H, d, } J= 6.4\text{Hz, CH}_3), 3.55 (3\text{H, s, OCH}_3), 3.69-3.85 (1\text{H, m, CH(CH}_3)_2), 5.00 (1\text{H, d(b), } J= 8.6\text{Hz, NH}), 5.72 (1\text{H, s, CHOCH}_3), 7.25-7.41 (5\text{H, m, C}_\text{quat}). \]

\[ ^{13}\text{C NMR (CDCl}_3) \delta 2 \times 23.0 (2 \times \text{CH}_3), 46.3 (\text{CH(CH}_3)_2), 54.9 (\text{OCH}_3), 96.2 (\text{C}_\text{quat-C}=\text{O}), 97.3 (\text{CHOCH}_3), 127.0 (\text{CH}_\text{ar}), 4 \times 128.6 (4 \times \text{CH}_\text{ar}), 130.8 (\text{C}_\text{quat}), 157.7 (\text{C}_\text{quat-NH}), 171.0 (\text{C}=\text{O}). \]

\[ \text{IR (KBr): } \nu_{\text{max}} \text{ 3344, 1732, 1634, 1447, 1130 \text{ cm}^{-1}. MS m/z (\%): 247 (M}^+\text{, 100), 200 (42), 144 (52), 117 (29).} \]
IV.7 Evaluation of new entries to substituted cyclopropenones

IV.7.1 Reactivity of α-chlorocinnamaldehyde 477 and the corresponding dimethyl acetal 482 in carbene addition reactions

IV.7.1.1 Reaction of α-chlorocinnamaldehyde 477 with trihalomethyl anions

To a solution of α-chlorocinnamaldehyde 477 (0.50 g, 3.00 mmol) in 20 ml of dry diethyl ether was added 0.91 g (9.01 mmol, 3 equiv.) Et₃N and the mixture was cooled to 0°C. Subsequently, a solution of 1.47 g (9.01 mmol, 3 equiv.) of trichloroacetic acid in 10 ml of dry diethyl ether was added dropwise. After addition, the reaction mixture was refluxed for 24 hours. Afterwards, the reaction mixture was poured in 20 ml water and extracted with diethyl ether (3 × 20 ml). Drying (MgSO₄) and evaporation of the solvent yielded a reaction mixture, from which tetrachlorobutenol 478 was separated by flash chromatography.

In another reaction setup, 0.50 g (3.00 mmol) of α-chlorocinnamaldehyde 477 was dissolved in 10 ml dry petroleum ether containing 2.28 g (9.01 mmol, 3 equiv.) bromoform. The mixture was cooled to -78°C and subsequently 1.01 g (9.01 mmol, 3 equiv.) of t-BuOK was added under N₂-atmosphere. After reaction for 4 hours, a brown oil was recovered after standard aqueous workup. Flash chromatography afforded the tribromomethyl adduct 479.

(3Z)-1,1,1,3-Tetrachloro-4-phenyl-3-buten-2-ol 478

Flash chromatography (hexane/EtOAc 95:5, Rₚ = 0.17); yield 61%. \(^1\)H NMR (CDCl₃): δ 3.53 (1H, s(b), OH), 4.89 (1H, s, CHO), 7.00 (1H, s, CH=, 7.33-7.42 (3H, m, 3 × CH₆), 7.65-7.68 (2H, m, 2 × CH₆).

\(^1\)H NMR (CDCl₃): δ 3.53 (1H, s(b), OH), 4.89 (1H, s, CHO), 7.00 (1H, s, CH=), 7.33-7.42 (3H, m, 3 × CH₆), 7.65-7.68 (2H, m, 2 × CH₆). IR (NaCl): \(ν_{max}\) 3434, 1609, 1493 cm\(^{-1}\). MS m/z (%): 284/86/88/90/92 (M⁺, 1), 167/69 (M⁺-CCl₃, 100), 149 (60), 131 (78), 103 (48).

(3Z)-1,1,1-Tribromo-3-chloro-4-phenyl-3-buten-2-ol 479

Flash chromatography (hexane/EtOAc 95:5, Rₚ = 0.19); yield 78%. \(^1\)H NMR (CDCl₃): δ 3.58 (1H, s(b), OH), 4.89 (1H, s, CHO), 7.10 (1H, s, CH=), 7.32-7.44 (3H, m, 3 × CH₆), 7.54-7.70 (2H, m, 2 × CH₆).

\(^1\)H NMR (CDCl₃): δ 3.58 (1H, s(b), OH), 4.89 (1H, s, CHO), 7.10 (1H, s, CH=), 7.32-7.44 (3H, m, 3 × CH₆), 7.54-7.70 (2H, m, 2 × CH₆). IR (NaCl):
\[ \nu_{\text{max}} 3522, 1606, 1492, 1447 \text{ cm}^{-1}. \textbf{MS} \text{ } m/z (\%) : 416/18/22/24 (M^+, 1), 167/69 (M^+-\text{CBr}_3, 100), 149 (23), 131 (34), 115 (33). \]

IV.7.1.2 Synthesis of (1Z)-2-chloro-3,3-dimethoxy-1-phenylpropene 482

To 5.00 g (0.03 mol) \( \alpha \)-chlorocinnamaldehyde 477 was added an excess (25 ml) of trimethyl orthoformate and a catalytic amount of sulfuric acid (0.1 ml). The mixture was refluxed for 5 hours and after cooling to room temperature, poured in 50 ml aq. 0.5M NaOH. After extraction with dichloromethane (3 \times 50 ml) the corresponding acetal 482 was obtained after drying (MgSO\(_4\)/K\(_2\)CO\(_3\)) and evaporation of the solvents.

\( (1Z)-2\text{-Chloro-3,3-dimethoxy-1-phenylpropene 482} \)

Distillation (96-102\(^\circ\)C, 0.9 mmHg); yield 72\%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 3.40 (6H, s, 2 \times \text{OCH}_3), 4.86 (1H, s, \text{CH(OCH}_3)_2\), 6.98 (1H, s, CH=C), 7.30-7.39 (3H, m, 3 \times \text{CH}_{ar}), 7.68-7.71 (2H, m, 2 \times \text{CH}_{ar}). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 2 \times 52.9 (2 \times \text{OCH}_3), 103.4 (\text{CH(OCH}_3)_2\), 127.3 (CH), 2 \times 128.3 (2 \times \text{CH}_{ar}), 128.5 (\text{CH}_{ar}), 128.7 (\text{C}_{quat}), 2 \times 129.5 (2 \times \text{CH}_{ar}), 133.9 (\text{C}_{quat}). \text{IR} (\text{NaCl}): \nu_{\text{max}} 1614, 1600, 1492, 1447 \text{ cm}^{-1}. \textbf{MS (ES+)} \text{ } m/z (\%) : 181 (M+H\(^+\)-MeOH, 1), 149 (M+H\(^+\)-2MeOH, 94).

IV.7.2 Reactivity of \( \beta \)-chlorocinnamaldehyde 484 and the corresponding dimethyl acetal 487 in carbene addition reactions

IV.7.2.1 Reaction of \( \beta \)-chlorocinnamaldehyde 484 with trihalomethyl anions

The synthesis of 1,1,1,4-tetrachloro-4-phenyl-3-buten-2-ol 485 and the corresponding tribromomethyl analogue 486 was identical to the synthesis of 1,1,1,3-tetrahalobutenols 478 and 479 (see above).

\( (3Z)-1,1,1,4\text{-Tetrachloro-4-phenyl-3-buten-2-ol 485} \)

Flash chromatography (hexane/EtOAc 95:5, \( R_f = 0.11 \)); yield 63\%. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 2.98 (1H, d, 5.9Hz, OH), \(^a\) 2.28 (1H, dd, J= 5.9Hz, 8.4Hz, CHO), \(^a\) 6.29 (1H, d, J= 8.4Hz, CH=CCI), 7.37-7.49 (3H, m, 3 \times \text{CH}_{ar}), 7.60-7.67 (2H, m, 2 \times \text{CH}_{ar}). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 80.5 (CHOH), 102.2 (CCl\(_3\)),
121.4 (CH<sub>ar</sub>), 2 × 127.0 (2 × CH<sub>ar</sub>), 2 × 128.6 (2 × CH<sub>ar</sub>), 130.0 (CH=CCl), 136.9 (C<sub>quat</sub>), 140.6 (C<sub>quat</sub>). **IR (NaCl):** ν<sub>max</sub> 3401, 1637, 1492, 1446 cm<sup>-1</sup>. **MS m/z (%):** 284/86/88/90/92 (M<sup>+</sup>, 1), 167/69 (M<sup>+</sup>-CCl<sub>3</sub>, 100), 149 (21), 103 (59).

<sup>a</sup> extra coupling was not always visible and disappeared when adding D<sub>2</sub>O to the sample.

(3Z)-1,1,1-Tribromo-4-chloro-4-phenyl-3-buten-2-ol 486

Flash chromatography (hexane/EtOAc 95:5, R<sub>f</sub> = 0.15); yield 38%. **<sup>1</sup>H NMR** (**CDCl<sub>3</sub>): δ 3.10 (1H, s(b), OH), 5.19 (1H, d, J= 8.3Hz, CH<sub>OH</sub>), 6.29 (1H, d, J= 8.3Hz, CH=CCl), 7.39-7.43 (3H, m, 3 × CH<sub>ar</sub>), 7.63-7.68 (2H, m, 2 × CH<sub>ar</sub>). **<sup>1</sup>C NMR** (**CDCl<sub>3</sub>): δ 51.6 (CBr<sub>3</sub>), 81.7 (CHOH), 122.6 (CH=CCl), 2 × 127.0 (2 × CH<sub>ar</sub>), 2 × 128.7 (2 × CH<sub>ar</sub>), 130.0 (CH<sub>ar</sub>), 137.0 (C<sub>quat</sub>), 140.0 (C<sub>quat</sub>). **IR (NaCl):** ν<sub>max</sub> 3401, 1636, 1446 cm<sup>-1</sup>. **MS m/z (%):** no M<sup>+</sup>, 167/69 (M<sup>+</sup>-CBr<sub>3</sub>, 100), 149 (19), 115 (26), 103 (31).

**IV.7.2.2 Synthesis of (1Z)-1-chloro-3,3-dimethoxy-1-phenylpropene 487**

The acetalization of β-chlorocinnamaldehyde 484 proceeds analogous to the synthesis of (1Z)-2-chloro-3,3-dimethoxy-1-phenylpropene 482. However to obtain the dimethyl acetal 487 of β-chlorocinnamaldehyde a 48 hour reaction time was needed (see Section IV.7.1.2).

(1Z)-1-Chloro-3,3-dimethoxy-1-phenylpropene 487

Distillation (113-118°C, 0.7 mmHg) or flash chromatography (hexane/EtOAc 98:2, R<sub>f</sub> = 0.28); yield 72%. **<sup>1</sup>H NMR** (**CDCl<sub>3</sub>): δ 3.42 (6H, s(b), OCH<sub>3</sub>), 5.35 (1H, d, J= 6.6Hz, CH(OCH<sub>3</sub>)<sub>2</sub>), 6.22 (1H, d, J= 6.6Hz, CH=CCl), 7.31-7.38 (3H, m, 3 × CH<sub>ar</sub>), 7.55-7.63 (2H, m, 2 × CH<sub>ar</sub>). **<sup>13</sup>C NMR** (**CDCl<sub>3</sub>): δ 2 × 53.4 (2 × OCH<sub>3</sub>), 5.35 (1H, d, J= 6.6Hz, CH(OCH<sub>3</sub>)<sub>2</sub>), 6.22 (1H, d, J= 6.6Hz, CH=CCl), 7.31-7.38 (3H, m, 3 × CH<sub>ar</sub>), 7.55-7.63 (2H, m, 2 × CH<sub>ar</sub>). **IR (NaCl):** ν<sub>max</sub> 1640, 1491, 1447, 1127 cm<sup>-1</sup>. **MS m/z (%):** 212/14 (M<sup>+</sup>, 2), 181/83 (M<sup>+</sup>-OMe, 100), 177 (61), 149 (43).
IV.7.3 Reactivity of α,α’-dihaloketones in ring closing reactions

IV.7.3.1 Synthesis of 3-bromo-1-methoxy-1-phenyl-2-propanone 494

To a solution of 1.70 g (5.82 mmol) α,α’-dibromophenylacetone 492 in 20 ml of dry methanol was added an excess of MgSO₄ and a catalytic amount of p-toluenesulfonic acid (0.02 g). The mixture was refluxed for 15 hours, filtered, poured in 25 ml water and extracted with diethyl ether (3 × 30 ml). After drying (MgSO₄/K₂CO₃) and evaporation of the solvent, the obtained 3-bromo-1-methoxy-1-phenyl-2-propanone 494 was purified by flash chromatography. The compound was not stable at room temperature (complete decomposition after 24 hours at room temperature).

3-Bromo-1-methoxy-1-phenyl-2-propanone 494

Flash chromatography (hexane/EtOAc 97:3, Rₚ = 0.09); yield 61%. ¹H NMR (CDCl₃): δ 3.41 (3H, s, OCH₃), 4.07 (1H, d, J = 14.0Hz, CHaHbBr), 4.17 (1H, d, J = 14.0Hz, CHaHbBr), 4.97 (CHOCH₃), 7.34-7.41 (5H, m, C₆H₅). ¹³C NMR (CDCl₃): δ 31.8 (CH₂Br), 57.6 (OCH₃), 87.3 (CH), 2 × 127.2 (2 × CH₃), 2 × 129.0 (2 × CH₃), 129.1 (CH₃), 135.0 (Cquat), 199.4 (C=O). IR (NaCl): νmax 1741 cm⁻¹. MS m/z (%): no M⁺, 121 (M⁺-COCH₂Br, 100), 105 (8), 91 (11), 77 (17).

IV.7.4 Evaluation of halogenated β-keto esters and derivatives as building blocks for cyclopropenones

IV.7.4.1 Synthesis of methyl (2-benzyl-5,5-dimethyl-1,3-dioxan-2-yl)acetate 503

A solution of 2.50 g (13.02 mmol) methyl 3-oxo-4-phenylbutanoate 502 in 50 ml of benzene containing 1.49 g (14.32 mmol, 1.1 equiv.) 2,2-dimethyl-1,3-propanediol and a catalytic amount of p-toluenesulfonic acid was refluxed for 15 hours using a Dean Stark apparatus for constant water removal by azeotropic distillation. After reaction, the mixture was poured in 30 ml of a saturated aq. NaHCO₃ solution and extracted with diethyl ether (3 × 30 ml). Drying (MgSO₄/K₂CO₃) and evaporation of the solvents yielded a crystalline compound which could be purified by recrystallization or flash chromatography.
Methyl (2-benzyl-5,5-dimethyl-1,3-dioxan-2-yl)acetate 503

Recrystallization (pentane) or flash chromatography (hexane/EtOAc 9:1, Rf = 0.28); yield 77%, mp 91-92°C. \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 0.89 (3H, s, CH\(_3\)), 0.90 (3H, s, CH\(_3\)), 2.67 (2H, s, CH\(_2\)), 3.21 (2H, s, CH\(_2\)), 3.57 (2H, d, J = 11.3Hz, 2 × CH\(_a\)H\(_b\)O), 3.60 (2H, d, J = 11.3Hz, 2 × CH\(_a\)H\(_b\)O), 3.70 (3H, s, OCH\(_3\)), 7.20-7.35 (5H, m, C\(_6\)H\(_5\)). \(^1^C\) NMR (CDCl\(_3\)): \(\delta\) 22.5 (CH\(_3\)), 22.6 (CH\(_3\)), 29.9 (C\(_{quat}\)), 38.1 (CH\(_2\)), 41.4 (CH\(_2\)), 51.9 (OCH\(_3\)), 2 × 70.7 (2 × CH\(_2\)O), 98.7 (O-C-O), 126.6 (CH\(_ar\)), 2 × 128.0 (2 × CH\(_ar\)), 2 × 131.0 (2 × CH\(_ar\)), 136.4 (C\(_{quat}\)), 170.1 (C=O). IR (KBr): \(\nu_{\text{max}}\) 1730, 1094 cm\(^{-1}\). MS m/z (%): 278 (M\(^+\), 1), 205 (29), 187 (100).

IV.7.4.2 Synthesis of methyl (2-(bromo(phenyl)methyl)-5,5-dimethyl-1,3-dioxan-2-yl)acetate 504

Methyl (2-benzyl-5,5-dimethyl-1,3-dioxan-2-yl)acetate 503 (2.00 g, 7.19 mmol) was dissolved in 20 ml of dry CCl\(_4\). To the solution was added 1.41 g (7.91 mmol, 1.1 equiv.) NBS and 0.12 g (0.72 mmol, 0.1 equiv.) AIBN. The heterogeneous mixture was refluxed for 2 hours and subsequently filtered after cooling to 0°C. The filtrate was washed with 10 ml water and 10 ml brine, and subsequently dried over MgSO\(_4\)/K\(_2\)CO\(_3\). After evaporation of the solvent, the obtained brominated ester 504 was purified by flash chromatography to give pale yellow crystals.

Methyl (2-(bromo(phenyl)methyl)-5,5-dimethyl-1,3-dioxan-2-yl)acetate 504

Flash chromatography (hexane/EtOAc 9:1, Rf = 0.25); yield 71%, mp 99-100°C. \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 0.79 (3H, s, CH\(_3\)), 1.07 (3H, s, CH\(_3\)), 2.64 (1H, d, J = 14.6Hz, CH\(_a\)H\(_b\)), 3.28 (1H, d, J = 14.6Hz, CH\(_Hb\)), 3.50 (1H, dd, J = 11.8Hz, 2.5Hz, CH\(_Hb\)C(CH\(_3\))\(_2\)CH\(_Hd\)), 3.54 (1H, dd, J = 11.8Hz, 2.5Hz, CH\(_Hb\)C(CH\(_3\))\(_2\)CH\(_Hd\)), 3.65 (1H, d, J = 11.4Hz, CH\(_Hb\)C(CH\(_3\))\(_2\)CH\(_Hd\)), 3.69 (3H, s, OCH\(_3\)), 3.75 (1H, d, J = 11.4Hz, CH\(_Hb\)C(CH\(_3\))\(_2\)CH\(_Hd\)), 5.54 (1H, s, CHBr), 7.25-7.32 (3H, m, 3 × CH\(_ar\)), 7.56-7.62 (2H, m, 2 × CH\(_ar\)). \(^1^C\) NMR (CDCl\(_3\)): \(\delta\) 22.3 (CH\(_3\)), 22.9 (CH\(_3\)), 29.8 (C\(_{quat}\)), 33.9 (CH\(_2\)), 52.1 (OCH\(_3\)), 57.3 (CHBr), 71.1 (CH\(_2\)O), 71.4 (CH\(_2\)O), 98.3 (O-C-O), 2 × 128.0 (2 × CH\(_ar\)), 128.4 (CH\(_ar\)), 2 × 130.4 (2 × CH\(_ar\)), 137.9 (C\(_{quat}\)), 169.3 (C=O). IR (KBr): \(\nu_{\text{max}}\) 1738, 1096 cm\(^{-1}\). MS m/z (%): 356/58 (M\(^+\), 1), 283/85 (10), 187 (100).
IV.7.4.3 Synthesis of methyl (2Z)-4-bromo-3-(3-hydroxy-2,2-dimethylpropoxy)-4-phenyl-2-butenoate 507

To a solution of 1.98 mmol (1.1 equiv.) LDA, freshly prepared from 0.20 g (1.98 mmol, 1.1 equiv.) diisopropylamine and 0.80 ml (1.98 mmol, 1.1 equiv.) 2.5M BuLi in hexane, in 10 ml of dry THF was added dropwise 0.50 g (1.80 mmol) methyl (2-benzyl-5,5-dimethyl-1,3-dioxan-2-yl)acetate 503 as a solution in 5 ml of dry THF at -78°C. After reaction for 30 minutes under N₂-atmosphere, 0.66 g (1.98 mmol, 1.1 equiv.) CBr₄ in 5 ml of dry THF was added via a dropping funnel under N₂-atmosphere. The mixture was stirred for 2 hours while cooling was stopped and the reaction mixture reached room temperature. Subsequently, the mixture was diluted with 3 ml ice water and poured in 10 ml water. Extraction was performed with diethyl ether (3 x 20 ml) and after drying (MgSO₄/K₂CO₃) and evaporation of the solvent, compound 507 was obtained. Purification was performed by flash chromatography.

Methyl (2Z)-4-bromo-3-(3-hydroxy-2,2-dimethylpropoxy)-4-phenyl-2-butenoate 507

Flash chromatography (hexane/EtOAc 4:1, Rₜ = 0.26); yield 48%.

1H NMR (CDCl₃): δ 0.86 (6H, s, 2 × CH₃), 3.29 (2H, s, CH₂), 3.50 (2H, s, HOCH₂), 3.70 (3H, s, OCH₃), 3.98 (2H, s, CH₂O), 5.08 (1H, s, CH=C), 7.20-7.34 (5H, m, C₆H₅). 13C NMR (CDCl₃): δ 2 × 21.2 (2 × CH₃), 35.9 and 37.3 (CH₂ and Cquat), 50.6 (OCH₃), 68.4 (CH₂O), 73.8 (CH₂O), 98.4 (CH=C), 126.2 (CH₃), 128.1 (2 × CH₃), 128.9 (2 × CH₃), 137.5 (Cquat), 167.9 (CH=C), 173.1 (C=O). IR (NaCl): νmax 3468, 1712, 1620, 1137 cm⁻¹. MS m/z (%): 278 (M⁺, 7), 246 (85), 187 (51), 160 (77), 101 (100).

IV.8 Synthesis of 2-alkyl- and 2-alkadienylcyclobutanones

IV.8.1 Synthesis of 2-alkylcyclobutanones

A solution of 1.00 g (9.01 mmol) N-(cyclobutylidene)isopropylamine 44a in 10 ml of dry THF was added to a solution of 1.05 equivalents (9.46 mmol) of LDA (in situ prepared from diisopropylamine and butyllithium) in 20 ml of dry THF at -78°C under N₂-atmosphere. After reaction for 30 minutes at this temperature, 1.49 g (9.01 mmol, 1 equiv.) hexyl bromide in 10 ml of THF was added via a syringe at the same temperature. After stirring the mixture for 1 hour at -78°C, the cooling bath was removed and the mixture was stirred for 1 hour at
room temperature. Without workup of the intermediate imine, an excess of aq. 2M HCl was added and the mixture was refluxed for 1 hour. After cooling, the mixture was extracted with $3 \times 50$ ml of diethyl ether. Drying ($\text{MgSO}_4$), filtration and evaporation of the solvent resulted in 2-hexylcyclobutanone $41a$, which was purified by flash chromatography.

### 2-Hexylcyclobutanone $41a^{295}$

![Chemical structure of 2-Hexylcyclobutanone](https://example.com/structure)

Flash chromatography (EtOAc/hexane 1:9, $R_f = 0.41$); yield: 75%. $^1\text{H}$ NMR, IR and MS data were in accordance with the literature data.$^{295}$ $^{13}\text{C}$ NMR ($\text{CDCl}_3$): (not reported)$^{295}$ $\delta$ 13.9 (CH$_3$), 16.8 (CH$_2$), 22.5 (CH$_2$), 26.9 (CH$_2$), 29.1 (CH$_2$), 29.5 (CH$_2$), 31.6 (CH$_2$), 44.3 (CH$_2$=O), 60.6 (CHC=O), 211.8 (C=O).

### 2-Decylcyclobutanone $41c^{43c}$

![Chemical structure of 2-Decylcyclobutanone](https://example.com/structure)

Flash chromatography (EtOAc/hexane 1:9, $R_f = 0.35$); yield: 80%. (No spectral data were reported)$^{43c}$ $^1\text{H}$ NMR ($\text{CDCl}_3$): $\delta$ 0.88 (3H, t, $J = 6.5$Hz, CH$_3$), 1.25 (16H, m, 8 × CH$_2$), 1.42-1.51 (1H, m, CH$_3$H$_6$CH$_2$C=O), 1.54-1.74 (2H, m, CH$_2$), 2.11-2.24 (1H, m, CH$_a$H$_b$CH$_2$C=O), 2.85-3.08 (2H, m, CH$_2$C=O), 3.21-3.34 (1H, m, CHC=O). $^{13}\text{C}$ NMR ($\text{CDCl}_3$): $\delta$ 14.1 (CH$_3$), 16.9 (CH$_2$), 22.7 (CH$_2$), 27.1 (CH$_2$), 29.4 (CH$_2$), 2 × 29.5 (2 × CH$_2$), 3 × 29.6 (3 × CH$_2$), 31.9 (CH$_2$), 44.3 (CH$_2$=O), 60.6 (CHC=O), 212.1 (C=O). IR (NaCl): $v_{\text{max}}$ 1780 cm$^{-1}$. MS $m/z$ (%): 210 (M$^+$, 1), 112 (24), 111 (11), 98 (100), 84 (23).

### IV.8.2 Synthesis of 2-[(5Z,8Z)-5,8-tetradecadienyl]cyclobutanone 43

#### IV.8.2.1 Synthesis of 5,8-tetradecadiyn-1-ol 48

To a suspension of 1.46 g (7.66 mmol, 2 equiv.) CuI, 1.15 g (7.66 mmol, 2 equiv.) NaI, 0.80 g (5.74 mmol, 1.5 equiv.) K$_2$CO$_3$ in 10 ml of DMF, 1-bromo-2-octyn $47$ (0.80 g, 4.21 mmol, 1.1 equiv.) and 5-hexyn-1-ol $46$ (0.38 g, 3.83 mmol, 1 equiv.) were added under N$_2$-atmosphere at room temperature.$^{277}$ After stirring for 15 hours, the suspension was filtered over Celite® and the filtrate was poured into 20 ml of saturated aqueous NH$_4$Cl and extracted with diethyl ether ($3 \times 30$ ml). Drying and evaporation of the solvent resulted in a pale oil which was chromatographed on silicagel.
5,8-Tetradecadiynol 48

Flash chromatography (diethyl ether/hexane 1:3, $R_f$ = 0.11); yield: 87%. $^1$H NMR (CDCl$_3$): $\delta$ 0.90 (3H, t, J = 6.8 Hz, CH$_3$), 1.25-1.40 (4H, m, 2 $\times$ CH$_2$), 1.43-1.79 (6H, m, 3 $\times$ CH$_2$), 2.05 (1H, s(br), OH), 2.15 (2H, tt, J = 7.2 Hz, 2.4 Hz, CH$_2$C=C), 2.21 (2H, tt, J = 6.7 Hz, 2.4 Hz, CH$_2$C=C), 3.12 (2H, quint, J = 2.4 Hz, C=CCH$_2$C=C), 3.66 (2H, t, J = 6.5 Hz, CH$_2$OH). $^{13}$C NMR (CDCl$_3$): $\delta$ 9.8 (CH$_3$), 14.0 (CH$_2$), 18.6 (CH$_2$), 18.7 (CH$_2$), 22.3 (CH$_2$), 25.0 (CH$_2$), 28.5 (CH$_2$), 31.1 (CH$_2$), 31.9 (CH$_2$), 62.4 (CH$_2$OH), 74.4 and 75.0 and 80.1 and 80.7 (2 $\times$ C=C). IR (NaCl): $\nu_{max}$ 3369 cm$^{-1}$. MS $m/z$ (%): 206 (M$^+$, 2), 205 (5), 191 (2), 149 (37), 110 (74), 91 (100), 79 (54). Anal. Calcd. for C$_{14}$H$_{22}$O: C, 81.50; H, 10.75. Found: C, 81.71; H, 10.94.

IV.8.2.2 Reduction of 5,8-tetradecadiyn-1-ol 48

A suspension of 1.03 g (20 mol% Pd) Lindlar catalyst in benzene was saturated with H$_2$ during 30 min at room temperature. After cooling the suspension to 10°C, a mixture of 0.50 g (2.43 mmol) tetradiynol 48, 1.10 g (8.51 mmol, 3.5 equiv.) quinoline and 30 ml of dry benzene were added. The flask was kept under H$_2$-atmosphere (atmospheric pressure) and stirred overnight. After filtration of the catalyst, the filtrate was washed with 2 $\times$ 20 ml aqueous 1M HCl and the solvent was evaporated.

$^{(5Z,8Z)}$-5,8-Tetradecadienol 49

Flash chromatography on a 3 cm silica column (diethyl ether/hexane: 1:3, $R_f$ = 0.16); yield: 94%. $^1$H NMR, $^{13}$C NMR, IR and MS data were in accordance with the literature data.$^{296}$

IV.8.2.3 Synthesis of $^{(5Z,8Z)}$-1-bromo-5,8-tetradecadiene 50

To a solution of 0.25 g (1.20 mmol) tetradecadienol 49 in 5 ml of dry CH$_2$Cl$_2$ at 0°C was added 0.47 g (1.79 mmol, 1.5 equiv.) triphenylphosphine and 0.59 g (1.79 mmol, 1.5 equiv.) dried CBr$_4$. The mixture was allowed to reach room temperature and was stirred for 8 hours at this temperature. The solids were filtered and the filtrate was evaporated in vacuo. Purification of the obtained bromide 50 was accomplished by flash chromatography.
(5Z,8Z)-1-Bromo-5,8-tetradecadiene 50

Flash chromatography (diethyl ether/hexane 1:4, R<sub>f</sub> = 0.75); yield: 90%. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.89 (3H, t, J= 6.7Hz, CH<sub>3</sub>), 1.29-1.41 (6H, m, 3 × CH<sub>2</sub>), 1.52 (2H, quint, J= 7.3Hz, CH<sub>2</sub>), 1.88 (2H, quint, J= 7.3Hz, CH<sub>2</sub>), 2.02-2.13 (4H, m, 2 × CHCH<sub>2</sub>), 2.77 (2H, t, J= 5.6Hz, CH<sub>2</sub>Br), 3.41 (2H, t, J= 6.7Hz, CHCH<sub>2</sub>CH), 5.27-5.44 (4H, m, 2 × CH=CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 14.2 (CH<sub>3</sub>), 22.9 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 31.6 (CHCH<sub>2</sub>), 32.4 (CH<sub>2</sub>CH), 33.9 (CHCH<sub>2</sub>CH), 127.7 (CH), 128.9 (CH), 129.2 (CH), 130.5 (CH). IR (NaCl): ν<sub>max</sub> 1648, 1457, 670 cm<sup>-1</sup>. MS m/z (%): 272/4 (M<sup>+</sup> +, 13), 188/90 (14), 95 (57), 81 (86), 67 (100). Anal. Calcd. for C<sub>14</sub>H<sub>25</sub>Br: C, 61.54; H, 9.22. Found: C, 61.78; H, 9.40.

IV.8.2.4 Synthesis of 2-[(5Z,8Z)-5,8-tetradecadienyl]cyclobutanone 43

The synthetic procedure is analogous to the synthesis of 2-alkylcyclobutanones 41a and 41c.

2-[(5Z,8Z)-5,8-Tetradecadienyl]cyclobutanone 43 <sup>269f</sup>

Flash chromatography (diethyl ether/hexane 2:8, R<sub>f</sub> = 0.51), yield: 69%. Spectral data were in accordance with literature data,<sup>269f</sup> but are given for the sake of completeness. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.89 (3H, t, J= 6.1Hz, CH<sub>3</sub>), 1.19-1.56 (13H, m, 6 × CH<sub>2</sub> and CH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub>C=O), 1.62-1.72 (2H, m, CH<sub>2</sub>), 2.01-2.24 (4H, m, 2 × CH<sub>2</sub>C=C), 2.77 (1H, m, CH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub>C=O), 2.84-3.09 (2H, m, C=CHCH<sub>2</sub>CH=C), 3.23-3.33 (1H, m, CHC=O), 5.28-5.46 (4H, m, 2 × CH=CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 14.2 (CH<sub>3</sub>), 17.0 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 2 × 29.5 (2 × CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 44.5 (CH<sub>2</sub>C=O), 60.6 (CHC=O), 127.9 (CH), 128.4 (CH), 129.8 (CH), 130.4 (CH), 212.5 (C=O). IR (NaCl): ν<sub>max</sub> 1782, 1652, 1462 cm<sup>-1</sup>. MS m/z (%): 262 (M<sup>+</sup>, 11), 247 (1), 234 (6), 219 (6), 205 (9), 191 (18), 95 (64), 81 (82), 67 (100).
V SUMMARY

The main objective of this PhD-thesis consists of the evaluation of halogenated cyclobutanones as building blocks for the synthesis of physiologically interesting carbocyclic and heterocyclic compounds. In the unabated search for new biologically active compounds, azaheterocycles still play a predominant role, which is reflected by the numerous applications of these compounds in agrochemistry and pharmacology. Also the study of small carbocyclic compounds such as cyclopropanes, cyclobutanes and cyclobutenes is worthwhile due to the specific properties associated with the ring strain of these compounds. In that respect, ‘micro’-cycles have already proven to be valuable synthons as intermediates for the synthesis of a variety of physiologically active compounds and natural products. In addition to their synthetic use, a wide diversity of small ring compounds display interesting biological activities. In this PhD-work, the reactivity of halogenated cyclobutanones and the corresponding imines, a class of compounds which is barely studied, was explored.

In a first part, new synthetic routes were developed towards substituted pyrroles. Especially 3-arylpyrroles and 3-halogenated pyrroles are of particular interest because of the existence of only a limited amount of synthetic pathways to reach these compounds and because of their physiological properties, e.g. fungicidal activities (Pyrrolnitrin \textit{i}), anticonvulsant activities (AWD 140-190 \textit{ii}), insecticidal activities (\textit{Pirate}® \textit{iii}) and fibrosis inhibition \textit{(iv)}.

Halogenated cyclobutanones \textit{v}, which are readily available from substituted styrenes via a [2+2]-cycloaddition with dihalogenated ketenes, were treated with various amines to induce a ring opening towards dichlorobutanamides \textit{vi}. These compounds were treated with base, \textit{in casu} sodium methoxide, resulting in 4-methoxybutenamides \textit{vii}, which cyclized towards new 3-pyrrolinones \textit{viii} upon treatment with aqueous HCl. 3-Pyrrolinones are
valuable synthons for further organic transformation towards other five membered azaheterocycles and, in that point of view, these compounds were treated with a variety of reducing agents to establish a new procedure for the synthesis of pyrroles. Surprisingly, only 9-BBN (9-borabicyclo[3.3.1]nonane) proved to be the reagent of choice and yielded 3-arylpyrrole \( \text{xi} \) in fair yield from 3-pyrrolinone \( \text{viiia} \), whereas other reductants like NaBH\(_4\), LiAlH\(_4\) or BH\(_3\) failed. To evaluate the generality of this procedure, other substituted 3-pyrrolinones were synthesized via alkylation of pyrrolinones \( \text{viii} \). Treatment of the latter with LDA and subsequent trapping of the formed anion with alkyl halides resulted in 3,4-disubstituted 3-pyrrolin-2-ones \( \text{ix} \), which in turn were reduced towards the corresponding pyrroles \( \text{x} \). Other 3-pyrrolinones \( \text{xv} \) were synthesized via optimized and modified literature procedures.

\[ \text{a)} \quad 2 \text{ equiv. } R^2\text{NH}_2, \text{Et}_2\text{O}, \text{ r.t., 4-8h.} \quad \text{b)} \quad 4 \text{ equiv. } 4\text{M NaOMe in MeOH, } \Delta, 2\text{h.} \quad \text{c)} \quad \text{excess aq. } 2\text{M HCl, } \Delta, 2\text{h.} \quad \text{d)} \quad 1) \quad 1.05 \text{ equiv. } \text{LDA, THF, } -78^\circ \text{C to } 0^\circ \text{C, 45 min.} \quad 2) \quad 1 \text{ equiv. } R^3\text{I or } R^3\text{Br, THF, } -78^\circ \text{C to r.t., 6h.} \quad \text{e)} \quad 3 \text{ equiv. } 9\text{-BBN, toluene, } \Delta, 15\text{h.} \]
To prepare new N-substituted pyrrolinones xva-c, phenylacetones xii were reacted with N-substituted chloroacetamides in the presence of base resulting in γ-ketoamides xiii, which cyclized towards 3-pyrrolinones xva-c by treatment with sulfuric acid in refluxing dichloromethane.

\[
\begin{align*}
\text{xii} \quad R^1 &= \text{C}_6\text{H}_4 \\
\text{xiiib} \quad R^1 &= 4-\text{MeOC}_6\text{H}_4 \\
\text{xiiic} \quad R^1 &= \text{C}_6\text{H}_4, R^2 = \text{n-Pr (not isolated)} \\
\text{xiiib} \quad R^1 &= \text{C}_6\text{H}_4, R^2 = \text{i-Pr (69%)} \\
\text{xiiic} \quad R^1 &= 4-\text{MeOC}_6\text{H}_4, R^2 = \text{i-Pr (72%)} \\
\text{xivb} \quad R^1 &= \text{C}_6\text{H}_5, R^2 = \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
xvi &= R^1 = \text{C}_6\text{H}_5, R^2 = \text{n-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (54%)} \\
xvib &= R^1 = \text{C}_6\text{H}_5, R^2 = \text{i-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (52%)} \\
xvict &= R^1 = 4-\text{MeOC}_6\text{H}_4, R^2 = \text{i-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (54%)} \\
xvig &= R^1 = \text{C}_6\text{H}_5, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{H (41%)} \\
xvix &= R^1 = \text{H}, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{C}_6\text{H}_5 (29%) \\
xvixf &= R^1 = \text{CH}_3, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{H (39%)} \\
xvixg &= R^1 = \text{H}, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{CH}_3 (32%) \\
\end{align*}
\]

\[
\begin{align*}
\text{xivb} \quad R^1 &= \text{C}_6\text{H}_5, R^2 = \text{i-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (50%)} \\
\text{xvib} &= R^1 = \text{C}_6\text{H}_5, R^2 = \text{i-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (53%)} \\
\text{xvict} &= R^1 = 4-\text{MeOC}_6\text{H}_4, R^2 = \text{i-Pr}, R^3 = \text{CH}_3, R^4 = \text{H (58%)} \\
\text{xvig} &= R^1 = \text{C}_6\text{H}_5, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{H (48-55%)} \\
\text{xvix} &= R^1 = \text{CH}_3, R^2 = \text{CH}_3, R^3 = \text{H}, R^4 = \text{H (12-15%)} \\
\end{align*}
\]

\[
\begin{align*}
\text{e) 3 equiv. 9-BBN, toluene, } \Delta, 15h. \\
\end{align*}
\]

N-Methylpyrrolinones xvd-g were synthesized via literature procedures and the resulting isomers were separated by chromatography for the first time. These pyrrolinones were reduced by 9-BBN in refluxing toluene yielding a diversity of substituted pyrroles xvi in
moderate to good yields. Encouraged by these results, also succinimide xivb was treated with 9-BBN to verify whether pyrrole xvid could be synthesized directly, and indeed, this proved to be the case albeit in rather low yield. In a second approach to synthesize 3-halogenated pyrroles, 3-aryl-2,2-dichlorocyclobutanones v were treated with sodium borohydride to induce a semi-benzilic Favorskii rearrangement towards new cis-2-aryl-1-chlorocyclopropanecarbaldehydes xvii. These substrates were used as starting material for the synthesis of various substituted azaheterocyclic compounds.

Having in hands these intriguing cyclopropanes xvii, efforts were performed to synthesize the corresponding cyclopropenes by dehydrochlorination. Unfortunately, the reaction with numerous bases did not yield any cyclopropenes. Transformation of the aldehyde moiety of xviia by Wittig or Knoevenagel reactions yielded cis-substituted chlorinated cyclopropanes xviii-xx. Analogous cyclopropanes were recently patented as insecticidal compounds.

To develop a new route to halogenated heterocycles, cyclopropanes xvii were treated with DMF-HCl to induce a ring opening. Subsequent reaction with chlorine yielded α,α,γ-trichlorobutanals xxi. The reaction of these aldehydes with amines in the presence of titanium(IV) chloride as an activator and dehydrating agent resulted in the formation of halogenated imines xxii, which were unstable at room temperature and were used immediately after workup. Via a cyanide induced cyclization of imines xxii by treatment with KCN in refluxing methanol, new substituted 2-pyrrolines xxiii were synthesized. A study of the reactivity of these interesting compounds resulted in the establishment of new entries towards pyrrolidinones xxiv and xxvi (via treatment with HCl or trichloroisocyanuric acid (TCIA), resp.) and several pyrroles xxv and xxvii with a specific substitution pattern (via reaction with base or DDQ, resp.). It is known that the presence of a halogen in β-position of pyrroles or an aryl moiety or electron withdrawing groups (e.g. carbonyl groups) in α-position often results in specific biological activities (e.g. anticonvulsant ii, insecticide iii and fibrosis inhibitor iv). For that reason, pyrroles were synthesized bearing all these functionalities. Pyrrolines xxiii were oxidized with DDQ to yield 2-cyanopyrroles xxvii. Attempts to hydrolyze the cyano function towards the corresponding carboxylic acid did not work out. Instead, the reaction with methyllithium and subsequent hydrolysis of the formed imine resulted in 2-acetylpyrrole xxxi. Also the polysubstituted pyrrole xxx was obtained by reaction of xxviiia with bromine.
Summary

\[ R^1 = C_6H_5 \]
\[ R^1 = 4-ClC_6H_4 \]

**va**

\[ R^1 = C_6H_5 \]
\[ R^1 = 4-ClC_6H_4 \]

**vb**

\[ \text{xxviii} (69\%) \]
\[ \text{xix} (68\%) \]
\[ \text{xx} (54\%) \]

**a)** 1) 1 equiv. NaBH₄, MeOH, 0°C, 2h. 2) excess aq. 1M NaOH, r.t., 15 min. **b)** 1) 2 equiv. DMF-HCl, 40-60°C, 20 min. 2) Cl₂-gas, DMF, CHCl₃, 40-70°C, 15 min. **c)** 2.5 to 4 equiv. R₂NH₂, 0.6 equiv. TiCl₄, Et₂O, 0°C to r.t., 15h. **d)** 1.1 equiv. KCN, MeOH, Δ, 4h. **e)** 1 equiv. dimethyl malonate, 0.05 equiv. piperidine, 0.03 equiv. HOAc, benzene, Δ, 20h. **f)** 1 equiv. Ph₃P=CHCOOEt, Et₂O, r.t., 6h. **g)** 6 equiv. Ph₃P, 3 equiv. CBr₄, CH₂Cl₂, 0°C to r.t., 4h. **h)** 1.1 equiv. DDQ, toluene, Δ, 3h. **i)** excess aq. 2M HCl/HOAc (1:1), r.t., 2h. **j)** 4 equiv. 2M NaOMe, MeOH, Δ, 2h. **k)** 1) 1.1 equiv. TCIA, CHCl₃/CH₃CN (1:1), Δ, 2h. 2) excess H₂O (workup). **l)** 1.2 equiv. POCl₃, DMF, CH₂Cl₂, 0°C, 5h. **m)** 1) 1 equiv. BuLi, THF, -78°C to 0°C, 10 min. 2) 3 equiv. ClCOOMe, THF, 0°C, 2h. **n)** 1 equiv. Br₂, 2 equiv. NaOAc, HOAc, Δ, 5h. **o)** 1) 1 equiv. MeLi, THF, r.t., 1h. 2) excess aq. 6M HCl, r.t., 2h.
When pyrrolines **xxiii** were treated with sodium methoxide as a base, pyrroles **xxv** were formed in good yields. Further transformation of pyrrole **xxva** towards methyl pyrrole-2-carboxylate **xxix** was accomplished via deprotonation of pyrrole **xxva** with BuLi and trapping of the anion with methyl chloroformate. Also a formylation was possible using DMF/POCl₃ resulting in 2-formylpyrrole **xxviii**. Besides the physiological interest of pyrroles **xxvii** and **xxviii**, they are also good substrates to synthesize 2-(hydroxymethyl)- (**xxxv**i) and 2-(aminomethyl)pyrroles (**xxxvi**), a class of compounds with current interest as physiologically active compounds, e.g. Viminol **xxxii**, a central analgesic and used for the treatment of drug dependency, DU 122290 **xxxiii**, an antipsychotic agent and FAUC 356 **xxxiv**, a selective dopamine D4 partial agonist, with potential for the treatment of ADHD. These compounds can also be used as building blocks for porphyrine analogues and related ‘pigments of life’.

![Chemical structures](image)

**xxxii** Viminol (central analgesic)  
**xxxiii** DU 122290 (antipsychotic agent)  
**xxxiv** FAUC 356 (dopamine D4 partial agonist)

Besides pyrroles **xxxv** and **xxxvi**, which were obtained by reduction of resp. 2-formylpyrrole **xxviii** and 2-cyanopyrrole **xxviia**, other pyrroles bearing methylene-spaced functional groups were synthesized using 5-(bromomethyl)pyrrolines **xxxvii** as starting material. Dichlorination of these compounds and subsequent reaction with sodium hydroxide, alkoxides or amines in the presence of K₂CO₃ yielded pyrroles **xxxix-xli** in good yields. Also, an Arbuzov reaction of 5-(bromomethyl)pyrrole **xxviiiib** with trimethyl phosphite in the presence of K₂CO₃ resulted in phosphonylated pyrrole **xlii**.

A second part of this PhD-thesis deals with the study of polyhalogenated cyclobutanones and the corresponding imines. Because a direct imination of 2,2-dichlorocyclobutanones **v** was not possible, the latter compounds were first dechlorinated using zinc in acetic acid. Imination of these cyclobutanones **xl** yielded imines **xliv**, which in turn, were chlorinated using NCS in CCl₄ towards **N**-(tetrachlorocyclobutylidene)-isopropylamines **xlvi**.
Having in hands these cyclobutylimines, reactions were performed to establish a synthesis of cis-substituted 3-arylcyclobutylamines xliv and xlvii. Substituted cyclobutylamines have attracted only limited attention in organic synthesis, despite the interesting anti-HIV properties of some cyclobutylamine derivatives.

The reaction of N-(3-aryl-2,2,4,4-tetrachlorocyclobutylidene)isopropylamines xlvi with sodium alkoxides resulted in a dehydrohalogenation and substitution of the remaining chloro atoms towards N-(trialkoxy)cyclobutenylidene)amines xlviii.
a) 4 equiv. Zn, HOAC, Δ, 5h. b) 4 equiv. R²NH₂, 0.6 equiv. TiCl₄, Et₂O, r.t., 14h. c) 1 equiv. LiAlH₄, Et₂O, r.t., 2h. d) 4.5 equiv. NCS, CCl₄, Δ, 30 min. e) 1 equiv. BH₃·SMe₂, THF, r.t., 3h. f) 4 equiv. 2-4M NaOR, ROH, Δ, 1h. g) excess aq. 2M HCl, CH₂Cl₂, Δ, 2h. h) excess HCl/HOAc (6:4), Δ, 2h. i) excess i-PrNH₂, r.t., 10 min. j) 4 equiv. RNH₂, 0.6 equiv. TiCl₄, Et₂O, -20°C to 0°C, 3h. k) 5 equiv. NCS, CCl₄, Δ, 30 min. l) 10 equiv. 4M NaOMe, MeOH, Δ, 1h. m) excess aq. 2M HCl, CH₂Cl₂, Δ, 1h.
Hydrolysis of the latter compounds xlviii yielded 3-substituted 4-arylcytclobutenediones xlix. With this new procedure for the synthesis of the cyclobutenedione skeleton, various derivatives were synthesized. Cyclobutenediones bearing alkoxy- or amino functionalities, often referred to as (semi)squarates or (semi)squaramides, are of renewed interest because of their wide diversity of physiological activities, e.g. the mycotoxin Moniliformin (lvii), dibutylsquarate lviii, used for the treatment of hair loss, semisquaramides lix and lx, a smooth muscle relaxant and antimigraine agent, resp. and EAA-090 (lxii), a neuroprotectant which can be used for the treatment of brain damage resulting from stroke.

With these interesting properties in mind, also 4-unsubstituted cyclobutenediones lvi were synthesized from the parent tetrachlorinated N-(cyclobutylidene)amines liv. Although the reaction by treatment with sodium methoxide proceeded via another mechanism as compared to the synthesis of xlix, different semisquaramides lvi were prepared via the procedure outlined above. A selective reduction of the α,β-unsaturated keto group of xlix with the use of zinc in acetic acid resulted in 4-hydroxy-2-cyclobutenones lxii. Reactions were performed to substitute the hydroxyl group (after tosylation) with N-nucleophiles towards cyclobutenones lxv. Unfortunately, the conversion of the formed 4-phthalimido- (lxva) and 4-azido-3-methoxy-2-phenyl-2-cyclobuten-1-one lxvb towards the corresponding free amine lxvi was not successful. Alkaline hydrolysis of the vinylogous ester lxviiia resulted in 3,4-dihydroxycyclobutenone lxiii. Via the same mechanism, treatment of lxviiia with isopropylamine yielded the corresponding vinylogous amide lxiv in good yield.

4-Hydroxy-3-alkoxy-2-cyclobutenones lxiii were acylated with different acid chlorides to yield new substituted cyclobutenones lxix. An evaluation of the reactivity of hydroxycyclobutenones lxii with electrophiles, in casu Br⁺ and Cl⁺, resulted in the synthesis of new furanones with an unusual substitution pattern. 4-Alkoxy-3-aryl-5-halo-2(5H)-furanones lxvii were synthesized from lxii via reaction with NBS or NCS in refluxing CCl₄.
a) 5 equiv. Zn, HOAc, r.t., 4h. b) 3 equiv. aq. 2M NaOH, MeOH, r.t., 4h. c) 2.1 equiv. i-PrNH₂, CH₂Cl₂, r.t., 4h. d) 1) 1.5 equiv. TosCl, 2 equiv. Ag₂O, 2 equiv. KI, CH₂Cl₂, 40°C, 45 min 2) 1 equiv. K-phthalimide or NaN₃, DMF, 50-60°C, 1h. e) 1 equiv. NXS, CCl₄, Δ, 1-2h. f) 3 equiv. MeLi, THF, -78°C, 15 min. g) 1 equiv. RCOCl, 1 equiv. Et₃N, CH₂Cl₂, 0°C, 2h. h) 1.5 equiv. Zn, HOAc, r.t., 2h. i) excess i-PrOH, r.t., 15h. j) 1 equiv. NaOR, ROH, r.t., 15h. k) excess i-PrNH₂, Δ, 12h. l) H₂ (4 bar), cat. Pd/C, THF, r.t., 15h.
These compounds were reduced with zinc in acetic acid towards dechlorinated furanones lxx, which in turn were hydrogenated to the corresponding new cis-dihydrofuranones lxxii. The reaction of lxvii with alkoxides resulted in a substitution of the chloro atom, yielding various new 4,5-dialkoxylated furanones lxxi. 5-Isopropoxy-4-methoxy-3-phenyl-2(5H)-furanone lxxiii was synthesized by simple treatment of lxviiib with isopropanol at room temperature. An analogous reaction of 4,5-dimethoxyfuranone lxxia with isopropylamine only resulted in a nucleophilic addition and subsequent elimination of methanol towards 4-isopropylamino-5-methoxyfuranone lxxiv.

In a third part of this thesis, new entries towards cyclopropenones were evaluated via dihalocarbene additions to selected olefins. Cyclopropenones bearing electron withdrawing groups, such as carboxylates are never synthesized before. Unfortunately, none of the performed reactions yielded cyclopropanes, as useful intermediates for the synthesis of new substituted cyclopropenones. Another approach towards these cyclopropenones via ring closure of suitably substituted α,α-dihaloketones also gave no results and further efforts to access these compounds were cancelled after the publication of analogous results by another research group during the course of this evaluation study.

A last topic deals with the alkylation of cyclobutanone liii with long-chain hydrocarbons. 2-Alkyl-, 2-(5-tetradecen-1-yl)- and 2-(5,8-tetradecadien-1-yl)cyclobutanones are compounds that are formed during the γ-irradiation of fatty foodstuffs. Ionizing radiation (γ-irradiation) for the disinfection and preservation of foods is not generally accepted and allowed. For that reason, it is of importance to rely on techniques that can detect whether foodstuffs are irradiated or not. One of these methodologies is the detection of 2-substituted cyclobutanones as markers for food-irradiation. Unfortunately, there exist no straightforward syntheses for these compounds, which are used as standards for food analysis. In this work, 2-alkycyclobutanones lxxvi were synthesized via deprotonation of N-(cyclobutylidene)-isopropylamine liiib and subsequent reaction with alkyl halides to yield the desired 2-alkycyclobutanones lxxvi. For the synthesis of (5Z,8Z)-2-(5,8-tetradecadien-1-yl)cyclobutanone lxxxiv, (5Z,8Z)-1-bromo-5,8-tetradecadiene lxxxi was synthesized via a Cu(I) catalyzed coupling of alkynes lxxvii and lxxviii, partial hydrogenation of the triple bonds of lxxix to lxxx and conversion of the hydroxyl moiety to the corresponding bromide. This bromide was used in the synthesis of 2-substituted cyclobutanone lxxxiv.
In this way, different cyclobutanones are made accessible via a short and efficient synthetic pathway. It should be emphasized that the synthesis of the unsaturated analogue **lxxiv** proceeds stereoselective to only the (5'Z,8'Z)-isomer, in contrast to earlier reported synthetic pathways.
In conclusion, cyclobutanones were used as starting material for the synthesis of a variety of physiologically promising new aza-heterocyclic compounds, \textit{i.e.} 15 new pyrrolinones, 6 new pyrrolines, 3 new pyrroolidinones and 26 new pyrroles. In addition, a novel synthetic pathway was developed towards cyclobutenediones, an intriguing class of small ring carbocycles with renewed interest in agrochemistry and pharmacology. A reactivity study of halogenated $N$-(cyclobutylidene)amines gave rise to 29 new cyclobutenones and cyclobutenediones and 15 new dihydrofuranones and 2(5$H$)-furanones with remarkable substitution patterns. In the framework of this small ring chemistry, efforts were also made to synthesize new cyclopropenones, however without success. In the last part of this thesis, a new synthetic pathway was developed to 2-substituted cyclobutanones as markers for $\gamma$-irradiated foodstuffs. In total, 145 new compounds were synthesized and completely characterized.
VI SAMENVATTING

Het hoofddoel van dit doctoraatswerk behelst de evaluatie van gehalogeneerde cyclobutanonen als bouwstenen voor de verdere synthese van fysiologisch interessante carbocyclische en heterocyclische verbindingen. Aza-heterocyclische verbindingen spelen een uiterst belangrijke rol in de zoektocht naar nieuwe biologisch actieve verbindingen, wat weerspiegeld wordt in de vele toepassingen van deze verbindingen in de agrochemische en farmaceutische sector. Ook de studie van microcyclische verbindingen, zoals cyclopropanen, cyclobutanen en cyclobutenen, is wegens hun specifieke reactiviteit al zeer waardevol gebleken voor de ontwikkeling van nieuwe fysiologisch actieve verbindingen. Naast het nut van deze microcyclische verbindingen als intermediairen in de synthetische organische chemie, vertonen tal van kleine carbocyclische verbindingen interessante fysiologische activiteiten.

In een eerste deel werden nieuwe synthesewegen ontwikkeld tot gesubstitueerde pyrrolen. Vooral 3-arylpyrrolen en 3-gehalogeneerde pyrrolen zijn zeer gegeerde verbindingen omwille van de beschikbaarheid van slechts enkele synthesewegen voor deze klasse verbindingen en omwille van hun unieke fysiologische eigenschappen, bijvoorbeeld Pyrrolnitrin \( \text{(i, fungicide)} \), AWD 140-190 \( \text{(ii, anticonvulsief)} \), Pirate\(^\circ\) \( \text{(iii, insecticide)} \) en 2-arylpyrrool \( \text{iv, een fibrose inhibitor} \).

\[
\begin{align*}
\text{i) Pyrrolnitrin (fungicide)} & \qquad \text{ii) AWD 140-190 (anticonvulsief)} & \qquad \text{iii) Pirate\(^\circ\) (insecticide)} & \qquad \text{iv) (fibrose inhibitor)}
\end{align*}
\]

2,2-Dichloorcyclobutanonen \( \text{v, die eenvoudig te bereiden zijn via een [2+2]-cycloadditie van digehalogeneerde ketenen aan gesubstitueerde styrenen, werden behandeld met primaire aminen om een ring opening te bewerkstelligen tot dichloorbutaanamiden vi. Reactie van deze laatste met base, } \text{in casu}, \text{ natrium methoxide, resulteerde in 4-methoxybutaanamiden vii, die op hun beurt aanleiding gaven tot een zuur-geïnduceerde ringsluiting met vorming van 3-pyrrolinonen viii. Naast tal van fysiologische activiteiten}
\]
geassocieerd met deze klasse van verbindingen, zijn 3-pyrrolinonen waardevolle bouwstenen voor verdere transformaties naar andere azaheterocyclische vijfringen. In dit opzicht, werd 3-pyrrolinon \textit{viiia} behandeld met verschillende reductantia om een nieuwe syntheseweg naar pyrrolen te bewerkstelligen. Verrassend genoeg bleek enkel de reductie van \textit{viiia} met 9-BBN aanleiding te geven tot pyrrool \textit{xi} in aanvaardbare rendementen, terwijl reactie met LiAlH₄, NaBH₄ of boraan geen bevredigend resultaat opleverde. Om de algemeenheid van deze procedure te evalueren werden 3-pyrrolinonen gesynthetiseerd met een diversiteit aan substituenten. 3,4-Digesubstitueerde pyrrolinonen \textit{ix} werden bekomen door alkylering van pyrrolinonen \textit{viii} en werden vervolgens behandeld met 9-BBN wat resulteerde in nieuwe pyrrolen \textit{x}. Andere 3-pyrrolinonen \textit{xv} werden gesynthetiseerd via geoptimaliseerde en gewijzigde reeds beschreven procedures.

\textbf{Schema 1}

- \textit{a)} 2 equiv. R²NH₂, Et₂O, k.t., 4-8h.
- \textit{b)} 4 equiv. 4M NaOMe in MeOH, Δ, 2h.
- \textit{c)} overmaat aq. 2M HCl, Δ, 2h.
- \textit{d)} 1) 1.05 equiv. LDA, THF, -78°C tot 0°C, 45 min. 2) 1 equiv. R³I of R³Br, THF, -78°C tot k.t., 6h.
- \textit{e)} 3 equiv. 9-BBN, tolueen, Δ, 15h.

\begin{align*}
\text{\textit{viiia} } & R¹ = H, R² = i\text{-Pr} (70\%) \\
\text{\textit{viiib} } & R¹ = Cl, R² = i\text{-Pr} (56\%) \\
\text{\textit{viiic} } & R¹ = H, R² = Bn (58\%) \\
\text{\textit{viiid} } & R¹ = Cl, R² = i\text{-Pr}, R³ = Bn (57\%) \\
\text{\textit{viia} } & R¹ = H, R² = i\text{-Pr} (69\%) \\
\text{\textit{viib} } & R¹ = Cl, R² = i\text{-Pr} (57\%) \\
\text{\textit{viic} } & R¹ = H, R² = Bn (60\%) \\
\text{\textit{viid} } & R¹ = Cl, R² = i\text{-Pr}, R³ = Bn (57\%) \\
\text{\textit{ixa} } & R¹ = H, R² = i\text{-Pr}, R³ = Et (50\%) \\
\text{\textit{ixb} } & R¹ = H, R² = i\text{-Pr}, R³ = n\text{-Pr} (46\%) \\
\text{\textit{ixc} } & R¹ = H, R² = Bn, R³ = Et (53\%) \\
\text{\textit{ixd} } & R¹ = Cl, R² = i\text{-Pr}, R³ = Bn (57\%) \\
\text{\textit{xi} } & (40\%)
\end{align*}
Reactie van fenylaceton xii met N-gesubsitueerde 2-chlooraceetamiden resulteerde in de vorming van γ-ketoamiden xiii die door behandeling met zuur cycliseerden tot 3-pyrrolinonen xva-c. Deze nieuwe verbindingen en N-methylpyrrolinonen xvd-g, gesynthetiseerd volgens geoptimaliseerde gekende procedures, werden eveneens behandeld met 9-BBN in tolueen onder reflux om zodoende een diversiteit aan pyrrolen xvi te synthetiseren. Ook succinimide xivb werd behandeld met 9-BBN resulterend in pyrool xvid, wat een uitbreiding van deze methode inhoudt.

\[
\text{xiiia } R^1 = C_6H_4 \\
\text{xiiib } R^1 = 4\text{-MeOC}_6H_4
\]

\[
\begin{align*}
\text{xiiia } R^1 & = C_6H_4, R^2 = n\text{-Pr (not isolated)} \\
\text{xiiib } R^1 & = C_6H_4, R^2 = i\text{-Pr (69\%)} \\
\text{xiiic } R^1 & = 4\text{-MeOC}_6H_4, R^2 = i\text{-Pr (72\%)}
\end{align*}
\]

\[
\begin{align*}
\text{xiva } R^1 & = R^2 = CH_3 \\
\text{xivb } R^1 & = C_6H_5, R^2 = CH_3
\end{align*}
\]

d)

\[
\begin{align*}
\text{xiva } R^1 & = C_6H_5, R^2 = n\text{-Pr, } R^3 = CH_3, R^4 = H (54\%) \\
\text{xivb } R^1 & = C_6H_5, R^2 = i\text{-Pr, } R^3 = CH_3, R^4 = H (52\%) \\
\text{xivc } R^1 & = 4\text{-MeOC}_6H_4, R^2 = i\text{-Pr, } R^3 = CH_3, R^4 = H (54\%) \\
\text{xvda } R^1 & = C_6H_5, R^2 = CH_3, R^3 = H, R^4 = H (41\%) \\
\text{xve } R^1 & = H, R^2 = CH_3, R^3 = H, R^4 = C_6H_5 (29\%) \\
\text{xvfb } R^1 & = CH_3, R^2 = CH_3, R^3 = H, R^4 = H (39\%) \\
\text{xvfg } R^1 & = H, R^2 = CH_3, R^3 = H, R^4 = CH_3 (32\%)
\end{align*}
\]

e)

\[
\begin{align*}
\text{xiva } R^1 & = C_6H_5, R^2 = n\text{-Pr, } R^3 = CH_3, R^4 = H (54\%) \\
\text{xivb } R^1 & = C_6H_5, R^2 = i\text{-Pr, } R^3 = CH_3, R^4 = H (52\%) \\
\text{xivc } R^1 & = 4\text{-MeOC}_6H_4, R^2 = i\text{-Pr, } R^3 = CH_3, R^4 = H (54\%) \\
\text{xvda } R^1 & = C_6H_5, R^2 = CH_3, R^3 = H, R^4 = H (48\%-55\%) \\
\text{xvfb } R^1 & = CH_3, R^2 = CH_3, R^3 = H, R^4 = H (12\%-15\%)
\end{align*}
\]

\[
\begin{align*}
\text{a) } & 1 \text{ equiv. } N\text{-isopropyl- of } N\text{-propylchlooracetamide, } 1.1 \text{ equiv. } t\text{-BuOK, DMSO, } 80^\circ C, 3h. \\
\text{b) } & \text{kat. } H_2SO_4, CH_2Cl_2, \Delta, 2h. \text{ c) } 1) 10 \text{ equiv. NaBH}_4, \text{EtOH/HCl, } 0^\circ C, 6h. 2) \text{overmaat HOAc, } \Delta, 24h. \text{ d) } 3 \text{ equiv. 9-BBN, toluuen, } \Delta, 15h. \text{ e) } 4 \text{ equiv. 9-BBN, toluuen, } \Delta, 15h.
\end{align*}
\]
In een tweede strategie om gesubstitueerde pyrrolen te bekomen, werden 3-aryl-2,2-dichlorocyclobutanonen \( \text{v} \) gereduceerd met natriumboorhydride om een ringcontractie tot cyclopropanen \( \text{xvii} \) te bewerkstelligen. Deze nieuwe \( \text{cis}-2\text{-aryl}-1\text{-chloorcyclopropa-} \text{carbaldehyden} \( \text{xvii} \) werden gebruikt als startproduct voor de synthese van verschillende gesubstitueerde azaheterocyclische verbindingen. Cyclopropanen \( \text{xvii} \) werden initieel aanzien als goede precursoren voor de synthese van nieuwe cyclopropenen, maar verschillende reacties met basen om een dehydrochlorering te bewerkstelligen resulteerde niet in de beoogde cyclopropenen. Andere reacties ter transformatie van de aldehydefunctie van \( \text{xvii} \) resulteerde in nieuwe cyclopropanen \( \text{xviii-xx} \) via Wittig en Knoevenagel reacties. Analoge cyclopropanen werden recent gepatenteerd omwille van hun insecticide activiteit.

Voor de ontwikkeling van een nieuwe route naar gehalogeneerde pyrrolen, werden cyclopropaancarbaldehyden in een eerste stap omgezet tot butanalen \( \text{xxi} \) via een tandem ringopening en chloorering door reactie met DMF-HCl en chloorgas. Vervolgens werden de bekomen \( \alpha,\alpha,\gamma\)-trichloorbutanalen \( \text{xxi} \) behandeld met aminen in aanwezigheid van titanium(IV)chloride, wat dienst doet als activator en dehydraterend agens, resulterend in overeenkomstige iminen \( \text{xxii} \) die onstabil waren bij kamertemperatuur en direct gebruikt werden in volgende reacties. Via een cyanide-geïnduceerde ringsluiting van iminen \( \text{xxii} \), werden nieuwe 2-pyrrolinen \( \text{xxiii} \) gesynthetiseerd. Een reactiviteitstudie van deze interessante verbindingen resulteerde in de ontwikkeling van nieuwe toetredingen tot pyrrolidinonen \( \text{xxiv} \) en \( \text{xxvi} \) (via reactie met aq. HCl of trichloorisocyanuuruurzuur (TCIA), resp.) en verschillende nieuwe pyrrolen \( \text{xxv} \) en \( \text{xxvii} \) (via reactie met base of DDQ, resp.) met specifieke substitutiepatronen. Vele pyrrolen met halogenen op de 3-plaats of aryl groepen of elektronenzuigende groepen, zoals esters, op de 2-plaats vertonen specifieke biologische activiteiten, bijvoorbeeld Pyrrolnitrin \( \text{(i), fungicide}, \text{AWD-190 (ii, anticonvulsief), } \text{Pirate}\textsuperscript{®} (\text{iii, insecticide}) \text{ en pyrrool iv, een fibrose inhibitor. Omwille van deze interessante eigenschappen werden verschillende pyrrolen gesynthetiseerd die deze kenmerkende substitutiepatronen bezitten of combineren. Pyrrolinen } \text{xxiii} \text{ werden geoxideerd met DDQ tot 2-cyaanpyrro-} \text{len } \text{xxvii}. \text{ Pogingen om de cyaanfunctie te hydrolyseren tot het overeenkomstige carbonzuur faalden, zodat werd overgegaan tot synthese van analoge 2-acylpyrro-} \text{len } \text{xxviii, xxix en xxx. Behandeling van } \text{xxviia} \text{ met MeLi en daaropvolgende hydrolyse van het gevormde imine leverde 2-acetylpyrrool } \text{xxxi}. \text{ Ook de reactie van } \text{xxviia} \text{ met broom resulteerde in het interessante polygesubstitueerd pyrrool } \text{xxx}. \text{ Wanneer pyrrolinen } \text{xxiii} \text{ werden behandeld met natriummethoxide als base, werden pyrrolen } \text{xxv} \text{ in goede rendementen gevormd.}
Samenvatting

\[ \text{OClClR}_1 \text{R}_1 \text{Cl} \text{O} \text{H} \]

\[ \text{Cl H Cl H Cl H} \]

\[ \text{R}_1 \text{HOClCl} \text{R}_1 \text{H} \]

\[ \text{N Cl ClCl R}_2 \text{N} \text{R}_2 \text{CN Cl} \]

\[ \text{N Cl} \text{Ph N OPh} \]

\[ \text{Br Br O} \text{OEt} \text{MeOOC COOMe} \]

\[ \text{Ph Ph Ph} \]

\[ \text{R}_1 \text{H}, \text{R}_2 \text{i-Pr} (58\%) \]

\[ \text{xxiia} \]

\[ \text{xxiib} \]

\[ \text{xxiic} \]

\[ \text{xxviiia} \]

\[ \text{xxviiib} \]

\[ \text{xxviiic} \]

\[ \text{xxv} \]

\[ \text{xxiv} \]

\[ \text{xxv} \]

\[ \text{xxvi} \]

\[ \text{xxvii} \]

\[ \text{xxviii} \]

\[ \text{xxix} \]

\[ \text{xxx} \]

\[ \text{xxxi} \]

\[ \text{a) 1) 1 equiv. NaBH}_4, \text{MeOH, 0°C, 2h. 2) overmaat aq. 1M NaOH, k.t., 15 min. b) 1) 2 equiv. DMF-HCl, 40-60°C, 20 min. 2) Cl}_2\text{-gas, DMF, CHCl}_3, 40-70°C, 15 min. c) 2.5 tot 4 equiv. R}_2\text{NH}_2, 0.6 equiv. TiCl}_4, \text{Et}_2\text{O, 0°C tot k.t., 15h. d) 1.1 equiv. KCN, MeOH, Δ, 4h. e) 1 equiv. dimethylmalonaat, 0.05 equiv. piperidine, 0.03 equiv. HOAc, benzene, Δ, 20h. f) 1 equiv. Ph}_3\text{P=CHCOOEt, Et}_2\text{O, k.t., 6h. g) 6 equiv. Ph}_3\text{P, 3 equiv. CBr}_4, \text{CH}_2\text{Cl}_2, 0°C tot k.t., 4h. h) 1.1 equiv. DDQ, toluen, Δ, 3h. i) overmaat aq. 2M HCl/HOAc (1:1), k.t., 2h. j) 4 equiv. 2M NaOMe, MeOH, Δ, 2h. k) 1) 1.1 equiv. TCIA, CHCl}_3/CH}_2\text{CN (1:1), Δ, 2h. 2) overmaat H}_2\text{O (opwerking). l) 1.2 equiv. POCl}_3, \text{DMF, CH}_2\text{Cl}_2, 0°C, 5h. m) 1) 1 equiv. BuLi, THF, -78°C tot 0°C, 10 min. 2) 3 equiv. CICOOME, THF, 0°C, 2h. n) 1 equiv. Br}_2, 2 equiv. NaOAc, HOAc, Δ, 5h. o) 1) 1 equiv. MeLi, THF, k.t., 1h. 2) overmaat aq. 6M HCl, k.t., 2h.} \]
Een verdere transformatie naar methyl-(2-pyrrool)carboxylaat **xxix** werd bekomen door deprotonering van **xxva** met BuLi en daaropvolgende reactie met methylchloroformiaat. Ook de formylering van pyrrool **xxva** door reactie met Vilsmeier reagens POCl₃/DMF werd gerealiseerd. Beide pyrrolen **xxviii** en **xxvii** zijn goede precursoren voor de synthese van 2-(hydroxymethyl)- (**xxxv**) en 2-(aminomethyl)pyrrolen **xxxvi**, klassen verbindingen die nog steeds in de belangstelling staan als fysiologisch actieve verbindingen, bijvoorbeeld Viminol (**xxxii**, centraal analgesicum), DU 122290 (**xxxiii**, antipsychoticum) en FAUC 356 (**xxxiv**, een dopamine D4 partiële agonist wat toekomst heeft als potentiële behandeling voor ADHD). 2-(Hydroxymethyl)- en 2-(aminomethyl)pyrrolen kunnen eveneens gebruikt worden als bouwstenen voor de synthese van porfyrine-analogen en andere ‘pigmenten des levens’.

![Chemical structures](image)

**xxxii** Viminol (centraal analgesicum)  
**xxxiii** DU 122290 (antipsychoticum)  
**xxxiv** FAUC 356 (partiële dopamine D4 agonist)

Naast pyrrolen **xxxv** en **xxxvi**, die bekomen werden door reductie van resp. **xxviii** en **xxviiia**, werden ook andere pyrrolen met 2-(alkoxymethyl)- en 2-(aminomethyl)groepen gesynthetiseerd uitgaande van 5-(broommethyl)-1-pyrrolinen **xxxvii**. Dichloorering van deze laatste resulteerde in pyrrolinen **xxxviii**, die op hun beurt behandeld werden met alkoxiden of met aminen in de aanwezigheid van K₂CO₃ resulterend in pyrrolen **xxxix-xli**. Ook een Arbusov-reactie van pyrroline **xxxviiiib** met trimethylfosfiet in aanwezigheid van K₂CO₃ resulteerde in perylolmethylfosfonaat **xlii**.

Een tweede deel van dit doctoraatswerk handelt over de reactiviteit van polygehalogeneerde cyclobutanonen en de overeenkomstige iminen. Omdat een rechtstreekse iminering van 2,2-dichloorcyclobutanonen **v** geen resultaat opleverde werden deze laatste eerst gedechloroerd door reactie met zink in azijnzuur. Een daaropvolgende iminering van cyclobutanonen **xliii** leverde wel **N-(cyclobutylideen)aminen xlv** op die op hun beurt gechloreerd werden met NCS in CCl₄ naar **N-(3-aryl-2,2,4,4-tetrachloorcyclobutylideen)-isopropylaminen xlv**.
Gehalogueerde en niet gehalogueerde iminen xlv en xlvii werden gereduceerd tot cyclobutylaminen xlv en xlvii, een klasse verbindingen die nog weinig bestudeerd is, niettegenstaande de interessante anti-HIV activiteiten van N-cyclobutyladenine derivaten.

De reactie van N-(3-aryl-2,2,4,4-tetrachloercyclobutyleen)isopropylaminen xlvii met natriumalkoxiden resulteerde in een initiële dehydrochlorering en daaropvolgende substitutie van de resterende chlooratomen door de respectievelijke alkoxiden wat N-(2,4,4-trialkoxy-2-cyclobutenyleen)aminen xlviii opleverde. Hydrolyse van deze laatste verbindingen leverde 3-gesubstitueerde 4-arylcyclobuteendionen xlix op. Met deze nieuwe procedure voor de synthese van het cyclobuteendion-skelet werden verschillende derivaten gesynthetiseerd.
Samenvatting

va, b  
\[
\begin{align*}
\text{xliia} & : R^1 = H (84\%) \\
\text{xliib} & : R^1 = Cl (89\%)
\end{align*}
\]

\[
\begin{align*}
\text{xliva} & : R^1 = H, R^2 = i-Pr (81\%) \\
\text{xlivb} & : R^1 = H, R^2 = Bn (74\%) \\
\text{xlvic} & : R^1 = Cl, R^2 = i-Pr (82\%)
\end{align*}
\]

\[
\begin{align*}
\text{xlvii} & : R^1 = H, R^2 = Bn (71\%) \\
\text{xlvib} & : R^1 = H, R^2 = i-Pr (58\%)
\end{align*}
\]

\[
\begin{align*}
\text{xlviiia} & : R^1 = H, R^2 = Me (88\%) \\
\text{xlviiib} & : R^1 = H, R^2 = Et (66\%) \\
\text{xlviiic} & : R^1 = H, R^2 = i-Pr (37\%)
\end{align*}
\]

\[
\begin{align*}
\text{xlviiid} & : R^1 = Cl, R^2 = Me (79\%) \\
\text{xlvie} & : R^1 = Cl, R^2 = i-Pr (58\%)
\end{align*}
\]

\[
\begin{align*}
\text{xlixa} & : R^1 = H, R^2 = Me (72\%) \\
\text{xlixb} & : R^1 = H, R^2 = Et (73\%) \\
\text{xlixc} & : R^1 = H, R^2 = i-Pr (60\%)
\end{align*}
\]

\[
\begin{align*}
\text{xlixd} & : R^1 = Cl, R^2 = Me (78\%) \\
\text{xlixe} & : R^1 = Cl, R^2 = i-Pr (58\%)
\end{align*}
\]

\[
\begin{align*}
\text{lii} & : R = n-Pr (n.i.) \\
\text{liib} & : R = i-Pr (78\%) \\
\text{liic} & : R = i-Bu (n.i.) \\
\text{liid} & : R = sec-Bu (73\%) \\
\text{liie} & : R = t-Bu (80\%)
\end{align*}
\]

\[
\begin{align*}
\text{liiva} & : R = n-Pr (n.i.) \\
\text{liivb} & : R = i-Pr (78\%) \\
\text{liivc} & : R = i-Bu (n.i.) \\
\text{liivd} & : R = sec-Bu (88\%) \\
\text{liive} & : R = t-Bu (90\%)
\end{align*}
\]

\[
\begin{align*}
\text{lviva} & : R = n-Pr (n.i.) \\
\text{lvivb} & : R = i-Pr (54\%) \\
\text{lvivc} & : R = i-Bu (n.i.) \\
\text{lvivd} & : R = sec-Bu (61\%) \\
\text{lvive} & : R = t-Bu (64\%)
\end{align*}
\]

\[
\begin{align*}
\text{li} & : R = n-Pr (n.i.) \\
\text{liib} & : R = i-Pr (78\%) \\
\text{liic} & : R = i-Bu (n.i.) \\
\text{liid} & : R = sec-Bu (88\%) \\
\text{liie} & : R = t-Bu (90\%)
\end{align*}
\]

\[
\begin{align*}
\text{liiva} & : R = n-Pr (n.i.) \\
\text{liivb} & : R = i-Pr (54\%) \\
\text{liivc} & : R = i-Bu (n.i.) \\
\text{liivd} & : R = sec-Bu (61\%) \\
\text{liive} & : R = t-Bu (64\%)
\end{align*}
\]

\[
\begin{align*}
\text{lii} & : R = n-Pr (n.i.) \\
\text{liib} & : R = i-Pr (54\%) \\
\text{liic} & : R = i-Bu (n.i.) \\
\text{liid} & : R = sec-Bu (61\%) \\
\text{liie} & : R = t-Bu (64\%)
\end{align*}
\]

\[
\begin{align*}
\text{liiia} & : R = n-Pr (n.i.) \\
\text{liiib} & : R = i-Pr (78\%) \\
\text{liiic} & : R = i-Bu (n.i.) \\
\text{liiie} & : R = sec-Bu (73\%) \\
\text{liiie} & : R = t-Bu (80\%)
\end{align*}
\]

a) 4 equiv. Zn, HOAc, Δ, 5h. b) 4 equiv. R₂NH₂, 0.6 equiv. TiCl₄, Et₂O, k.t., 14h. c) 1 equiv. LiAlH₄, Et₂O, k.t., 2h. d) 4.5 equiv. NCS, CCl₄, Δ, 30 min. e) 1 equiv. BH₃·SMe₂, THF, k.t., 3h. f) 4 equiv. 2-4M NaOR, ROH, Δ, 1h. g) overmaat aq. 2M HCl, CH₂Cl₂, Δ, 2h. h) overmaat HCl/HOAc (6:4), Δ, 2h. i) overmaat i-PrNH₂, r.t., 10 min. j) 4 equiv. RNH₂, 0.6 equiv. TiCl₄, Et₂O, -20°C tot 0°C, 3h. k) 5 equiv. NCS, CCl₄, Δ, 30 min. l) 10 equiv. 4M NaOMe, MeOH, Δ, 1h. m) overmaat aq. 2M HCl, CH₂Cl₂, Δ, 1h.
Cyclobutanonen gesubstitueerd met alkoxy- of aminogroepen, ook (semi)squaraten en (semi)squaramiden genoemd, zijn recent weer in de belangstelling gekomen door de brede waaier fysiologische activiteiten die geassocieerd is met deze klasse verbindingen, bijvoorbeeld Moniliformin **lvii**, een mycotoxine geïsoleerd uit *Fusarium moniliforme*, dibutylsquaraat **lviii**, gebruikt voor de behandeling van haaruitval, semisquaramiden **lix** en **lx**, respectievelijk een relaxant voor zacht spierweefsel en antimigraine agens, en EAA-090 **lx**i, een neuroprotector dat kan gebruikt worden om hersenbeschadiging tegen te gaan na een hartaanval.

**Deze biologische activiteiten indachtig,** werden eveneens verschillende cyclobuteendionen zonder substituent op C-4 gesynthetiseerd vertrekkende van *N*-(tetrachloorcyclobutylideen)aminen **liv**. Hoewel behandeling van deze laatste met NaOMe niet resulteerde in eenzelfde reactieverloop als bij de reactie van **xlvi** met NaOMe, werden toch verschillende cyclobuteendionen **lvi** bekomen na hydrolyse van 4,4-dimethoxycyclobutenonen **lv**.

Een selectieve reductie van het α,β-onverzadigd keton in **xlx** was mogelijk door reactie met zink in azijnzuur en leverde nieuwe 4-hydroxycyclobutenonen **lx**ii op. Pogingen werden ondernomen om de gevormde hydroxylgroep te substitueren met *N*-nucleofielen na tosylering. Hoewel deze substitutie uiteindelijk toch verbindingen **lxv** opleverde, was de daaropvolgende conversie van **lxv** naar het vrije amine **lxvi** niet mogelijk.

Een basische hydrolyse van 3-methoxycyclobutenon **lx**iia leverde 3,4-dihydroxycyclobutenon **lx**iii en volgens een analoog reactieverloop werd 3-(isopropylamino)cyclobutenon **lx**iv gesynthetiseerd door reactie van **lx**iia met isopropylamine. 4-Hydroxycyclobutenonen **lx**ii werden eveneens geacyleerd teneinde nieuwe derivaten **lxix** te synthetiseren. In een verdere evaluatie van de reactiviteit van hydroxycyclobutenonen **lx**ii met elektrofielen, *in casu* Br⁺ en Cl⁺, werden nieuwe furanon met een ongewoon substitutiepatroon ter beschikking gesteld.
a) 5 equiv. Zn, HOAc, k.t., 4h. b) 3 equiv. aq. 2M NaOH, MeOH, k.t., 4h. c) 2.1 equiv. i-PrNH₂, CH₂Cl₂, k.t., 4h. d) 1) 1.5 equiv. TosCl, 2 equiv. Ag₂O, 2 equiv. KI, CH₂Cl₂, 40°C, 45 min 2) 1.1 equiv. K-itaalimide of NaN₃, DMF, 50-60°C, 1h. e) 1.1 equiv. NXS, CCl₄, D, 1-2h. f) 3 equiv. MeLi, THF, -78°C, 15 min. g) 1 equiv. RCOCl, 1 equiv. Et₃N, CH₂Cl₂, 0°C, 2h. h) 1.5 equiv. Zn, HOAc, k.t., 2h. i) overmaat i-PrOH, k.t., 15h. j) 1 equiv. NaOR, ROH, k.t., 15h. k) overmaat i-PrNH₂, Δ, 12h. l) H₂ (4 bar), cat. Pd/C, THF, k.t., 15h.
4-Alkoxy-3-aryl-5-chloor-2(5\text{H})-furanonen \text{lxvii} werden bekomen door ringexpansie van 4-hydroxycyclobutanonen \text{lxii} onder invloed van NCS. Deze merkwaardige verbindingen konden gedechloreerd worden naar furanonen \text{lx} door reactie met zink en werden verder gehydrogeneerd naar nieuwe \text{cis}-dihydrofuranonen \text{lxii}. Reacties van \text{lxvii} met alkoxiden resulteerde in een substitutie van het chlooratoom met vorming van dialkoxyfuranonen \text{lx}. Op analoge wijze gaf de reactie van \text{lxviib} met isopropanol 5-isopropoxy-4-methoxyfuranon \text{lxxiii}. Behandeling van 4,5-dimethoxyfuranone \text{lxxia} met isopropylamine resulteerde in 4-isopropylamino-5-methoxyfuranon \text{lxxiv}.

In een derde deel werden nieuwe toetredingen geëvalueerd naar cyclopropenonen via dihalogeencarbeen addities aan geselecteerde olefienen. Cyclopropenonen gesubsitueerd met elektronenzuigende groepen (zoals een carbonylgroep) werden nog nooit gesynthetiseerd en vormen een intrigerende nieuwe klasse van microcyclische verbindingen. Geen enkele van de uitgevoerde reactie leverde echter cyclopropanen op als intermediairen voor de synthese van nieuwe cyclopropenonen. In een andere strategie werden \text{a,a'}-dihalogeenketonen, en derivaten daarvan, gebruikt om via ringsluiting cyclopropenonen te bekomen. Omdat in de loop van dit onderzoek analoge resultaten werden gepubliceerd door een andere onderzoeksgroep werden verdere reacties gestaakt.

Het laatste hoofdstuk van dit doctoraatswerk handelt over de alkylering van cyclobutanon \text{lii} met lineaire alkanen en alkenen. 2-Alkyl-, 2-(5-tetradecen-1-yl)- en 2-(5,8-tetradecadien-1-yl)cyclobutanonen zijn verbindingen die gevormd worden gedurende de bestraling van voedingsmiddelen met \text{γ}-stralen. Het gebruik van ioniserende stralen voor de desinfectie en als conserveringsmethode voor voedingsmiddelen is niet overal toegelaten. Omwille van deze reden is het van belang om te beschikken over technieken waarmee kan nagegaan worden indien voeding bestraald werd of niet. Een van deze methoden is de detectie van 2-gesubstitueerde cyclobutanonen als merkstoffen voor \text{γ}-bestraling. Merkwaardig genoeg bestaat tot nog toe geen algemene en efficiënte methode om deze verbindingen te synthetiseren zodat deze kunnen gebruikt worden als standaardmateriaal voor analyses. Vanwege de industriële vraag naar deze verbindingen werd een efficiënte methode ontwikkeld om 2-gesubstitueerde cyclobutanonen gemakkelijker toegankelijk te maken.

In de uitgewerkte strategie werden 2-hexyl- (\text{lxxvia}) en 2-decycyclobutanon \text{lxxvib} gesynthetiseerd via deprotonering van imine \text{liiiib} en daaropvolgende reactie met de respectievelijke alkylbromiden. Voor de synthese van 2-(5,8-tetradecadien-1-yl)cyclobutanon \text{lxxxiv}, werd eerst een synthese bewerkstelligd van het corresponderende alkadienylbromide.
als alkyleringsreagens. 5,8-Tetradecadiyn-1-ol werd gesynthetiseerd via een Cu(I)
gekatalyseerde koppeling van alkynen en. Een daaropvolgende partiële
hydrogenering resulteerde in tetradecadiënom, waarbij dient benadrukt te worden dat op
deze wijze enkel het (5Z,8Z)-isomeer werd gevormd, in tegenstelling tot andere
gerapporteerde synthesen waarbij steeds een chromatografische scheiding nodig was van
verschillende isomeren. Functionele groep transformatie van alcohol naar (5Z,8Z)-5,8-
tetradecadien-1-ylbromide werd verwezenlijkt door reactie met trifenylfosfine en CBr₄.
Dit bromide werd vervolgens gebruikt voor de alkylering van cyclobutanon, analoog aan de
synthesen van en.
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