Syntheses of 3-, 4- and 5-Membered Carbocycles - New Methodology on Old Methods

Synteser av 3-, 4- og 5-rings karbosykler - ny metodologi på gamle metoder

Philosophiae Doctor (PhD) Thesis

Runa Berg Østby

Department of Chemistry, Biotechnology and Food Science
Faculty of Veterinary Medicine and Bioscience
Norwegian University of Life Sciences

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AIMS OF THE STUDY

The three smallest carbocyclic rings, cyclopropane, cyclobutane and cyclopentane, are recognized as substructures of many biologically active, synthetically challenging natural products. They are also important as intermediates in organic synthesis, and new methods of preparation of these cyclic compounds are still in demand.

The unifying objective of this thesis was to use new methodology in order to improve old methods for the synthesis of 3-, 4- and 5-membered cyclic compounds.

The thesis involves the following partial objectives:

1. To use flow chemistry in a microreactor in order to prepare different *gem*-dibromocyclopropanes by using a well-established method (dihalocyclopropanation under phase-transfer catalysis) in a new way (by using a microreactor).

2. To subject allene-ene esters to microwave irradiation (a new methodology) in order to improve the Lewis acid catalysed intramolecular [2+2] cycloaddition of these compounds and obtain cyclobutane compounds.

3. To investigate a ring expansion reaction of isopropylidenecyclobutanes to yield bicyclo[3.3.0]octanes.

ABSTRACT

The main focus of this thesis was to use new methodology on already well-established methods of preparation of 3-membered, 4-membered and 5-membered carbocyclic compounds with the emphasis on improving them.

Traditional batch dibromocyclopropanations by reaction of bromoform and alkenes under phase-transfer conditions usually require strong base (50% NaOH (aq)), vigorous stirring, and often long reaction times. When flow chemistry in a microreactor was used, the reactions were found to be smooth, rapid, and high-yielding under ambient conditions when 40% (w/w) NaOH was used as the base. A key requirement for the success of this method was the use of the slug flow technique and an aqueous-to-organic flow ratio (AO ratio) of 4. A representative selection of alkenes, displaying a variety of structural features, was used as substrates. When unsaturated alcohols were used as substrates, the yields obtained were dependent on the structure of the alcohol.

Methyl 2,3,8-nonatrienoate (**12**) undergoes a Lewis acid ($EtAlCl_2$) catalysed [2+2] cycloaddition to give a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13a)** and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13b**) (2.5 : 1) in 83 % yield when microwave irradiation is applied at 130 °C for 30 seconds. In the literature 14 days at 25°C was used. The cyclisation did not work for 3-methyl-3-buten-1-yl buta-2,3-dienoate (**68a**) or 3-methyl-3- buten-1-yl 4-methylpenta-2,3-dienoate (**68c**) although several catalysts and different temperatures and reaction times were tried.

When subjected to HBr/HOAc in polar solvents like acetic acid, 6-(1-methyl-ethylidene)bicyclo[3.2.0]heptane (**76a**) did undergo a ring expansion reaction yielding 2-bromo-3,3-dimethylbicyclo[3.3.0]octane (**77a**) and 3-bromo-2,2-dimethyl-bicyclo[3.3.0]octane (**78a**). Several other isopropylidenecyclobutanes gave similar results with high stereoselectivity, but moderate regioselectivity. In less polar solvents like diethyl ether the ring expansion reaction was suppressed, and bromides resulting from addition of HBr to the isopropylidene double bond were obtained.

SAMMENDRAG

Hovedfokus i denne avhandlingen har vært å bruke ny metodologi på allerede veletablerte metoder for fremstilling av karbosykliske 3- og 4- og 5-ringsforbindelser med håp å forbedre dem.

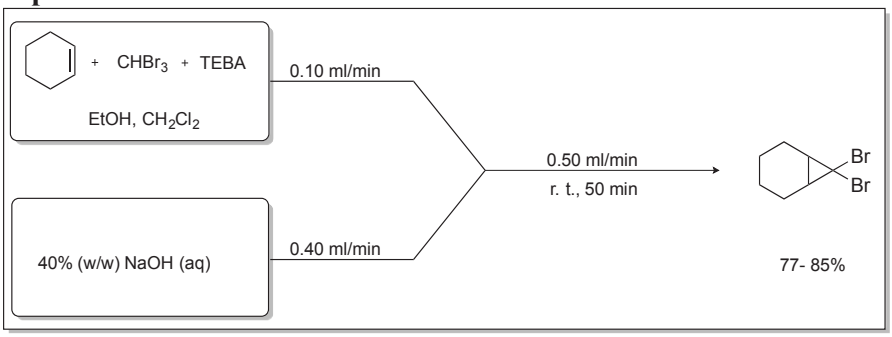
Tradisjonelle metoder for dibromsyklopropaneringer i vanlige reaksjonskolber ved reaksjon med bromoform og alkener under faseoverføringsbetingelse krever vanligvis sterk base (50% NaOH (aq)), svært kraftig røring og ofte lange reaksjonstider. Ved å benytte "flow"-kjemi i en mikroreaktor, ble reaksjonene funnet å være enkle å utføre i tillegg til at de var raske og gav høyt utbytte under normale betingelser, men hvor det var nødvendig med en basestyrke på kun 40% (w/w) NaOH. Et nøkkelkrav for denne metodens suksess, var bruk av "slug flow"-teknikken og et vannfase-organiskfase-forhold (AO forhold) på 4. Et representativt utvalg av alkener med forskjellige strukturelementer ble brukt som substrater. Med umettede alkoholer som substrat, viste det seg at utbyttene var svært avhengige av strukturen til alkoholen.

Ved å benytte mikrobølgestråling ved 130 °C i kun 30 sekunder, ga methyl-2,3,8-nonatrienat (**12**) undergår en Lewis-syrekatalysert ($EtAlCl_2$) [2+2] sykloaddisjon. Produktblandingen besto av en blanding av *(Z)*-metyl-2-bisyklo[3.2.0]hept-6-ylidene acetat (**13a)** og *(E)*-metyl-2- bisyklo[3.2.0]hept-6-ylidene acetat (**13b**) (2.5 : 1) i 83 % utbytte. Tidligere er det rapportert av andre at 14 dager ved 25°C var nødvendig for å få til tilsvarende resultat. Sykliseringen fungerte ikke for 3-metyl-3-buten-1-yl buta-2,3-dienat 68**a**) eller 3-metyl-3- buten-1-yl 4-metylpenta-2,3-dienat (**68c**) selv om flere katalysatorer og forskjellige temperaturer og reaksjonstider ble forsøkt.

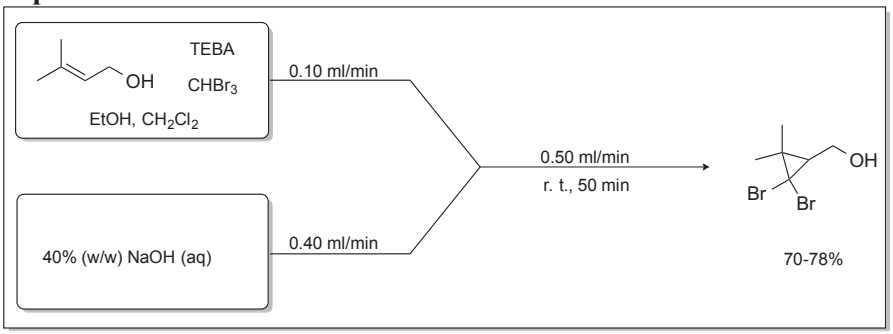
Da 6-(1-metyl-etylidene)bicyclo[3.2.0]heptane (**76a**) ble behandlet med HBr/HOAc i polare løsningsmidler som eddiksyre, ble resultatet en ringekspansjonsreaksjon som gav 2-brom-3,3-dimetylbisyklo[3.3.0]oktan (**77a**) og 3-brom-2,2-dimetyl-bisyklo[3.3.0]oktan (**78a**). Flere andre isopropylidenesyklobutaner undergikk den samme reaksjonen med høy stereoselektivitet, men moderat regioselektivitet. I mindre polare løsemidler som dietyleter, ble ringekspansjonsreaksjonen undertrykt. I stedet ble bromider som skyldes addisjon av HBr til isopropyliden-dobbeltbindingen dannet.

GRAPHICAL ABSTRACTS

Paper I



Paper II



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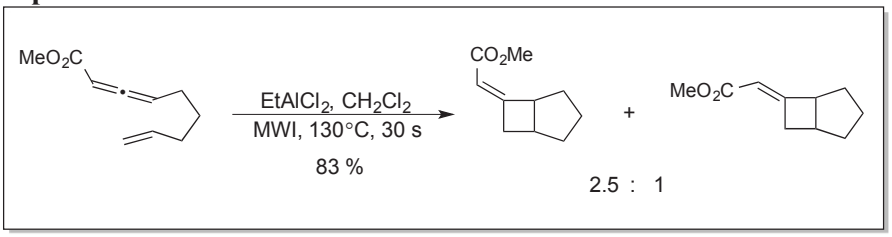
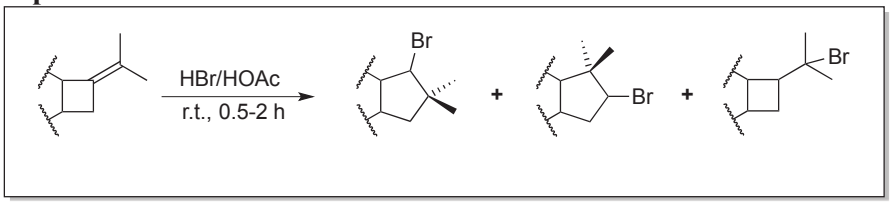


Paper IV



LIST OF PAPERS

I. *The Use of Flow Chemistry for Two-Phase Dibromocyclopropanation of Alkenes*
Østby, R. B.; Stenstrøm, Y. H.; Didriksen, T.
Journal of Flow Chemistry **2015**, *5*, 69-73

II. *Two-Phase Dibromocyclopropanation of Unsaturated Alcohols Using Flow Chemistry*
Østby, R. B.; Stenstrøm, Y. H.; Didriksen, T.,
manuscript.

III. *Synthetic Studies towards Cyclobutanes by Microwave Assisted Intramolecular [2+2] Cycloaddition of Allene-Ene Esters*
Østby, R. B.; Sørensen, R. L.; Stenstrøm, Y. H.; Westerås, S.; Antonsen, S.,
manuscript.

IV. *Syntheses of bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes by ring expansion of isopropylidenecyclobutanes*
Østby, R. B., Stenstrøm, Y. H.,
ARKIVOC **2014**, (iv), 266-284.

ABBREVIATIONS

EWG	Electron Withdrawing Group
GLC	Gas Liquid Chromatography
HATR	Horizontal Attenuated Total Reflectance
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
LG	Leaving Group
MAOS	Microwave Assisted Organic Synthesis
MIRC	Michael Induced Ring Closure
MS	Mass Spectroscopy
MWI	Microwave irradiation
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
PCTFE	Polychlorotrifluoroethene
PTC	Phase-transfer catalysis
PTFE	Polytetrafluoroethylene
ppm	Parts per million
ROESY	Rotating Overhouser Effect Spectroscopy
r.t.	Room temperature
TBAB	Tetra-n-butylammonium bromide
TEBA	Benzyltriethylammonium chloride
TMS	Trimethylsilyl

CHAPTER 1 - INTRODUCTION

1.1 Introduction to 3-, 4, and 5-Membered Carbocyclic Compounds

The three smallest carbocyclic rings, cyclopropane, cyclobutane and cyclopentane, are recognized as substructures of many biologically active, synthetically challenging natural products belonging to several different product classes, like fatty acids, terpenes and alkaloids, and the number is still growing.[1-8] Examples include e.g. the antifungal nucleoside FR-900848, a fermentation product from *Streptoverticillium fervens*,[9-11] containing an aglycon with five cyclopropyl groups, Pasteurestin A, an antibacterial fermentation product from the basidiomycetes *Agrocybe cylindracea and A. aegeritta,*[12-13] and (±)-1-desoxyhypnophilin, a biologically active terpene isolated from the East African mushroom *Lentinus crinitus* (L. ex Fr.) Fr.[14]

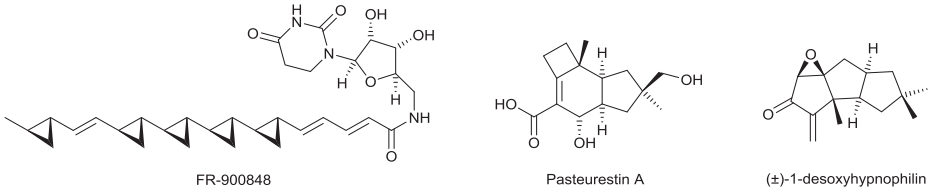


Figure 1.1 Some natural products containing 3-, 4- and 5-membered rings.

A number of active pharmaceutical ingredients also contain 3- to 5-membered carbocyclic rings, e.g. ciprofloxacin, a broad-spectrum antibiotic containing a cyclopropane ring, carboplatin, an anticancer drug containing a cyclobutane ring, and glycopyrronium bromide (Seebri ® Breezhaler®), a bronchodilator, containing a cyclopentane ring.

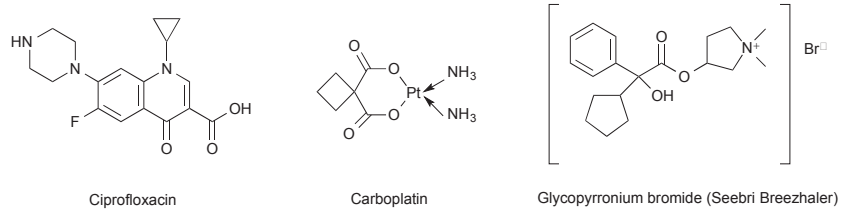


Figure 1.2 Three drugs currently marketed in Norway.

In addition to being important structural elements in natural products as such,[15] cyclopropanes, cyclobutanes and cyclopentanes are also important substrates as versatile intermediates for the syntheses of both natural products and other interesting compounds.[16-19] New methods for synthesis of these compounds are still in demand.[1,17]

Although the cyclopropyl group is stable enough to be found in natural products, cyclopropanes are more reactive than their acyclic counterparts and larger cycloalkanes.[20] Cyclopropanes often resemble alkenes in their behaviour,[21] e.g.:

1. They interact with electrophiles like bromine, whereas their acyclic counterparts and cyclobutanes and larger cycloalkanes generally do not.[21]
2. They are generally more efficient than cyclobutanes and larger cycloalkanes in interacting with a proton or an adjacent cationic center where cyclopropanes acts like a base. Cyclobutanes and larger cycloalkanes are much less basic than cyclopropanes since they do not stabilize the positive charge equally well.[21]
3. The C-C bonds in cyclopropanes are thermally more easily cleaved than C-C bonds in cyclobutanes are, which again are more easily cleaved than the C-C bonds in cyclopentanes and cyclohexanes are.[21]
4. The methylene protons in cyclopropane usually have an increased acidity compared to their acyclic counter parts and larger cycloalkanes.[21]
5. Cyclopropanes form metal complexes, undergo catalytic hydrogenation and cycloadditions.[22]
6. The ^{13}C-H coupling constant ($^{1}J_{C\text{-}H}$) of cyclopropane is found to be 161 Hz, resembling $^{1}J_{C\text{-}H}$ of ethene (157 Hz), and is much larger than $^{1}J_{C\text{-}H}$ of ethane (126 Hz). In contrast, $^{1}J_{C\text{-}H}$ of cyclobutane (134 Hz) and of cyclopentane (128) resemble $^{1}J_{C\text{-}H}$ of cyclohexane (124 Hz) more.[23]
7. In cyclopropanes both the C-C and C-H bonds normally are shorter than those in other cycloalkanes like cyclohexane, while for cyclobutanes the opposite is true, usually having bonds that are longer.[21]

In contrast to acyclic alkanes, cyclic alkanes experience varying degrees of ring strain. (Table 1.1)[20]

Table 1.1 Strain Energy of Some Cyclic Alkanes[20]

Entry	Alkene	Strain Energy (kcal/mol)
1	cyclopropane	27.5
2	cyclobutane	26.5
3	cyclopentane	6.2
4	cyclohexane[a]	0.0

[a] Chair conformation

The strain energies of the cycloalkanes of small and medium sizes (3-6 membered rings) may result from:[20]

1) Angle strain: The deformation of bond path angles (interorbital angles) from the tetrahedral angle of 109.5°, which is normal for unstrained alkanes.
2) 1,3 repulsion between cross-ring carbons.
3) Torsional interactions arising when bonds are not ideally staggered.

Cyclohexane in its chair conformation is regarded as strain free since its bond path angles are near identical to the tetrahedral angle, the bonds are almost perfectly staggered, and there is no 1,3 repulsion between cross-ring carbons (Table 1.1, Entry 4).[21]

In cyclopentanes there usually are no angular strain, but strain due to eclipsing of methyl groups exist. (Table 1.1, Entry 3 for cyclopentane.) Cyclopentanes adopt conformations that alleviate this transannular strain.[24]

Cyclopropanes and cyclobutanes (Table 1.1, Entries 1 and 2 for the parent hydrocarbons) in general have higher strain energy than larger cyclic alkanes (and acyclic alkanes). Since the cyclopropane ring contains only three atoms, it must be planar, and the C-C-C bond angles should be 60°, something that would lead to a severely strained molecule with rather weak bonds.[20,25]

The Förster-Coulson-Moffitt model[26-28] suggests that the C-C bonds in cyclopropanes are formed by orbitals relatively rich in p character, giving sp^5 hybridized carbons, (bent bonds) in order to minimize the angle strain (Figure 1.3).[21] Several other studies, both

experimental[29-32] and theoretical,[33-37] have confirmed that the interorbital angle (α) of cyclopropane is larger than its geometric angle (60°), and that the bonding regions of cyclopropane lies outside the triangle made by the three carbon atoms, although there have been some discussion about the magnitude of the interorbital angle in literature.[29-37]

The increased reactivity and many of the unique properties of cyclopropanes, and to some extent cyclobutanes, can be explained in terms of these bent bonds that can act similarly to π bonds.

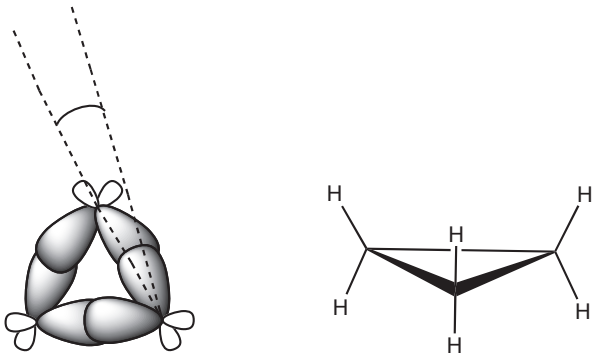


Figure 1.3 Bent bonds in cyclopropane and eclipsed conformation of cyclopropane.

As a consequence of the increased p character (decreased s character) of the C-C bonds in cyclopropane, the C-H bonds gets an increased s character, compared to what is found in acyclic alkanes, and resemble sp^2 hybridised bonds. The HCH angle is increased compared to the tetrahedral angle. The high s character of C-H bonds in cyclopropanes generally leads to increased acidity of the methylene groups and makes the ^{13}C-H coupling constant in cyclopropanes resemble that of alkenes.[21]

Cyclopropanes generally have upfield shifts in NMR compared to other carbocycles: δ_H for cyclopropane is 0.12 ppm, considerably upfield from cyclohexane (δ_H = 1.44), while for cyclobutane the hydrogens are shifted downfield (δ_H = 1.96 ppm). δ_C for cyclopropane is -2.9 ppm, for cyclohexane 27 ppm, and for cyclobutane 23 ppm. The upfield shifts are general features of cyclopropanes and can be used in structure determination.[21] The upfield

shifts of cyclopropanes have been attributed to shielding arising from a ring current in cyclopropane that involves the six electrons in the three C-C bonds (σ-aromaticity) and is induced when cyclopropane is subjected to a perpendicular magnetic field.[38,39] A similar explanation of the downfield shifts of cyclobutanes does not seem to exist.[39]

In addition to the angle strain, cyclopropanes in general experience torsional strain[20] since all the hydrogens are eclipsed (Figure 1.3.)

Cyclobutane contains bonds that are bent to a lesser extent than for cyclopropane and therefore generally behaves more like an ordinary alkane compared to cyclopropane (Figure 1.4).[25] Cyclobutanes also experience torsional strain, but they can relieve some of the torsional strain caused by eclipsing CH_2 groups by adopting a puckered conformation where the C-C-C bond angle is reduced from 90° (for cyclobutane itself from 90° to 88°).[21]

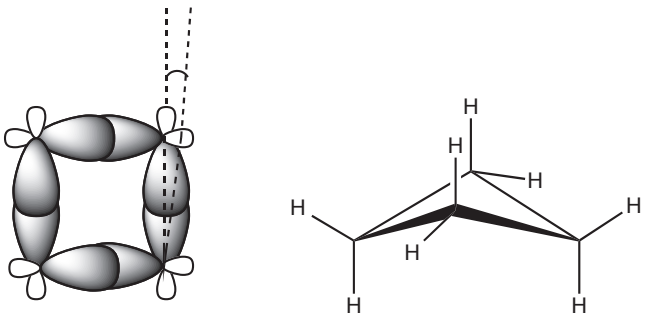


Figure 1.4 The slightly bent bonds and puckered conformation of cyclobutane.

In addition, cyclobutanes also experience 1,3 cross-ring repulsion between methylene groups. It is this cross-ring repulsion that causes the bonds in cyclobutanes to be longer than normal.[21]

The strain energies of cyclopropane and cyclobutane are of similar value. The reasons for this is that while cyclopropane has a much larger angle strain and torsional strain than

cyclobutane, it lacks the 1,3 repulsion between the cross-ring carbons. In addition, the C-H bonds in cyclopropane are stronger than those of cyclobutane, in part compensating for the weaker C-C bonds.[20]

The presence of 3- to 5- membered rings in natural products of biological significance, and the special characteristics of these rings have made them into targets for synthetic chemists, and several methods for their synthesis exist.

1.2 Synthesis of 3-Membered Carbocyclic Compounds

The first preparation of a cyclopropane ring was described in 1882 when August Freund reported the synthesis of cyclopropane by treating 1,3-dibromopropane with sodium in an intramolecular Wurtz coupling.[40] Since then a huge number of methods for preparing these interesting and useful compounds have been developed.[2,17,41-44] Only a few of these methods will be briefly mentioned here, and readers are encouraged to consult the literature[41-44] for details concerning these and other existing cyclopropanation methods.

1.2.1 Some general methods for construction of the cyclopropyl carbon skeleton

Some of the most frequently used general methods for construction of the cyclopropyl carbon skeleton are listed in Table 1.2 on page 13 and 14. A few typical experimental characteristics are included in the table. The new C-C bonds that are formed in these reactions are shown in red.

1.2.1.1 Intramolecular Reductive 1,3-elimination of Two Heteroatoms

As mentioned earlier, an intramolecular Wurtz reaction on 1,3-dibromopropane was used for the first preparation of cyclopropane.[40] The reductive elimination of 1,3-dihalides[41a] is a general reaction and has been achieved by metal reduction with e.g. Zn, Mg or Na, or by employing organometallic reducing agents like ^{t}BuLi or $LiAlH_4$ (Table 1.2, Entry 1). The reaction runs smoothly with 1,3-diiodides and 1,3-dibromides,[41a] whereas sodium iodide has been used as a mediator to complement the relative low reactivity of the 1,3-dichlorides.[41a,42b] Primary halides usually work well in this reaction, while the secondary and, and particularly tertiary halides are hampered by production of alkene sideproducts.[42b] Mixed 1,3-dihalides give lower yields than the corresponding dibromides.[41a] Other heteroatoms than halides may participate in the reaction, and while the 1,3-debromination is a non-stereospecific reaction, 1,3-deoxystannylation is a stereospecific method.[41a,42b]

1.2.1.2 The Simmons-Smith Cyclopropanation

The stereochemical terms are according to those defined by Hellquist.[44a] For more details see Appendix 1.

Since the zinc reagents are weakly electrophilic, the cyclopropanation using the Simmons-Smith protocol[45-46] (Table 1.2, Entry 2) is accelerated by electron-donating substituents at the double bond and retarded by electron-withdrawing groups.[42c] The Simmons-Smith reaction is usually stereospecific with regard to the transfer of methylene and free from side-reactions. The zinc reagents tend to coordinate to oxygen or nitrogen functional groups that are appropriately positioned in the alkene substrate,[42c,47-49] and such coordination may accelerate and direct the cyclopropanation, thus influencing the syn/anti product ratios (diastereofacial selectivity). The reaction occurs at the more accessible face of the double bond with respect to functional groups and coordinated zinc reagent.

The Simmons-Smith cyclopropanation usually is less efficient for tetrasubstituted than for less substituted double bonds due to steric congestion.[50] A number of chiral ligands have been used for asymmetric Simmons-Smith cyclopropanation.[2] A major drawback of the Simmons-Smith reaction is the expense of diiodomethane, although in some cases dibromomethane can be used together with promotors.[50]

1.2.1.3 Metal Catalysed Diazomethane Cyclopropanation

Catalytic decomposition of diazomethane in the presence of an alkene[41b,42c,44b] (Table 1.2, Entry 3) is another way of constructing the cyclopropane skeleton. When $Pd(OAc)_2$ is used as the catalyst, only mono- and disubstituted alkenes react.[2] Since non-activated, internal double bonds does not react easily, a selective cyclopropanation may be obtained when different types of double bonds are present in a molecule.[42c] The reaction is generally stereospecific with respect to the addition of the methylene group.[44b] With cyclic alkenes, the Pd-carbene species approaches the less hindered face of the alkene. Acyclic alkenes show low diastereoselectivity (low diastereofacial selectivity) under these conditions.[2] Other catalysts have also successfully been used, and asymmetric reactions have been accomplished by using optically active catalysts or different chiral auxiliaries (either in the alkene or in the diazocompound).[44b] Large scale syntheses using this protocol is inconvenient since diazomethane is poisonous and explosive.[44b] Alkyl- and dialkylcarbenes

are susceptible to rapid intramolecular insertion reactions and give acceptable yields of cyclopropanes only for intramolecular cyclopropanations.[42c]

1.2.1.4 Metal Catalysed Diazo-carbonyl Cyclopropanation

Many different transition metal complexes (e.g. copper salts or rhodium salts) catalyse the decomposition of diazocarbonyl compounds (like diazoacetate) into acyl- and alkoxycarbonyl carbenes[2,42d] (Table 1.2, Entry 4). The reaction of acyl- and alkoxycarbonyldiazomethanes with alkenes is in general stereospecific under catalytic conditions (i.e. retention of the cis-trans relationship of the double bond substituents in the cyclopropane product).[42d] Usually, the addition preferentially occurs to the less hindered side of the double bond, and the less sterically congested anti-isomer of the product predominates.[42d] Possible problems concerning diastereoselectivity (anti vs. syn) and enantioselectivity, may often be solved by varying the metal-ligand system and the steric bulk of substituents such as the ester group.[2]

1.2.1.5 Cyclopropanation by Michael Induced Ring Closure (MIRC) Reaction

Michael acceptors may be cyclopropanated by conjugate addition of a nucleophile, followed by intramolecular cyclization and elimination of a leaving group (LG).[41c,42e-f] The leaving group may be located in the Michael acceptor (Entry 5) or in the nucleophile (Entry 6).[41c] Stabilized ylides, e.g. sulfur ylides are frequently used as nucleophiles in the latter type of Michael Induced Ring Closure (MIRC) reaction.[42f] The reaction is base induced and generally racemic mixtures of cyclopropanes are obtained,[41c] although in some cases the reaction may be stereospecific.[44c] The stereoselectivity of the reaction is determined by the cyclization step on the intermediate Michael adduct, and the cis/trans ratio of the bond that is formed is dependent on the solvent polarity, the degree of anion-cation association and steric interactions, and under phase-transfer conditions, whether a catalyst is used or not.[41c]

1.2.1.6 Ring Contractions

Cyclopropanes may also be prepared by ring contraction of larger rings, e.g. by nitrogen extrusion from 1-pyrazolines,[42g-h] or by ring contraction of cyclobutyl derivatives.[42i] Several other methods for achieving ring contractions can be found in the literature.[41d-g]

1.2.1.6.1 Nitrogen Extrusion from 1-Pyrazolines

The thermal, or photochemical, extrusion of N_2 from 1-pyrazolines (Table 1.2, Entry 7) is a useful method for preparation of alkylsubstituted cyclopropanes,[42g] since preparation of these compounds from alkyl- and dialkylcarbenes is impractical due to rapid intramolecular insertion reactions (See chapter 1.2.1.3).[42c]

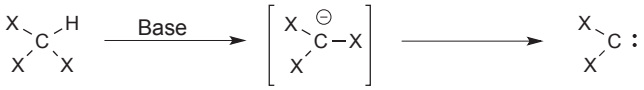
The pyrazolines are usually prepared by a concerted, stereospecific 1,3-cycloaddition of a diazo compound to an alkene containing an activated double bond.[42g-h,3744b] For certain pyrazolines acid catalysis is used.[42g] The photochemical decomposition generally gives better results than the thermal decomposition due to thermal side reactions. Direct photolysis usually gives cyclopropanes with retention of the relative stereochemistry of the starting pyrazolines, whereas triplet sensitized photolysis tends to give an extensive loss of stereochemistry, but better yields of cyclopropanes.[42g]

1.2.1.6.2 Ring Contraction of Cyclobutyl Derivatives

Cyclobutanes that are vicinally disubstituted by an electron-donating group and a leaving (or electron receiving) group, undergo facile ring contractions yielding cyclopropyl derivatives.[51,52] (Table 1.2, Entry 8) Two examples of such reactions are: [42i] Treatment of 2-substituted cyclobutanols with base to give cyclopanecarbaldehydes or cyclopropyl ketones, and nucleophilic addition and subsequent ring contraction of α-substituted cyclobutanones to give cyclopropanecarboxylic acids and their derivatives. Generally, this ring contraction is stereospecific and occurs with inversion of configuration at the carbon substituted with the leaving group. However, in some cases epimerization of this carbon prior to ring contraction result in a stereochemically more complex mixture of products.

1.2.1.7 Addition of Dihalocarbenes to Alkenes

Another method of synthesis of 3-membered rings is by [1+2]cycloaddition of dihalocarbenes to alkenes to yield *gem*-dihalocyclopropanes.[41h,53] (Table 1.2, Entry 9) The dihalocarbene is formed by elimination of hydrogen halide from the haloform using a strong base (Scheme 1.1).



X = halogen

Scheme 1.1 α-elimination of hydrogen halide

The cycloaddition of dihalocarbenes to alkenes is usually a stereospecific process that preserves the configuration of the alkenes in the products. Dihalocarbenes are electrophilic species that react readily with nucleophilic (electron-rich) alkenes. The more highly substituted the alkene is, the faster the reaction generally is:

The reactivity of simple alkenes towards dihalocarbenes decreases in this order: tetrasubstituted > trisubstituted > unsymmetric-disubstituted > symmetric-disubstituted > monoalkyl-substituted,[42j] and generally:[53]

- 1,1-disubstituted alkenes has a higher reaction rate than 1,2-disubstituted alkenes
- Straigth chain *(Z)*-alkenes react faster than the corresponding *(E)*-isomers, and
- Cyclic *(E)*-alkenes react at a higher rate than the corresponding *Z*-isomers.

With electrophilic (electron-poor) alkenes, the reaction is much slower, and if the double bond is fairly unreactive, the dihalocarbene may participate in side reactions like insertion into C-H bonds. Dibromocarbene is more reactive (and less selective) than dichlorocarbene.

Usually chloroform or bromoform are used, and only routes leading to dichloro- and dibromocyclopropanes are discussed here. For preparation of other dihalocyclopropanes, readers are referred to the literature.[41h,44d,53] Two of the most important methods for

preparation of dichloro- and dibromocyclopropanes are the Doering-Hoffmann method[54] and the Makosza method[55] (and modifications of these).

In the Doering-Hoffmann protocol the α-elimination is achieved by the use of ^{t}BuOK. Addition of the resulting dihalocarbenes to alkenes (typically in a hydrocarbon solvent or in an excess of alkene) gives the dihalocyclopropanes in good yields, except for relatively unreactive alkenes. Replacing ^{t}BuOK with lithium triethylmetoxide gives good yields also for these alkenes. Strictly anhydrous conditions are required.

When the Makosza protocol is used, however, the α-elimination is achieved by the use of a concentrated *aqueous* solution (50 % (w/w)) of NaOH (or KOH) under phase-transfer catalysis (PTC). Details of the Makosza reaction will be discussed in the next section (Section 1.2.2).

Another method that has been used for preparation of dichloro- or dibromocarbenes is thermal decomposition of Seyferth's reagents,[55] *e.g.* trihalomethyl(phenyl)mercury ($PhHgCX_3$, X= Cl or Br).[42j,53,56] The method is very efficient, giving good yields of *gem*-dichlorocyclopropanes prepared from base-sensitive alkenes or alkenes of low reactivity, e.g. allyl halides, esters and nitriles. This method is however, hampered by the high cost and toxicity of the carbene precursors and toxicity of the waste produced.

Several other methods[42j, 53] have been used to prepare the *dichloro*carbenes, *e.g.*: reaction of ethyl trichloroacetate with sodium methoxide,[57], thermal decomposition of sodium trichloroacetate,[58] treatment of CBr_4/CCl_4 with an iron/copper couple in acetonitrile,[59] and oxidative addition of CCl_4 to a low-valent titanium species generated from Ti(IV)chloride with metallic magnesium.[60]

Table 1.2 Some Methods for Preparation of Cyclopropane Rings[a]

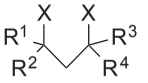
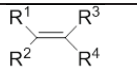
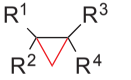
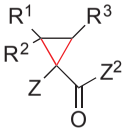
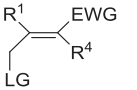
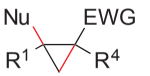
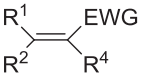
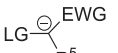
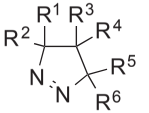
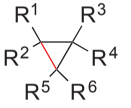
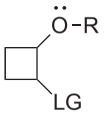
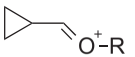
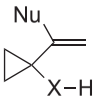
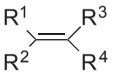
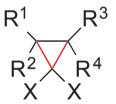
Entry	Name of Reaction	Substrate	Typical Reagents/Catalysts	Product	Ref.
1	Intramolecular reductive 1,3-elimination of two heteroatoms		- Metals Na, Zn, Mg or - Organometallic reagents, e.g. ^{t}-BuLi or - Metal hydride, e.g. $LiAlH_4$		40 41a 42b
2	Simmons-Smith cyclopropanation	 electron rich alkenes favoured	- e.g. $Zn(Cu)/CH_2I_2$, $Zn(Ag)/CH_2I_2$ or - Et_2Zn/CH_2I_2		2 42c 45-50
3	Metal catalysed diazo-methane cyclopropanation	For Pd(OAc)2: mono or disubstituted alkenes[b]	Excess CH_2N_2 and $Pd(OAc)_2$, copper salts or copper complexes		2 41b 42c 44b
4	Metal catalysed diazo-carbonyl cyclopropanation	Mono or disubstituted double bonds	Diazocarbonyl compound and - $Pd(OAc)_2$ or - rhodium salts e.g. $Rh_2(OAc)_4$ or - copper salts e.g. $Cu(TBS)_2$		2 42d
5	Cyclopropanation of γ-substituted Michael acceptors/MIRC[c]		Nu:-		41c 42e 44c
6	Cyclopropanation of Michael acceptors with carbon nucleophiles containing a LG		 e.g. stabilized ylides		41c 42f 44c

Table 1.2 continued…

Entry	Name of Reaction	Substrate	Typical Reagents/Catalysts	Product	Ref.
7	Nitrogen extrusion from 1-pyrazolines		- Δ or - λν (direct or triple sensitized)		42g 42h 44b
8	Ring contraction of cyclobutanol or cyclobutanone derivatives	 	base Nu:-	 	42i 51 52
9	Dihalocyclopropanation		$:CX_2$		41h 42j 44d 53 55 56

[a]R^1-R^6 = H or functional groups, X = heteroatom, Z = H or functional group

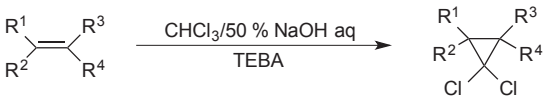
[b]With copper salts electron rich alkenes are favoured.

[c]MIRC = Michael Induced Ring Closure, EWG = Electron-withdrawing group: -COR, -COOR, $-CONH_2$, -CN, $-SO_2R$, $-NO_2$ etc., LG = leaving group, Nu:- = nucleophile.

1.2.2 Addition of Dihalocarbenes to Alkenes by The Makosza Reaction and derivatives of this

Until 1969 strictly anhydrous conditions were assumed necessary for the α-elimination of hydrogen halide from haloform to prevent rapid hydrolysis of dihalocarbene. In 1969, however, Makosza published a new and convenient way of synthesizing *gem*-dichlorocyclopropanes that made them more easily available to chemists.[61]

Makosza found that both the α-elimination of hydrogen chloride from chloroform and the addition of the resulting dichlorocarbene to alkenes, could be performed in a two-phase system using a concentrated aqueous solution of NaOH as the base, in the presence of a quaternary ammonium salt acting as a phase-transfer catalyst. Only a small amount of the generated dihalocarbene was hydrolysed in the reaction. (Scheme 1.2)



R^1, R^2, R^3, R^4 = H or functional group
X = halogen

Scheme 1.2 The Makosza reaction.

Dibromocarbene is more reactive than dichlorocarbene, and hydrolyses to a greater extent.[43] In 1973 Skattebøl *et al.*[62] found that the poor yields of *gem*-dibromocyclopropanes previously obtained, could be improved if excess $CHBr_3$ and long reaction times were used. Since then addition of small amounts of a lower alcohol (e.g. ethanol, ca. 0.4 mL per 0.1 mol of alkene[41h]) has been reported to increase the yields of the dibromocyclopropanes as well.[63]

Two different mechanisms were suggested for the catalytic processes: an extraction mechanism of inorganic anions for PTC reactions was proposed by Starks,[64] while Makosza proposed an interfacial mechanism for the same reaction.[65]

I) The Extraction Mechanism

In this mechanism the lipophilic cation of the phase-transfer catalyst is considered to form a complex with hydroxide anion and transfer it to the organic phase. The CCl_3^- anion or dichlorocarbene is suggested to be maintained in the organic phase away from water sufficiently long to react with the alkene. The mechanism can be summarized as follows (Figure 1.5):

1. The phase-transfer catalyst cation, Q^+, forms a complex with the OH^- anion.
2. The Q^+OH^- complex passes the boundary between the aqueous phase and the organic phase.
3. Chloroform is deprotonated to give the lipophilic salt of the trichloromethyl anion and water.
4. The trichloromethyl anion dissociates to give dichlorocarbene and the lipophilic ammonium salt, $Q^+Cl^-_{org}$, that may go back to the aqueous phase.
5. The dichlorocarbene adds irreversibly to the alkene, forming the dichlorocyclopropane.

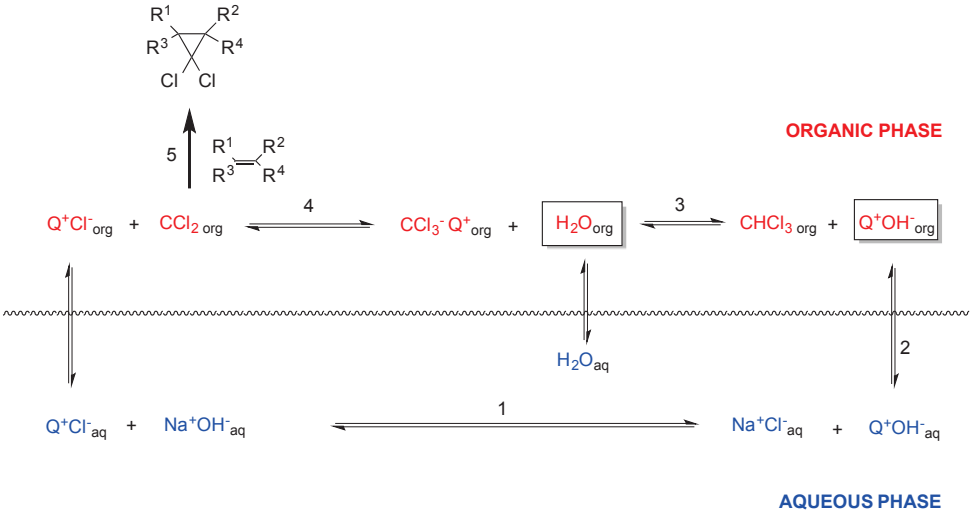


Figure 1.5 The Extraction Mechanism. Q^+Cl^- denotes the quaternary ammonium salt.

II) The Interfacial Mechanism

The phase boundary between the two immiscible phases, *e.g.* the organic phase and the aqueous phase, is considered an anisotropic region (with a concentration gradient) in which there is a diffusion of components from the organic phase, into the aqueous phase, and vice versa. In this interface region, components of the two phases can meet and react.[66] The interface region comprises a very small volume, and the residence time of the reacting species there is short, thus only reactions with a very high rate constant can be observed.

Since the details of this mechanism is not sufficiently known,[66] an outline of the mechanism is presented in figure 1.6 (which is an adaptation of a figure in the literature[66]) and summarized in the following steps:

1. In the interfacial region:
   Rapid deprotonation of chloroform ($CHCl_{3,int}$) to give water and the sodium salt of the carbanion ($CCl_3^- Na^+_{int}$), that is absorbed at the phase boundary and cannot migrate to the organic phase, nor to the aqueous phase.

2. Ion exchange between $CCl_3^- Na^+_{int}$ and the lipophilic quaternary ammonium salt ($Q^+Cl^-_{int}$, the phase-transfer catalyst) producing $Na^+Cl^-_{int}$, and a lipophilic salt of the carbanion ($CCl_3^- Q^+_{int}$)

3. $CCl_3^- Q^+_{int}$ passes over to the organic phase.

4. In the organic phase:
   $CCl_3^- Q^+_{org}$ dissociates *reversibly* to CCl_2 and the quaternary ammonium salt. Since water and hydroxide ions are absent in the organic phase, the fast, reversible reaction is "kept ready for use" when the addition to the alkene is a slow process.

5. CCl_2 add irreversibly to the alkene (rate determining step).The higher the nucleophilicity of the alkene, the higher the rate of the reaction.

6. In the interfacial region:
   The trichloromethyl anions ($CCl_3^-{}_{int}$) that are generated in the interfacial region also dissociate into dichlorocarbene and chloride ions. The dichlorocarbene produced

there immediately dissociates, shifting the equilibrium 6 to the right. Since the chloride ions produced have lower hydration energy than the hydroxide ions, they prefer to be located at the interface, and shift the equilibrium to the left, thus inhibiting the dissociation of the $CCl_3^-{}_{int}$.

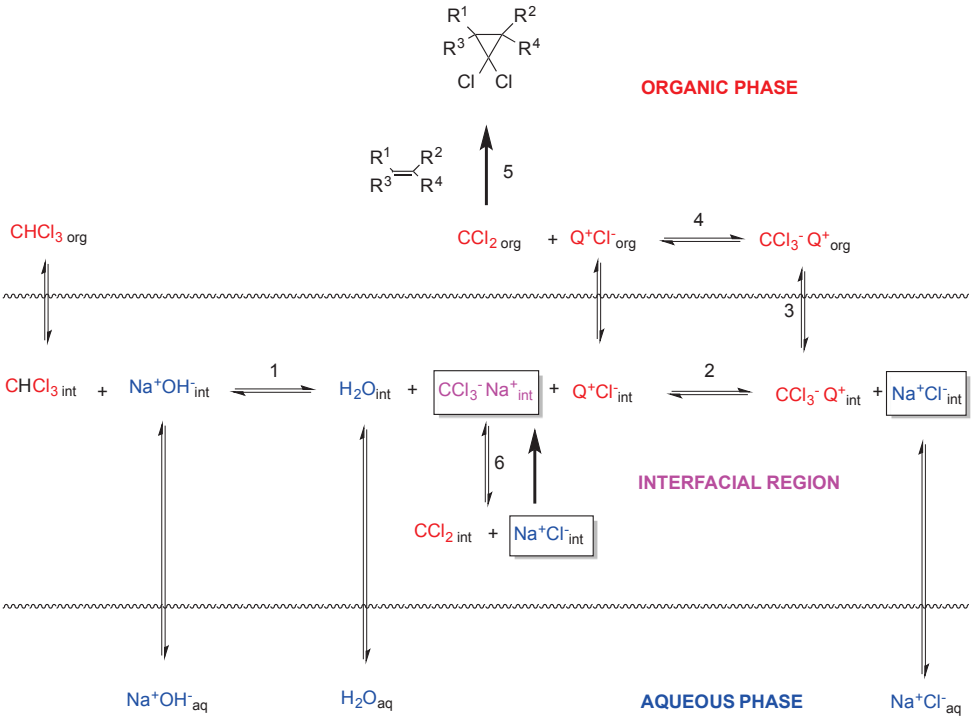


Figure 1.6 The Interface Mechanism. Q^+Cl^- denotes the quaternary ammonium salt.

The mechanism is less thoroughly investigated for the addition of CBr_2 than for the reaction of CCl_2, but is likely to be very similar,[53] although the mechanism of this dihalocarbene addition is still in debate.[66-68]

The phase-transfer catalysed two-phase dichloro- and dibromo addition, have successfully been applied for many different alkenes, polyenes and allenes,[42j] and is especially attractive for the dihalocyclopropanation of tetrasubstituted alkenes.[56] As seen in Chapter 1.2.1.7 the

dihalocarbenes are electrophilic, and the more highly substituted alkenes react more quickly. The order of reaction is the same as shown in Chapter 1.2.1.7.

The phase-transfer catalyst facilitates mass transport across the interface between the two immiscible phases, and vigorous stirring is very important to ensure that this interface is as large as possible. Stirring-speed is an important parameter for the reaction rate, conversion and yield.[62,69,70] An inert organic solvent is often used in addition to the haloform. Quaternary ammonium salts like benzyltriethylammonium chloride (TEBA) and tetrabutylammonium bromide (TBAB) are commonly used as catalysts, but other catalysts e.g. tertiary amines, crown ethers are also in use.[53]

While the traditional Makosza conditions are still in use, some successful adaptions to the procedure have been made. The use of solid potassium hydroxide (pellets or powder) instead of aqueous base, has been shown to increase reaction rates and the yields of dibromocyclopropanes,[71] and the combination of solid sodium hydroxide, phase-transfer catalysis and sonication has in shortened the reaction time increased the yields even further.[72] The Makosza method is a convenient method for the preparation of dibromocyclopropanes since strictly anhydrous conditions is not required, and the reagents used for this reaction is of low toxicity and cost compared to other methods for the preparation of cyclopropanes.[55,56,65]

1.2.3 Flow Chemistry in a Microreactor

Microreactor technology is a relatively new technology that over the last couple of decades has emerged as an attractive alternative to conventional batch chemistry,[73-77] and in 2003 the capillary-microreactor was introduced as a new reactor concept.[78]

Microreactors are usually defined as "miniaturized reaction systems fabricated by using, at least partially, methods of microtechnology and precision engineering." The internal structures of microreactors like fluid channels typically have characteristic dimensions ranging from the sub-micrometer to the sub-millimeter range.[79] The internal volumes are often of several milliliters. While surface-to-volum ratios for batch reactions usually do not exceed 1 000 m^2/m^3 (laboratory vessels) and 100 m^2/m^3 (production vessels). Surface-to-volume ratios of microchannels typically amount to 10 000 - 50 000 m^2/m^3.

In microreactors, where reactants are mixed in narrow channels, short diffusion lengths and a high surface-to-volume ratio result in rapid mass and heat transfer. This in turn improves control of reaction conditions and may contribute to increased rate and selectivity of reactions. The low reactor volumes are advantageous with respect to safety and allows for the use of minimal amounts of reagents under precisely controlled conditions to rapidly screen reaction conditions.[74]

The conventional batch synthesis is a space limited process where the outcome of the reaction is determined by the size of the reaction vessel. However, in flow chemistry synthesis is a time limited process where reagents constantly are pumped into a flow reactor, mixed and allowed to react. The residence time is in the microreactor is the equivalent of reaction time in batch reactions and is defined by the combined volume of the microreactor and the flow rate. The products leave the reactors as a continuous stream, and scale of the synthesis is determined by the flow rate and operation time.[74] Continuous flow processes allow rapid transfer from laboratory scale to industrial scale without the need for re-optimisation of the process.[75]

Microreactor technology has also been used successfully for two-phase reactions.[78,80,81] When two immiscible liquids are introduced into a micro- channel, they naturally separate into distinct phases with a large specific interface area, often in the form of alternating liquid slugs flowing through the microchannel.[82] Internal circulation within these slugs results in an increased mass transfer compared to, e.g., parallel flow[83,84] (Figure 1.7).

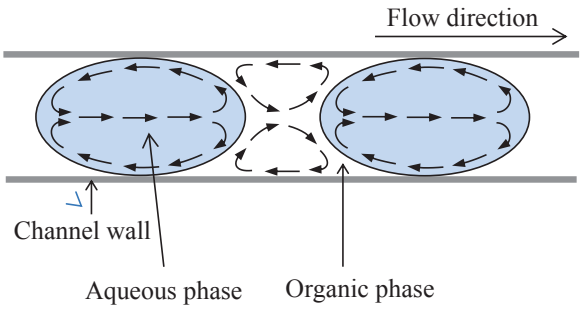


Figure 1.7 Internal circulation in alternating slugs of two immiscible liquids in a microchannel. The internal flow is shown relative to the bulk velocity.

In the present work a microreactor consisting of a Y-mixer (PCTFE) connected to a 25-mL tube reactor (PTFE, 0.8 mm i.d.) was used (Figure 1.8).

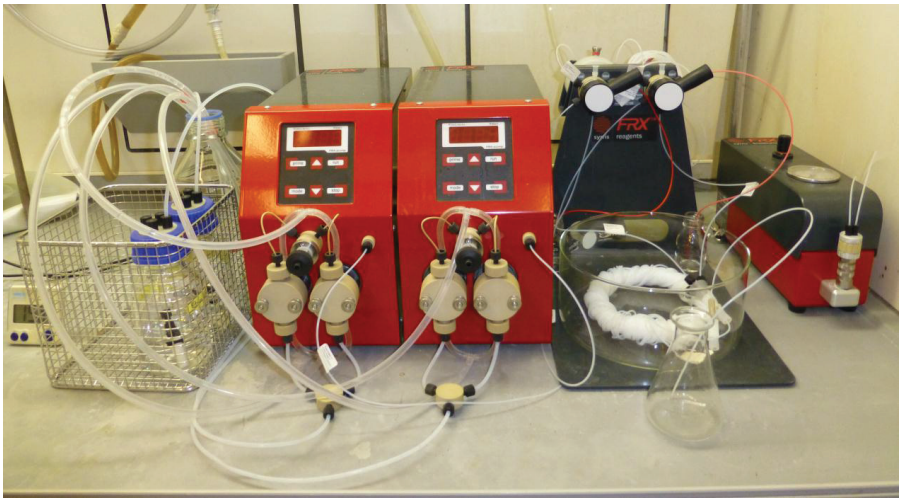


Figure 1.8 Modified Flow Chemistry Toolkit FRX200 from Syrris Ltd.

1.3 Synthesis of 4-Membered Carbocyclic Compounds

Even though cyclobutanes were first described 120 years ago, it is only during the last four decades that cyclobutanes have found use as versatile intermediates in organic synthesis.[1] The inherent ring strain found in the 4-membered rings (See Chapter 1.1) facilitates selective bond breakage, making the cyclobutane derivatives important intermediates for further manipulations. Only a few of the methods that exist for preparation of these four-membered carbocyclic rings will be briefly mentioned here, and for more details of these and other methods excellent reviews exist.[85-87]

1.3.1 Some General Methods for Construction of the Cyclobutyl Carbon Skeleton

Some of the most frequently used general methods for construction of the cyclobutyl carbon skeleton are listed in Table 1.3 on page 27. A few typical experimental characteristics are included in the table. The new C-C bonds that are formed in these reactions are shown in red. The principal strategies for formation of the cyclobutane ring system are [2+2] cycloadditions, cyclization of acyclic precursors, and ring expansion of cyclopropanes.[85]

1.3.1.1 [2+2] Cycloadditions

In these cycloadditions two C-C bonds and up to four new stereogenic centers are formed in a single step, making this method very useful.[85] The thermal concerted version of this cyclization is normally forbidden by orbital symmetry considerations* and must proceed via intermediates (biradicals or zwitterions) that are sufficiently long lived to undergo stereochemical equilibration. Mixtures of regio- and stereoisomers often result when non-activated alkenes are used, and usually this method cannot be used for preparation of configurationally defined cyclobutanes, and cycloadditions with ketenes (or ketene equivalents) are used instead. Methods for catalysed cycloadditions have also been developed.

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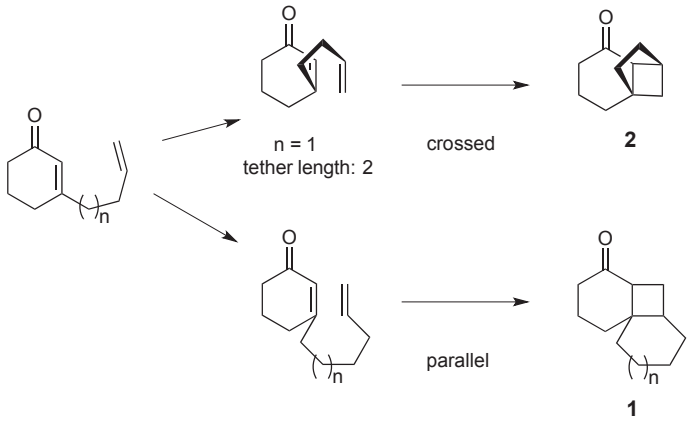
* It has been considered that orthogonal transition states can overcome this obstacle.

Two examples of the thermal [2+2] cycloaddition, the catalysed cycloadditions and the ketene additions, are discussed further together with the [2+2] photochemical cycloaddition.

1.3.1.1.1 Photochemical [2+2] cycloadditions

The photochemically induced [2+2] cycloaddition is allowed by orbital symmetry. The method cannot be used for non-conjugated alkenes, and when conjugated alkenes or enones are used, the compounds often undergo intersystem crossing to the triplet state producing biradicals that can undergo stereochemical equilibration.[85] Non-symmetrical alkenes with little stereoelectronic differentiation can in addition give regioisomeric mixtures. However, the intramolecular photochemical [2+2] cycloaddition reactions (Table 1.3, Entry 1) generally show much larger regio- and stereoselectivities since the mobility of the two reacting moieties is decreased. For the intramolecular alkene-enone photocyclisation the parameters that influence regioselectivities are the tether length between enone and alkene, and the substitution pattern of the reacting functional groups. Two regioisomers, the "parallel" cyclobutane **1** (1,2-disubstituted) and the "crossed" cyclobutane **2** (1,3-disubstituted), may be formed. (Scheme 1.3). In general, tether lengths possessing two centers between alkene units give the "crossed" product, whereas those of three or more centers give the "parallel" product, but strain factors and substitution patterns also influence the regioselectivity.



Scheme 1.3 Regioselectivity related to tether length.

Photochemical cycloadditions of allenes yield alkylidenecyclobutanes.[85] Mixtures of regio- and stereoisomers are often obtained. Alkynes are also used in this cycloaddition reaction.

1.3.1.1.2 Catalysed Cycloadditions

Alkenes that are thermally unreactive to cycloaddition may undergo cycloaddition reactions when exposed to catalysts (metals, Lewis acids, Brønsted acids).[85,86a] (Table 1.3, Entry 2) The substrates are often converted to reactive intermediates like metalated alkenes, cations, or radical cations that can undergo cyclisation more efficiently. The mild conditions used permit the cycloaddition of alkene combinations that would not otherwise react. A number of these catalysts may cause decomposition of the cyclobutanes formed in the initial reaction, and such catalysed reactions are limited to allyl cations, strained alkenes and donor-acceptor substituted alkenes. Alkenes possessing a nucleophilic site for coordination to a metal or Lewis acid, may undergo stereochemical equilibration to give mixtures of products. Intramolecular reactions are generally more selective than the intermolecular ones. Zwitterionic intermediates have been proposed for some of these processes, and the selectivity is often dependent on the nature of the metal catalyst used. Highly stereoselective examples are known.[88]

Takasu *et al.*[89-91] found that silyl enol ethers undergo hard Lewis acid (e.g. $EtAlCl_2$) catalysed [2+2] cycloaddition reactions with α,β-unsaturated esters to produce substituted cyclobutanes. Although the reactions are highly efficient and highly regio- and stereoselective, large amounts of the catalyst (ca. 20 mol%) is needed and the process is not applicable to substrates that contain Lewis acid sensitive functionality.

Recently, it has been shown that trifluoromethanesulfonimide (Tf_2NH) serves as a highly efficient catalyst for the [2+2] cycloaddition of silylenol ethers and α,β-unsaturated esters.[92-93] The reaction is an alternative to the photochemical reaction for these compounds, producing highly substituted and structurally complex cyclobutanes using only 1.0 mol% of Tf_2NH. The yields have been found to vary inversely with the catalyst concentration. The reaction is reversible, and the kinetic product possesses the *trans*-configuration, whereas the thermodynamic product has the *cis*-configuration. The Tf_2NH acts as a precatalyst to produce the real catalyst $TBDMSNTf_2$ through reaction with the *tert*-butyldimethylsilyl enol ethers.

1.3.1.1.3 Cycloadditions with Ketenes and Ketene Equivalents

The cycloaddition of ketenes to alkenes is the most widely used method for the synthesis of cyclobutanes.[85,86b] The popularity of the method may be due to the fact that ketenes are available from different routes, and that the reactions are highly regio- and stereoselective (Table 1.3, Entry 3).

The reactivities of ketenes differ widely depending on the substituents. The regio- and stereochemistry of the ketene addition can be predicted on the basis of orbital symmetry considerations, and during initial bond formation the ketene fragment acts as the electrophilic component, and electron-withdrawing substituents on the ketene enhance reactivity. Cycloadditions of electrophilic ketenes and nucleophilic alkenes are the most facile. Dichloroketene is sufficiently activated to react with non-activated alkenes (*e.g.* cyclohexene). Electron-deficient alkenes do not undergo cycloaddition to ketenes at all. However, ketene equivalents such as ketene acetals or ketene iminium salts may be used for these alkenes and also non-activated alkenes. A common side reaction for ketenes is dimerization, and in the original procedures the ketenes are usually generated *in situ* in the presence of a large excess of the alkene. An exception to this was the ketene iminium salts that do not dimerize like the ketenes do. Development of novel methodologies has overcome some of these obstacles.[86,94]

The cyclobutanones formed in the ketene addition are formed regioselectively with the more nucleophilic carbon of the alkene bonded to the ketene carbonyl carbon.[85] The stereochemistry of the alkene substituents is generally maintained in the product. The relative stereochemistry of the ketene substituents to the alkene substituents may be predicted on the basis of a concerted mechanism, and in the product formed from unsymmetrical ketenes with cycloalkanes the larger of the two substituents occupies the endo position in the bicycloalkane.

In intramolecular ketene to alkene cycloadditions, the efficiency of the addition depends on the nature and rigidity of the tether length. When alkene and ketene moieties are held rigidly and in close proximity, good yields of cycloaddition products are obtained, and three carbon tethers give the best results. The intramolecular reaction proceeds with retention of alkene

configuration, whereas the regiochemistry depends on the substitution pattern of the alkene unit.

1.3.1.2 1,4-Cyclisation of Acyclic Precursors

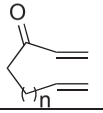
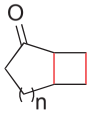
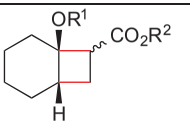
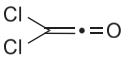
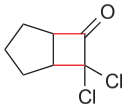
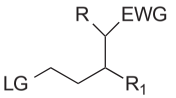
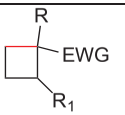
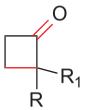
The cyclisation of acyclic precursors is a general method for the synthesis of cyclobutanes as for the cyclopropanes (Section 1.2.1.1) Several strategies for this 1,4-cyclisation have been developed, e.g. dehalogenation of 1,4-dihalobutanes, 1,4-dehydrohalogenations or dehydrotosylations, intramolecular electrophilic or nucleophilic addition to alkenes or alkynes.[85,86c] The 1,4-cyclisation of acyclic precursors can take place by radical or ionic mechanisms and often proceed with stereochemical equilibration of the stereogenic termini.

Intramolecular nucleophilic substitution of carbanions by the S_N2 or the S_N2' mechanism, using a carbanionic nucleophile, is an often used method. The carbanion is generated by deprotonation of acidic C-H functions (e.g. a-hydrogens to carbonyl or nitrile groups), or by metal halogen exchange processes (e.g. the Wurtz reaction). Substituents that will enhance the acidity of the C-H group and is easily removed from the product, is used. The carbanion attacks the electrophilic carbon center that is bonded to an efficient leaving group (*e.g.* halogen).

1.3.1.3 Ring Expansions of Cyclopropylcarbinyl Precursors

Cyclopropylmethyl systems that are substituted with an electrondonating substituent at C-1 may undergo ring enlargement to give cyclobutane compounds (Table 1.3, Entry 4).[85,86d] The regioselectivity in substituted cyclopropane derivatives is determined by the migration of the more substituted carbon. A number of substrates can be used for these reactions, *e.g*. alkylidenecyclopropanes, vinylcyclopropanes, cyclopropylmethanol or any cyclopropylmethyl compound containing a leaving group and cyclopropyl carbonyl derivates. The transformation of alkylidenecyclopropanes to cyclobutanes is generally carried out by oxidation (epoxidation or hydroxylation) of the alkene group followed by a thermal or cationic induced rearrangement. The oxidized intermediate is most often not isolated. The reagents used to induce the ring expansion depends on the nature of the electrondonating substituent at C-1.

Table 1.3 Some Methods for Preparation of Cyclobutane Rings[a]

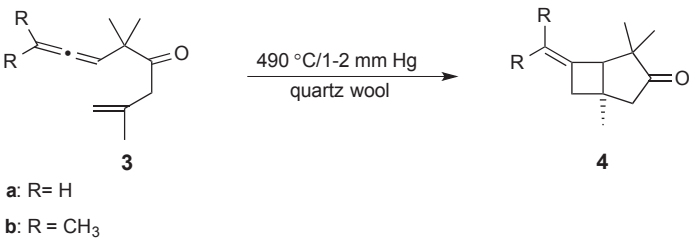
Entry	Name of Reaction	Substrate	Typical Reagents	Product	Ref.
1	Photochemical [2+2] cycloaddition	- Enones (especially cyclic) (intramolecular reaction best) 	- hν		85
2	Thermal catalysed [2+2] cycloaddition	- especially good for thermally unreactive alkenes	- metals - Lewis acids - Brønsted acids	 R^1 = TBS	85 86a 88-93
3	Thermal ketene [2+2] cycloaddition	- alkenes	e.g.: 		85 86 94
4	1,4-Cyclisation of acyclic precursors		- base (e.g. LiHMDS, LDA, NaH), - SmI_2, Bu_3SnH, metals		85 86c
5	Ring expansion of cyclopropylcarbinyl precursors		- oxidants (e.g. OsO_4/NMO, mCPBA, ^{t}BuOOH)		85 86d

[a]R-R^2 = H or functional groups

[b]EWG = Electron-withdrawing group, LG = leaving group.

1.3.2 Thermal [2+2] Cyclisations of Allenes

Allenes are generally considerably more reactive than non-conjugated alkenes in undergoing cycloadditions with other isolated, non-activated double bonds since the strain associated with the central sp hybridised carbon in allenes can be relieved in the cycloaddition reaction.[85] However, the regio- and stereoselectivities of the allene cycloadditions are low, largely due to the occurrence of diradical and zwitterion intermediates in these processes. Usually mixtures of isomeric cyclobutanes are obtained, and separation of the isomers is often difficult. An example of a successful thermal [2+2] allene-ene cycloaddition that was one of the intermediate steps in the synthesis of the pheromone component lineatin[95,96] is shown in scheme 1.4.



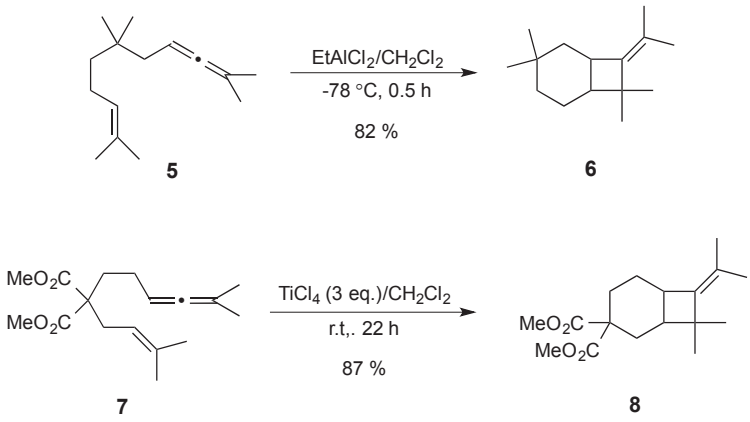
Scheme 1.4 Thermal [2+2] cycloaddition.

It is also observed that donor-acceptor cyclisation between electrophilic allenes and nucleophilic alkenes, or vice versa, proceed more efficiently and with high regioselectivity.[85]

1.3.2.1 Catalytic [2+2] cycloadditions of allene-enes

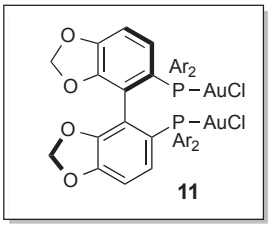
As seen in Chapter 1.3.1.1.2 Lewis acid catalysis may allow reaction between alkenes that are thermally unreactive to cycloaddition. Hiroi *et al.* achieved an intramolecular [2+2] cycloaddition of inactivated allene and ene functionality by the assistance of Lewis acids.[97] The [2+2] cycloaddition reactions of 1,2,7-triene systems were found to be largely dependent upon the acidity of the Lewis acid used and the reaction temperature. The 1,2,7-triene compound **5** having no other functional groups, underwent a [2+2] cycloaddition

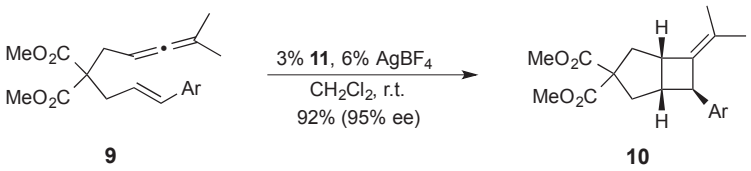
reaction when treated with a strong Lewis acid ($EtAlCl_2$) at low temperature (at -78°C). Using higher temperatures (0°C), polymerisation was the major reaction path. The 1,7-allene-ene **7** having a *gem*-diester group gave a [2+2] cycloaddition product when treated with weaker Lewis acids, e.g. $TiCl_4$ (3.0-7.0 equivalents) at room temperature. On the other hand the more acidic Lewis acids, like $EtAlCl_2$ (0 °C) gave no reaction at all with this compound (Scheme 1.5).



Scheme 1.5

The first transition-metal-catalysed cycloaddition of allene-enes to alkylidene cyclobutanes was reported in 2007 when Luzung *et al.*[98] published an intramolecular [2+2] cycloaddition of allene-enes **9** to give high yields of enantioenriched bicyclo[3.2.0]heptanes **10**, using chiral bisarylphosphine-gold(I) complexes **11** as catalysts (Scheme 1.6). Other gold(I) ligands have been used in enantioselective [2+2] cycloadditions of allene-enes.[99] Nickel complexes have also successfully been applied to allene reactions.[85]



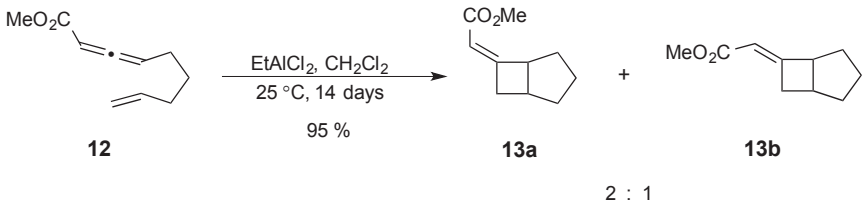


Scheme 1.6 Luzung's synthesis.[98]

Zhao *et al.* identified $In(OTf)_3$ in $MeNO_2$ as the best conditions in a highly efficient acid-catalysed intramolecular [2+2] cycloaddition between the less activated distal allenic double bond and unactivated alkene moieties of ene-allenones.[100] The reaction displays excellent chemo-, regio-, and diastereoselectivities under very mild conditions and enables the stereocontrolled construction of complex polycyclic compounds containing the methylenecyclobutane framework.

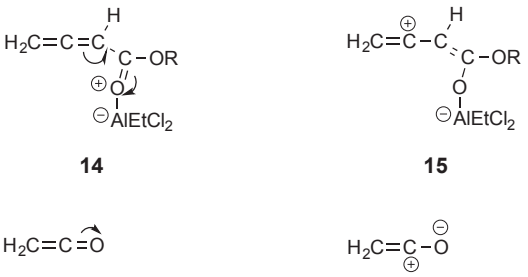
1.3.2.2 Catalytic [2+2] cycloadditions of allenic esters to alkenes

Snider *et al.*[101,102] investigated the Lewis acid catalysed inter- and intramolecular [2+2] cycloaddition of conjugated allenic esters to alkenes. They found $EtAlCl_2$ to be optimal for the Lewis acid catalysed reactions of unsaturated esters. An example is shown in Scheme 1.7.



Scheme 1.7

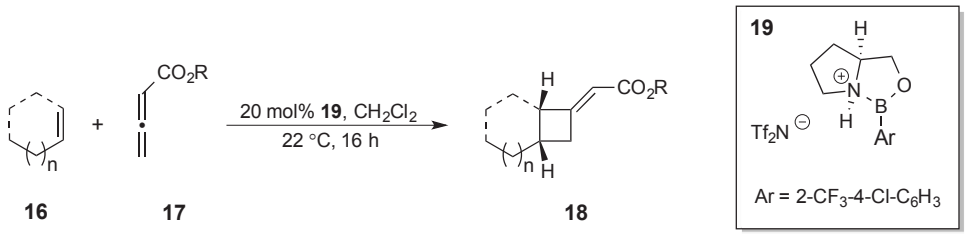
The results indicate that these cycloadditions occur at carbons 3 and 4 of the allene, and the stereo- and regioselectivities of these Lewis acid catalysed reactions are remarkably similar to thermal cycloaddition reaction of the corresponding ketenes, which can be looked upon as a heterocumulene (Scheme 1.8). The mechanistic models used to describe ketene cycloaddition reactions, are probably also applicable to allenic ester cycloaddition.



Scheme 1.8 Comparison between the $EtAlCl_2$ complex and ketene.

An $AlCl_3$ promoted regio- and stereoselective [2+2] cycloaddition of ethyl 2,3-butadienoate and alkenes have also appeared.[103] The yields were low to excellent, depending on the alkene used.

In 2015, Conner *et al.* introduced a new and highly enantioselective method for catalytic [2+2] cycloadditions between readily available allenoates and alkenes.[104] Using the catalyst **19** a wide variety of alkenes undergo cycloaddition with good yields and enantioselectivity, an example is shown in scheme 1.9 Unactivated alkenes may be used, which is in sharp contrast to the majority of reported catalytic enantioselective methods. Strained alkenes give higher yields than the non-strained alkenes. The catalyst is readily available in one step from commercially available starting materials. Limitations of the method are the use of trisubstituted alkenes or α,γ-unsaturated alkenes where low selectivity has been obtained.



Scheme 1.9

The intra-molecular allenic ester cycloadditions complement intramolecular ketene cycloadditions that often proceed in reasonable yields only when activated ketenes are used (See chapter 1.3.1.1.3).

1.3.3 Microwave Assisted Organic Synthesis

Microwave irradiation (MWI) has become a well established and frequently used source of thermal energy for many organic reactions.[105] In 1986 Gedye[106] and Giguere/Majetic[107] published pioneering work in this field, and since then the technique has become increasingly popular. More than 3500 articles in the field of Microwave Assisted Organic Synthesis (MAOS) have appeared.[108]

The microwave heating technique has been shown to dramatically reduce reaction times (from days or hours to minutes or seconds) and side reactions, increase yields, and improve reproducibility of organic reactions.[105]

Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz, corresponding to wavelengths of 1m to 1mm. Both domestic microwave ovens and microwave reactors that are dedicated to chemical synthesis, operate at a frequency of 2.45 GHz. At this frequency the microwave photon has an energy of 0.0016 eV, which is too low to break chemical bonds.

The traditional way of heating an organic reaction is by using conductive heating with an external heat source (oil-bath, heating mantle). Compared to microwave heating this method

is slow and inefficient since it depends on convection currents and the thermal conductivities of the materials that must be penetrated (Figure 1.9). This generally results in the temperature of the reaction vessel being higher than that of the reaction mixture (wall effect) and may lead to the formation of a temperature gradient within the mixture. The reaction mixture that is in contact with the vessel wall is heated first, and local overheating may result in decomposition of *e.g.* products or reactants.

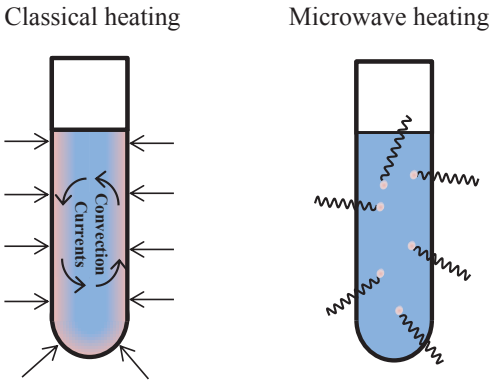


Figure 1.9 Classical conventional heating compared to microwave heating.

Microwave irradiation, however, can produce very efficient, internal heating by the direct transfer of microwave energy to the molecules (solvents, reagents, catalysts etc.) in the reaction mixture. The temperature of the whole mixture is raised simultaneously, thus minimizing the wall effects.

Microwave enhanced chemistry, however, is based on the heating of materials by "microwave dielectric heating" effects. Microwave dielectric heating is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. Irradiation of a reaction mixture is at microwave frequencies, causes substances with dipole moments to align in the applied electric field. When the applied field oscillated, the dipole field attempts to realign itself with the alternating electric field, thereby loosing energy in the form of heat, through molecular friction and dielectric loss. The ability of a

substance (e.g. a solvent) to convert electromagnetic energy to heat at a given frequency and temperature, is given by the loss factor, tanδ.

$$\tan\delta = \varepsilon''/\varepsilon'$$

where ε" is the dielectric loss, which is an indication of the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant which indicates the ability of the molecules to be polarized by the electric field.

In order to efficiently absorb the microwave energy and effect rapid heating of the reaction, the medium must have a high tanδ. Solvents are classified as having a high (tanδ > 0.5, *e.g.* ethylene glycol), medium (tanδ 0.1-0.5, *e.g.* water) or low (tanδ < 0.1, *e.g.* dichloromethane). The overall dielectric properties of the reaction medium will in most cases allow sufficient microwave heating even if solvents with low tanδ are used. In addition polar additives, such as doping with ionic liquids,[109] may also be used to increase absorbance level of the medium. The microwave irradiation technique sometimes displays accelerations that cannot be achieved or duplicated by conventional heating, e.g. a high microwave absorbing solvent may be superheated to temperatures >100 °C above its boiling point when heated by microwaves in a sealed vessel.

In the beginning, the microwave assisted organic synthesis was performed in a sealed vessel in ordinary kitchen microwave ovens, without accurate temperature or pressure measurements and no safety controls. Nowadays advanced instruments that are dedicated specifically to organic synthesis is most often used. These modern microwave reactors usually has online monitoring of temperature and pressure and gives a much better control of reaction conditions, and this is one of the major reasons for the success of the technique.

1.4 Synthesis of 5-Membered Carbocyclic Compounds

The synthesis of 5-membered carbocycles is not a trivial matter and until the 1960's rather few general methods existed. However, the quest for reliable stereoselective methods was spurred by the increasing knowledge of the impact prostaglandins and prostacyclines have in human health. Both of these groups of compound contain the cyclopentane motif. This lead to a large interest in their synthesis. In 1969 Corey published several total syntheses of prostaglandins that are now considered classics in the development of the syntheses of five-membered carbocycles.[110,111] Several recent reviews summarize these and other methods.[112-115] Of other protocols that have grown popular the Pauson-Khand originally published in 1971 should also be mentioned.[116] This is a formal [2+2+1] reaction between an alkyne, an alkene and carbon monoxide to form cyclopentenones. The reaction has been done both inter- and intramolecularly and can to some extent be compared to the more classic Nazarov reaction[117,118] (*vide infra*) since both give cyclopentenones. Many recent reviews summarising this reaction has also been published.[119-121] However, in the enclosed thesis none of these will be specifically mentioned since they are rather different from the corresponding protocol that is described herein. Likewise will standard methods like intramolecular S_N2 reactions and intramolecular Michael reactions that also may be used for preparation of the cyclopentanes not be encountered herein. Readers are encouraged to consult the literature[113-115] for details concerning these and other existing methods. But a few other methods used to prepare 5-membered rings will be briefly mentioned in the next sections.

1.4.1 Some General Methods for Construction of the Cyclopentane Carbon Skeleton

Some of the most frequently used general methods for construction of the cyclopentane carbon skeleton are listed in Table 1.4 on page 39. A few typical experimental characteristics typical experimental characteristics are included in the table. The new C-C bonds that are formed in these reactions are shown in red.

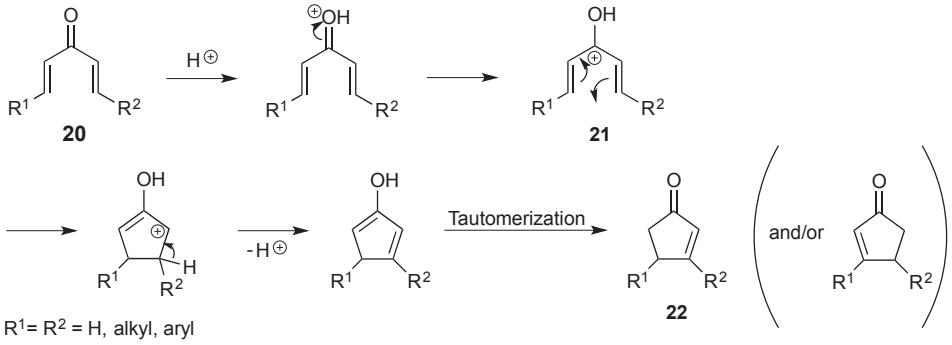
1.4.1.1 Preparation by Standard Carbonyl Chemistry

Five-membered carbocyclic rings are often synthesized by standard carbonyl condensations from 1,4-dicarbonyl compounds, 1,5-dicarbonyl compounds and 1,6-dicarbonyl compounds, as their formation from acyclic precursors are kinetically and thermodynamically favoured.[122]

For instance, the aldol condensation has been used to prepare cyclopent-2-enones from 1,4-dicarbonyl compounds. (Table 1.4, Entry 1) Unless the substrates are chosen carefully, the regioselectivity of the cyclisation to form the ring may be an issue.

1.4.1.2 Preparation by Electrocyclic Reactions - The Nazarov Reaction

Electrocyclic reactions are defined as the formation of a new σ-bond across one of the ends of a conjugated π-system or the breaking of such a bond.[122] The Nazarov[117] reaction is an example of such a reaction: an acid promoted, cationic four-electron electrocyclic, conrotatory cyclisation reaction in which a divinyl ketone **20** is transformed into a 2-cyclopentanone **22** via a 3-oxy-pentadienylic cation **21**.[118] (Table 1.4, Entry 2). The thermodynamically favoured cyclopentenone is formed, however, the classical reaction protocol generally lacks control over the position of the endocyclic double bond (Scheme l.10).



Scheme 1.10 Proposed mechanism for the protic acid induced Nazarov reaction.

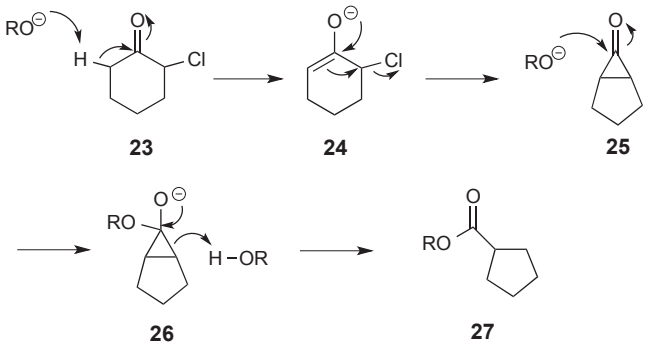
The presence of an electron-donating group (like an alkoxy or vinyl group) or a bridge-headed proton on the endocyclic intermediate, facilitates the protic acid promoted

cyclisation. One 1 equivalent of a Brønsted or Lewis acid is required. $MeSO_3H$ was found to be a superior protic acid for the Nazarov reaction, and Lewis acids like $BF_3{\cdot}Et_2O$, $SnCl_4$, TiCl4 and $AlCl_3$, TMSOTf, $Cu(OTf)_2$ and more complicated ones have been used for this reaction. The regiochemistry of the reaction has been controlled by using the β-cation stabilizing effect and having an electrofuge of silicon,[123-125] or by application of the β-cation destabilizing effect and the α-electron-donating effect of fluorine.[126-127]

1.4.1.3 Ring Contraction

1.4.1.3.1 The Favorskii Rearrangement

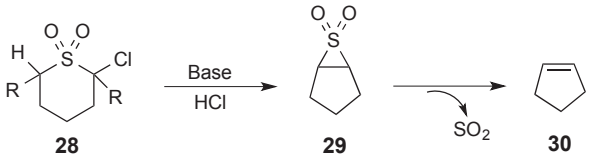
In this rearrangement an α-haloalkanone e.g. **23** is treated with a nuclophilic alkoxide RO^-.[128-130] The enolate **24** cyclises to give an unstable cyclopropane **25** that is immediately attacked by the alkoxide resulting in cleavage of the week C-C bond in the 3-membered ring. For cyclic compounds the result is a ring-contracted ester **27** (Table 1.4, Entry 3).



Scheme 1.11 The Favorskii Rearrangement.

1.4.1.3.2 Ramberg-Bäcklund

The Ramberg-Bäcklund reaction is a method for transforming α-halosulfones into alkenes (Scheme 1.12).[131,132] The first step may in fact be considered as a type of Favorskii reaction mentioned in the previous section. Abstraction of a proton from the non-halogenated α-carbon of the α-halosulfone **28** yields an episulfone **29** which extrudes SO_2 to provide the product alkene **30**. (Table 1.4, Entry 4).



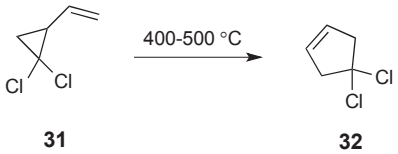
Scheme 1.12 The Ramberg-Bäcklund reaction.

1.4.1.4 Preparation by Ring expansions

Ring expansion of Cyclobutylmethyl Carbocations are treated separately in Chapter 1.4.2.

1.4.1.4.1 The Vinyl Cyclopropane to Cyclopentene Rearrangement

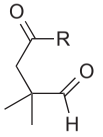
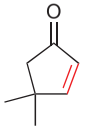
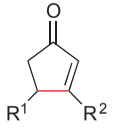
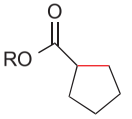
When subjected to strong heating, vinyl cyclopropanes rearrange to cyclopentenes.[122] In 1959 Neureiter[133] discovered that 1,1-dichloro-2-vinylcyclopropane (**31**) when heated above 400 °C rearranged thermally to dichlorocyclopentene (**32**) (Scheme 1.13 and Table 1.4, Entry 5).



Scheme 1.13 Vinylcyclopropyl rearrangement

A year later the rearrangement of vinylcylopropane to cyclopentene was also reported.[134-136] The mechanism of the reaction is still being debated, and both a diradical-mediated two-step mechanism and a fully concerted orbital symmetry controlled mechanism has been suggested.[137] Both thermal, photochemical and transition metal catalysed versions of this reaction have been developed.[137] Heteroatoms attached to the ring have been found to greatly accelerate the rate of the reaction, and when strong Lewis acids (e.g. Et_2AlCl) are used as catalysts, the reactions may be performed at low temperatures (-78 °C), and the substrate scope of the reaction was expanded. The reaction has been used with several different substituents on the vinylcyclopropanes, e.g. with thiophenyl or trimethylsiloxy substituents.[137,138]

Table 1.4 Some Methods for Preparation of Cyclopentane Rings[a]

Entry	Name of Reaction	Substrate	Typical Reagents	Product	Ref.
1	Standard carbonyl chemistry	*e.g.:* 	Base		122
2	The Nazarov Reaction	Divinyl ketone	H^+,$MeSO_3H$, $BF_3{\cdot}Et_2O$, $SnCl_4$, TiCl4, $AlCl_3$, TMSOTf, $Cu(OTf)_2$	 and regioisomer	117 118 122-127
3	Favorskii rearrangement	α-haloalkanones	Nucleophilic alkoxide		128-130
4	Ramberg - Bäcklund	α-halosulfones	Base		131 132
5	Vinyl Cyclopropane to Cyclopentene Rearrangement		- Δ - hν - Lewis acids, transition metals		122 133-138

[a] R, R^1, R^2 = H or functional group.

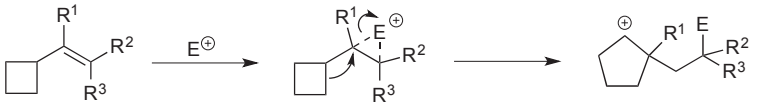
1.4.2 Ring Expansions of Cyclobutylmethyl Carbocations

Some of the most used methods of synthesizing 5-membered rings are ring-expansion reactions, and the driving force in many of these methods are the relief of ring strain combined with the generation of a positive charge on the carbon atom adjacent to a 4-membered ring (Scheme 1.14).[115] The relief of ring strain associated with expansion from a cyclobutane ring to a cyclopentane ring is larger than for the expansion from a cyclopropane ring to a cyclobutane ring (or from a cyclopentane ring to a cyclohexane ring).

Scheme 1.14 Ring expansion of cyclobutylmethyl carbocations.

1.4.2.1 Ring Expansion of Cyclobutylmethyl carbocation through Activation of a C=C bond

Alkenylcyclobutanes like **33** are interesting substrates for preparation of 5-membered rings as they are prone to attack by an electrophile, E^+ under Markovnikov rules. An electrondeficiency is created, thereby triggering a ring expansion.[115] (Scheme 1.15) The formation of the cyclobutylmethyl carbocation by activation of a C=C bond may be promoted by *e.g.* an acid, by halogen/selenium or by metals.



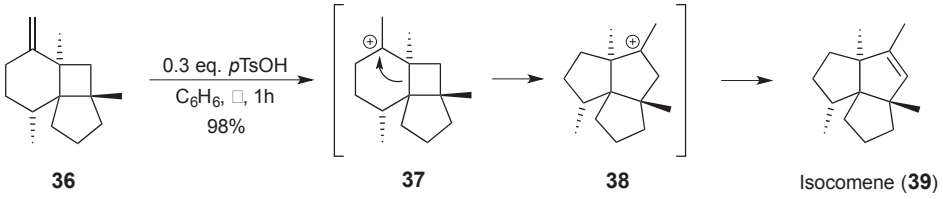
33 **34** **35**

Scheme 1.15

Allenes and alkynes may also be activated toward ring-enlargement.

An example of this type of ring expansion is the acid promoted ring expansion of different types of vinylcyclobutanes. Both protic acid and Lewis acid-catalysed rearrangements of α-vinylcyclobutanes by use of methanesulfonic acid or $BF_3 \cdot Et_2O$ are known, and *e.g.* ring-

annelated bicyclo[3.1.0]hexanones, bicyclo[4.3.0]nonenones have been prepared in this way. The last step in the total synthesis of isocomene (**39**) involved an acid-catalysed cyclobutylmethyl to cyclopentyl carbocation rearrangement.[139,140]



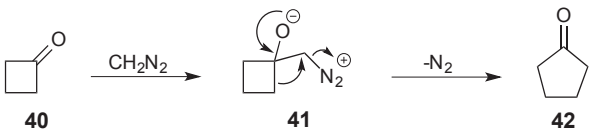
Scheme 1.16 Pirrung's synthesis of isocomene (**39**)

1.4.2.2 Ring Expansion of Cyclobutylmethyl carbocation by Expulsion of a Leaving Group

Another way of forming the cyclobutylmethyl carbocation is through the expulsion of a leaving group. Different kinds of leaving groups are used, e.g. halogens, nitrogen, activated hydroxy and alkoxy groups, sulfur or selenium groups.

The semipinacol-type rearrangement of diazoalkanes.

The diazomethane method is the most extensively used protocol for the ring expansion of cyclobutanones to cyclopentanones.[115] (Scheme 1.17) The rearrangement of the intermediate zwitterion **41** is usually highly regioselective generally yielding only one product, especially when using α-chloro- or α,α-dichlorocyclobutanones and substituted diazomethanes are used. Migration of the less substituted α-carbon is favoured, but migration of α-carbons bearing electronegative halogens is disfavoured. However, other factors like steric effects, ring strain, steric hindrance related to approach of the diazomethane may influence the regioselectivity.



Scheme 1.17 Semipinacol type rearrangement of diazomethanes.

CHAPTER 2 - RESULTS AND DISCUSSION

2.1 Relationship between Papers.

As part of our continued interest in the synthesis of natural products, we are interested in developing new methods or make amendments to already well-established methods for the synthesis of different cyclic compounds. The unifying theme of this thesis is to use new methodology in order to improve old methods.

Dibromocyclopropanes, the three-membered ring compounds that are the subjects of **Papers I** and **II**, are especially interesting since they are versatile intermediates for the synthesis of other interesting compounds, like natural products. In **Paper I** a flow chemistry method using a microreactor was developed, which can be used as an easy and rapid alternative to the already existing methods. In **Paper II** the scope and limitations of this flow chemistry method was investigated further when unsaturated alcohols were included as substrates. The dibromocyclopropanes are interesting as precursors for allenes, the subject of **Paper III**.

In **Paper III** the microwave irradiation technique was used in a Lewis acid catalysed intramolecular [2+2] cycloaddition of allene-ene esters. A particularly interesting result was obtained for one of the substrates where the reaction time was reduced from 14 days to 30 seconds. The results obtained here are, however, preliminary and work is on going to develop the methodology further to establish a fast method for the synthesis of 4-membered ring compounds, for instance isopropylidenecyclobutanes like the compounds used in **Paper IV**.

Paper IV reports the results obtained when several isopropylidenecyclobutanes (4-membered rings) were subjected to HBr/HOAc under different reaction conditions. In polar solvents the isopropylidenecyclobutanes were found to undergo a ring expansion reaction yielding cyclopentanes (5-membered rings).

2.2 Two-Phase Dibromo-Cyclopropanation of Alkenes by Use of Flow Chemistry in a Microreactor (Paper I and II)

The aim of this part of the thesis was to prepare *gem*-dibromocyclopropanes by using a well-established method (dihalocyclopropanation under phase-transfer catalysis) in a new way (by using a microreactor). The following chapter describes the results obtained for several different alkenes.

The use of gem-dibromocyclopropanes as versatile intermediates for the synthesis of other useful compounds like allenes[141,142] cumulenes[143] and furans,[144] has rendered them important substrates in organic synthesis. Their usefulness in the synthesis of natural products is also acknowledged, and new methods for their profitable use has been developed in recent years.[145] Our interest in the dibromocyclopropanes stems especially from the fact that they can be used in the synthesis of allenes,[146-148] compounds that are used in paper (III).

2.2.1 The Use of Flow Chemistry for Two-Phase Dibromocyclopropanation of Alkenes (Paper I)

2.2.1.1 Strategic Considerations

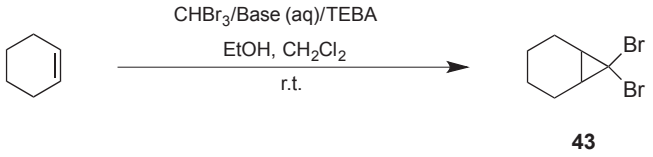
The conventional two-phase Makosza method[61] (Chapter 1.2.2.) is still one of the most efficient methods for the preparation of dibromocyclopropanes,[53,145,149] using a phase-transfer catalyst to facilitate mass transport between the two phases, and vigorous stirring to make the interface between the two phases as large as possible.

In microreactors (Chapter 1.2.3) the reactants are mixed in narrow channels, and rapid mass and heat transfer is obtained as a result of the high surface-to-volume ratio and short diffusion lengths. In slug-flow reactors (Chapter 1.2.3) internal circulation in alternating slugs result in an increased mass transfer compared to *e.g.* parallel flow reactors,[83,84] and the slug-flow method seemed to be an interesting method to use for the two-phase dibromocyclopropanation of alkenes. To our knowledge this is the first time the two-phase dibromocyclopropanation of alkenes has been done using flow chemistry in a microreactor.

2.2.1.2 Results and Discussion

2.2.1.2.1 Choice of System and Optimisation of Reaction Conditions

For the initial experiments cyclohexene was chosen as the substrate, TEBA was used as the phase-transfer catalyst, bromoform was the dibromocarbene precursor and dichlorometane was used as the organic solvent. (Scheme 2.1) Cyclohexene was chosen as a convenient substrate since its reaction is well known, and the product is easily identified. Dibromocyclopropanes are more reactive than dichlorocyclopropanes, and since we also are interested in their use as allene precursors our focus was on the dibromo compounds.



Scheme 2.1 Dibromocyclopropanation of cyclohexene.

In preliminary studies, 50 % (w/w) NaOH was used as the base, since this base concentration is used in traditional two-phase systems. However, when using this viscous base solution, severe clogging of the flow reactor resulted. The problem was resolved by reducing the base concentration to 40 % (w/w).

Initially, a ratio of cyclohexene-bromoform-TEBA of 1:1: 0.009 was mixed with 40 % (w/w) NaOH (aq) in a 1 mL glass microchip reactor. The aqueous to organic flow ratio (AO ratio) was 1. Low yields of the dibromocyclopropane adduct **43** (7-18 %) resulted, even though the reaction time was increased (up to 85 min), either by adding a tube reactor, or by lowering the flow rate (Table 2.1, Entry 1).

Some improvement in the yields could be seen when the ratio of cyclohexene-bromoform-TEBA was 1:1.5: 0.026. However increasing the concentration of TEBA to 4.2 mol% (relative to cyclohexene) only left the microreactor more prone to clogging (Table 2.1, Entry 2), even when the solution was diluted by the addition of more CH_2Cl_2 and the glass

microchip reactor was replaced by a Y-mixer. (Table 2.1, Entry 3). Although ultrasonication has been shown to increase the yield both in phase-transfer dibromocyclopropanation reactions using Brinker's method[72] and in reactions using flow chemistry,[150] we did not observe an increase in the yield when our tube reactor was subjected to sonication, and best yields obtained were 31-34 %.

A solution of 45 % (w/w) KOH in water is less viscous/concentrated than a 40 % (w/w) NaOH solution in water,[151] and we decided to try this KOH solution as the base. TEBA was added to the water phase in a concentration (0.12 wt %, 0.014 mol% relative to the KOH solution) that was used with success in another phase-transfer reaction in the literature.[80] The yields obtained were discouragingly low (4-6 %), although reaction times from 6 to 50 minutes were tried, by changing either the tube lengths or the flow rates (Table 2.1, Entry 4).

Jovanovic *et al.*[80] found that increasing the AO ratio (from 1 to 4) in a PTC alkylation of phenylacetonitrile (using 45 % (w/w) KOH (aq) containing 0.12 wt % TEBA) increased the yield of the product. This can be attributed to the decreased organic slug size and increased average surface-to-volume ratio yielding an increased rate of catalyst transfer across the liquid-liquid interface area, and also increasing the internal circulation of the organic interslug.[80] When we increased the AO ratio, an increase of the yield of dibromocyclopropane adduct **1** was obtained at an AO ratio of 4, but not at an AO ratio of 9. (Table 2.1, Entries 5-6) This is in accordance with the existence of an optimum flow ratio with a maximum productivity.[80] The yields obtained were still quite low, and further optimization with this KOH solution was abandoned.

When an AO ratio of 4 was used with 40 % (w/w) NaOH (aq), however, the yields were greatly increased (Table 2.1, Entry 7). The clogging problems previously experienced, was solved by removing the backpressure regulator since the same yields were obtained with the backpressure regulator as without. During this optimisation phase, teflon tube reactors of several different lengths were tried. The best yields were obtained with a 25 mL tube reactor used in combination with a teflon Y-mixer, and after a lengthy trial and error phase, the yields obtained had increased from 7 to 78%. Increasing the bromoform amount from 1.5 to

2 equivalents gave only a minor increase in yield (from 78 % to 85 %). A picture of our flow chemistry system is shown in Figure 1.8 in Chapter 1.2.3.

Table 2.1 Dibromocyclopropanation of cyclohexene.[a]

Entry	[Alkene] (M)	Base[b]	EtOH (Vol%)	TEBA[c] (mol%)	AO Ratio[d]	Reaction time (min)	Yield (%)
1	2.2[e]	NaOH	1.6	0.9	1	1-85	7-18
2	2.8	NaOH	1.2	2.6-4.2	1	26-52	22-29
3	1.4	NaOH	0.6	4.2	1	50-52	31-34[f]
4	2.8	KOH	1.2	0.3	1	6-50	4-6
5	2.8	KOH	1.2	1.1	4	40	22
6	2.8	KOH	1.2	2.5	9	40	7
7	2.8	KOH	1.2	1.1	4	40	11[g]
8	1.4	NaOH	0.6	4.2	4	50	78

[a]Conditions used unless otherwise stated: room temperature, back pressure 1.5-3 bar, 1.5 eq $CHBr_3$ relative to cyclohexene.
[b]Base concentrations: NaOH (aq): 40 % (w/w), KOH (aq): 45% (w/w) containing 0.12 wt. % TEBA.
[c]Relative to cyclohexane
[d]Aqueous to organic flow ratio (AO ratio)
[e]1 eq. $CHBr_3$ relative to cyclohexene.
[f]Clogging occurred.
[g]$CHBr_3$ was used as solvent instead of dichloromethane.

2.2.1.2.2 Scope and Limitations

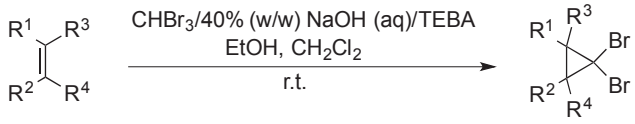
In order to test the scope and limitations of this method, a selection of alkenes containing a variety of structural features were tested with our optimized conditions:

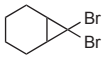
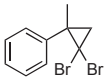
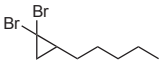
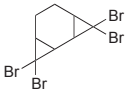
- an alkene concentration of 1.4 M
- an alkene-bromoform-TEBA ratio of 1:1.5-2: 0.042
- a total flow rate of 0.50 mL/min (aqueous + organic flow rate)
- an AO ratio of 4

using 40% (w/w) NaOH (aq) as the base.

Representative yields are shown in Table 2.2.

Table 2.2 Dihalocyclopropanation of a selection of alkenes using the optimised conditions.[a]



Entry	Substrate	Product		Yield (%)[b]	Lit. yield (%)[c]
1			**43**	77-85	76[152]
2			**44**	78	80[63]
3			**45**	82	73[153]
4			**46**	47	-
5			**47**	92	-
6			**48**	81	77[154]
7			**49**	65	38[155]
			**50**	9	
8			**51**	57	58[156]
9			**52**	63	-

[a]Conditions unless otherwise stated: [alkene]=1.4 M, 1.5-2 eq. $CHBr_3$ (relative to alkene), 4.2 mol% TEBA (relative to alkene), 0.6 vol% ethanol (in CH_2Cl_2); room temperature, 25 mL PTFE tube reactor; total flow rate: 0.50 mL/min; AO ratio: 4; reaction time: 50 min.

[b]Estimated using ^{1}H NMR spectra of the isolated reaction mixture.

[c]Literature yields are only given for Makosza conditions using TEBA.

High yields were obtained, except when the monosubstituted alkene, 1-heptene, was used as the substrate (Table 2.2, Entry 4), a result that is in accord with known order of reacting the alkenes with dihalocarbenes (See Chapter 1.2.2). Even a *gem*-dichlorocyclopropane **52** was prepared in good yield. This indicates that the reaction may also be used with chloroform as the dihalocarbene precursor. The yields obtained were comparable to yields found in the literature when using the same phase-transfer catalyst in the Makosza protocol.

2.2.1.3 Conclusions

Good to excellent yields in less time than for batch chemistry were obtained when flow chemistry in a microreactor was used for the dibromocyclopropanation of alkenes under phase-transfer catalysis (PTC) using 40% (w/w) NaOH (aq) as the base. The yields obtained were comparable to the ones reported from ordinary batch reactions using the same phase-transfer catalyst.

Thus, the use of flow chemistry in a microreactor should be an interesting alternative for the Makosza reaction (compared to the traditional batch chemistry).

2.2.2 Two-Phase Dibromocyclopropanation of Unsaturated Alcohols Using Flow Chemistry (Paper II)

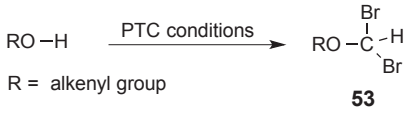
The following chapter describes the results obtained when using the method developed in paper I with unsaturated alcohols as substrates. Having successfully used flow chemistry in a microreactor to prepare different alkenes in high yields, we wanted to investigate the scope and limitation of the method even further by including unsaturated alcohols as substrates.

2.2.2.1 Choice of Strategy

With unsaturated alcohols, the dibromocyclopropanation reaction is known to be strongly dependent upon the structure of the alcohol and also the exact conditions used.[53] The yields of the alcohols in the literature are varying from excellent to low. For two main reasons the

hydroxyl group is often protected as an acetal[53,157] or an ether[53,158] when used in this reaction:

1. The hydroxy group (or alkoxy anion) has been known to compete with the double bond for the dihalocarbene to give an O-H insertion product **53**. (Scheme 2.2)[53]
2. The unsaturated alcohols are also known to form other side products that make the purification of the main product difficult.



53

Scheme 2.2 Insertion of dibromocarbene at the O-H bond.

We wanted to investigate the possibility of performing the dibromocyclopropanation in a microreactor without the use of protecting groups.

2.2.2.2 Results and Discussion

2.2.2.2.1 Choice of System and Substrates

The same reaction conditions and system that was used in paper I (an alkene concentration of 1.4 M, a ratio of alkene-bromoform-TEBA of 1:1.5: 0.042-0.043, 40% (w/w) NaOH (aq), 0.6 vol.% EtOH, AO ratio 4, total flow rate 0.50 mL/min) was tried. However, we found that the yields increased when 2-2.5 equivalents of bromoform was used (*i.e*. a ratio of alkene-bromoform-TEBA of 1:2-2.5: 0.042-0.043).

Kleveland *et al.*[159] observed an intriguing difference between the allylic alcohols, linalool (**54**) and geraniol (**55**) (Figure 2.1) when these alcohols were used in the conventional batch version of the Makosza reaction (with dichlorocarbene). When linalool (**54**) was used, an excellent yield of the dichlorocyclopropane monoadduct, 5-(2,2-dichloro-3,3-

dimethylcyclopropyl)-3-methyl-1-penten-3-ol (**56**), (89%) was obtained in a rapid and regioselective reaction, whereas geraniol was less reactive and gave a low yield of a mixture containing at least six components that partially decomposed under the attempted separations. The difference in reactivity has been explained as a result of the primary allylic hydroxyl group competing for the dihalocarbene, and its retarding effect of the rate of addition of dihalocarbene.[159]

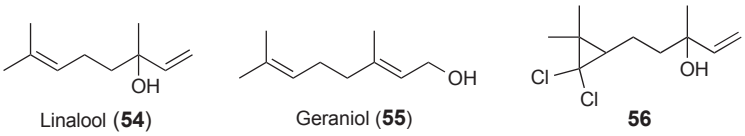
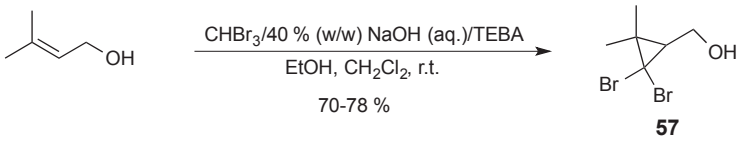


Figure 2.1 The allylic alcohols linalool and geraniol, and the dichlorocarbene adduct **56**.

These two beautifully scented unsaturated alcohols seemed to be interesting substrates to test with our optimised flow chemistry conditions.

2.2.2.2.2 Scope and Limitations

Several other unsaturated alcohols were tested with our optimized conditions flow chemistry conditions. The results are shown in Table 2.3, and the reaction is shown for 3-methyl-2-buten-1-ol in Scheme 2.3.



Scheme 2.3 Dibromocyclopropanation of 3-methyl-2-buten-1-ol under PTC conditions.

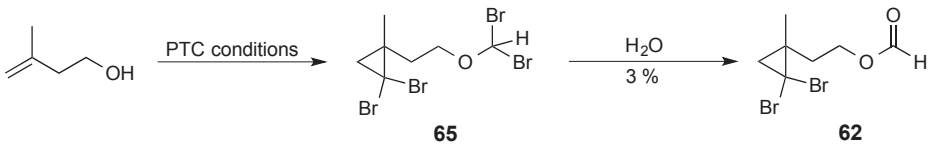
The reactions were generally rapid, and the yields obtained were comparable to yields reported in the literature for the conventional batch reaction. All products, except the ones that were obtained with geraniol, were easily identified by their spectral data. (Table 2.3, Entry 1)

When the tertiary dienol linalool was used as a substrate, regioselective addition to the trisubstituted double bond occurred, and the dibromocyclopropane **58** was obtained in excellent yield as a mixture of diastereomers (approximately 1:1). (Table 2.3, Entry 2). Due to overlap of signals in the ^{1}H NMR spectrum, only an estimation of the diastereomeric ration could be done. Geraniol, however, yielded a mixture of several products, (Table 2.3, Entry 3) as was also observed by Kleveland *et al.*[159] with dichlorocarbene. No attempts were made to separate the complex mixture of geraniol adducts. The difference in the outcome of the reaction of these two terpenoid allylic alcohols is probably that geraniol has two trisubstituted double bonds and a primary hydroxyl group that will easily compete in a reaction with a dibromocarbene, while linalool has two very differently substituted double bonds, and a sterically congested tertiary alcohol give little or no competition in the reaction with the same dibromocarbene.

Interestingly, citronellol that only differ structurally from geraniol by the absence of the allylic double bond, yielded the dibromocyclopropane **60** as a mixture of diastereomers (approximately 1:1) in 57 % yield. (Table 2.3, Entry 4).

The dibromocyclopropane **60** was easily identified from its ^{1}H NMR spectrum by a characteristic doublet at δ 0.89 ppm corresponding to the methyl group at the metin carbon, the broad singlet at δ 1.75 ppm corresponding to the hydroxyl proton and from its ^{13}C NMR spectrum by resonance at δ 60.9 ppm corresponding to the carbon bearing the OH-group. The other features of the spectra were in accord with the structure. The molecular ion was obtained in high resolution MS.

From 3-methyl-3-buten-1-ol, the dibromocyclopropyl alcohol **61** was obtained in moderate yield (47%) after chromatography (Table 2.3, Entry 5) together with a small amount of the formate ester **62** (3%). The presence of the formate ester can be explained by insertion of dibromocarbene at the O-H bond and subsequent hydrolysis (Scheme 2.4).



Scheme 2.4 Insertion of dibromocarbene at the O-H bond and subsequent hydrolysis.

The formate ester **63** was identified from its spectral data, particularly the singlet at δ 8.05 ppm in ^{1}H NMR (the formate ester proton), the resonance at δ 160.9 ppm in ^{13}C NMR (the formate ester carbon) and the strong peak at 1725 cm^{-1} in IR (characteristic of a formate ester.).

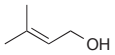
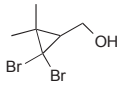
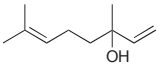
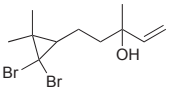
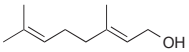
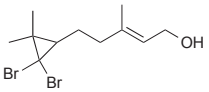
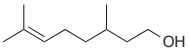
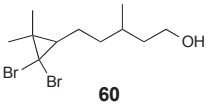
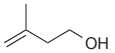
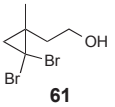
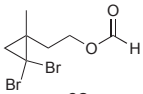
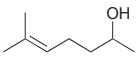
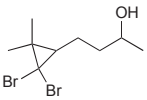
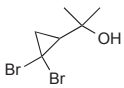
The secondary alcohol, 6-methyl-5-hepten-2-ol, gave a good yield of the dibromocarbene adduct **64** as a mixture of diastereomers (approximately 1:1) (Table 2.3, Entry 6).

The tertiary alcohol, 2-methyl-3-buten-2-ol, has been reported to react sluggishly when subjected to dichlorocarbene under phase-transfer conditions,[159] and when we used this alcohol as a substrate, only small amounts of the starting material could be isolated (Table 2.3, Entry 7).

2.2.2.3 Conclusion

Flow chemistry in a microreactor has been used with success for the dibromocyclo-propanation of several unsaturated alcohols under phase-transfer catalysis (PTC) using 40% (w/w) NaOH (aq) as the base. Depending of the structure of the alcohol, moderate to excellent yields in less time than for batch chemistry were obtained. The reactions were generally rapid, and the yields were comparable to yields reported in the literature for the conventional batch reaction. The best yields were obtained with the trisubstituted alkenes (Table 2.3, Entries 1-4, 6). This has been explained as resulting from the increased nucleophilicity of the trisubstituted double bonds compared to di- and monosubstituted double bonds when the substituents are electron donating.[41h]

Table 2.3 Dibromocyclopropanation of a selection of unsaturated alcohols using 40% (w/w) NaOH (aq) at AO ratio: 4.[a]

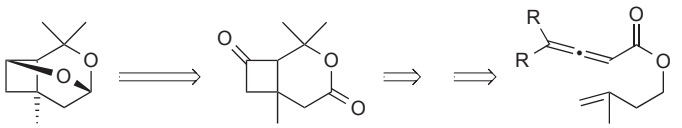
Entry	Substrate	Product	Yield (%)	Litt. yield (%)[c]
1		 **57**	70-78 [d]	(36[160])
2		 **58**	98[d]	(93[159])
3		 **59**	-	(-[159])
4		 **60**	57[e]	(-)
5		 **61**	47[e]	(58[161])
		 **62**	3[e]	(-)
6		 **63**	77[e]	(-)
7		 **64**	-	(2[162])

[a]Conditions unless otherwise stated: [alkene] = 1.4 M, 4.2-4.3 mol% TEBA (relative to alkene), 0.6 vol% ethanol (in CH_2Cl_2). Room temperature, 25 mL PTFE tube reactor. Total flow rate 0.50 mL/min. Aqueous to Organic flow ratio (AO ratio): 4. Reaction time 50 min. [b]Relative to alkene. [c]Literature yields are only given for Makosza conditions using TEBA. [d]Estimated using ^{1}H NMR spectra of the isolated reaction mixture. [e]Isolated yield.

2.3 Synthetic Studies towards Cyclobutanes by Microwave Assisted Intramolecular [2+2]-Cycloaddition of Allene-ene Esters (Paper III)

The aim of this part of the thesis was to subject allene-ene esters to microwave irradiation to improve the intramolecular [2+2] cycloaddition of these compounds and obtain cyclobutane compounds. The following chapter describes the preliminary results obtained. Part of this work is also based on the work published in a Master thesis.[163]

We are interested in the cycloaddition products from the intramolecular [2+2] cycloaddition of allene-ene esters for two main reasons: 1) They can be used in ring expansion of isopropylidenecyclobutanes, the subject of paper IV (Chapter 2.4) to yield *e.g.* diquinanes, and 2) They are interesting as intermediates in natural product synthesis, e.g. of the insect pheromone component lineatin **66** (Scheme 2.5).[95,96]



Lineatin **66** **67** **68**

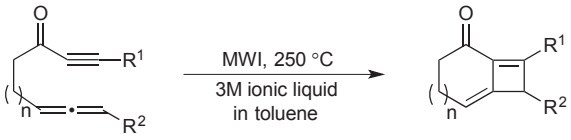
R = H or CH_3.

Scheme. 2.5 Retrosynthesis of the pheromone component lineatin (**66**).

2.3.1 Choice of Strategy

At the start of this project, only a few papers on the thermal Lewis acid catalysed [2+2] cycloaddition of allenoate esters and alkenes had been published (Chapter 1.3.2.2).[101-103] Although high yields of the [2+2] adducts were sometimes achieved, high temperatures and/or long reaction times were usually required.[102] The use of microwave irradiation as a heat source in synthetic organic chemistry has been found to decrease the required reaction time, as well as reduce the amounts of side products, in several types of reactions. (Chapter 1.3.3).[105,108]

Brummond *et al.*[164] found an efficient route to bicyclomethylenecyclobutenes by using microwave irradiation of alkynyl allenes (Scheme 2.6), and the use of the microwave heating technique seemed interesting also for the Lewis acid catalysed [2+2] cycloaddition of allene-ene esters.



69 **70**

Scheme 2.6 Brummond's microwave heated synthesis

2.3.2 Results and Discussion

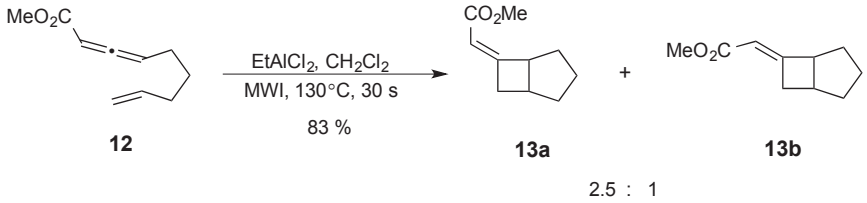
2.3.2.1 Choice of System and Optimisation of Reaction Conditions

The allene-ene ester **12** was chosen as the model molecule in a CH_2Cl_2 solution since it had already been tested in the thermal Lewis acid catalysed [2+2] cycloaddition by Snider and Ron,[102] using this solvent. Although CH_2Cl_2 is a low microwave absorbing solvent[105,108] the overall dielectric properties of the reaction medium (including polar reagents and catalysts) will in most cases allow sufficient heating by microwaves.[105]

When Snider and Ron subjected this allene-ene ester to $EtAlCl_2$ at 25 °C, a reaction time of 14 days were required to give a 95 % yield of a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13a**) and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13b**) in a ratio of 2 : 1.[102]

The extremely long reaction time of two weeks spurred us to see if this could be improved. Several Lewis acids, temperatures and reaction times were tested in the microwave irradiated optimization trials. The best result was obtained when microwave heating was applied to this reaction at 130 °C for only 30 s, yielding >96% conversion and a mixture of the esters **13a** and **13b** (2.5 : 1) (according to GLC) in 83% isolated yield. (Scheme 2.7 and Table 2.4, Entry 3) Although several attempts were made for chromatographic separation of

the esters **13a** and **13b**, none were successful. A selection of the parameters used for optimization and representative results are presented in Table 2.4.



Scheme 2.7 Microwave assisted Lewis acid catalysed reaction of **12**.

Table 2.4: Parameters for optimization of the microwave assisted Lewis acid catalyzed [2+2]-cycloaddition of methyl 2,3,8-nonatrienoate (**12**).

Entry	Lewis acid[a]	Temperature [°C]	Reaction time [s]	Conversion/ (Isolated yield) [%]
1	$EtAlCl_2$	80	1200	poor
2	$EtAlCl_2$	100	10	83[b]
3	$EtAlCl_2$	130	30	>96[b] (83)
4	$EtAlCl_2$	140	10	>96[b]
5	$AlCl_3$	130	10	< 50[d]
6	$AlCl_3$	140	30	>96[b]
7	$FeCl_3$	100	600	Small amounts
8	BF_3	100	600	-
9	-	120	1200	0[c]

[a] CH_2Cl_2 was used as the solvent.

[b] According to GLC analyses

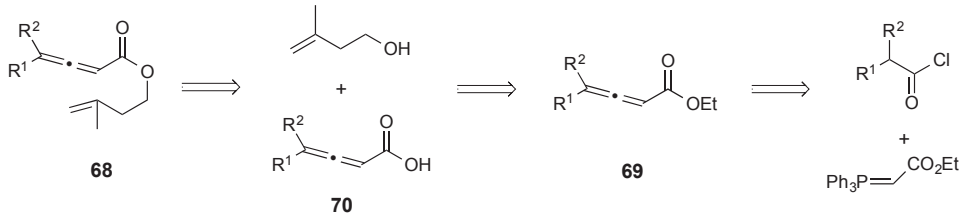
[c] According to ^1H NMR analyses

[d] According to IR analyses

$EtAlCl_2$ was found to be a better catalyst for the reaction than $AlCl_3$, since a temperature of 140 °C was required to get full conversion when $AlCl_3$ was used (Table 2.4, compare Entry 3 with entries 5 and 6). Such a high temperature may be difficult to obtain in the microwave oven when using the low microwave absorbing solvent CH_2Cl_2.[105] As a control experiment the reaction was attempted without any Lewis acid present. But even with extended MW heating no detectable conversion was observed. (Table 2.4, Entry 9).

2.3.2.2 Scope and Limitations

To explore the scope and limitations of this microwave irradiated reaction, we wanted to test it for alkenyl allenoic esters, and a strategy for the synthesis of these starting materials was devised (Scheme 2.7).]

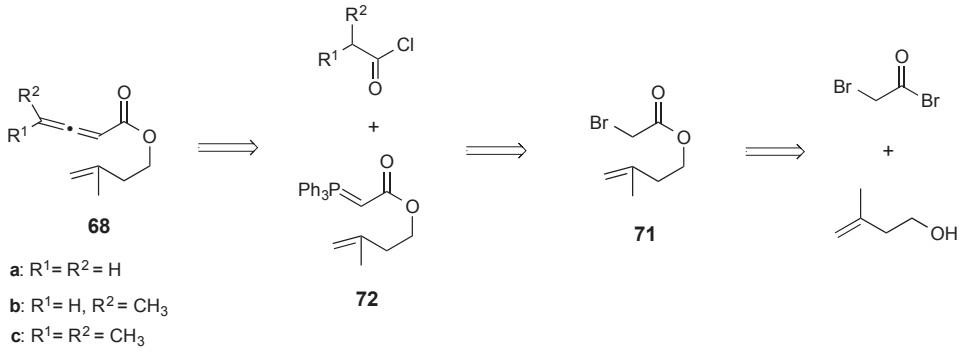


a: R^1= H, R^2 = H

b: R^1= H, R^2 = CH_3

Scheme 2.7 Strategy for the synthesis of model molecules **68**.

The esters **69a** and **69b** were prepared in 30 % and 63 % yield, respectively, using a literature procedure.[165,166] Hydrolysis (using $LiOH•H_2O$ in a mixture of glyme and water (1: 1)), yielded the acid **70a** in 78 % yield. With the ester **69b**, however, a mixture of the allenic acid **70b** and 3-propionic acid (20:80) was obtained. Approximately the same mixture of acids were obtained in the literature when the hydrolysis was done in ethanol.[167] Given the poor yields of the ester **69a** and allenoic acid **70b**, we decided to change strategy for the synthesis of our model compounds (Scheme 2.8), and since the allene ester **68b** is prone to rearrangement to 3-pentynoic acid, we decided to use the ester **68c** instead.



Scheme 2.8 Revised strategy for the preparation of allene esters **68**.

(3-methyl-3-buten-1-yl) 2-bromoacetate (**71**) was prepared by a general literature procedure for production of bromoacetates.[168] Reaction with PPh_3 and subsequent treatment by base afforded the phosphonium ylide **72** in good yield. Reaction of **72** with acyl chlorides provided the allene esters **68a** and **68c** in in 62 % and 14 % yield, respectively. The yields have not been optimized.

To explore the scope of the reaction, the allene esters **68a** and **68c** were treated with several different Lewis acids (e.g. $EtAlCl_2$, $AlCl_3$, Tf_2NH) using different concentrations of allene esters and amounts of Lewis acids during microwave irradiation. Temperatures ranging from 120 to 200 °C and prolonged reaction times were attempted. The reactions are summarised in Table 2.5 and Table 2.6 below. In most cases the allene esters were unconverted, as seen by taking out aliquots and checking for the characteristic allene-stretch in the IR spectrum (at approximately 1950 cm^{-1}). For an additional check the reaction mixture was worked up, and the NMR spectra were recorded, confirming that no cyclobutanes had been formed.

Work to optimise the Lewis acid catalysed [2+2] cycloaddition is still on going in our group, and we are looking into the possibility to change solvents or dope the solution with an ionic liquid[109] in order to increase the microwave absorbance level of the liquid.

Table 2.5 Attempts on intramolecular Allene-ene cycloaddition of (3-Methyl-3-buten-1-yl) 2,3-butadienoate (**68a**) using different Lewis acids

Entry	Allene [M]	Lewis acid	Lewis acid [mol%][a]	Solvent	Temperature[b] [°C]	Reaction time at each T [min]
1	0.4	$EtAlCl_2$[c]	0.9	CH_2Cl_2	120 - 200	10
2	0.6	$EtAlCl_2$[d]	9	CH_2Cl_2	100-130	0.5
3	0.4	$EtAlCl_2$[d]	9	CH_2Cl_2	135-160	0.5
4	0.6	Tf_2NH	1.9	CH_2Cl_2	100-180	5
5	0.6	Tf_2NH	1.9	CH_2Cl_2	130-170	30
6	0.42	Tf_2NH[e]	0.1	Toluene-CH_2Cl_2 (1:4)	100, 250	10
7	neat[f]	$AlCl_3$	0.5	Benzene or CH_2Cl_2	100-180	30

[a]Related to alkene.

[b]Reactions were cooled down and sampled after the reaction time was over, then heated to the next temperature.

[c]0.1 M in hexane.

[d]1 M in hexane.

[e]0.01 M Tf_2NH in CH_2Cl_2.

[f]0.160 g allene, no solvent.

Table 2.6 Attempts on intramolecular Allene-ene cycloaddition of allene (3-Methyl-3-buten-1-yl) 4-methyl-2,3-pentadienoate (**68c**) using different Lewis acids

Entry	Allene conc. [M]	Lewis acid	Lewis acid [mol%][a]	Solvent	Temperature [°C][b]	Reaction time at each T [min]
1	0.5	$EtAlCl_2$[c]	4.8	CH_2Cl_2	120 140 160 180	20
2	0.4	Tf_2NH	2 grains	CH_2Cl_2	100 120	10

[a]Related to alkene.

[b]Reactions were cooled down and sampled after the reaction time was over, then heated to the next temperature.

[c]0.1 M in hexane.

2.3.3 Conclusions

When methyl 2,3,8-nonatrienoate (**12**) is irradiated with microwaves at 130 °C for 30 seconds a Lewis acid catalysed [2+2] cycloaddition takes place to give a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13a)** and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13b**) (2.5 : 1) in 83 %. Several Lewis acids were tried, and $EtAlCl_2$ was found to give best yield and conversion.

The [2+2] cycloaddition reaction was unsuccessful for 3-methyl-3-buten-1-yl buta-2,3-dienoate (**68a**) and 3-methyl-3-buten-1-yl 4-methylpenta-2,3-dienoate (**68c**), although several catalysts, temperatures and reaction times were attempted.

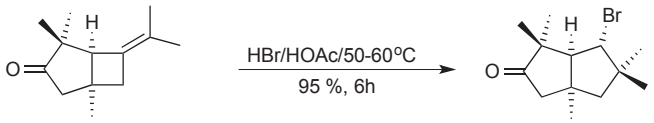
2.4 Syntheses of Bicyclo[3.3.0]octanes and Bicyclo[4.3.0]nonanes by Ring Expansion of Isopropylidenecyclobutanes (Paper IV)

Many compounds of high synthetic and biological relevance contain the cyclopentane unit as a substructure, for instance the bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane skeletons are structural moieties of many biologically active natural products, like *e.g.* capnellenes, hirsutanes, and pasteurestins.[5-8,14,18-19] The structural variety of these compounds urge for a variety of methods for the synthesis of this motif.

2.4.1 Choice of Strategy.

This part of the thesis describes work that was inspired by a previous work in our group, namely the work towards a synthesis of the insect pheromone component lineatin. Here it was discovered that the epoxide of **73** gave an acid catalysed ring expansion.[96]

Previous attempts to achieve this ring expansion of compound **73** using protic acids (e.g. HCl, *p*-toluenesulfonic acid or CF_3COOH) or Lewis acids (e.g. BF_3, $AlCl_3$, $HgSO_4$) were unsuccessful.[169] However, it was found that treatment of the cyclobutylisopropylidene compound **73** with 45 % HBr in acetic acid a stereo- and regioselective reaction gave a near quantitative yield of the ring expanded product **74**.[169]



73 **74**

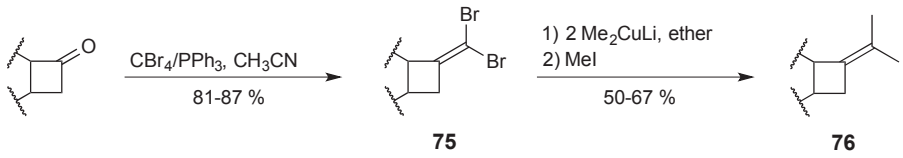
Scheme 2.9 Ring expansion reaction of **73**.

These results encouraged us to investigate the reaction further, since such a high yielding, regio- and stereoselective reaction would be very useful in the synthesis of natural products containing the bicyclo[3.3.0]octane moiety.

2.4.2 Results and Discussion

2.4.2.1 Choice of Method and Preparation of Model Compounds

The model compounds were prepared by the reaction sequence shown in Scheme 2.10.



Scheme 2.10 Preparation of the isopropylidenecyclobutanes **76a-e**.

The dibromomethylenecyclobutanes **75a-e** were prepared in excellent yields (81-87 %) by treatment of known ketones[170-173] with PPh_3 and CBr_4 in acetonitrile using a modified literature procedure.[174] Acetonitrile has been found to be the best solvent for the reaction of ketones with PPh_3/CCl_4 and was also the chosen solvent here.[175] Dimethylation of the dibromomethylenecyclobutanes **75a-e** with lithium dimethylcuprate[174] yielded the isopropylidene cyclobutanes in good yield (50-67 %). In order to minimise loss of product, the solvent (diethyl ether) was distilled at ambient pressure when the products were low boiling. In this way the isopropylidenecyclobutanes **76a-e** were prepared. (Figure 2.2).

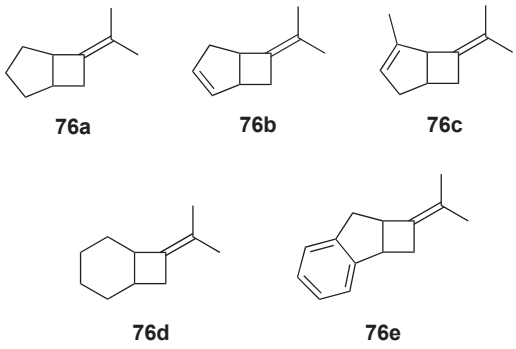
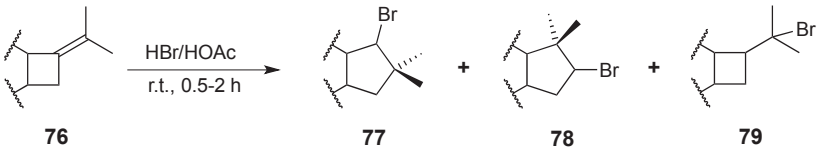


Figure 2.2 Model compounds for the ring expansion reaction.

2.4.2.2 Optimisation of Reaction Conditions - Scope and Limitations

At first the reaction was carried out with 33 % HBr in acetic acid at room temperature using the same amount of HBr (~8 eq.) as in the literature.[169] The reactions were finished in 0.5-2h, and three products were observed: the ring expanded compounds **77** and **78**, and variable amounts of the compound **79**. The compound **79** resulted from addition of HBr across the double bond. (Scheme 2.11) Representative examples are depicted in Table 2.6.



Scheme 2.11. Preparation of **77**, **78** and **79.**

Table 2.6 Treatment of the isopropylidenecyclobutanes with excess 33 % HBr in acetic acid at room temperature

Entry	Substrate	Ratio (%)[a]		Ratio (%)[a]	
		77	**78**	**77+78**	**79**
1	**76a**	64	36	-	-
2	**76b**	small amounts	small amounts	-	-
3	**76c**	small amounts	small amounts	-	-
4	**76d**	58	42	70	30
5	**76e**	74	26	90	10

[a]Conversion 100%. Ratio based on NMR analysis (of the crude mixture). GLC analysis indicated the same ratio.

[b]Based on GLC analysis.

The compounds **79** were observed to rearrange on the GLC, and for this reason it was not possible to give exact amounts of these compounds. The ^{1}H NMR spectrum of the product mixture resulting when the alkene **76d** was used as the substrate, indicated that the ratio of the ring expanded compounds (**77d** + **78d**) to **79d** was approximately 70:30 (Table 2.6, Entry 4). Prolonged reaction times did not change the ratio **77d** : **78d**. When substrate **76e** was used, the ratio of the ring expanded compounds (**77e**+**78e**) to **79e** was approximately 90:10 (Table 2.6, Entry 5). The compound **79a** was not seen in the NMR spectrum of the reaction mixture resulting from compound **76a** (Table 2.6, Entry 1).

Generally a high stereoselectivity was achieved. According to both ^{1}H NMR and GLC analyses mainly one stereoisomer was formed, and only a few per cent of the other isomer could be detected.

The reaction was only moderately regioselectiv, and the best regioselectivity was obtained with compound **76e**, assumed to be the most strained substrate. The least strained substrate **76d** yielded the lowest selectivity. However, for substrates **76b** and **76c** the reaction was unsuccessful, and only small amounts of the desired products were seen (GLC). This was probably due to addition of HBr to the *endocyclic* double bond. Separation and structure elucidation of the complex mixtures were not attempted.

Only minor effects were obtained from changing the temperature of the reaction (table 2.7). Both the stereo- and regioselectivity of the reaction was the same as at room temperature when temperatures ranging from 0-5 °C to 70 °C degrees were tried. However, for substrate **76d** lowering the temperature slowed the ring expansion reaction down, and the major product was **79d** (Table 2.7, Entry 6). For substrate **76c** the reaction was still unsuccessful.

Table 2.7 Temperature effects

Entry	Substrate	Temperature	Ratio (%)[a]		
			77	**78**	**79**
1	**76a**	50-60 °C	65	35	-
2	**76a**	0-5 °C	66	34	trace amounts
3	**76c**	50-60 °C	-	-	-
4	**76c**	0-5 °C	small amounts[b]	small amounts[b]	small amounts[b]
5	**76d**	50-60 °C	52	39	8[c]
6	**76d**	0-5 °C	30	25	45[c]

[a] Conversion 100 %. Ratio based on GLC data. [b] i. e. <15%

[c] Rearranges to a certain extent on the GLC.

Since the temperature effects was observed to be minimal for this reaction, we tried to change the polarity of the reaction medium using substrate **76a** as a model substance. When the reaction was performed with the same amount of HBr (in acetic acid) as before (~8 eq.), no improvement in the regioselectivity was seen when solvents with polarities from hexane to CH_2Cl_2 were added in a ratio of HBr/HOAc : solvent of ~1:3 (Table 2.8, entries 1 and 2). However, when diethyl ether was used as the solvent, the ring expansion reaction was suppressed completely yielding **79a** as as the only product identified.

Substrates **76b**, **76c** and **76d** were also tried using ether as the solvent. The reactions were performed at room temperature except for Table 2.8, entry 6 (substrate **76c**) that was performed in refluxing ether. Comparison of GLC chromatograms of the reactions of the bromide **76c** at room temperature and at reflux, indicated that the temperature change only resulted in minor differences in the product ratio. All attempts on purification of **79a** by flash chromatography and preparative GLC failed, and only the ring expanded products **77a** and **78a** were isolated.

When the reaction in diethyl ether was performed using only 2-4 equivalents of HBr (HBr/HOAc : ether, ~1:20), the ring expansion reaction was suppressed for all substrates,

and the only product observed was **79** No attempts were made to purify **79b-d** since the purification of **79a** failed. The compound **79c** was only identied from its ^{1}H NMR spectrum since it could not be obtained pure (only as the major product). Slower addition of the HBr/HOAc solution only resulted in a slower addition, and in accordance with the literature,[176] an excess of 2-3 eq. of HBr was needed to complete the reaction. The yields of the products **79a-d** have not been optimised.

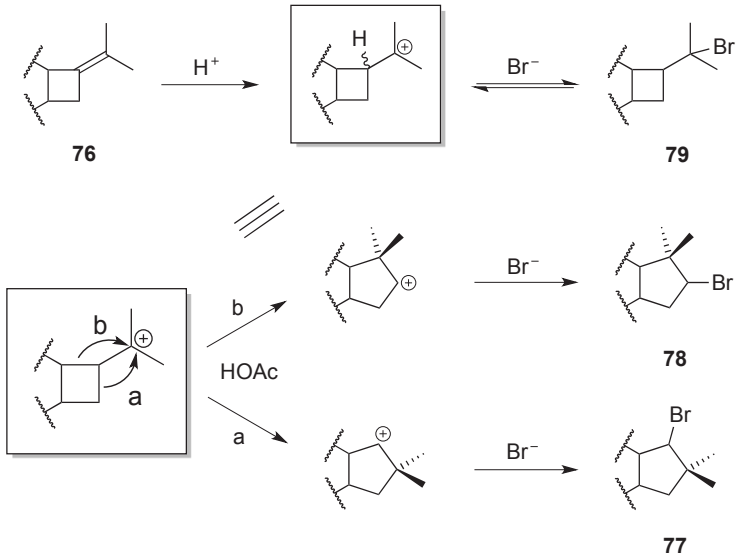
Table 2.8 Solvent effects

Entry	Substrate	Conditions	Ratio (%)[a]			Conversion
			77	**78**	**79**	**(%)[a]**
1	**76a**	Et_2O, 1 h[b]	-	-	~100	~100
2	**76a**	CH_2Cl_2, 1 h[b]	52 (58)	48 (42)	-	100
3	**76a**	Hexane, 1 h[b]	(40)	(28)	(32)	95
4	**76a**	Et_2O, 4 h[c]	-	-	~100	94
5	**76b**	Et_2O, 3 h[c]	-	-	~100	100
6	**76c**	Et_2O, Δ, 22 h[c,d,e]	-	-	major	94
7	**76d**	Et_2O, 8 h[c,d]	-	-	~100	91

[a] Ratio based on ^{1}H NMR data or GLC data (in parenthesis), conversion based on GLC data. [b] HBr/HOAc: solvent, ~1:3; [c] HBr/HOAc: solvent, ~1:20; [d] Slow addition of HBr in acetic acid; [e] Reaction performed at reflux

At last an attempt to achieve ring expansion on **79b** and **79c** were made by treating them with acetic acid at elevated temperatures. The substrate **79b** yielded the ring expanded compounds **77b** and **78b** in moderate regioselectivity (72 : 28, according to NMR). With the crude **79c** a complex mixture containing only moderate amounts of **77c** and **78c** (in a ratio of 63 : 37, according to GLC) was obtained. Analytical samples of **77b**, **78b** and **77c** could be obtained.

Scheme 2.12 depicts a possible mechanism of the ring expansion reaction where the intitially formed tertiary carbocation can rearrange through either pathway **a** or **b** yielding **77** or **78**, respectively.



Scheme 2.12 Possible mechanism of the ring expansion reaction.

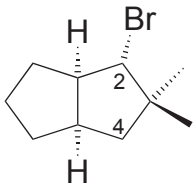
However, this mechanism fails to explain the high stereoselectivity exhibited by the reaction. Sterical congestion alone cannot explain the high stereoselectivity, and possibly a cage type mechanism is at work. A higher regioselectivity was obtained when isopropylidenecyclobutane **73** was used as the substrate in the reaction.[175] This may be explained by the fact that if substrate **73** were to undergo a ring expansion reaction by pathway **b**, a severely sterically congested bromide with adjacent *gem*-dimethyl substituted carbon atoms would result. The mechanism was, however, not studied in this work.

2.4.2.3 Discussion of NMR spectra of 77, 78 and 79.

The compounds **77**, **78** and **79** could easily be identified from their respective ^{1}H NMR spectra. In the ^{1}H NMR spectra of **77** a characteristic doublet at δ 3-4 ppm was seen (CH-Br). In the spectra of **78** the corresponding signal appeared as a doublet of doublet at δ 3.8-4.5 ppm. The compounds **79** could be identified from the two methyl singlets at δ 1.6-1.7 ppm consistent with a *gem*-dimethyl group situated on the same carbon atom as the bromine

atom. The other features of the spectra were confirmed the structures. Since only an impure sample could be obtained for compound **78c**, this compound was merely identified from the ^{1}H NMR spectrum of the impure sample by the singlets at δ_H 0.96 and 1.16 ppm (the *gem*-dimethyl groups), a multiplet at δ_H1.69-1.77 ppm (alkene CH_3 group), a doublet of doublet at δ_H 4.11 ppm (CHBr proton, *J* 5.4 and 5.9 Hz) and a multiplet at δ_H 5.25-5.35 ppm (alkene proton).

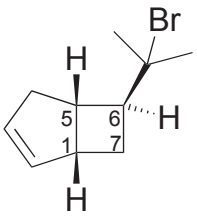
Mainly one stereoisomer was obtained in this rearrangement, but due to the flexibility of the two fused 5-membered rings it was not possible to use coupling constants to confirm which stereoisomer was predominantly formed. However, thorough analysis of the NMR spectra of **77a** made it possible to distinguish the two protons on C4. A fairly strong interaction between the *endo* H4 proton and the α-proton (H2) based on the ROESY spectra could be seen, tentatively showing the stereochemistry of the bromine substituted carbon atom (H2) as depicted in Figure 2.3.



77a

Figure 2.3 Stereochemistry of **77a**.

The stereochemistry of the bromides **79** was also difficult to establish, but the ROESY spectrum of **79b** shows a strong coupling between the two bridgehead protons H1 and H5, and a weaker coupling between the bridgehead proton H5 and the α-proton (H6). Molecular models (ball-and-stick models) indicate that due to the rigidity of this bicyclic compound, the coupling between protons H5 and H1 and between protons H5 and H6 should be of similar strength if the α-proton (H6) and the bridgehead protons are *syn*. This indicates that **79b** has the stereochemistry depicted in Figure 2 with the $(CH_3)_2$CBr-group situated *exo* which is confirmed by the ROESY spectrum revealing correlations between the $(CH_3)_2$CBr-group and both the bridgehead proton H5 and the *exo* H7 proton.



79b

Figure 2.4 Stereochemistry of **79b**.

2.4.3 Conclusions

When the isopropylidenecyclobutane, 6-(1-methylethylidene)-bicyclo[3.2.0]heptane (**76a**), are subjected to HBr/HOAc in polar solvents like acetic acid, a ring expansion reaction results yielding 2-bromo-3,3- dimethylbicyclo[3.3.0]octane (**77a**) and 3-bromo-2,2-dimethylbicyclo[3.3.0]octane (**78a**) result. Several other isopropylidenecyclobutanes have been found to undergo the same reaction with high stereoselectivity and moderate regioselectivity.

When less polar solvents like diethyl ether is used the ring expansion reaction is suppressed, and bromides resulting from addition of HBr to the isopropylidene double bond are obtained.

CHAPTER 3 - SUMMARY AND FUTURE WORK

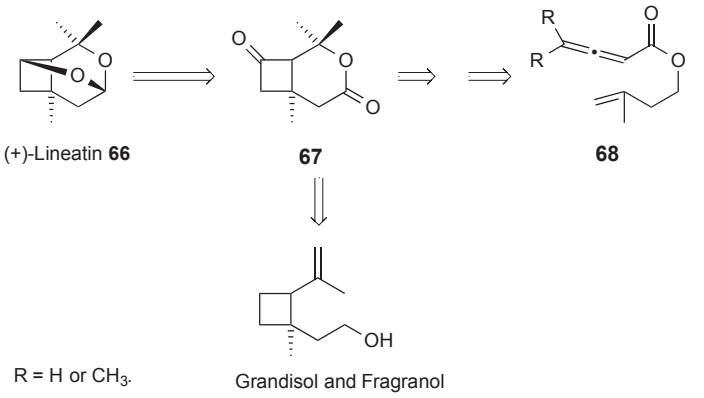
In this thesis new methodology has been used in an effort to improve old and well-established methods for synthesising 3- and 4-membered cyclic compounds. In addition, a ring expansion reaction of 4-membered rings to yield 5-membered rings has been studied.

Flow chemistry in a microreactor has successfully been used for the dibromocyclopropanation of several different alkenes under phase-transfer conditions using 40 % (w/w) NaOH (aq) as the base, TEBA as the phase-transfer catalyst, and bromoform as the dibromocarbene precursor. The phase-transfer catalyst facilitates mass-transport between the two immiscible liquid phases (organic phase and NaOH (aq)), and vigorous stirring is crucial to make this interface as large as possible. In microreactors the short diffusion lengths and high surface-to-volume ratios ensures rapid mass and heat transfer. With the use of the slug flow technique at an AO ratio of 4, good to excellent yields were obtained in less time than for ordinary batch chemistry when using the same catalyst. Unsaturated alcohols (without protection of the hydroxyl group) have also been included in the substrate scope of this flow chemistry method. The use of microreactor technology should be an interesting alternative for the Makosza conditions compared to the traditional batch chemistry.

It would be interesting for future work to include more substrates, and also to develop a continuous flow method for these reactions. A functioning and reliable setup with continuous extraction could also be of interest since it would be both time- and space-saving.

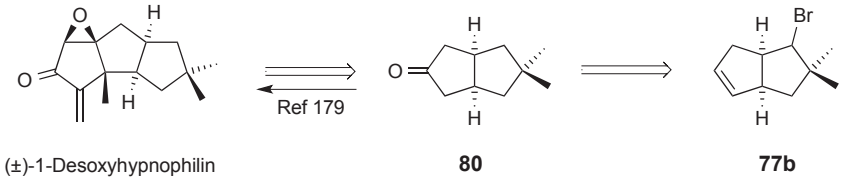
The use of microwave irradiation as a heat source is known to decrease the required reaction time in many different types of reactions, and also reduce the amount of side products obtained.[105] When the allene-ene ester, methyl 2,3,8-nonatrienoate (**12**) was subjected to $EtAlCl_2$ under microwave irradiation at 130 °C, a reaction time of only 30 seconds were required to give a 83 % yield of a mixture of *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13a**) and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**13b**) (2.5 : 1). The reaction time reported in the literature was 14 days. Preliminary efforts to test the other two

allene-ene esters under the same conditions have been without success, and work to develop the methodology further is ongoing, e.g. by doping the reaction medium with an ionic liquid.[109] The cycloaddition products from this intramolecular [2+2] cycloaddition of allene-ene esters could perhaps be used as precursors for the insect pheromone component, lineatin[95-96] as shown in the retrosynthesis in Scheme 3.1 It should also be possible to extend this to other cyclobutane containing natural products like grandisol,[177] fragranol[178] and others.



Scheme 3.1 Retrosynthesis of lineatin, grandisol and fragranol.

Finally, several isopropylidenecyclobutanes were found to undergo a ring expansion reaction from 4-membered to 5-membered rings. For instance, 6-(1-methylethylidene)-bicyclo[3.2.0]heptane (**76a**) was found to undergo a ring expansion reaction yielding 2-bromo-3,3-dimethylbicyclo[3.3.0]octane (**77a**) and 3-bromo-2,2-dimethylbicyclo-[3.3.0]octane (**78a**). The reaction was highly stereoselective, but moderately regioselective. The highest regioselectivity was achieved for the most strained substrate tested. In less polar solvents like diethyl ether the ring expansion reaction was suppressed, and bromides resulting from addition of HBr to the isopropylidene double bond were obtained. The products from this ring expansion reaction are interesting as possible precursors for natural products like, (±)-1-desoxyhypnophilin,[14] a project for future work.



(±)-1-Desoxyhypnophilin **80** **77b**

Scheme 3.2. Retrosynthetic analysis of (±)-1-desoxyhypnophilin.

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APPENDIX

A1: Some Stereochemical Definitions Regarding the Addition of Carbenes and Carbenoids to C-C Double Bonds as Summarized by Hellquist

A2: Paper I

A3: Paper II

A4: Paper III

A5: Paper IV

Appendix 1:

Some Stereochemical Definitions Regarding the Addition of Carbenes and Carbenoids to C-C Double Bonds as Summarized by Hellquist

APPENDIX 1

Some Stereochemical Definitions Regarding the Addition of Carbenes and Carbenoids to C-C Double Bonds as Summarized by Hellquist.[44a]
(See also Figure A1):

1) «The term *stereoselectivity* refers to the degree of selectivity for formation of cyclopropane products having *endo versus exo* or, alternatively *syn versus anti* stereochemistry of the substituents originating in the alkylidene group relative to substituents originating in the alkene substrate.»

2) «The term *stereospecificity* refers to the stereochemistry of vicinal cyclopropane substituents originating as double-bond substituents in the starting alkene, *i.e.* a cyclopropane-forming reaction is stereospecific if the *cis/trans* relationship of the double-bond substituents is retained in the cyclopropane product.»

3) «*Diastereofacial selectivity* refers to the face of the alkene to which addition occurs relative to other substituents in the alkene substrate.»

4) «*Entantioselectivity* refers to the formation of a specific enantiomer of the cyclopropane product.»

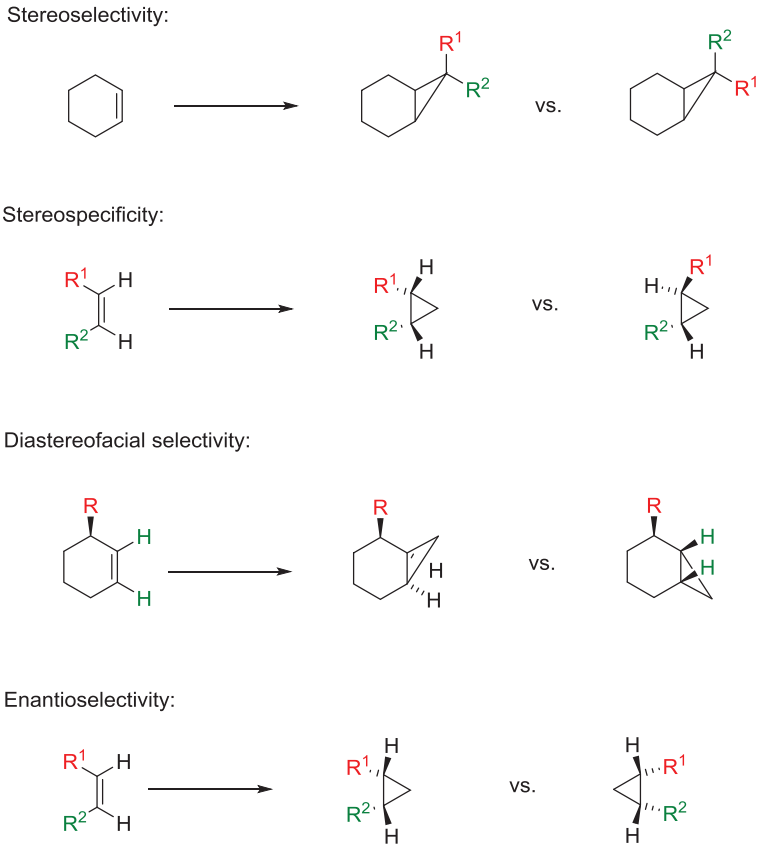

Figure A1. Definition of some stereochemical terms related to carbene addition.[44a]

Appendix 2:

Paper I

The Use of Flow Chemistry for Two-Phase Dibromocyclopropanation of Alkenes

Østby, R. B.; Stenstrøm, Y. H.; Didriksen, T.,

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The Use of Flow Chemistry for Two-Phase Dibromocyclopropanation of Alkenes

Runa B. Østby[1]*, Yngve H. Stenstrøm[1]* and Terje Didriksen[2]

[1]*Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, P.O. Box 5003, NO-1432 Ås, Norway*
[2]*SINTEF Materials and Chemistry, P.O. Box 124 Blindern, NO-0314 Oslo, Norway*

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Conventional batch dibromocyclopropanations by reaction of bromoform and alkenes under phase-transfer conditions require strong base (50% NaOH (aq)), vigorous stirring, and often long reaction times. Using flow chemistry in a microreactor, the reactions were found to be smooth, rapid, and high-yielding under ambient conditions when 40% (w/w) NaOH was used as the base. The reaction has been tested with a representative selection of alkenes, displaying a variety of structural features.

Keywords:: dibromocyclopropanation, $CHBr_3$, Makosza reaction, phase-transfer catalysis, microreactor, flow chemistry

1. Introduction

gem-Dibromocyclopropanes are important substrates in organic synthesis where they have been used as versatile intermediates for the syntheses of other interesting compounds like allenes [1, 2], cumulenes [3], cyclopentadienes [4, 5], cyclic acetals [6, 7], and furans [8]. They have also been found useful in the syntheses of many natural products, as emphasized in several reviews [9–11]. New methods for their exploitation are still under development [11].

The phase-transfer catalyzed two-phase dihalocyclopropanation of alkenes, since its discovery by Makosza [12], has become a well-established, widely used method in organic synthesis, and is still one of the most effective methods for preparation of *gem*-dibromocyclopropanes [9, 11, 13].

Traditionally, the Makosza conditions involve vigorous stirring of a solution of the alkene substrate and haloform (CHX_3, X=Cl, Br) with a concentrated (50% (w/w)) solution of NaOH (aq) under phase-transfer catalysis (PTC) conditions.

The phase-transfer catalyst facilitates mass transport across the interface between the two immiscible liquid phases (organic phase and NaOH (aq)), which is essential for the reaction, and vigorous stirring is crucial to make this interface as large as possible. Stirring-speed is an important parameter for the reaction rate, conversion, and yield [14–16].

During the last decade or two, microreactor technology has emerged as an attractive alternative to conventional batch chemistry [17–21], and in 2003, the capillary-microreactor was introduced as a new reactor concept [22].

In microreactors, where reactants are mixed in narrow channels, short diffusion lengths and a high surface-to-volume ratio result in rapid mass and heat transfer. This in turn improves control of reaction conditions and may contribute to increased rate and selectivity of reactions.

When two immiscible liquids are introduced into a microchannel, they naturally separate into distinct phases with a large specific interface area, often in the form of alternating liquid slugs flowing through the microchannel [23]. Internal circulation within these slugs results in an increased mass transfer compared to, e.g., parallel flow [24, 25] (Figure 1). Slug-flow reactors have been used, e.g., for nitration of aromates [22], arylation of arylbromides [26], and Wittig reactions [27], and, thus, seemed to be an interesting method also for the two-phase dibromocyclopropanation of alkenes.

* Authors for correspondence: runa.berg@nmbu.no (R.B. Østby) and yngve.stenstrom@nmbu.no (Y.H. Stenstrøm)

2. Results and Discussion

Cyclohexene was used as a model substance in the initial experiments, with benzyl triethylammonium chloride (TEBA) as the phase-transfer catalyst and bromoform as the dibromocarbene precursor (Scheme 1).

The setup for our experiments is shown in Figure 2. In the traditional two-phase system, a 50% (w/w) solution of NaOH is used [10–12, 14]. During initial experiments using this viscous base solution, clogging was a severe problem, and for this reason, we used only 40% (w/w) NaOH (aq) as the base. Initially, equimolar amounts of cyclohexene and bromoform and 0.9 mol% TEBA (relative to cyclohexene) were mixed in a 1-mL glass microchip reactor (reaction time: 1 min). The aqueous-to-organic volumetric flow ratio (AO ratio) was 1. This resulted in very low yields of the dibromocarbene adduct **1** (Table 1, Entry 1). Increasing the reaction time (up to a maximum of 85 min), by adding a tube reactor and/or lowering the flow rate, did not increase the yield to an acceptable value (Table 1, Entries 2–4).

When the amounts of bromoform and phase-transfer catalyst were increased to give a ratio of cyclohexene–bromoform–TEBA of 1:1.5:0.026, some improvement in the yield could be seen (Table 1, Entry 5). Increasing the concentration of TEBA to 4.2 mol% (relative to cyclohexene), only left the reaction more prone to clogging, even when the solution was diluted to half its original concentration and the microchip was changed to a Y-mixer (Table 1, Entries 6–9). The best yields of dibromocyclopropane **1** obtained were 31–34%. These yields were obtained when the microreactor chip (acting as a micromixer) or a Y-mixer was used together with the 25 mL tube reactor. Exchanging the microreactor chip for a Y-mixer did not significantly improve the yield, and clogging also occurred.

Ultrasonication has been reported to increase the yield in a phase-transfer catalyzed reaction between cyclohexene, bromoform, and solid NaOH [28]. Also, Ahmed-Omer et al. [29] found that sonication increased the reaction rate of a hydrolysis reaction in combination with segmented flow. In addition, ultrasound has been used to prevent clogging in a microreactor [26]. However, we did not observe an increase in yield when our tube reactor was subjected to sonication (Table 1, Entry 6).

Since a solution of 45% (w/w) KOH in water is less viscous/concentrated than a 40% (w/w) NaOH solution in water [30], we decided to try to use this KOH solution as the base. The catalyst (0.12 wt.% TEBA) was added to the water phase. The amount of TEBA relative to the cyclohexene was only 0.3 mol% (and 0.014 mol% relative to the KOH solution) which is close to the maximum amount (0.0157 mol% relative to the KOH solution) that is soluble in the 45% (w/w) KOH (aq) according to literature

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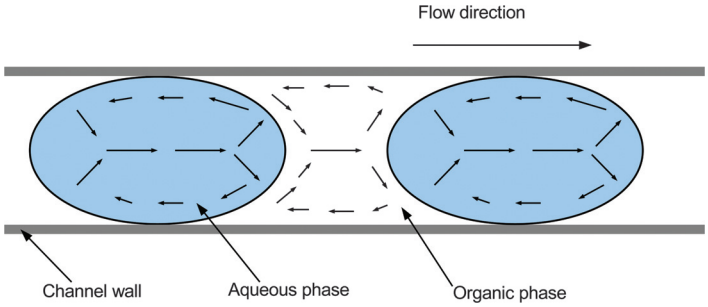


Figure 1. Internal circulation in alternating slugs of two immiscible liquids in a microchannel. Internal flow is shown relative to the bulk velocity

[31]. Different tube reactor lengths and flow rates were tried, giving reaction times from 6 to 50 min. Only low yields resulted (Table 1, Entries 10–13).

Jovanovic et al. [31] successfully used a solution of 45% (w/w) KOH (aq) containing 0.12 wt.% TEBA (aq) for the PTC alkylation of phenylacetonitrile. They found that increasing the AO ratio increased the yield of alkylation product. This can be attributed to the decreased organic slug size and increased average surface-to-volume ratio yielding an increased rate of catalyst transfer across the liquid–liquid interface area, and also increasing the internal circulation of the organic interslug [31].

When we increased the AO ratio to 4, using 45% (w/w) KOH (aq) as the base, an increase in the yield of dibromocyclopropane was observed (Table 1, entry 14), but at AO ratio of 9, the yield decreased (Table 1, Entry 15). This is in accordance with the existence of an optimum flow ratio with a maximum productivity as described in the literature [31]. Using $CHBr_3$ as the solvent instead of CH_2Cl_2 (Table 1, Entry 16) resulted in lower yields. With the rather poor yields, further optimization using the 45% (w/w) KOH (aq) solution was abandoned.

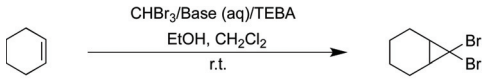
However, when the base was changed to 40% (w/w) NaOH (aq) with an AO ratio of 4, the yield was drastically improved (Table 2, entry 1). Since the equipment still got clogged from time to time, we tried the reaction without using a backpressure regulator. The same yields were achieved without any clogging (Table 2, compare entries 1 and 3, and entries 4 and 5). Utilizing these conditions on several other alkenes, excellent yields were obtained. The only exception was the monosubstituted alkene, 1-heptene, where moderate yields were observed, even when the amount of bromoform was increased from 1.5 equivalents to 2 equivalents relative to the alkene (Table 2, Entries 8–9). This is in accord with the well-known observations that the rate of reaction will increase with increased alkene substitution [38, 39].

Using 1,3-cyclohexadiene as a substrate, a small amount of the bisadduct **8** was observed (^{1}H NMR). This is probably due to the fact that a ratio of $CHBr_3$ to alkene of 1.5 was used, but this has not been investigated further.

To extend the scope of the reaction we did one experiment with chloroform as the carbene precursor reacting this with 2,3-dimethyl-2-butene. The yield is comparable to previously reported ones (Table 2, Entry 14), clearly showing that also dichlorocyclopropanes are achievable by this method.

However, since the *gem*-dibromocyclopropanes are reported to be generally more reactive than the corresponding *gem*-dichlorocyclopropanes [9] and, thus, are more interesting as intermediates in organic synthesis, we focused our attention on the *gem*-dibromocompounds and did not elaborate further along synthesizing the dichlorocompounds.

Scheme 1. Dibromocyclopropanation of cyclohexene



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3. Conclusions

Flow chemistry in a microreactor was successfully used for dibromocyclopropanation of alkenes under phase-transfer catalysis (PTC) using 40% (w/w) NaOH (aq) as the base. Good to excellent yields in less time than for batch chemistry were obtained. Yields comparable to the ones reported from ordinary batch reactions using the same phase-transfer catalyst were achieved.

Emulsion problems often reported to occur during workup [40] was under the conditions reported herein, only an issue for 1,1-dibromo-2-(chloromethyl)-2-methylcyclopropane (**9**).

Thus, the use of microreactor technology should be an interesting alternative for the Makosza reaction (compared to the traditional batch chemistry).

4. Experimental

4.1. General. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Benzyltriethylammonium chloride was purchased from Sigma-Aldrich. Flash column chromatography was performed on silicagel (Merck Kieselgel 60, (0.040–0.063 mm, 230–400 Mesh ASTM)/Celite 545 coarse (calcined) or aluminum oxide (Fluka, type 507C neutral, 100–125 mesh (pH 7.0 ± 0.5)). In order to degas the dichloromethane, it was sonicated for 15 min prior to use in the flow system. The routine NMR spectra were recorded using $CDCl_3$ as a solvent and TMS as a reference. ^{1}H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at 75 or 100 MHz. NMR resonances are given only when literature spectra are not found or when our spectra have significantly better resolution than previously reported spectra. The flow

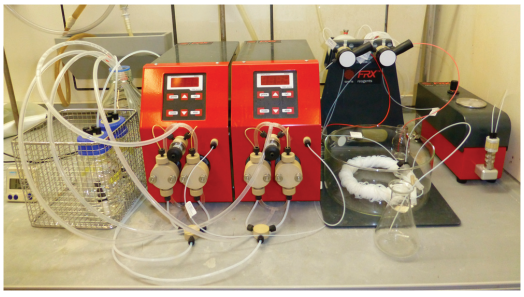


Figure 2. Modified Flow Chemistry Toolkit FRX200 from Syrris Ltd.

Table 1. Dibromocyclopropanation of cyclohexene[a]

Entry	[Alkene] (M)	$CHBr_3$[b] (eq.)	Base[c]	Ethanol (vol%)	TEBA[b] (mol%)	Reactor[d]	AO ratio[e]	Reaction time (min)	Yield (%)[f]
1	2.2	1	NaOH	1.6	0.9	1	1	1	7
2	2.2	1	NaOH	1.6	0.9	1	1	2	10
3	2.2	1	NaOH	1.6	0.9	2	1	34	17
4	2.2	1	NaOH	1.6	0.9	2	1	85	18
5	2.8	1.5	NaOH	1.2	2.6	2	1	34	29
6	2.8	1.5	NaOH	1.2	4.2	3	1	26	22[g,h]
7	2.8	1.5	NaOH	1.2	4.2	3	1	52	25[h]
8	1.4	1.5	NaOH	0.6	4.2	3	1	52	31[h]
9	1.4	1.5	NaOH	0.6	4.2	6	1	50	34[h]
10	2.8	1.5	KOH	1.2	0.3	4	1	6	4
11	2.8	1.5	KOH	1.2	0.3	5	1	16	4
12	2.8	1.5	KOH	1.2	0.3	6	1	50	6
13	2.8	1.5	KOH	1.2	0.3	5	1	40	5
14	2.8	1.5	KOH	1.2	1.1	5	4	40	22
15	2.8	1.5	KOH	1.2	2.5	5	9	40	7
16	2.8	1.5	KOH	1.2	1.1	5	4	40	11[i]

[a] Conditions used unless otherwise stated: room temperature, backpressure: 1.5–3 bar.
[b] Relative to cyclohexene.
[c] Base concentrations: NaOH: 40% (w/w), KOH: 45% (w/w) containing 0.12 wt.% TEBA.
[d] Reactors 1: 1 mL glass microchip reactor, 2: a 16-mL PTFE tube reactor in addition to the 1 mL glass microchip reactor, 3: 25 mL PTFE tube reactor in addition to the 1 mL glass microchip reactor, 4: 3 mL PTFE tube reactor, 5: 8 mL PTFE tube reactor, and 6: 25 mL PTFE tube reactor.
[e] Aqueous to organic flow ratio (AO ratio).
[f] Estimated using ^{1}H NMR spectra of the isolated reaction mixture.
[g] Sonication.
[h] Clogging occurred.
[i] $CHBr_3$ was used as solvent instead of dichloromethane.

instrumentation apparatus used was the Flow Chemistry Toolkit FRX200 from Syrris Ltd. fitted with 2 Frx200 pumps, a reagent module containing one Syrris sample loop (PTFE, 5 mL, 0.5 mm i.d.), one additional sample loop (either a 5 mL PTFE sample loop (Syrris), 0.5 mm i.d., or a 1.0-mL sample loop (PTFE, 0.5 mm i.d.) or a 0.52-mL sample loop (PTFE, 0.5 mm i.d.)). The microreactor setup is shown in Figure 2. The following modules were used, either separately or in combination: (1) a 1-mL 3-inlet glass microchip Microreactor fitted with a Microreactor Header (0.6 mm i.d., Syrris Ltd.), (2) a 25-mL tube reactor (PTFE, 0.8 mm i.d.), (3) a 16-mL tube reactor (PTFE, 0.8 mm i.d., Syrris Ltd.), (4) a 8-mL tube reactor (PTFE, 0.8 mm i.d.), and (5) a 3-mL tube reactor (PTFE, 0.8 mm i.d.). When the glass microchip reactor was omitted, the tube reactors were fitted with a Y-mixer (Tube Reactor 3 input Adaptor (PCTFE) from Syrris Ltd.). The pressurization module used was Syrris FRX Pressurization Module with a backpressure regulator.

4.2. Representative Procedure

4.2.1. 7,7-DIBROMOBICYCLO[4.1.0]HEPTANE (1) [41]. The flow chemistry system described above was used with the Y-mixer, the 25 mL tube reactor, a 1.0-mL sample loop containing a solution of cyclohexene (1.44 mmol), $CHBr_3$ (2.15 mmol), 4.2 mol% TEBA (relative to alkene) and 0.6 vol% ethanol (absolute) in CH_2Cl_2, and a 5-mL sample loop (PTFE, Syrris Ltd.) containing the 40% (w/w) NaOH (aq) solution (**CAUTION:** strong, viscous base). The sample loop containing the 40% (w/w) NaOH (aq) solution was filled very slowly and with great care, due to the high viscosity of the strongly basic NaOH solution and danger of spillage due to pressure buildup. No backpressure regulator was used. The two solutions were simultaneously introduced into the flow system at a total flow rate of 0.50 mL/min (flow rate NaOH: 0.40 mL/min, flow rate organic solution: 0.10 mL/min) at room temperature, i.e., a residence time of 50 min and an AO flow ratio of 4. The mixture was fed into brine (50 mL), and the flow was collected for 77 min at this flow rate and then for 4 min at 2 × 1 mL/min (to flush the system). The pressure in the system was 1–4 bar. Pentane (100 mL) was added to the reaction mixture, and the two layers were separated. The aqueous phase was extracted with pentane (or hexane) (3 × 50 mL), and the combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by filtering it through a plug made of 0.5 cm silica and 0.5 cm Celite using pentane as the eluent. Concentration in vacuo yielded a mixture (0.31 g) containing 7,7-dibromobicyclo[4.1.0]heptane (**1**)–bromoform–pentane, 91:8:1, according to ^{1}H NMR. Estimated yield of **1** was 0.28 g, 77%. The spectral data were in accordance with the literature [42, 43].

4.2.2. (2,2-Dibromo-1-methylcyclopropyl)benzene (2) [44]. Yield was 0.40 g of a mixture containing the dibromide **2**–α-methylstyrene–bromoform, 82:7:11, according to ^{1}H NMR. Estimated yield of the dibromide **2** was 0.32 g, 78%. The spectral data were in accordance with the literature [45].

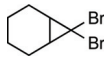
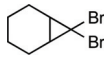
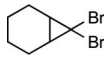
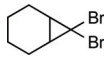
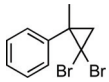
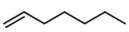
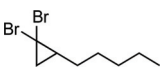
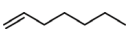
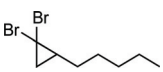
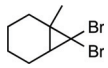
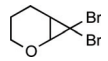
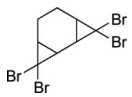
4.2.3. 1,1-Dibromo-2,2,3,3-tetramethylcyclopropane (3) [38]. Yield was 0.30 g, 82%, as a white solid that was pure according to ^{1}H and ^{13}C NMR, and the spectral data were in accordance with the literature [43], mp. 78–80 °C (lit. 79–80 °C [34]).

4.2.4. 1,1-Dibromo-2-pentylcyclopropane (4) [46]. Yield was 0.23 g of a mixture containing the dibromide **4**–1-pentene–bromoform, 79:1:20, according to ^{1}H NMR. Estimated yield of **4** was 0.18 g, 47%. The spectral data were in accordance with the literature [47]. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.89 (t, *J* 6.9 Hz, 3H), 1.17 (t, *J* 7.2 Hz, 1H), 1.25–1.37 (m, 4H), 1.37–1.65 (m, 5H), 1.71 (dd, *J* 9.9 and 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0, 22.6, 28.0, 28.5, 29.7, 31.4, 31.5, 32.6.

4.2.5. 7,7-Dibromo-1-methylbicyclo[4.1.0]heptane (5) [48]. Yield was 0.40 g of a mixture containing the dibromide **5**–bromoform–pentane, 89:10:1, according to ^{1}H NMR. Estimated yield of **5** was 0.36 g, 92%. The spectral data were in accordance with the literature [49]. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.13–1.28 (m, 2H), 1.28–1.48 (m, 2H), 1.40 (s, 3H), 1.43 (dd, *J* 9.0 and 2.2 Hz, 1H), 1.53–1.64 (m, 1H), 1.70–1.82 (m, 2H), 1.88–2.02 (m, 1H).

4.2.6. 7,7-DIBROMO-2-OXABICYCLO[4.1.0]HEPTANE (6) [50]. **CAUTION:** It has been reported that this compound may decompose violently while distilled (vacuum distillation/90 °C) [35, 50]. In the work-up procedure, ethyl acetate replaced pentane, and the product mixture was purified by filtration through a plug made of 1 cm aluminum oxide, using pentane as the eluent. Yield was 0.32 g of a mixture containing the dibromide **6**–bromoform, 94:6, according to ^{1}H NMR. Estimated yield of **6** was 0.30 g, 81%. The spectral data were in accordance with the literature [35].

Table 2. Dihalocyclopropanation of a selection of alkenes using 40% (w/w) NaOH (aq) at AO ratio: 4[a]

Entry	Substrate	Equivalents $CHBr_3$[b]	Product		Yield (%)[c]	Lit. yield (%)[d]
1		1.5		**1**	78[e]	76 [32]
2		1.5		**1**	77[e,f]	76 [32]
3		1.5		**1**	77	76 [32]
4		2		**1**	82[e]	76 [32]
5		2		**1**	85	76 [32]
6		1.5		**2**	78	80 [33]
7		1.5		**3**	82	73 [34]
8		1.5		**4**	47	–
9		2		**4**	45	–
10		2		**5**	92	–
11		1.5		**6**	81	77 [35]
12		1.5		**7**	65	38 [36]
				**8**	9	
13		1.5		**9**	57	58 [37]
14		1.5		**10**	63	–

[a] Conditions unless otherwise stated: [alkene]=1.4 M, 4.2 mol% TEBA (relative to alkene), 0.6 vol% ethanol (in CH_2Cl_2); room temperature, 25 mL PTFE tube reactor; total flow rate: 0.50 mL/min; AO ratio: 4; reaction time: 50 min.
[b] Relative to alkene.
[c] Estimated using ^{1}H NMR spectra of the isolated reaction mixture.
[d] Literature yields are only given for Makosza conditions using TEBA.
[e] Back pressure regulator was used. Backpressure: 2–3 bar.
[f] Sonication was used at 20–25 °C.

4.2.7. 7,7-Dibromobicyclo[4.1.0]hept-2-ene (7) [51] and 3,3,8,8-Tetrabromotricyclo[5.1.0.02,4]octane (8) [52]. Yield was 0.26 g of a mixture containing the dibromide **7**–tetrabromide **8**–bromoform in a ratio of 83:14:3 according to ^{1}H NMR. Estimated yield of **7** was 0.22 g, 65%, and of tetrabromide **8**, 0.038 g, 9%. The spectral data were in accordance with the literature [53].

4.2.8. 1,1-Dibromo-2-(chloromethyl)-2-methylcyclopropane (9) [54]. The solvents were carefully removed in vacuo at/or just below room temperature. Yield was 0.34 g of a mixture containing the dibromide **9**–bromoform, 63:37, according to ^{1}H NMR. Estimated yield of **9** was 0.21 g, 57%. The spectral data were in accordance with the literature [37].

4.2.9. 1,1-Dichloro-2,2,3,3-tetramethylcyclopropane (10) [55]. Purification was done by careful removal of solvents by distillation at ambient pressure to give a residue of white crystals of **10** (0.15 g, 63%), mp. 49–50 °C (lit. 49.8–50.5 °C [55]). The spectral data were in accordance with the literature [56].

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Appendix 3:

Paper II

Two-Phase Dibromocyclopropanation of Unsaturated Alcohols Using Flow Chemistry

Østby, R. B.; Stenstrøm, Y. H.; Didriksen, T.,

Manuscript.

Two-Phase Dibromocyclopropanation of Unsaturated Alcohols Using Flow Chemistry

Runa B. Østby,[a]* Yngve H. Stenstrøm[a]* and Terje Didriksen[b]

[a]*Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, P.O. Box 5003, NO-1432 Ås, Norway*
[b]*SINTEF Materials and Chemistry, P.O. Box 124 Blindern, NO-0314 Oslo, Norway*

ABSTRACT

When dibromocyclopropanations by addition of dibromocarbene to alkenes under phase-transfer conditions is done in conventional batch reactions, strong base (50 % NaOH (aq)), vigorous stirring and long reaction times are often required. Using flow chemistry in a microreactor, cyclopropanation of a selection of unsaturated alcohols have been tested under ambient conditions using 40% (w/w) NaOH as the base. The reactions were generally rapid, and the yields were comparable to yields reported in the literature for the conventional batch reaction.

Keywords: Dibromocyclopropanation; $CHBr_3$; Makosza reaction; Phase-transfer catalysis; Microreactor; Flow Chemistry; unsaturated alcohols.

* Corresponding authors:

Tel: +47 67232559; fax: +47 64965001, *E-mail address:* yngve.stenstrom@nmbu.no

Tel: +47 64966132; fax: +47 64965001, *E-mail address:* runa.berg@nmbu.no

1. Introduction

gem-Dibromocyclopropanes in general are important substrates in organic synthesis and have been used as versatile intermediates for the syntheses of other interesting compounds like allenes,[1,2] cumulenes,[3] cyclopentadienes,[4,5] cyclic acetals,[6,7] furans,[8] and also for the synthesis of natural products.[9-11]

The phase-transfer catalysed two-phase dihalocyclopropanation of alkenes[12] is a well-established, widely used method in organic synthesis, and is still one of the most effective methods for preparation of *gem*-dihalocyclopropanes.[9,11,13]

The traditional Makosza conditions involve vigorous stirring of a solution of the alkene substrate and haloform (CHX_3, X = Cl, Br) with a concentrated (50% (w/w)) solution of NaOH (aq) under phase-transfer catalysis (PTC) conditions. The phase-transfer catalyst facilitates mass transport across the interface between the two immiscible liquid phases (organic phase and NaOH (aq)), which is essential for the reaction, and vigorous stirring is crucial to make this interface as large as possible. Stirring-speed is an important parameter for the reaction rate, conversion and yield.[14-16]

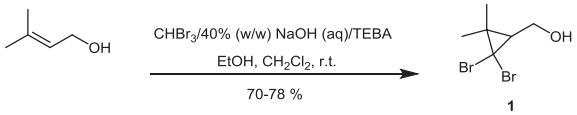
When the Makosza conditions are used with unsaturated alcohols as substrates the outcome of the reaction depends strongly on the structure of the alcohol and the presise conditions used since the hydroxyl group/alkoxy anion may compete with the double bond for the dibromocarbene[9] and the yields of dibromocyclopropyl alcohols are varying (from excellent to low). Since unsaturated alcohols also may form side products that make purification of the main product difficult, the hydroxyl group is often protected as an acetal[9,17] or ether[9,18] when used in this reaction.

Recently we have shown[19] that flow chemistry under slug flow conditions can be an interesting alternative to batch chemistry for the Makosza reaction, giving moderate to excellent yields of different dibromocyclopropanes in a short reaction time. This encouraged

us to react several unsaturated alcohols under the same conditions to get an indication of the obtainable yields when the hydroxy group is not protected.

2. Results and Discussion

The unsaturated alcohols selected for testing under Makosza conditions are shown in Table 1. Benzyltriethylammonium chloride (TEBA) was used as the phase-transfer catalyst, and bromoform was the dibromocarbene-precursor, as shown for 3-methyl-2-buten-1-ol in Scheme 1.



Scheme 1. Dibromocyclopropanation of 3-methyl-2-buten-1-ol under PTC conditions.

In the traditional two-phase system, a 50% (w/w) solution of NaOH is used.[9-11,13] However, in earlier experiments we observed that when using this viscous base solution in a flow reactor, clogging was a severe problem. This problem, however, could be solved by reducing the base concentration to 40% (w/w)[19] Using a ratio of alkene:bromoform:TEBA of 1:1.5:0.044 together with the diluted base solution in an aqueous-to-organic flow ratio (AO ratio) of 4, good to excellent yields of dibromocyclopropanes could be obtained.

Employing the same conditions to the 3-methyl-2-buten-1-ol gave a yield of 70 % of the corresponding dibromocyclopropane **1** (Table 1, Entry 1). By increasing the amount of bromoform from 1.5 to 2 equivalents, the yield could be increased to 74 %. Adding even more bromoform did not significantly increase the yield (from 74% to 78%) (Table 1, entries 2-3). Thus a 1:2-2.5 ratio of alkene to bromoform was used for subsequent experiments. Several unsaturated alcohols where subjected to these conditions.

When Kleveland *et al.*[20] used the allylic alcohols linalool and geraniol as substrates in the conventional batch version of the Makosza reaction (with dichlorocarbene), they observed a supprising difference in the outcome of the reaction for the two alcohols: Linalool gave rapid and regioselectiv reaction resulting in an excellent yield of the dichlorocyclopropane monoadduct, 5-(2,2-dichloro-3,3-dimethylcyclopropyl)-3-methyl-1-penten-3-ol, (89%), while geraniol was less reactive and gave a low yield of a mixture containing at least six components that partially decomposed under the attempted separations.

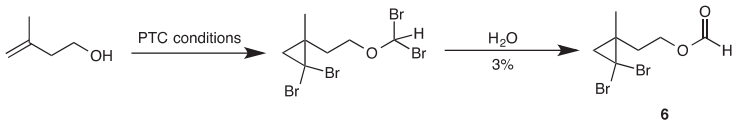
When the tertiary dienol linalool was subjected to our flow chemistry conditions, regioselective addition to the trisubstituted double bond occured, and the dibromocyclopropane **2** was obtained as mixture of diastereomers (approximately 1:1) in excellent yield. (Table 1, Entry 4). Due to overlap of signals in the ^{1}H NMR spectrum, only an estimation of the diastereomeric ration could be done. The primary dienol geraniol, however, yielded a mixture of several products, according to ^{1}H NMR and ^{13}C NMR data, (Table 1, Entry 5) as was observed by Kleveland *et al.*[20] with dichlorocarbene. No attempts were made to separate the complex mixture.

Intrigued by this result, we subjected several other alcohols to this reaction. From citronellol, that only differ structurally from geraniol by the absence of the allylic double bond, the dibromocyclopropane **4** was obtained as a mixture of diastereomers (approximately 1:1) in 57 % yield when 2.5 equivalents of bromoform (compared to alkene) were used (Table, Entry 6). With only two equivalents, the reaction did not go to completion.

The dibromocyclopropane **4** was easily identified from its ^{1}H NMR spectrum by a characteristic doublet at δ 0.89 ppm corresponding to the methyl group at the metin carbon, the broad singlet at δ 1.75 ppm corresponding to the hydroxyl proton and from its ^{13}C NMR spectrum by resonance at δ 60.9 ppm corresponding to the carbon bearing the OH-group. The

other features of the spectra were in accord with the structure. The molecular ion was obtained in high resolution MS.

When 3-methyl-3-buten-1-ol was used as the substrate, the dibromocyclopropyl alcohol **5** was obtained in moderate yield (47%) after chromatography (Table, Entry 7). In addition, a small amount of the formate ester **6** (3%) was isolated. The presence of the formate ester can be explained by insertion of dibromocarbene at the O-H bond and subsequent hydrolysis (Scheme 2).



6

Scheme 2. Insertion of dibromocarbene at the O-H bond and subsequent hydrolysis.

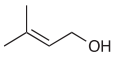
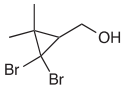
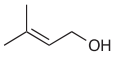
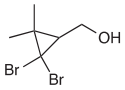
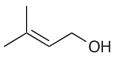
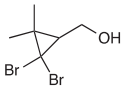
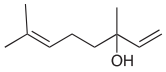
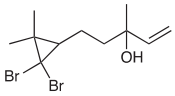
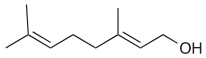
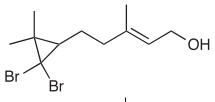
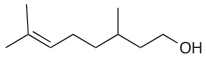
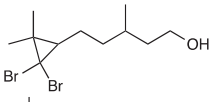
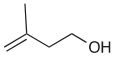
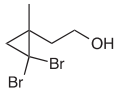
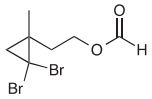
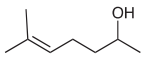
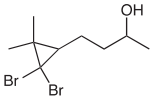
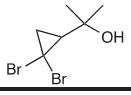
The formate ester was identified from its ^{1}H NMR spectrum by a triplet at δ 4.36 ppm (*J* 7.0 Hz) corresponding to the methyl protons on the carbon atom bearing the formate ester group, and a singlet at δ 8.05 ppm corresponding to the formate ester proton. In the ^{13}C spectrum a characteristic resonance at δ 61.3 ppm corresponds to the methyl group bearing the fomate ester group, and the resonance at δ 160.9 ppm corresponds to the formate ester carbon. The other features of the spectra confirmed the structure. In IR a strong peak at 1725 cm^{-1} characteristic of a formate ester was seen.
The molecular ion could not be obtained in MS, and the [M-HCOOH] ion was used for confirmation of the structure by high resolution MS.

The secondary alcohol, 6-methyl-5-hepten-2-ol, gave a good yield of the dibromocarbene adduct **7** as a mixture of diastereomers (approximately 1:1), which was identified from its ^{1}H NMR spectrum by the doublet at δ 1.20 (*J* 6.2 Hz) corresponding to the methyl group on the carbon bearing the OH-group, the singlet at δ 1.58 corresponding to the OH-group, and by its

^{13}C NMR spectrum by the resonances at δ 67.6 & δ 67.7 (CH) corresponding to the CH-OH carbon in the two diastereomers. The other features of the spectra also were in accord with the structure. The molecular ion could not be obtained in MS, which is not uncommon for alcohols, and the [M-H_2O] ion was used for confirmation of the structure by high resolution MS.

However, when the tertiary alcohol, 2-methyl-3-buten-2-ol, was used as a substrate, only small amounts of the starting material could be isolated (Table, Entry 9). This is in accord with in the literature reports where this alcohol has been reported to react sluggishly when subjected to dichlorocarbene under phase-transfer conditions.[20]

Table 1. Dibromocyclopropanation of a selection of unsaturated alcohols using 40% (w/w) NaOH (aq) at AO ratio: 4.[a]

Entry	Substrate	$CHBr_3$ (eq.)[b]	Product (number)	Yield (%)	Litt. yield (%)[c]	Ref
1		1.5	 (**1**)	70[d]	36	21
2		2	 (**1**)	74[d]	36	21
3		2.5	 (**1**)	78[d]	36	21
4		2	 (**2**)	98[d]	93	20
5		2	 (**3**)	-	-	20
6		2.5	 (**4**)	57[e]	-	-
7		2	 (**5**)	47[e]	58	22
			 (**6**)	3[e]	-	-
8		2	 (**7**)	77[e]	-	-
9		2	 (**8**)	-	2	23

[a]Conditions unless otherwise stated: [alkene] = 1.4 M, 4.2-4.3 mol% TEBA (relative to alkene), 0.6 vol% ethanol (in CH_2Cl_2). Room temperature, 25 mL PTFE tube reactor. Total flow rate 0.50 mL/min. Aqueous to Organic flow ratio (AO ratio): 4. Reaction time 50 min. [b]Relative to alkene. [c]Literature yields are only given for Makosza conditions using TEBA. [d]Estimated using ^{1}H NMR spectra of the isolated reaction mixture. [e]Isolated yield.

3. Conclusions

Flow chemistry in a microreactor was successfully used for dibromocyclopropantion of several unsaturated alcohols under phase-transfer catalysis (PTC) using 40% (w/w) NaOH (aq) as the base. Moderate to excellent yields in less time than for batch chemistry were obtained, depending on the structure of the alcohol. The trisubstituted alkenes (Table, Entries 1-6, 8) generally gave better yields than the disubstituted (Table, Entry 7) and monosubstituted alkenes (Table, Entry 9). This has been explained as resulting from the increased nucleophilicity of the trisubstituted double bonds compared to di- and monosubstituted double bonds when the substituents are electron donating.[24] Yields comparable to the ones reported from ordinary batch-reactions were achieved.

Thus, the use of microreactor technology should be an interesting alternative for the Makosza reaction (compared to the traditional batch chemistry).

4. Experimental

4.1 General. All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise stated. Benzyltriethylammonium chloride was purchased from Sigma-Aldrich. Flash column chromatography was performed on silicagel (Merck Kieselgel 60, (0.040-0.063 mm, 230-400 Mesh ASTM) or VWR Chemicals/BDH Prolabo Normasil 60 (40-63 μm)/Celite 545 coarse (calcined). Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F254. Compounds were stained with $KMnO_4$ solution, followed by heating. MS was performed on an Autospec Ultima (Micromass Ltd. Manchester, England) equipped with an electron ionisation (EI) ion source producing 70 eV electrons. For HRMS the resolution was tuned to 12 000. GC/MS was performed on the same instrument (tuned to a resolution of 2000) in combination with an Agilent 6890 Series gas chromatograph (Agilent Technology, Wilmington, DE, USA). In order to degas the dichloromethane, it was sonicated for 15 min prior to use in the flow system. The routine NMR spectra were recorded using $CDCl_3$ as a

solvent and TMS as a reference. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz. Corresponding signals from pairs of diastereomers are separated by "&". IR spectra were recorded on a ZnSe HATR cell (Horizontal Attenuated Total Reflectance). The flow instrumentation apparatus used was the Flow Chemisty Toolkit FRX200 from Syrris Ltd. fitted with 2 Frx200 pumps, a reagent module containing one Syrris sample loop (PTFE, 5 mL, 0.5 mm i.d.), a 1.0 mL sample loop (PTFE, 0.5 mm i.d.), a 25 mL tube reactor (PTFE, 0.8 mm i.d.), a Y-mixer (Tube Reactor 3 input Adaptor (PCTFE) from Syrris Ltd.).

4.2. Representative Procedure.

(2,2-Dibromo-3,3-dimethylcyclopropyl)methanol (1)[25]

A 1.0 mL sample loop containing a solution of 3-methyl-2-buten-1-ol (1.43 mmol), $CHBr_3$ (2.86 mmol), 4.2 mol% TEBA (relative to the alkene) and 0.6 vol% ethanol (absolute) in CH_2Cl_2, and a 5 mL sample loop (PTFE, Syrris Ltd.) containing 40% (w/w) NaOH (aq) solution, was used. **CAUTION:** Strong, viscous base. The sample loop containing the 40% (w/w) NaOH (aq) solution was filled very slowly and with great care, due to the high viscosity of the strongly basic NaOH solution and danger of spillage due to pressure build-up. The two solutions were simultaneously introduced into the flow system at a total flow rate of 0.50 mL/min (flow rate NaOH (aq): 0.40 mL/min, flow rate organic solution: 0.10 mL/min) at room temperature, *i.e.* a residence time of 50 min and an AO flow ratio of 4. The mixture was fed into brine (50 mL) and the flow was collected for 77 min at this flow rate, and then for 4 min at 2x1.5 mL/min (to flush the system). The pressure in the system was 1-4 bar. To the reaction mixture was added ethyl acetate (100 mL), and the two layers were separated. The aqueous phase was extracted with ethyl acetate (3x50 mL), and the combined organic phases were washed with brine (2x50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by filtering it through a plug made of 0.5 cm silica and 0.5 cm Celite using ethyl acetate as the eluent. Concentration *in vacuo* yielded a mixture (0.31g) containing (2,2-dibromo-3,3-dimethylcyclopropyl)methanol (**1**) : 3-methyl-2-buten-1-ol : bromoform; 88:2:10 according to ^{1}H NMR. Estimated yield of **1**: 0.27g, 74%. The spectral data were in accordance with the literature.[26]

5-(2,2-Dibromo-3,3-dimethylcyclopropyl)-3-methyl-1-penten-3-ol (2).[20]
Yield: 0.48g of a mixture containing the dibromide **2** : linalool: bromoform; 87:9:5, as a mixture of diastereomers (estimated diastereomeric ratio: 1:1), according to ^{1}H NMR. Estimated yield of the dibromide **2**, 0.42g, 89%. The spectral data were in accord with the literature.[20]

5-(2,2-Dibromo-3,3-dimethylcyclopropyl)-3-methylpentan-1-ol (4). 2.5 equivalents of $CHBr_3$ per equivalent of 3,7-dimethyl-6-octen-1-ol was used. The crude mixture was purified by column chromatography (silica, hexane : ethyl acetate; 80:20) yielding the dibromide **4** (0.27 g, 57%) as a mixture of diastereomers (approximately 1:1), according to ^{1}H and ^{13}C NMR. IR (HATR) ν_{max}: 3338 (br, s), 2954 (s), 2926 (s), 2870 (s), 1456 (s), 1375 (s), 1147 (m), 1109 (m), 1060 (s, shoulder), 1006 (m), 963 (m), 756 (s), 740 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J* 6.5 Hz, 3H), 1.07-1.52 (m, 6H), 1.14 (s, 3H), 1.34 (s, 3H), 1.52-1.65 (m, 2H), 1.75 (br s, 1H), 3.57-3.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 & 19.3 (CH_3), 19.5 & 19.6 (CH_3), 25.4 & 25.5 (CH_2), 27.4 (CH_3), 27.9 & 28.0 (C), 29.3 & 29.4 (CH), 35.5 & 35.6 (CH_2), 39.6 (CH_2), 40.0 (CH), 48.3 & 48.4 (C), 60.9 (CH_2). MS, *m/z* (%) = 246 (M-HBr, 1)/248 (M-HBr, 1), 228 (10)/230 (10), 167 (40), 163 (34), 162 (33), 149 (28), 107 (13), 109 (14), 93 (24), 95 (23), 83 (100), 81 (56), 69 (74) and 67 (49). HRMS: $C_{11}H_{20}O^{79}Br_2$ requires *m/z* = 325.9881. Found *m/z* = 325.9878.

2-(2,2-Dibromo-1-methylcyclopropyl)-etan-1-ol (5)[22] and **2-(2,2-Dibromo-1-methylcyclopropyl)-etyl formate (6)**.
The crude mixture was purified by column chromatography (silica, pentane: ethylacetate; 85:15) yielding the dibromide **5** (0.17g, 47%) and 2-(2,2-dibromo-1-methylcyclopropyl)ethyl formate **(6)** (0.01g, 3%), both as oils. The spectral data for the dibromoalcohol **5** were in accordance with literature.[22]

2-(2,2-Dibromo-1-methylcyclopropyl)-etyl formate (6).
IR (HATR) ν_{max}: 2963 (s), 2928 (s), 2873 (m), 1725 (s), 1454 (m), 1430 (m), 1383 (m), 1260 (m), 1167 (s), 733 (s), 694 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.44 (d, *J* 7.5 Hz, 1H), 1.51 (d, *J* 7.5 Hz, 1H), 1.92-2.13 (m, 2H), 4.36 (t, *J* 7.0 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6 (CH_3), 27.4 (C), 34.5 (CH_2), 36.9 (CH_2), 37.7 (C), 61.3 (CH_2), 160.9 (CH). MS, *m/z* (%) = 238 (M-HCOOH, 14)/240 (M-HCOOH, 28)/242 (M-

HCOOH, 14), 211 (10)/213 (18)/215 (9), 159 (72)/161 (70), 131 (11)/133 (12), 119 (4)/121 (3), 80 (100) and 79 (87). HRMS: $C_6H_8{}^{79}Br_2$ requires *m/z* = 237.8993. Found *m/z* = 237.8994.

4-(2,2-Dibromo-3,3-dimethylcyclopropyl)-butan-2-ol (7).

The crude product was purified by column chromatography (silica, pentane: ethylacetate; 80:20), yielding the dibromide **7** as a mixture of diastereomers (approximately 1:1) as an oil (0.33g, 77%). IR (HATR) ν_{max}: 3343 (br, s), 2962 (s), 2926 (s), 2868 (s), 1456 (s), 1374 (s), 1335 (m), 1308 (m), 1128 (s, shoulder), 1090 (s), 773 (s), 745 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 & 1.17 (s, 3H), 1.20 (d, *J* 6.2 Hz, 3H), 1.35 (s, 3H), 1.58 (s, 1H), 1.15-1.75 (m, 5H), 3.75-3.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3 (CH_3), 23.7 (CH_3), 24.2 & 24.4 (CH_2), 27.42 & 27.43 (CH_3), 28.0 & 28.1 (C), 37.6 & 37.8 (CH_2), 39.7 & 39.9 (CH), 48.0 & 48.3 (C), 67.6 & 67.7 (CH). MS, *m/z* (%) = 280 (M-H_2O, 18)/282 (M-H_2O, 34)/284 (M-H_2O, 16), 238 (3)/240 (5)/242 (2), 173 (37)/175 (35), 159 (4)/161 (4), 122 (40), 121 (83), 107 (46), 94 (100), 79 (53) and 77 (40). HRMS: $C_9H_{14}{}^{79}Br_2$ requires *m/z* = 279.9462. Found *m/z* = 279.9461.

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Appendix 4:

Paper III

Synthetic Studies towards Cyclobutanes by Microwave Assisted Intramolecular [2+2]-Cycloaddition of Allene-Ene Esters

Østby, R. B.; Sørensen, R. L.; Stenstrøm, Y. H.; Westerås, S.; Antonsen, S.,

Manuscript.

Synthetic Studies towards Cyclobutanes by Microwave Assisted Intramolecular [2+2]-Cycloaddition of Allene-Ene Esters

Runa B. Østby, Rita L. Sørensen, Stephen Westerås, Simen Antonsen and Yngve Stenstrøm*

Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, PO Box 5003, NO-1432 Ås, Norway
E-mail: yngve.stenstrom@nmbu.no

Abstract

When subjected to microwave irradiation at 130 °C for 30 seconds, methyl 2,3,8-nonatrienoate undergoes a Lewis acid catalysed [2+2]cycloaddition to give a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (2.5 : 1) in 83 % yield. $EtAlCl_2$ was found to give the best yield and conversion. The reaction was unsuccessful for 3-methyl-3-buten-1-yl 4-methylpenta-2,3-dienoate and 3-methyl-3-buten-1-yl buta-2,3-dienoate, even though several catalysts, temperatures and reaction times were attempted.

Keywords: Microwave Assisted; [2+2] Cycloaddition; Allene Esters; Cyclobutanes

Introduction

The cyclobutane ring is a known moiety of many naturally occurring, biologically significant compounds.[1] Ring strain found in the 4-membered rings is substantial and facilitates selective bond breakage, making the cyclobutane derivatives important intermediates for further manipulations.

Many methods exist for the syntheses of these carbocyclic rings. Dichloroketene and [2+2] photocycloaddition probably being the most pronounced.[2] However, the allene-ene intramolecular reaction has also been found to be efficient as an alternative strategy.[3-9]

The use of microwave irradiation as a heat source is known to decrease the required reaction time in different types of reactions and may also reduce the amount of side products in the reactions.[10,11]

The main objective of this project was to study the microwave assisted [2 +2] cycloaddition reactions of allene-ene esters in the presence of Lewis acids.

Results and Discussion

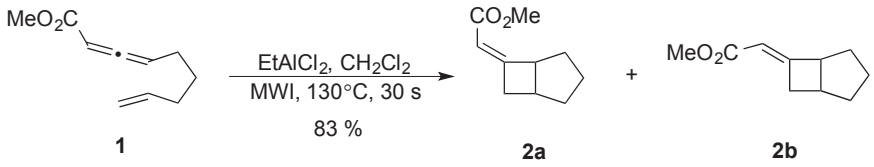
The model substance, methyl 2,3,8-nonatrienoate (**1**), was synthesized from 6-heptenoic acid in two steps, via the acid chloride, according to a literature procedure[12] (Scheme 1).

When Snider and Ron[12] subjected the allene ester (**1**) to the Lewis acid, $EtAlCl_2$, an intramolecular [2+2]-cycloaddition reaction resulted. The reaction time was 14 days at 25 °C, giving a 95% yield of a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**2a**) and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**2b**) in a ratio of 2 : 1.

Inspired by Brummond and Chen's successful use of microwave irradiation of alkynyl allenes to afford intramolecular [2+2]-cycloadditions,[13] we wanted to improve the intramolecular [2+2] allene-ene reaction by using microwave heating.

To find optimal conditions, several Lewis acids, temperatures and reaction times were tested. Parameters for optimization and representative results are presented in the Supplementary information.

We found that when microwave heating was applied to this reaction at 130 °C, only 30 s was needed for >95 % conversion, and a mixture of the esters **2a** and **2b** (2.5 : 1) (according to GLC) in 83 % isolated yield resulted. (Scheme 1).

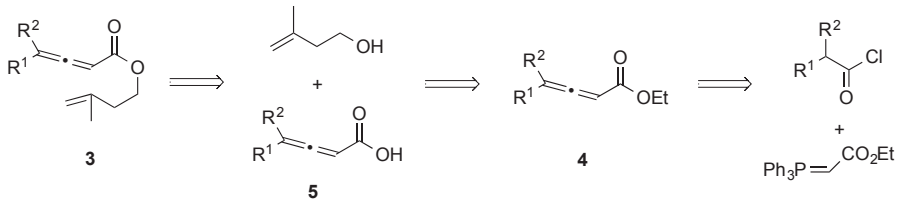


Scheme 1. Microwave assisted Lewis acid catalysed reaction of **1**.

Several attempts were made for chromatographic separation of the esters **2a** and **2b**, but none were successful.

During the optimization of the microwave assisted [2+2] cycloaddition reaction, we found $EtAlCl_2$ to be a better catalyst for the reaction than $AlCl_3$. When $AlCl_3$ was used as the catalyst, a temperature of 140 °C was required to get full conversion. Such a high temperature can be difficult to obtain in the microwave oven when using CH_2Cl_2 as a solvent since it is a low microwave absorbing solvent.[14] Careful handling is required during work-up when using $EtAlCl_2$, since it reacts violently during the deactivation step. As a control experiment the reaction was attempted without any Lewis acid present. But even with extended MW heating no detectable conversion was observed.

To explore the scope and limitations of this microwave irradiated reaction, we wanted to test it for alkenyl allenoic esters, and a strategy for the synthesis of these starting materials was devised (Scheme 2).

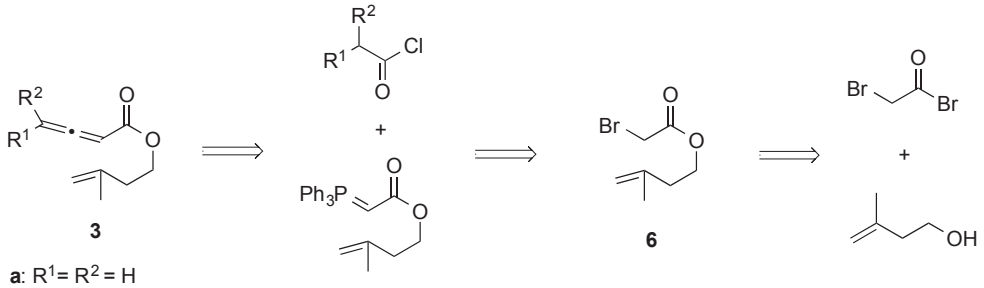


a: R^1 = H, R^2 = H
b: R^1 = H, R^2 = CH_3

Scheme 2. Strategy for the synthesis of model molecules **3**.

The esters **4a** and **4b** were prepared by acylation of ethyl(triphenylphosphoranylidene) acetate, using a literature procedure.[15,16] Purification by flash column chromatography gave **4a** and **4b** in 30 % and 63 % yield, respectively. The esters were hydrolysed using LiOH•H_2O in a mixture of glyme and water (1: 1), yielding the acid **5a** in 78 % yield. With the ester **4b**, however, a mixture of the allenic acid **5b** and 3-propionic acid (20:80) was obtained.

A mixture of allenic acid **5b** and 3-propionic acid (25:75) was also obtained when **4b** was hydrolysed in ethanol.[17] Given the poor yields of the ester **4a** and allenoic acid **5b**, we decided that a new strategy for the synthesis of our model compounds was needed (Scheme 3). Since the allene ester **3b** is prone to rearrangement to 3-pentynoic acid, we decided to use the ester **3c** instead.



a: R^1 = R^2 = H
b: R^1 = H, R^2 = CH_3
c: R^1 = R^2 = CH_3

Scheme 3. Revised strategy for the preparation of allene esters **3**.

(3-methyl-3-buten-1-yl) 2-bromoacetate (**6**) was prepared by a general literature procedure for production of bromoacetates.[18] Addition of PPh_3 and subsequent treatment with base, afforded the phosphonium ylide **7** in good yield. Reaction of **7** with acyl chlorides provided the allene esters **3a** and **3c** in in 62 % and 14 % yield, respectively. The yields have not been optimized.

The allene esters **3a** and **3c** were treated with several different Lewis acids (e.g. $EtAlCl_2$, $AlCl_3$, Tf_2NH) using different concentrations of allene esters and amounts of Lewis acids during the microwave irradiation. Several different temperatures and reaction times were attempted. The reaction was monitored by taking out aliquots and checking the characteristic allene stretch in the infrared spectrum at approximately 1950 cm^{-1}. However, no cycloaddition products were seen. For an additional check the reaction mixture was worked up and the NMR spectra were recorded, confirming that no cyclobutanes had been formed. In most cases the allene esters was unconverted.

Conclusion

Methyl 2,3,8-nonatrienoate (**1**) undergoes a Lewis acid catalysed [2+2]cycloaddition to give a mixture containing *(Z)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**2a)** and *(E)*-methyl-2-bicyclo[3.2.0]hept-6-ylidene acetate (**2b**) (2.5 : 1) in 83 % yield when microwave irradiation is applied at 130 °C for 30 seconds. Several Lewis acids were tried, and $EtAlCl_2$ was found to give best yield and conversion.

The cyclisation did not work for 3-methyl-3-buten-1-yl buta-2,3-dienoate (**3a**) or 3-methyl-3-buten-1-yl 4-methylpenta-2,3-dienoate (**3b**) and, even though several catalysts, temperatures and reaction times were attempted.

Experimental

General. IR was performed on a Perkin Elmer, Spectrum Bx, FT-IR system. using a diamond or ZnSe API-cell, or a ZnSe HATR cell (Horizontal Attenuated Total Reflectance). Only selected absorption bands in IR are reported. UV analyses were performed on a Biochrom, Libra S32 PC spectrophotometer. The routine NMR spectra were recorded at 25 °C on a

Varian Gemini 300 instrument and a Bruker AscendTM 400 instrument using $CDCl_3$ as a solvent and TMS as a reference. ^1H NMR spectra were recorded at 300 and 400 MHz and ^{13}C NMR spectra were recorded at 75 and 100 MHz. MS spectra were recorded on an Autospec Ultima (Micromass Ltd. Manchester, England) using electronic ionisation (EI) at an ionisation potential of 70 eV, unless otherwise stated. For GC/MS an Agilent 6890 Series gas chromatograph (Agilent Technology, Wilmington, DE, USA) was used in combination with the MS instrument. Only selected peaks in MS are reported. Analytical GLC was carried out on a Shimadzu GC-14B gas chromatograph and using a Varian CP-Wax 52CB capillary column (30 m, i.d. 0.32 mm, film: 0.50 μm). The temperature program used was 100 °C for 30 s, an increase of 4 °C/min until 225 °C and then 25 °C/ min until 250 °C. Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254}. Compounds were visualized by UV light and/or stained with *p*-anisaldehyde solution or $KMnO_4$ solution, followed by heating. For the microwave assisted reactions a Biotage Initiator microwave oven or a Biotage Initiator+ EU microwave oven were used. Flash column chromatography was performed using Versa flash™ with a Supelco Versa Pak™ silica cartridge column (40 x 75 mm) or on silicagel (Merck Kieselgel 60, (0.040–0.063 mm, 230–400 Mesh ASTM). All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. When required, the solvents were dried (by standard procedures) and distilled and the reactions performed under an atmosphere of nitrogen. Anhydrous solvents purchased in sure seal bottles over molecular sieves were used without further drying.

Methyl 2,3,8-nonatrienoate (1)[12]

6-Heptenoic acid (4.73 g , 36.9 mmol) and oxalylic chloride (11.69 g, 92.2 mmol) was stirred for 12 h. Oxalylic chloride was removed by distillation, however, due to severe foaming during distillation of 6-heptenoyl chloride (Short-path distillation) the compound was dissolved in acetonitrile (50 mL) and used without further purification in a literature procedure[10]) Triethylamine (7.38 g, 72.9 mmol) in acetonitrile (50 mL) and (carbomethoksymethyl)triphenylphosphonium bromide (12.70 g, 36.5 mmol) in acetonitrile (150 mL) was used. The residue was filtered through a small column (silica, 25 % ethyl acetate in hexane), concentrated *in vacuo* and the residue was purified by flash column

chromatography (Versa Flash, silica, 10 % ethyl acetate in hexane) yielding the ester **1** (3.7 g, 60 %). The spectra were in accordance with the literature.[10]

Typical procedure for the microwave assisted [2+2]-cycloaddition reactions:

(Z)-methyl-2-(bicyclo[3.2.0]heptan-6-ylidene) acetate (2a) and (E)-methyl-2-(bicyclo[3.2.0]heptan-6-ylidene) acetate (2b)

The methyl ester **1** (0.190 g, 1.15 mmol) was dissolved in CH_2Cl_2 (predried with $MgSO_4$, 2 mL) in a microwave reactor vial (8 mL) in an atmosphere of nitrogen, and $EtAlCl_2$ in hexane (1M, 1 mL) was added. **CAUTION:** $EtAlCl_2$ is pyrophoric and reacts violently with water! The mixture was irradiated with microwaves at 130 °C for 30 s (fixed hold time: ON). The catalyst was deactivated by addition of saturated aq sodium dihydrogenphosphate-1-hydrate, and the organic phase was filtered through a small plug of silica/$MgSO_4$ using CH_2Cl_2 as the eluent. Concentration *in vacuo* yielded a mixture (0.165 g, 83 %) containing the acetates **2a** and **2b** in a ratio of 2.5 : 1 (according to GLC analysis). Several attempts on separation of **2a** and **2b** by flash column chromatography were made, but they were all unsuccessful. The spectroscopical data for **2a** og **2b** was in accordance with literature,[12]

General procedure for the preparation of the allene esters 3 and 4:

The allene esters were prepared according to the procedure of Lang and Hansen,[15,16] and purified by flash column chromatography.

(3-Methyl-3-buten-1-yl) 2,3-butadienoate (3a)

The allene ester **3a** was prepared from (3-methyl-3-buten-1-yl) triphenylphosphoranyliden-acetate (**7**) (39.7 g, 0.102 mol) in dry CH_2Cl_2 (380 mL), triethylamine (14.5 mL, 0.104 mol) in dry CH_2Cl_2 (150 mL), acetyl chloride (7.4 mL, 0.105 mol) in CH_2Cl_2 (150 mL). The crude products were purified by column chromatography (silica, pentane : ethyl acetate (80:20)) to give pure 3-methyl-3-buten-1-yl 2,3-butadienoate (**3a**) (9.7 g, 62 %) as a colourless oil.
IR (HATR) (ν_{max}, cm^{-1}): 3033 (m), 2969 (s), 2914 (s), 1970 (s), 1942 (s), 1720 (s), 1651 (s), 1452 (m) and 1425 (m). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.68 (3H, s), 2.89 (2H, t, *J* 6.9 Hz), 4.18 (2H, t, *J* 6.9 Hz), 4.67 (1H, s), 4.73 (1H, s), 5.13 (2H, d *J* 6.5 Hz) and 5.55 (1H, t *J* 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.9, 36.1, 62.6, 78.5, 87.3, 111.8, 141.0, 164.7 and 215.3. MS, *m/z* (%) = 152 (M^+, 0.1), 137 (2), 107 (20), 97 (7), 91 (8), 85 (31), 69 (55), 68 (100), 67 (99), 66 (26) and 53 (49).

(3-Methyl-3-buten-1-yl) 4-methyl-2,3-pentadienoate (3c)

The allene ester **3c** was prepared from (3-methyl-3-buten-1-yl) triphenylphosphoranyliden-acetate (**7**) (51.1 g, 0.132 mol) in dry CH_2Cl_2 (450 mL), triethylamine (19 mL, 0.136 mol) in dry CH_2Cl_2 (180 mL), isobutyryl chloride (14 mL, 0.134 mol) in CH_2Cl_2 (180 mL). The crude products were purified by column chromatography (silica, pentane : ethyl acetate (80:20)) to give **3c** (3.3 g, 14 %) as a colourless oil.

IR (HATR) (ν_{max}, cm^{-1}): 3074 (m), 2970 (m), 2907 (m), 1970 (m), 1942 (m), 1718 (s), 1652 (w), 1442 (m) and 1399 (m). ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.71 (3H, s), 1.75 (3H, s), 1.75 (3H, s), 2.31 (2H, t, *J* 6.8 Hz), 4.18 (2H, t, *J* 6.8 Hz), 4.70 (1H, s), 4.75 (1H, s), 5.35-5.45 (1H, m).. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.2 (2xCH_3), 22.5, 36.7, 62.9, 85.9, 100.0, 112.1, 141.8, 166.5 and 210.7.

MS, *m/z* (%) = 180 (M^+, 14), 165 (19), 150 (24), 137 (19), 135 (22), 119 (12), 113 (38), 112 (26), 107 (13), 95 (86), 93 (35), 69 (57), 68 (93), 67 (96), 65 (25), 53 (31), 51 (29) and 41 (100).

Ethyl buta-2,3-dienoate (4a)[19]

Flash column chromatography (Silica, pentane: EtOAc; 95 : 5) yielded the ester **4a** (3.41 g, 30 %) as an oil. The spectra confirmed the structure.[20]

Ethyl penta-2,3-dienoate (4b)[15]

Flash column chromatography (Silica, hexane) yielded the ester **4b** (7.94 g, 63 %) as an oil. The spectra were in accordance with the literature.[15,21]

General procedure for the preparation of the allene acids 5a and 5b:

2.3-butadienoic acid (5a)[22]

Ethyl 2,3-butadienoate (**4a**) (1.5 g, 12 mmol) was added to a solution of $LiOH \bullet H_2O$ (1.02 g, 24 mmol) in water (24 mL) and glyme (24 mL) and stirred at room temperature for 3h. Water (30 mL) was added and the mixture was extracted with ether (50 mL). Hydrochloric acid (5-10 %) was added to the aqueous phase until a pH of 3-4. The water phase was extracted with ether (3x), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Residual glyme was removed by azotropic distillation with hexane, yielding the allene acid **5a** (0.788 g, 78 %) as a white solid. The spectra were in accord with the literature.[23]

2,3-pentadienoic acid (5b)[24] and 3-pentynoic acid[25]

Ethyl 2,3-pentadienoate (**4b**) (0.755 g, 6 mmol), LiOH•H_2O (0.505 g, 12 mmol) in water (13 mL) and glyme (13 mL). Crude yield: 0.52 g, 88 % of a mixture containing the allenic acid **5b** and 3-pentynoic acid in a ratio of 20:80 (according to NMR) as a white solid. The spectra of 3-pentynoic acid was in accordance with the literature.[26]

2,3-pentadienoic acid (5b)

^{1}H NMR (400 MHz, $CDCl_3$): The signals that could be distinguished were: δ_H 1.75 (1H, dd, *J* 3.2 and 7.4 Hz), 5.48-5.55 (1H, m), 5.57-5.66 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 12.4, 87.1, 90.6, 172.5, 214.4.

(3-methyl-3-buten-1-yl) 2-bromoacetate (6)[27]

3-methyl-3-butenol (2.15 g, 25.0 mmol), dry triethyl amine (2.28 g, 22.5 mmol) and 4-(dimethylamino)-pyridine (0.31 g, 2.51 mmol) were dissolved in benzene (30 mL).[18] The solution was cooled in an ice-bath, and 2-bromoacetyl bromide (5.05 g, 25.0 mmol) in benzene (20 mL) was added dropwise. The mixture was refluxed for 0.5 h. The precipitated salt was removed by filtration, the mixture was concentrated *in vacuo*, and the residue was distilled to give bromoacetate **6** (3.48 g, 67%) as a colourless oil. Bp. 103-108 °C/15-20 torr. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.72 (3H, m), 2.30-2.40 (2H, m), 3.79 (2H, s), 4.20-4.30 (2H, m), 4.71 (1H, br s), 4.78 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.3, 25.8, 36.3, 64.3, 112.6, 141.0, and 167.2.

(3-methyl-3-buten-1-yl) triphenylphosphoranylidenacetate (7)

(3-methyl-3-buten-1-yl) 2-bromoacetate (**6**) (1.04 g, 5 mmol) was dissolved in ether (5 mL), and PPh_3 (1.31 g, 5 mmol) was slowly added.[11] Ether (4 mL) was used to rinse the transfer vessel. Vigorous stirring was maintained for 24 h, and then the solution was allowed to stand for additional 12 hours. The white precipitate was collected by filtration, washed with diethyl ether and dried *in vacuo* to afford the phosphonium salt as a fine, white powder (crude yield 2.02 g) that was used without further purification.

The crude phosphonium salt was dissolved in CH_2Cl_2 (25 mL) and the solution was shaken gently with aq. KOH (1N, 25 mL) in a separatory funnel for 5 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated, and dried *in vacuo* to give the phosphonium ylide **7** (crude yield 1.48 g) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.63 (3H, s), 2.10 (2H, t, *J* 7.0 Hz), 2.40-2.80 (1H, br s), 4.01 (2H, t, *J* 7.0 Hz), 4.57 (1H, br s), 4.62 (1H, br s) and 7.30-8.00 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.5, 29.4/31.0, 37.3, 60.6, 111.3, 128.3/128.5, 128.6/128.7, 131.8/131.9, 132.9/133.0, 142.7 and 171.1/171.2.

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Supplementary Material for

Synthetic Studies towards Cyclobutanes by Microwave Assisted Intramolecular [2+2]-Cycloaddition of Allene-Ene Esters

Runa B. Østby, Rita L. Sørensen, Stephen Westerås, Simen Antonsen and Yngve Stenstrøm*

Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, PO Box 5003, NO-1432 Ås, Norway

E-mail: yngve.stenstrom@nmbu.no

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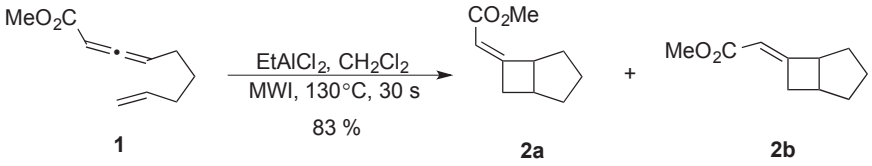
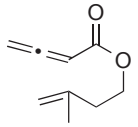


Table 1. Parameters for optimization of the microwave assisted Lewis acid catalyzed [2+2]-cycloaddition of methyl 2,3,8-nonatrienoate (**1**)

Lewis acid[a]	Temperature [°C]	Reaction time [s]	Conversion/ (Isolated yield) [%]
$EtAlCl_2$	80	1200	poor
$EtAlCl_2$	100	10	83[b]
$EtAlCl_2$	120	10	92[b]
$EtAlCl_2$	130	30	>96[b] (83)
$EtAlCl_2$	140	10	>96[b]
$AlCl_3$	130	10	< 50[d]
$AlCl_3$	140	10	>90[b]
$AlCl_3$	140	600	complete (47)
$AlCl_3$	140	30	>96[b]
$FeCl_3$	100	600	Small amounts
BF_3	100	600	-
-	120	1200	0[c]

[a] CH_2Cl_2 was used as the solvent.
[b] According to GLC analyses
[c] According to ^1H NMR analyses
[d] According to IR analyses

Table 2. Attempts on intramolecular Allene-ene cycloaddition of (3-Methyl-3-buten-1-yl) 2,3-butadienoate (**3a**) using different Lewis acids

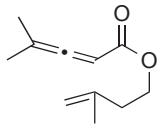


3a

Entry	Allene [M]	Lewis acid	Lewis Acid [mol%][a]	Solvent	Temperature[b] [°C]	Reaction time at each T [min]
1	0.4	$EtAlCl_2$[c]	0.9	CH_2Cl_2	120, 140, 160, 180 200	10
2	0.6	$EtAlCl_2$[d]	9	CH_2Cl_2	100, 110, 115, 120, 125, 130	0.5
3	0.4	$EtAlCl_2$[d]	9	CH_2Cl_2	135, 140, 145, 150, 160	0.5
4	0.6	Tf_2NH	1.9	CH_2Cl_2	100, 110, 120, 130, 140, 150, 160, 170, 180	5
5	0.6	Tf_2NH	1.9	CH_2Cl_2	130, 150, 170	30
6	0.42	Tf_2NH[e]	0.1	Toluene-CH_2Cl_2 (1:4)	100, 250	10
2	neat[f]	$AlCl_3$	0.5	Benzene or CH_2Cl_2	100 140 180	30

[a]Related to alkene.
[b]Reactions were cooled down and sampled after the reaction time was over, then heated to the next temperature.
[c]0.1 M in hexane.
[d]1 M in hexane.
[e]0.01 M Tf_2NH in CH_2Cl_2.
[f]0.160 g allene, no solvent.

Table 3. Attempts on intramolecular Allene-ene cycloaddition of allene (3-Methyl-3-buten-1-yl) 4-methyl-2,3-pentadienoate (**3c**) using different Lewis acids



3c

Entry	Allene conc. [M]	Lewis acid	Lewis Acid [mol%][a]	Solvent	Temperature [°C][b]	Reaction time at each T [min]
1	0.5	$EtAlCl_2$[c]	4.8	CH_2Cl_2	120 140 160 180	20
2	0.4	Tf_2NH	2 grains	CH_2Cl_2	100 120	10

[a]Related to alkene.
[b]Reactions were cooled down and sampled after the reaction time was over, then heated to the next temperature.
[c]0.1 M in hexane.

Appendix 5:

Paper IV

Syntheses of bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes by ring expansion of isopropylidenecyclobutanes

Østby, R. B., Stenstrøm, Y. H.,

ARKIVOC **2014**, (iv), 266-284.

Syntheses of bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes by ring expansion of isopropylidenecyclobutanes

Runa B. Østby and Yngve Stenstrøm*

Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, PO Box 5003, NO-1432 Ås, Norway
E-mail: yngve.stenstrom@numb.no

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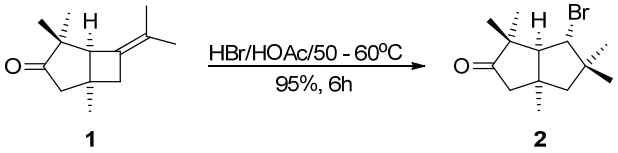
Abstract
When subjected to HBr/HOAc in polar solvents like acetic acid, 6-(1-methylethylidene)-bicyclo[3.2.0]heptanes undergo a ring expansion reaction yielding 2-bromo-3,3-dimethylbicyclo[3.3.0]octane and 3-bromo-2,2-dimethylbicyclo[3.3.0]octane. Several other isopropylidenecyclobutanes have been found to undergo the same reaction with high stereoselectivity and moderate regioselectivity. In less polar solvents like diethyl ether the ring expansion reaction is suppressed, and bromides resulting from addition of HBr to the isopropylidene double bond are obtained.

Keywords: Ring expansion reaction, HBr, acetic acid, isopropylidenecyclobutanes, bicyclo[3.3.0]octanes

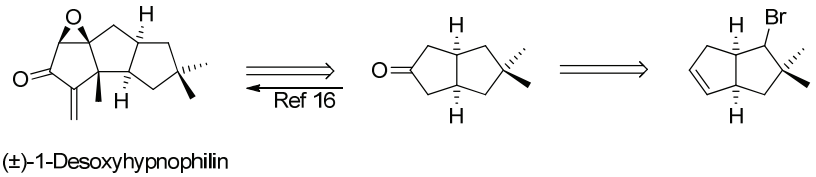
Introduction

The bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane skeletons are recognized as substructures of many biologically active, synthetically challenging compounds like capnellanes, hirsutanes and pasteurestins.[1-7] Several other examples of ring expansions of four-membered carbocycles to give useful five-membered rings can be found in the literature.[8-12] Despite several existing methods, the structural variety of these compounds still calls for new practical procedures to be developed.[13] While working on a synthesis of the insect pheromone component lineatin, we found that the epoxide of **1** gave an acid catalysed ring expansion.[14] Later we found that using HBr in acetic acid gave a near quantitative yield of the ring expanded product **2**.[15] The reaction was found to be both stereo- and regioselective as seen from both spectroscopic data and X-ray crystallography.



Scheme 1. Ring expansion reaction of **1**.

Inspired by these results, we decided to investigate the reaction further. Such a regio- and stereoselective, high yielding reaction would be very useful in the syntheses of natural products, e.g. (±)-1-desoxyhypnophilin a biologically active linear triquinane isolated from the East African mushroom *Lentinus crinitus* (L. ex Fr.) Fr.[1]

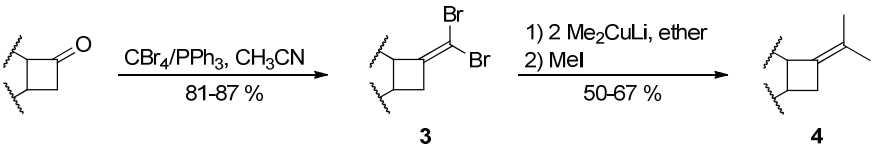


Scheme 2. Retrosynthetic analysis of (±)-1-desoxyhypnophilin.

In the present paper we would like to report a study in which several isopropylidene-cyclobutane derivatives were tested for the ring expansion reaction.

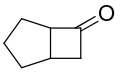
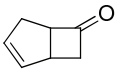
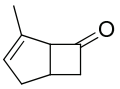
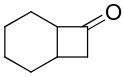
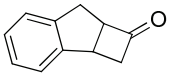
Results and Discussion

The dibromomethylenecyclobutanes were prepared in excellent yields (81-87 %) by treatment of known ketones[17-20] with PPh_3 and CBr_4 in acetonitrile using a modified literature procedure.[21] Acetonitrile was used since it has been found to be the best solvent for the reaction of ketones with PPh_3/CCl_4.[22] The dibromomethylenecyclobutanes were then methylated twice with lithium dimethylcuprate.[21] With low boiling products, the solvent was distilled at ambient pressure in order to minimise loss of product. The yields of the isopropylidenecyclobutanes were fairly good (50-67 %). In this way the isopropylidenecyclobutanes **4a-e** were prepared. (Scheme 3 and Table 1).

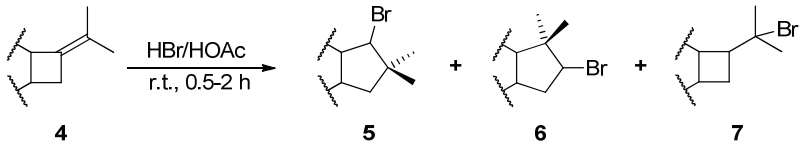


Scheme 3. Preparation of the isopropylidenecyclobutanes **4a-e**.

Table 1. Starting materials

Substrate	Dibromomethylenecyclobutane (isolated yield)	Isopropylidenecyclobutane (isolated yield)
	**3a** (87%)	**4a** (60%)
	**3b** (81%)	**4b** (60%)
	**3c** (87%)	**4c** (67%)
	**3d** (85%)	**4d** (50%)
	**3e** (85%)	**4e** (62%)

Previous attempts in our group to achieve ring expansion of compound **1** using protic acids like HCl, *p*-toluenesulfonic acid or CF_3COOH, and Lewis acids like BF_3, $AlCl_3$, $HgSO_4$, $Hg(OAc)_2$ or $AgNO_3$ were unsuccessful.[15] However, using 45 % HBr in acetic acid a near quantitative yield of a product corresponding to compound **5** was achieved. When the reaction was carried out with 33 % HBr in acetic acid at room temperature using the same amount of HBr (~8 eq.), a mixture of products were obtained.



Scheme 4. Preparation of **5**, **6** and **7.**

The reactions were finished in 0.5-2 h and three products were observed. Two of these were ring expanded compounds **5** and **6**. In addition variable amounts of **7** resulting from addition of HBr across the double bond, were also seen (Scheme 4). It was observed that **7** rearranged on the GLC, and for this reason it was not possible to give exact amounts of these compounds. The ^1H NMR spectrum of the product mixture resulting when the alkene **4d** was used as the substrate, indicated that the ratio of the ring expanded compounds (**5d** + **6d**) to **7d** was approximately 70:30, and that the ratio of **5d** to **6d** was 58:42 (^1H NMR). Prolonged reaction times did not change the ratio **5d**:**6d**. When substrate **4e** was used, the ratio of the ring expanded compounds

(**5e+6e**) to **7e** was approximately 90:10. The *gem*-dimethyl singlets are easily detectable in the ^{1}H NMR spectra of the product **7**. So when none of these resonances were seen in the spectrum of the reaction mixture using **4a** as substrate, this was clearly indicating that none or only small amounts of **7a** could have been formed.

Attempts to isolate **5a** and **6a** by column chromatography failed since no separation was achieved, and separation of **5** and **6** by chromatography was not attempted. Instead analytical samples of **5** and **6** were isolated using preparative GLC.

Generally a high stereoselectivity was achieved. According to both ^{1}H NMR and GLC analyses mainly one stereoisomer was formed, and only a few per cent of the other isomer could be detected. Representative examples are depicted in Table 2.

Table 2. Treatment of the isopropylidenecyclobutanes with excess 33 % HBr in acetic acid at room temperature

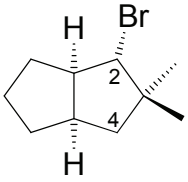
Substrate	Method	Ratio (%)[a]	
		5	**6**
4a	GLC	65	35
4a	NMR	64	36
4b	GLC	small amounts	small amounts
4c	GLC	small amounts	small amounts
4d	GLC	56	44
4d	NMR	58	42
4e	GLC	79	21
4e	NMR	74	26

[a] Conversion 100 %. Ratio based on GLC analyses (at full reaction time) and ^{1}H NMR data (of the crude mixture).

The compounds **5**, **6** and **7** are easily identified from their respective ^{1}H NMR spectra. The ^{1}H NMR spectra of **5** exhibited a characteristic doublet at δ 3-4 ppm due to the CH-Br signal. In the spectra of **6** the corresponding signal appeared as a doublet of doublet at δ 3.8-4.5 ppm. The compounds **7** could be identified from the two methyl singlets at δ 1.6-1.7 ppm consistent with a *gem*-dimethyl group situated on the same carbon atom as the bromine atom. The other features of the spectra were also in accord with the structures.

The rearrangement gave mainly one stereoisomer, but due to the flexibility of the two fused

5-membered rings it was not possible to use coupling constants to confirm which stereoisomer was predominantly formed. However, thorough analysis of the NMR spectra of **5a** made it possible to distinguish the two protons on C4. A fairly strong interaction between the *endo* H4 proton and the α-proton (H2) based on the ROESY spectra could be seen, tentatively showing the stereochemistry of the bromine substituted carbon atom (H2) as depicted in Figure 1.



5a

Figure 1

The regioselectivity, however, was only moderate and best for the isopropylidene-cyclobutane **4e**, assumed to be the most strained substrate. The least strained substrate **4d** yielded the lowest selectivity. With the substrates **4a** and **4e** only minor amounts (<10 %, GLC) of side products were observed. With the substrate **4d** up to 18% side products were present (GLC), but some of them may result from decomposition of **7d** in the injector. The substrates **4b** and **4c**, however, gave mixtures of several unidentified products where the ring expanded products **5** and **6**, according to GLC analyses, constituted only small amounts. This was probably due to addition of HBr to the *endocyclic* double bond. Small amounts of two unidentified compounds could be isolated by preparative GLC from the complex mixture resulting from substrate **4b**. The ^{1}H NMR spectra indicated that no double bonds were present in these compounds, and no attempts were made to further elucidate the structures. The reaction mixture resulting from substrate **4c** was so complex that separation was not attempted.

Changing the temperature of the reaction resulted in only minor effects. (Table 3) Both the stereo- and regioselectivity of the reaction was the same as at room temperature. Temperatures ranging from 0-5 °C to 70 °C were tried. For substrate **4d** (entry 7), however, lowering the temperature to 0-5 °C slowed the ring expansion reaction down, and the major product was **7d** (GLC) where the ring expansion had not taken place. The amounts of side products formed were approximately the same as at room temperature. Unfortunately, lowering the temperature did not affect the outcome of the reaction for the substrate **4c** (entry 5), and a complex mixture containing only minor amounts of **5c** and **6c** resulted. Elevation of the temperature (entry 4) gave no trace of **5c** and **6c**.

Table 3. Temperature effects

Entry	Substrate	Temperature	Ratio (%)[a]		
			5	**6**	**7**
1	**4a**	70 °C	65	35	-
2	**4a**	50-60 °C	65	35	-
3	**4a**	0-5 °C	66	34	trace amounts
4	**4c**	50-60 °C	-	-	-
5	**4c**	0-5 °C	small amounts[b]	small amounts[b]	small amounts[b]
6	**4d**	50-60 °C	52	39	8[c]
7	**4d**	0-5 °C	30	25	45[c]

[a] Conversion 100 %. Ratio based on GLC data. [b] i. e. <15%

[c] Rearranges to a certain extent on the GLC.

Since the temperature effects were minimal, changing the polarity of the reaction medium was tried. Representative results are presented in Table 4.

At first the reaction was performed using the same amount of HBr (in acetic acid) as before (~8 eq.). Using substrate **4a** as a model, solvents with polarities ranging from hexane to CH_2Cl_2 were added in a ratio of HBr/HOAc : solvent, ~1:3 (eg. entries 1 and 2). The regioselectivity did not improve. Moreover, using diethyl ether as the solvent, the ring expansion reaction was suppressed completely yielding **7a** as the only product identified. Only minor amounts of side products (<10%) were observed. The reactions were performed at room temperature except for entry 6 (substrate **4c**) that was performed in refluxing ether. Comparison of GLC chromatograms of the reactions of the bromide **4c** at room temperature and at reflux, indicated that the temperature change only resulted in minor differences in the product ratio. Purification of **7a** by preparative GLC or flash chromatography failed, and only the ring expanded products **5a** and **6a** were isolated. Even at direct injection on the MS, rearrangement of **7a** was observed. The compound **7b** gave a spectrum that was tentatively associated with the structure depicted for this compound, but for **7c** and **7d** no attempts to measure MS spectra were made since they all rearranged as easily as **7a**.

Table 4. Solvent effects

Entry	Substrate	Conditions	Ratio (%)[a]			Conversion
			5	**6**	**7**	(%)[a]
1	**4a**	Et_2O, 1 h[b]	-	-	~100	~100
2	**4a**	CH_2Cl_2, 1 h[b]	52 (58)	48 (42)	-	100
3	**4a**	Hexane, 1 h[b]	(40)	(28)	(32)	95
4	**4a**	Et_2O, 4 h[c]	-	-	~100	94
5	**4b**	Et_2O, 3 h[c]	-	-	~100	100
6	**4c**	Et_2O, Δ, 22 h[c,d,e]	-	-	major	94
7	**4d**	Et_2O, 8 h[c,d]	-	-	~100	91

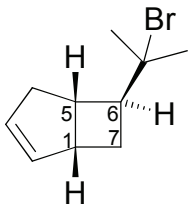
[a] Ratio based on ^{1}H NMR data or GLC data (in parenthesis), conversion based on GLC data.
[b] HBr/HOAc: solvent, ~1:3; [c] HBr/HOAc: solvent, ~1:20; [d] Slow addition of HBr in acetic acid;
[e] Reaction performed at reflux

When the reaction was performed in diethyl ether using an excess of only 2-4 eq. of HBr (HBr/HOAc:ether, ~1:20) (entries 4 to 7) no change in the outcome of the reaction was observed; the ring expansion reaction was suppressed for all the substrates, and only **7** were obtained. No attempts were made to purify **7b**-**d** since the purification of **7a** failed. The compound **7c** was not isolated, but merely identified from the ^{1}H NMR spectrum of the crude product by resonances at δ ~1.6-1.7 ppm corresponding to the *gem*-dimethyl group situated on the bromine substituted carbon atom, a singlet at δ 1.85 ppm corresponding to the vinylic methyl group and a multiplet at 5.27-5.37 ppm (alkene proton). Signals due to formation of the rearranged bromides **5c** and **6c** could not be seen in the spectrum. The yields of the products **7a-7d** have not been optimized.

Slower addition of the HBr/HOAc solution resulted only in a slower reaction, and in accordance with literature,[23] an excess of 2-3 eq. of HBr was necessary to complete the reaction.

The stereochemistry of the bromides **7** was difficult to establish, but the ROESY spectrum of **7b** shows a strong coupling between the two bridgehead protons H1 and H5, and a weaker coupling between the bridgehead proton H5 and the α-proton (H6). Molecular models (ball-and-stick models) indicate that due to the rigidity of this bicyclic compound, the coupling between protons H5 and H1 and between protons H5 and H6 should be of similar strength if the α-proton (H6) and the bridgehead protons are *syn.* This indicates that **7b** has the stereochemistry depicted in Figure 2 with the $(CH_3)_2$CBr-group situated *exo*. This is confirmed by the ROESY spectrum

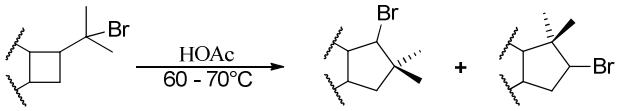
revealing correlations between the $(CH_3)_2CBr$-group and both the bridgehead proton H5 and the *exo* H7 proton.



7b

Figure 2

Finally, attempts to achieve ring expansion on **7b** and **7c** were made treating them with acetic acid at elevated temperatures. The substrate **7b** yielded the ring expanded compounds **5b** and **6b** in moderate regioselectivity. The substrate **7c** gave a complex mixture containing moderate amounts of **5c** and **6c** (Table 5 and Scheme 5).



7 **5** **6**

Scheme 5. Ring expansion of **7** in HOAc.

Table 5. Ring expansion of HBr adducts

Substrate	Reaction time (h)	Ratio (%)		Method	Conversion (%)
		5	**6**		
7b	1.5	71	29	GLC	96[a]
		72	28	NMR	90[b]
7c	8	63	37	GLC	89[a]

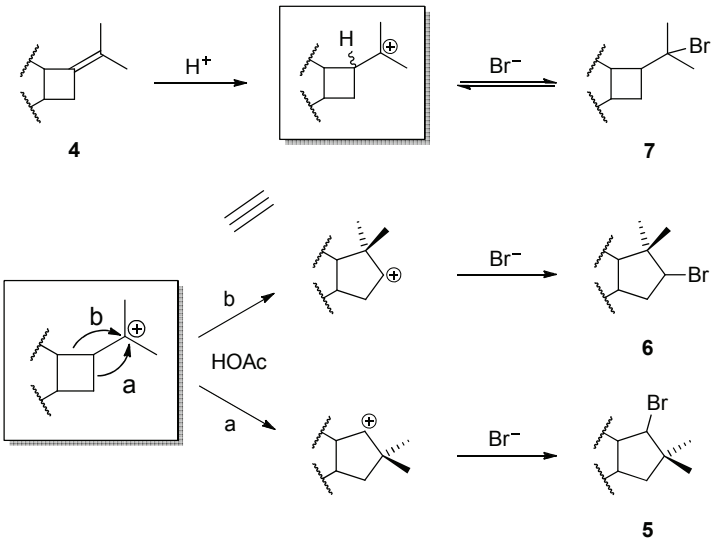
[a] Conversion based on GLC data. [b] Conversion based on ^{1}H NMR data.

The reaction gave an impure mixture, and the ^{1}H NMR spectrum of this was too complex to indicate the conversion of **7c** or the ratio of **5c** and **6c** formed. On the other hand, the crude mixture obtained from **7b** gave consisting results, when analysed by GLC and NMR, both with respect to conversion of the starting material and the ratio of **5b** to **6b**. This information is

indicative of both the conversion of **7c** and the ratio of **5c** and **6c**, although the bromide **7c** has been found to rearrange on the GLC.

Preparative GLC yielded analytical samples of **5b**, **6b** and **5c**. For **6c** an impure sample was obtained, and **6c** was merely identified from the ^{1}H NMR spectrum of this sample by the singlets at δ 0.96 and 1.16 ppm (the *gem*-dimethyl groups), a multiplet at δ 1.69-1.77 ppm (alkene CH_3 group), a doublet of doublet at δ 4.11 ppm (CHBr proton, *J* 5.4 and 5.9 Hz) and a multiplet at δ 5.25-5.35 ppm (alkene proton).

A possible mechanism of the ring expansion reaction is depicted in Scheme 6.



Scheme 6. Possible mechanism of the ring expansion reaction.

The initially formed tertiary carbocation can rearrange through either pathway **a** or **b** yielding **5** or **6**, respectively. This mechanism fails to explain the high stereoselectivity exhibited by the reaction, however. Sterical congestion alone cannot explain the high stereoselectivity, and possibly a cage type mechanism is at work.

When the reaction was performed with the isopropylidenecyclobutane **1**, a higher regioselectivity was reported.[15] This may be due to the fact that if substrate **1** were to undergo a ring expansion reaction by pathway **b**, a severely sterically congested bromide with adjacent *gem*-dimethyl substituted carbon atoms would result. However, the mechanism of the reaction was not studied.

Experimental Section

General. Melting points were measured on an Electrothermal 9100 apparatus. IR was performed on a Perkin Elmer Paragon 500 FT-IR spectrophotometer or a Magna-IR 550 Nicolet FT-IR spectrophotometer. Only selected absorption bands in IR are reported. The routine NMR spectra were recorded on a Varian Gemini 200 instrument or Bruker DPX 200, DPX 300 or DRX 500 instruments using $CDCl_3$ as a solvent and TMS as a reference. ^{1}H NMR spectra were recorded at 200, 300 and 500 MHz, and ^{13}C NMR spectra were recorded at 50, 75 and 125 MHz. MS spectra were recorded on a JEOL DX-303 mass spectrometer, and HRMS spectra were recorded on a Fisons VG ProSpec Q mass spectrometer using electronic ionisation (EI) at an ionisation potential of 70 eV unless otherwise stated. Only selected peaks in MS are reported. Analytical GLC was carried out on a Varian 3400 gas chromatograph and a Chrompack CP9001 gas chromatograph using Chrompack WCOT fused silica capillary columns (25 m, i.d. 0.32 mm, CP-sil-8 CB 1.20 μm), and preparative GLC was carried out on a Varian 3300 and a Varian 3400 gas chromatograph using a 10% SP-2100 packed column (2.5 m, i.d. 4 mm). Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254}. Compounds were visualized by UV light and/or stained with *p*-anisaldehyde solutions followed by heating. Flash column chromatography was performed on silicagel (Merck Kieselgel 60, (0,040-0,063 mm, 230-400 Mesh ASTM). All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. When required, the solvents were dried (by standard procedures) and distilled and the reactions performed under an atmosphere of nitrogen. Anhydrous solvents purchased in sure seal bottles over molecular sieves were used without further drying.

Bicyclo[3.2.0]heptan-6-one,[17] bicyclo[3.2.0]hept-2-en-6-one,[18] bicyclo[4.2.0]octan-7-one[20] and 2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]inden-1-one[18] were prepared from the corresponding dichloroketene adducts according to literature.[24,25] 4-Methylbicyclo[3.2.0]hept-3-en-6-one[19] was prepared from 3-hydroxy-3-methyl-6-heptenoic acid according to literature procedures.[26]

Typical procedure for the preparation of the (dibromomethylene)bicyclic compounds[21,22]

6-(Dibromomethylene)bicyclo[3.2.0]heptane (**3a**). A mixture of triphenylphosphine (24.13 g, 92.0 mmol) and bicyclo[3.2.0]heptan-6-one[17,24] (1.983 g, 18.0 mmol) in acetonitrile (140 mL) was cooled to 0 °C, and CBr_4 (15.22 g, 45.9 mmol) was added in one portion. The mixture was stirred at room temperature under nitrogen for 4 h. Solid material was removed by vacuum filtration, and the solvent was removed *in vacuo*. The residue was dissolved in a minimal quantity of dichloromethane and added dropwise to hexane (dichloromethane:hexane 1:5). Precipitated solid was filtered and washed with hexane. Solvents were removed *in vacuo*, and the procedure was repeated twice. Purification of the residue by chromatography (silica, hexane) yielded the pure dibromomethylenecyclobutane **3a** (4.16 g, 87%) as a colourless oil. IR (film) ($\nu_{max,}$ cm^{-1}): 2952 (s, shoulder), 2858 (m), 1660 (w), 1444 (w), 1413 (w), 840 (m) and 799 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.30-1.88 (5H, m), 1.88-2.10 (2H, m), 2.53-2.73 (2H, m) and 3.10-

3.24 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 24.6 (CH_2), 29.9 (CH_2), 31.7 (CH), 32.5 (CH_2), 36.7 (CH_2), 49.4 (CH), 79.1 (C) and 148.6 (C). MS, *m/z* (%) = 264 (M^+, 10)/266 (M^+, 22)/268 (M^+, 9), 236 (13)/238 (22)/240 (12), 185 (30)/187 (29), 157 (17)/159 (16), 106 (82), 105 (100), 79 (39), 77 (40), 51 (43) and 39 (53). HRMS: $C_8H_{10}{}^{79}Br^{81}Br$ requires *m/z* = 265.9129. Found *m/z* = 265.9132.

6-(Dibromomethylene)bicyclo[3.2.0]hept-2-ene (3b). Triphenylphosphine (10.25 g, 39.1 mmol), bicyclo[3.2.0]hept-2-en-6-one[18,24] (0.830 g, 7.68 mmol), CBr_4 (6.495 g, 19.6 mmol), acetonitrile (30 mL). The dibromomethylenecyclobutane **3b** (1.64 g, 81%) was obtained as a colourless oil. IR ($CDCl_3$) (ν_{max}, cm^{-1}): 3056 (m), 2948 (s, shoulder), 2852 (m), 1747 (m, br), 1713 (m, br), 1665 (m, br), 1607 (m, br), 848 (s) and 802 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.24 (1H, dt, *J* 16.5 and 3.4 Hz), 2.43-2.62 (1H, m), 2.66-2.84 (2H, m), 3.14-3.30 (1H, m), 3.32-3.46 (1H, m) and 5.70-5.80 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 36.4 (CH_2), 39.3 (CH), 39.8 (CH_2), 46.2 (CH), 80.9 (C), 131.7 (CH), 132.2 (CH) and 149.8 (C). MS, *m/z* (%) = 262 (M^+, 31)/264 (M^+, 58)/266 (M^+, 29), 247 (16)/249 (29)/251 (15), 183 (92)/185 (92), 104 (97), 103 (100), 77 (56), 66 (98) and 51 (60). HRMS: $C_8H_8{}^{79}Br^{81}Br$ requires *m/z* = 263.8972. Found *m/z* = 263.8979.

7-(Dibromomethylene)-2-methylbicyclo[3.2.0]hept-2-ene (3c). Triphenylphosphine (24.13 g, 92.0 mmol), 4-methylbicyclo[3.2.0]hept-3-en-6-one[19,26] (2.199 g, 18.0 mmol), CBr_4 (15.22 g, 45.9 mmol), acetonitrile (140 mL). The dibromomethylenecyclobutane **3c** (4.33 g, 87%) was obtained as a colourless oil. IR (film) (ν_{max}, cm^{-1}): 3037 (w), 2967 (s), 2908 (s), 2847 (m), 1660 (w, br), 1442 (m), 1413 (m), 1117 (m), 840 (m) and 788 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.79-1.87 (3H, m), 2.09-2.37 (2H, m), 2.44-2.63 (1H, m), 2.63-2.87 (2H, m), 3.59-3.73 (1H, m) and 5.33-5.42 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 17.1 (CH_3), 31.0 (CH), 39.6 (CH_2), 39.9 (CH_2), 60.5 (CH), 78.0 (C), 125.8 (CH), 138.7 (C) and 148.8 (C). MS, *m/z* (%) = 276 (M^+, 23)/278 (M^+, 44)/280 (M^+, 22), 261 (16)/263 (30)/265 (14), 248 (8)/250 (15)/252 (8), 197 (31)/199 (30), 118 (100), 117 (90), 80 (35) and 79 (33). HRMS: $C_9H_{10}{}^{79}Br^{81}Br$ requires *m/z* = 277.9129. Found *m/z* = 277.9127.

7-(Dibromomethylene)bicyclo[4.2.0]octane (3d). Triphenylphosphine (24.13 g, 92.0 mmol), bicyclo[4.2.0]octan-7-one[20,25] (2.235 g, 18.0 mmol), CBr_4 (15.22 g, 45.9 mmol), acetonitrile (150 mL). The dibromomethylenecyclobutane **3d** (4.27 g, 85%) was obtained as a colourless oil. IR (film) (ν_{max}, cm^{-1}): 2933 (s), 2855 (m), 1665 (w), 1449 (m, shoulder) and 802 (m, shoulder). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.13-1.60 (5H, m), 1.60-1.90 (3H, m), 2.15-2.45 (2H, m), 2.45-2.68 (1H, m) and 2.75-3.00 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 21.6 (CH_2), 21.8 (CH_2), 24.1 (CH_2), 26.6 (CH), 26.9 (CH_2), 37.9 (CH_2), 43.4 (CH), 77.3 (C) and 148.8 (C). MS, *m/z* (%) = 278 (M^+, 49)/280 (M^+, 100)/282 (M^+, 50), 250 (12)/252 (23)/254 (12), 236 (8)/238 (16)/240 (8), 224 (9),/226 (17)/228 (8), 199 (19)/201 (23), 119 (32), 91 (20) and 67 (22). HRMS: $C_9H_{12}{}^{79}Br^{81}Br$ requires *m/z* = 279.9285. Found *m/z* = 279.9288.

1-(Dibromomethylene)-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene (3e). Triphenylphosphine (8.973 g, 34.2 mmol), 2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]inden-1-one[18,24] (1.063 g, 6.72 mmol), CBr_4 (5.683 g, 17.1 mmol), acetonitrile (56 mL). The dibromomethylenecyclobutane **3e**

(1.79 g, 85%) was obtained as a white solid, mp. 105-108 °C. IR (CCl_4) (ν_{max}, cm^{-1}): 3073 (w), 3024 (w), 2929 (m), 2852 (w), 1661 (w), 1480 (w), 837 (w) and 798 (s). ^1H NMR (200 MHz, $CDCl_3$): δ_H 2.42 (1H, dt, *J* 16.7 and 3.4 Hz), 3.05 (1H, dd, *J* 16.7 and 8.4 Hz), 3.18 (1H, dd, *J* 17.2 and 9.1 Hz), 3.36-3.52 (1H, m), 3.56-3.72 (1H, m), 3.74-3.88 (1H, m) and 7.16-7.32 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 36.2 (CH_2), 39.3 (CH), 41.3 (CH_2), 47.5 (CH), 81.4 (C), 124.3 (CH), 124.6 (CH), 126.5 (CH), 126.6 (CH), 142.8 (C), 144.4 (C) and 147.9 (C). MS, *m/z* (%) = 312 (M^+, 8)/ 314 (M^+, 14)/316 (M^+, 8), 233 (8)/235 (8), 154 (16), 153 (25), 152 (14), 117 (11), 116 (100) and 115 (29). HRMS: $C_{12}H_{10}{}^{79}Br_2$ requires *m/z* = 311.9149. Found *m/z* = 311.9143.

Typical procedure for the preparation of the isopropylidene bicyclic compounds using a modified literature procedure[21]

6-(1-Methylethylidene)bicyclo[3.2.0]heptane (4a). An etheral solution of lithium dimethylcuprate was prepared at 0 °C by suspending CuI (15.36 g, 80.7 mmol) in dry diethyl ether (80 mL) and adding a 1.5 M solution of MeLi in diethyl ether until the mixture was colourless. To this solution **3a** (2.178 g, 8.19 mmol) in dry diethyl ether (96 mL) was added, and the mixture was stirred at room temperature overnight. Then methyl iodide (24 mL) was added dropwise under cooling (ice/water), and stirring was continued at room temperature for 1 h. Saturated aq ammonium chloride was carefully added, and the aqueous phase was extracted with ether (3x). The combined etheral extracts were washed with brine and dried (Na_2SO_4). For solids: The solvents were removed *in vacuo*, and the crude material was purified by chromatography (silica, hexane). For liquids: The solvent was removed by careful distillation at ambient pressure and finally by flushing with N_2 while cooled (ice-water). The residue was distilled bulb-to-bulb at 0.7 mmHg and an oil bath temperature of 40 °C slowly rising to 70 °C, yielding the isopropylidenecyclobutane **4a** (0.665 g, 60%) as a colourless oil. IR (film) (ν_{max}, cm^{-1}): 2948 (s), 2922 (s), 2851 (m), 1446 (m, shoulder) and 1369 (m). ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.44 (3H, s), 1.51 (3H, s), 1.20-1.80 (6H, m), 1.85-2.08 (1H, m), 2.52-2.74 (2H, m) and 3.13-3.30 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 18.7 (CH_3), 19.0 (CH_3), 25.2 (CH_2), 32.5 (CH_2), 33.5 (CH, CH_2), 33.6 (CH_2), 46.0 (CH), 122.4 (C) and 133.4 (C). MS, *m/z* (%) = 136 (M^+, 70), 121 (100), 107 (57), 94 (43), 93 (88), 79 (52), 67 (70) and 41 (36). HRMS: $C_{10}H_{16}$ requires *m/z* = 136.1252. Found *m/z* = 136.1247.

6-(1-Methylethylidene)bicyclo[3.2.0]hept-2-ene (4b). CuI (10.77 g, 56.6 mmol) in dry diethyl ether (70 mL), 1.6 M methyllithium in diethyl ether and **3b** (1.510 g, 5.72 mmol) in dry diethyl ether (70 mL). MeI (17 mL). The isopropylidenecyclobutene **4b** (0.457 g, 60%) was obtained as a colourless oil. IR (film) (ν_{max}, cm^{-1}): 3047 (m), 2967 (m), 2918 (s), 2849 (m), 1609 (w), 1444 (m) and 1369 (m). ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.45 (3H, s), 1.55 (3H, s), 2.20-2.34 (1H, m), 2.36-2.65 (2H, m), 2.70-2.91 (1H, m), 3.12-3.32 (1H, m), 3.35-3.55 (1H, m) and 5.68-5.87 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 19.0 (CH_3), 19.3 (CH_3), 36.4 (CH_2), 38.9 (CH_2), 41.2 (CH), 43.0 (CH), 124.9 (C), 130.6 (CH), 133.4 (CH) and 135.0 (C). MS, *m/z* (%) = 134 (M^+, 58), 119

(62), 105 (20), 92 (56), 91 (99), 79 (21), 78 (30), 77 (20), 68 (23), 67 (41), 66 (100), 41 (31) and 39 (34). HRMS: $C_{10}H_{14}$ requires *m/z* = 134.1096. Found *m/z* = 134.1089.

2-Methyl-7-(1-methylethylidene)bicyclo[3.2.0]hept-2-ene (4c). CuI (15.36 g, 80.7 mmol) in dry diethyl ether (80 mL), 1.6 M methyllithium in diethyl ether and **3c** (2.268 g, 8.16 mmol) in dry diethyl ether (96 mL). MeI (24 mL). The isopropylidenecyclobutene **4c** (0.814 g, 67%) was obtained as a colourless oil. IR (film) (ν_{max}, cm^{-1}): 3034 (w), 2963 (s), 2909 (s), 2848 (s), 1648 (w), 1445 (m) and 1373 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.47 (3H, s), 1.62 (3H, s), 1.73 (3H, br s), 2.02-2.36 (2H, m), 2.43-2.65 (1H, m), 2.65-2.86 (2H, m), 3.60-3.73 (1H, m) and 5.25-5.34 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 16.4 (CH_3), 18.9 (CH_3), 19.4 (CH_3), 32.6 (CH), 36.2 (CH_2), 39.9 (CH_2), 57.3 (CH), 121.0 (C), 123.8 (CH), 134.6 (C) and 141.0 (C). MS, *m/z* (%) = 148 (M^+, 93), 133 (100), 106 (52), 105 (100), 92 (59), 91 (66), 80 (53), 79 (49) and 41 (40). HRMS: $C_{11}H_{16}$ requires *m/z* = 148.1252. Found *m/z* = 148.1254.

7-(1-Methylethylidene)bicyclo[4.2.0]octane (**4d**).[27] CuI (15.36 g, 80.7 mmol) in dry diethyl ether (80 mL), 1.6 M methyl lithium in diethyl ether and **3d** (2.285 g, 8.16 mmol) in dry diethyl ether (96 mL). MeI (24 mL).The isopropylidenecyclobutane **4d** (0.610 g, 50%) was obtained as a colourless oil, and the spectral data were in accordance with the literature.[27]

1-(1-Methylethylidene)-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene (4e). CuI (10.48 g, 55.0 mmol) in dry diethyl ether (60 mL), 1.6 M methyl lithium in diethyl ether, **3e** (1.749 g, 5.57 mmol) in dry diethyl ether (60 mL) and MeI (17 mL). The isopropylidenecyclobutane **4e** (0.633 g, 62%) was obtained as a white solid, mp. 42-45 °C. IR (CCl_4) (ν_{max}, cm^{-1}): 3070 (w), 3022 (w), 2924 (s, br), 2851 (m), 1479 (m), 1450 (m) and 1371 (w). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.41 (3H, br s), 1.60 (3H, br s), 2.32-2.50 (1H, m), 2.95-3.27 (3H, m), 3.57-3.82 (2H, m) and 7.07-7.26 (4H, m). ^{13}C (50 MHz, $CDCl_3$): δ_C 19.1 (CH_3), 19.3 (CH_3), 37.7 (CH_2), 38.5 (CH_2), 41.2 (CH), 44.1 (CH), 124.2 (CH), 124.5 (CH), 125.1 (C), 125.9 (CH), 126.1 (CH), 133.4 (C), 143.6 (C) and 146.6 (C). MS, *m/z* (%) = 184 (M^+, 40), 141 (27), 128 (16), 117 (12), 116 (100), 115 (45), 73 (11) and 41 (18). HRMS: $C_{14}H_{16}$ requires *m/z* = 184.1252. Found *m/z* = 184.1252.

Typical methods for the preparation of the bromobicyclo[3.3.0]octanes, the bromobicyclo-[4.3.0]nonanes, and the HBr adducts (**7**)

Method A: **2-Bromo-3,3-dimethylbicyclo[3.3.0]octane (5a) and 3-bromo-2,2-dimethyl-bicyclo[3.3.0]octane (6a)**

A solution of **4a** (0.191 g, 1.40 mmol) in 33% HBr in acetic acid (1.83 mL, 10.4 mmol) was stirred at room temperature for 1 h. Diethyl ether (25 mL) and water (10 mL) was added. The organic layer was separated, and the water phase was extracted with diethyl ether (3 × 5 mL). The combined etheral phases were washed with water (10 mL), saturated aq $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a mixture (Crude yield: 0.277 g, 91%) consisting of **5a** (64%) and **6a** (36%) according to NMR and GLC. Analytical samples of **5a** and **6a** were obtained by preparative GLC.

2-Bromo-3,3-dimethylbicyclo[3.3.0]octane (5a). IR (ATR) (ν_{max}, cm^{-1}): 2949 (s, shoulder), 2864 (s), 1458 (m), 1445 (m), 1385 (m), 1368 (m), 802 (m) and 752 (m). ^{1}H NMR (500 MHz,

$CDCl_3$): δ_H 0.90-1.00 (1H, m), 0.98 (6H s, 2 × CH_3), 1.28-1.37 (1H, m), 1.39-1.63 (5H, m), 1.87 (1H, dd, *J* 12.7 and 8.9 Hz), 2.49-2.60 (1H, m), 2.67-2.76 (1H, m) and 3.40 (1H, d, *J* 9.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.7 (CH_3), 24.4 (CH_2), 26.2 (CH_3), 30.6 (CH_2), 33.0 (CH_2), 39.5 (CH), 44.1 (C), 44.8 (CH_2), 52.3 (CH) and 69.3 (CH). MS, *m/z* (%) = 216 (M^+, 5)/218 (M^+, 4), 138 (14), 137 (100), 121 (7), 95 (35), 81 (71), 79 (15), 69 (50), 67 (22), 55 (17) and 41 (23). HRMS: $C_{10}H_{17}{}^{79}Br$ requires *m/z* = 216.0514. Found *m/z* = 216.0504.

3-Bromo-2,2-dimethylbicyclo[3.3.0]octane (6a). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.97 (3H, s), 0.98 (3H, s), 0.85-1.42 (3H, m), 1.46-1.72 (2H, m), 1.75-2.34 (4H, m), 2.37-2.60 (1H, m) and 3.94 (1H, dd, *J* 11.2 and 7.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 23.1 (CH_3), 26.2 (CH_3), 28.0 (CH_2), 30.1 (CH_2), 35.7 (CH_2), 39.2 (CH), 42.6 (CH_2), 44.6 (C), 52.5 (CH) and 61.0 (CH). MS, *m/z* (%) = 216 (M^+, 3)/218 (M^+, 3), 148 (5)/150 (5), 138 (16), 137 (100), 121 (9), 110 (100), 95 (59), 81 (75), 69 (94) and 67 (68). HRMS: $C_{10}H_{17}{}^{79}Br$ requires *m/z* = 216.0514. Found *m/z* = 216.0512.

Method B: 6-Bromo-7,7-dimethylbicyclo[3.3.0]oct-2-ene (5b) and 7-bromo-6,6-dimethylbicyclo[3.3.0]oct-2-ene (6b). A solution of **7b** (0.127 g, 0.590 mmol) in acetic acid (0.13 mL, 2.26 mmol) was stirred for 1.5 h at 70 °C and worked up as in method A yielding a mixture (crude yield: 0.096 g, 76%) that contained **5b** (65%), **6b** (25%) and **7b** (10%) (^{1}H NMR). Analytical samples of **5b** and **6b** were obtained by preparative GLC.

6-Bromo-7,7-dimethylbicyclo[3.3.0]oct-2-ene (5b). IR (ATR) (ν_{max}, cm^{-1}): 3050 (m), 2956 (s), 2923 (s), 2853 (m), 1460 (m, shoulder), 1384 (m), 1368 (m), 810 (m) and 724 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.00 (3H, s), 1.02 (3H, s), 1.14 (1H, dd, *J* 12.7 and 8.2 Hz), 1.96 (1H, dd, *J* 12.7 and 9.3 Hz), 2.15-2.35 (1H, m), 2.45-2.70 (1H, m), 2.85-3.05 (1H, m), 3.05-3.25 (1H, m), 3.48 (1H, d, *J* 10.1 Hz) and 5.48-5.64 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 23.7 (CH_3), 27.0 (CH_3), 37.2 (CH_2), 43.8 (CH_2), 44.2 (C), 47.2 (CH), 49.7 (CH), 70.1 (CH), 127.1 (CH) and 133.7 (CH). MS, *m/z* (%) = 214 (M^+, 33)/216 (M^+, 32), 199 (11)/201 (10), 173 (43)/175 (41), 135 (67), 119 (24), 107 (42), 93 (55), 91 (34), 79 (100) and 77 (38). HRMS: $C_{10}H_{15}{}^{79}Br$ requires *m/z* = 214.0357. Found *m/z* = 214.0361.

7-Bromo-6,6-dimethylbicyclo[3.3.0]oct-2-ene (6b). IR (ATR) (ν_{max}, cm^{-1}): 2956 (m), 2922 (s), 2852 (s), 1464 (m), 1456 (m), 804 (m) and 724 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.75-1.10 (1H, m), 1.00 (3H, s), 1.04 (3H, s), 1.87-2.65 (4H, m), 3.10-3.30 (1H, m), 3.90 (1H, dd, *J* 10.1 and 7.0 Hz) and 5.47-5.67 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 23.3 (CH_3), 26.4 (CH_3), 35.0 (CH_2), 41.0 (CH_2), 45.3 (C), 47.3 (CH), 49.4 (CH), 61.5 (CH), 129.7 (CH) and 132.6 (CH). MS, *m/z* (%) = 214 (M^+, 7)/216 (M^+, 7), 135 (32), 119 (12), 107 (15), 93 (28), 91 (18), 79 (23), 77 (18), 69 (72), 66 (100) and 41 (33). HRMS: $C_{10}H_{15}{}^{79}Br$ requires *m/z* = 214.0357. Found *m/z* = 214.0347.

8-Bromo-2,7,7-trimethylbicyclo[3.3.0]oct-2-ene (5c) and 7-bromo-2,8,8-trimethylbicyclo-[3.3.0]oct-2-ene (6c). Preparation according to Method B: 0.261 g of a crude mixture containing mainly the bromide **7c** was added acetic acid (0.30 mL, 5.21 mmol) and stirred at 50 °C for 2.5 h. Since GLC analysis indicated that 37% of **7c** still remained, more acetic acid (0.30 mL, 5.21 mmol) was added. The mixture was stirred for another 3.5 h at 50 °C and for 2 h at 60 °C and

worked up as in Method A. An impure mixture (0.183 g) containing moderate amounts of **5c** and **6c** was obtained. An analytical sample of **5c** was obtained by preparative GLC. Attempts to isolate other components in the mixture failed.

8-Bromo-2,7,7-trimethylbicyclo[3.3.0]oct-2-ene (5c). IR (ATR) (ν_{max}, cm^{-1}): 3036 (w), 2957 (s), 2931 (s), 2894 (m), 2850 (s), 1455 (m), 1443 (m), 1384 (m), 1369 (m), 798 (m), 794 (m) and 752 (m). ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.00 (3H, s), 1.02 (3H, s), 0.90-1.20 (1H, m), 1.81 (3H, br s), 1.94 (1H, dd, *J* 12.4 and 8.4 Hz), 1.65-2.10 (1H, m), 2.38-2.60 (1H, m), 2.70-2.94 (1H, m), 3.11-3.30 (1H, m), 3.53 (1H, d, *J* 7.9 Hz) and 5.11-5.21 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 15.7 (CH_3), 23.8 (CH_3), 26.4 (CH_3), 38.5 (CH_2), 39.1 (CH), 44.6 (C), 46.6 (CH_2), 62.6 (CH), 67.5 (CH), 123.7 (CH) and 140.3 (C). MS, *m/z* (%) = 228 (M^+, 16)/230 (M^+, 18), 149 (7), 148 (15), 133 (23), 93 (100), 91 (41), 79 (43), 77 (37), 41 (47) and 39 (24). HRMS: $C_{11}H_{17}{}^{79}Br$ requires *m/z* = 228.0514. Found *m/z* = 228.0514.

7-Bromo-8,8-dimethylbicyclo[4.3.0]nonane (5d), 8-bromo-7,7-dimethylbicyclo[4.3.0]nonane (6d) and 7-(1-bromo-1-methylethyl)bicyclo[4.2.0]octane (7d). Preparation according to Method A. Isopropylidenecyclobutane **4d** (0.210 g, 1.40 mmol) and 33% HBr in acetic acid (1.83 mL, 10.4 mmol) was stirred at room temperature for 2 h. Work-up as in Method A yielded an impure mixture (0.316 g) containing (**5d+6d)** to **7d** in a ratio of 70 : 30. (^1H NMR). The ratio of **5d** to **6d** was 58:42. (^1H NMR). Analytical samples of **5d** and **6d** were obtained by preparative GLC. The bromide **7d** was identified by GLC analysis and comparison with a ^1H NMR spectrum of a sample of **7d** prepared by using ether as the solvent (*vide infra*).

7-Bromo-8,8-dimethylbicyclo[4.3.0]nonane (5d). IR (ATR) (ν_{max}, cm^{-1}): 2951 (s), 2925 (s), 2856 (s), 1459 (m), 1448 (m), 1387 (w), 1366 (m), 802 (m), 795 (m) and 734 (m). ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.03 (3H, s), 1.09 (3H, s), 0.85-2.10 (11H, m), 2.11-2.35 (1H, m) and 3.97 (1H, d, *J* 11.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 20.7 (CH_2), 24.7 (CH_2), 24.8 (CH_2), 28.2 (CH_3), 29.3 (CH_3), 30.5 (CH_2), 35.3 (CH), 40.6 (C), 45.2 (CH), 45.4 (CH_2) and 67.1 (CH). MS, *m/z* (%) = 230 (M^+, 12)/232 (M^+, 13), 151 (100), 135 (23), 109 (13), 95 (73), 81 (30), 69 (49), 67 (25) and 41 (32). HRMS: $C_{11}H_{19}{}^{79}Br$ requires *m/z* = 230.0670. Found *m/z* = 230.0671.

8-Bromo-7,7-dimethylbicyclo[4.3.0]nonane (6d). IR (ATR) (ν_{max}, cm^{-1}): 2975 (s), 2930 (s), 2852 (s), 1463 (m), 1455 (m), 1387 (m), 1366 (m), 809 (m) and 655 (m). ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.94 (3H, s), 1.07 (3H, s), 0.70-1.35 (3H, m), 1.35-1.75 (6H, m), 2.00-2.35 (2H, m), 2.40-2.70 (1H, m) and 4.23 (1H, dd, *J* 9.4 and 7.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 21.4 (CH_2), 22.5 (CH_3), 25.0 (CH_2), 25.5 (CH_2), 27.2 (CH_3), 27.9 (CH_2), 34.6 (CH), 39.3 (CH_2), 46.7 (C), 47.1 (CH) and 62.5 (CH). MS, *m/z* (%) = 230 (M^+, 1)/232 (M^+, 1), 151 (34), 135 (11), 124 (20), 109 (17), 95 (50), 81 (23), 69 (100), 67 (48), 55 (29) and 41 (73). HRMS: $C_{11}H_{19}{}^{79}Br$ requires *m/z* = 230.0670. Found *m/z* = 230.0667.

1-Bromo-2,2-dimethyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene (5e) and 2-bromo-1,1-dimethyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene (6e) and 1-(1-bromo-1-methylethyl)-2,2a,7,7a-tetrahydro-1*H*-cyclobuta[*a*]indene (7e). Preparation according to Method A. Isopropylidenecyclobutane **4e** (0.217 g, 1.18 mmol) in 33% HBr in acetic acid (1.53 mL, 8.72 mmol) was stirred at room temperature for 1 h and worked up as in Method A yielding a mixture

(crude yield: 0.292 g, 94%) consisting of **5e + 6e** (90%) and **7e** (10%) (^{1}H NMR). The ratio of **5e** to **6e** was 74:26 (^{1}H NMR). Analytical samples of **5e** and **6e** were obtained by preparative GLC.

1-Bromo-2,2-dimethyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene (5e). IR (ATR) (ν_{max}, cm^{-1}): 3072 (w), 3022 (m), 2958 (s, br), 2928 (s, shoulder), 2868 (m), 2851 (m), 1482 (s), 1459 (s), 1447 (m), 1386 (m), 1372 (m), 807 (s) and 751 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.03 (3H, s), 1.13 (3H, s), 1.48 (1H, dd, *J* 12.9 and 7.2 Hz), 2.36 (1H, dd, *J* 12.8 and 9.9 Hz), 2.81-3.05 (1H, m), 3.05-3.35 (2H, m), 3.57 (1H, d, *J* 10.1 Hz), 3.73 (1H, q, *J* 7.3 Hz) and 7.07-7.27 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 24.0 (CH_3), 26.9 (CH_3), 36.2 (CH_2), 44.7 (C), 45.1 (CH_2), 46.4 (CH), 50.7 (CH), 68.9 (CH), 124.1 (CH), 124.8 (CH), 126.3 (CH), 126.5 (CH), 140.8 (C) and 146.8 (C). MS, *m/z* (%) = 264 (M^+, 31)/266 (M^+, 30), 185 (32), 169 (11), 155 (21), 141 (30)/143 (30), 129 (100), 128 (93), 116 (36), 115 (76), 91 (19), 69 (31) and 41 (43). HRMS: $C_{14}H_{17}{}^{79}Br$ requires *m/z* = 264.0514. Found *m/z* = 264.0519.

2-Bromo-1,1-dimethyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]indene (6e). IR (ATR) (ν_{max}, cm^{-1}): 3070 (w), 3021 (w), 2964 (s), 2934 (s), 2870 (m), 2852 (w), 1482 (m), 1459 (m), 1385 (m), 1368 (m), 835 (w) and 750 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.99 (3H, s), 1.13 (3H, s), 2.18-2.36 (1H, m), 2.48-2.70 (1H, m), 2.72-2.90 (2H, m), 2.90-3.10 (1H, m), 3.70-3.86 (1H, m), 3.97 (1H, dd, *J* 9.4 and 7.0 Hz) and 7.10-7.19 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 23.0 (CH_3), 26.5 (CH_3), 34.6 (CH_2), 43.2 (CH_2), 45.7 (C), 47.3 (CH), 50.7 (CH), 61.9 (CH), 123.69 (CH), 123.73 (CH), 126.1 (CH), 126.2 (CH), 142.4 (C) and 145.9 (C). MS, *m/z* (%) = 264 (M^+, 11)/266 (M^+, 13), 185 (14), 141 (16)/143 (18), 129 (29), 128 (31), 116 (82), 115 (80), 69 (100) and 41 (37). HRMS: $C_{14}H_{17}{}^{79}Br$ requires *m/z* = 264.0514. Found *m/z* = 264.0525.

6-(1-Bromo-1-methylethyl)bicyclo[3.2.0]heptane (7a). Typical procedure: To a solution of isopropylidenecyclobutane **4a** (0.051 g, 0.374 mmol) in diethyl ether (3 mL) was added 33% HBr in acetic acid (0.20 mL, 1.14 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was worked up as in Method A above yielding crude bromide **7a** (0.040 g, 49%). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.36-1.60 (5H, m), 1.65 (3H, s), 1.67 (3H, s), 1.63-1.94 (3H, m), 1.95-2.13 (1H, m) and 2.42-2.68 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 25.8 (CH_2), 28.4 (CH_2), 31.3 (CH_3), 31.4 (CH_3), 33.3 (CH_2), 33.4 (CH), 33.6 (CH_2), 42.5 (CH), 51.7 (CH) and 73.2 (C).

6-(1-bromo-1-methylethyl)bicyclo[3.2.0]hept-2-ene (7b). Typical procedure: To a solution of **4b** (0.185 g, 1.38 mmol) in diethyl ether (8 mL) was added 33% HBr in acetic acid (0.27 mL, 1.54 mmol), and the mixture was heated at reflux overnight. Since 19% of **4b** was left according to GLC, more 33% HBr in acetic acid (0.03 mL, 0.171 mmol) was added, and the mixture was refluxed for 7 h. Then the mixture was worked up as in Method A, yielding crude **7b** (0.224 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.62 (3H, s), 1.66 (3H, s), 1.70-1.88 (1H, m), 1.97-2.28 (3H, m), 2.45-2.62 (1H, m), 2.82 (1H, q, *J* 7.1 Hz), 2.95-3.10 (1H, m) and 5.65-5.83 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.2 (CH_2), 31.2 (CH_3), 31.4 (CH_3), 40.01 (CH), 40.05 (CH_2), 40.4 (CH), 54.0 (CH), 72.2 (C), 130.5 (CH) and 134.2 (CH). MS, *m/z* (%) = 214 (M^+, 41)/ 216 (M^+, 37), 175 (16), 135 (69), 134 (28), 119 (24), 107 (24), 105 (24), 93 (33), 79 (38), 77 (26), 69 (42) and 66 (100).

7-(1-Bromo-1-methylethyl)-2-methylbicyclo[3.2.0]hept-2-ene (7c). To a solution of isopropylidenecyclobutane **4c** (0.210 g, 1.42 mmol) in diethyl ether (7 mL) was added 33% HBr in acetic acid (0.29 mL, 1.65 mmol), and the mixture was heated at reflux for 12h. GLC indicated that 37% of **4c** still remained, and more 33% HBr in acetic acid (0.06 mL, 0.342 mmol) was added. The mixture was stirred for another 5.5 h at reflux. There was still 17% of **4c** left, and more 33% HBr in acetic acid (0.06 mL, 0.342 mmol) was added. The mixture was stirred for another 4 h at reflux (still 6% of **4c** left) and worked up as in Method A yielding a crude mixture (0.278 g) containing mainly **7c** (NMR). The crude product was used without further purification.

7-(1-Bromo-1-methylethyl)bicyclo[4.2.0]octane (7d). To a solution of isopropylidenecyclobutane **4d** (0.030 g, 0.200 mmol) in diethyl ether (2 mL) was added 33% HBr in acetic acid (0.07 mL, 0.399 mmol), and the mixture was stirred for 1h at room temperature. As there was still 58% of **4d** left, more 33% HBr in acetic acid (0.04 mL, 0.228 mmol) was added, and the mixture was stirred for another 5 h. Still 9% of **4d** remained, and more 33% HBr in acetic acid (0.04 mL, 0.228 mmol) was added. The mixture was stirred for 1h (8% of **4d** left) when more 33% HBr in acetic acid (0.01 mL, 0.057 mmol) was added, and finally the mixture was stirred for another 1h. In total 4.6 equivalents of HBr were added (0.160 mL, 0.912 mmol), and the total reaction time was 8 h. Work-up as in Method A above yielded the bromide **7d** (crude yield: 0.028 g, 61%). ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.74-2.12 (11H, m), 1.67 (3H, s), 1.68 (3H, s), 2.22-2.40 (1H, m) and 2.40-2.58 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 22.1(CH_2), 23.6 (CH_2), 26.8 (CH_2), 27.4 (CH), 29.8 (CH_2), 30.0 (CH_2), 31.8 (CH_3), 32.2 (CH_3), 36.2 (CH), 49.3 (CH) and 73.0 (C).

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