SYNTHESIS OF BICYCLIC COMPOUNDS USING SEQUENTIAL HYDROFORMYLATION AND ALDOL CONDENSATION OF CYCLIC KETONES WITH UNSATURATED SIDE CHAINS

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"Ricordati che dietro ogni problema c'è un'opportunità."

Galileo Galilei

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for Sonia

Index of abbreviations and symbols

abs.	absolut, dry
Ac	acetyl
acac	acetylacetonato
br	broad (FTIR)
br s	broad singulet (NMR)
Bu	butyl
cod	1,5-cyclooctadienyl
C_q	quaternary carbon (NMR)
Cy	cyclohexyl
d	doublet (NMR)
dd	doublet of doublets (NMR)
ddd	doublet of a doublet of doublets (NMR)
δ	delta (NMR shift designator)
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIA	diisopropylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DS	diastereoisomer
EI	Electron impact (MS)
Et	ethyl
eV	electronvolt (MS)
FAB	Fast-Atom Bombardment
FTIR	Fourier–Transform infrared spectroscopy
GC	gas chromatography
Hz	Hertz
i-	iso
IR	infrared spectroscopy
J	NMR coupling constant (Hz)
LDA	lithium diisopropylamide
m	multiplet (NMR), medium intensity (IR)
M^+	Molecular peak (MS)

MARDi	Michael addition retro-Dieckmann
Mat.	material
Me	methyl
Ms	Mass spectroscopy
MTBE	*t*-butylmethylether
n-	normal
NMR	Nuclear magnetic resonance spectroscopy
p	total pressure
ppm	parts per million (NMR)
q	quartet (NMR)
R	reaction
RT	room temperature
s	singlet (NMR), strong (IR)
Start.	starting (material)
t	reaction time, triplet (NMR)
t	tertiary
T	temperature
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin liquid chromatography
TMS	trimethylsilyl
vs	very strong (IR)
w	weak (IR)
$\tilde{\nu}$	wave number [cm^{-1}]

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1 Introduction

Alicyclic compounds such as prostaglandins, steroids or pheromones hold a dominant position in organic chemistry; e.g. as natural products with important biological activities, others find use as perfumes or are important as antibiotics, cytotoxic agents and antifeedants. The terpenoids, which are perhaps the most numerous and varied class of organic compounds found in nature, are containing a broad variety of ring systems[1] and have decisively influenced modern developments in synthetic organic chemistry. Recent years have revealed the increasingly important biological role of many terpenoids and the need of powerful new synthetic methods, e.g. for the formation of bridged or fused compounds containing rings with 5, 6, or 7 carbon atoms[2]. Several natural products like *Clovene*[3], *Pallescensin-C*[4], *β–Barbatene*[5], Ingenane[6], Taxol[7], Portulal[8,9] contain this kind of skeleton as depicted in Figure 1.

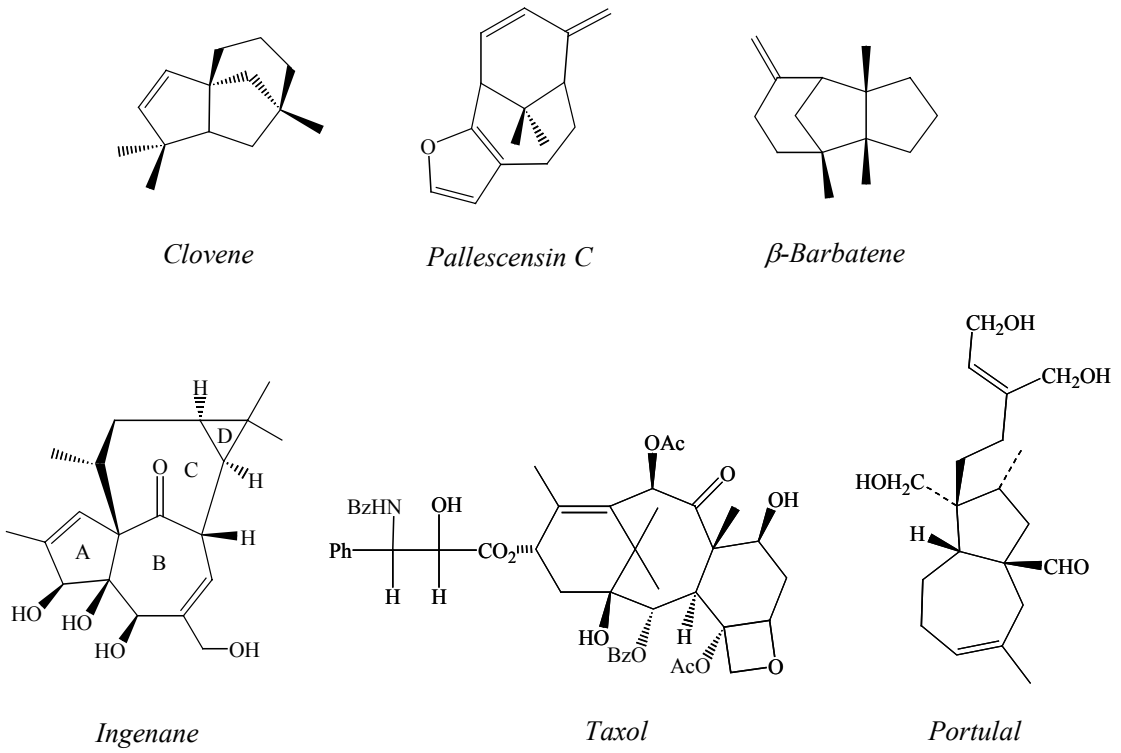
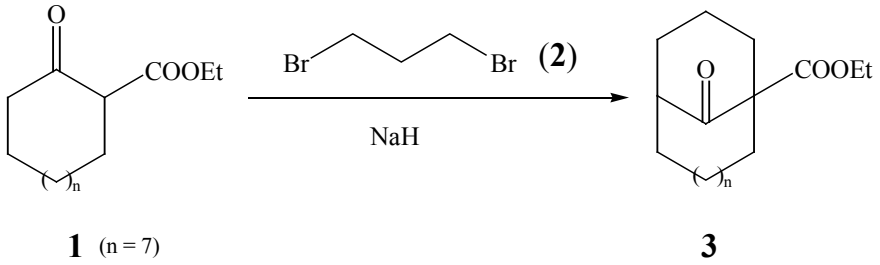


Figure 1: Examples of natural products containing a multi-rings skeleton.

The ingenane diterpenes comprise a structurally novel group of highly oxygenated tetra-cyclic diterpene esters with a broad spectrum of biological activities, ranging from the tumor-promoting properties[10,11] of some derivatives to the powerful antileukemic

activity of others. Central to the novel structure of the ingenanes, which are synthesized by a long sequence of reactions, is the highly strained bicyclo[4.4.1]undecan-11-one which possesses the unusual inside-outside intrabridgehead (BC rings) stereochemical relationship[6] (Figure 1).

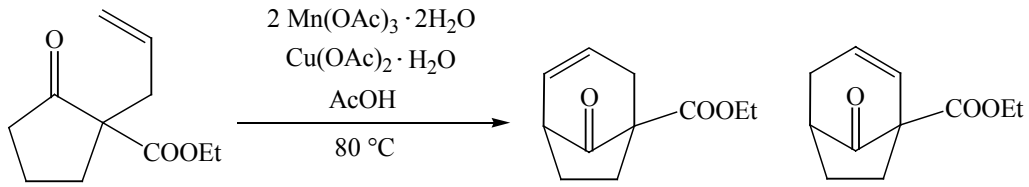
The synthesis of bridged systems of types as reported above by means of cyclization of cycloalkanones is performed using different reaction-types. Formation of [m.3.1] bridged system like **3** (Scheme 1) could be accomplished by alkylation of β-ketoester **1** with 1,3-dibromopropane (**2**)[12].



1 (n = 7) **3**

Scheme 1: Formation of [m.3.1] bridged system by 1,3-dibromopropane addition.

Alternatively, Mn(III)-based oxidative free-radical cyclization of unsaturated β-ketoesters (Scheme 2) is another versatile synthetic procedure towards the synthesis of bicyclo[m.3.1] alkane skeletons[13]. For example, oxidation of cycloalkanones of type **4a** with 2 eq. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 eq. of $Cu(OAc)_2 \cdot H_2O$ at 80 °C (Scheme 2) affords 75 % yield of ethyl 8-oxo-bicyclo[3.2.1]oct-3-ene-1-carboxylate (**5**) and 15 % of ethyl 8-oxo-bicyclo[3.2.1]oct-2-ene-1-carboxylate (**6**).

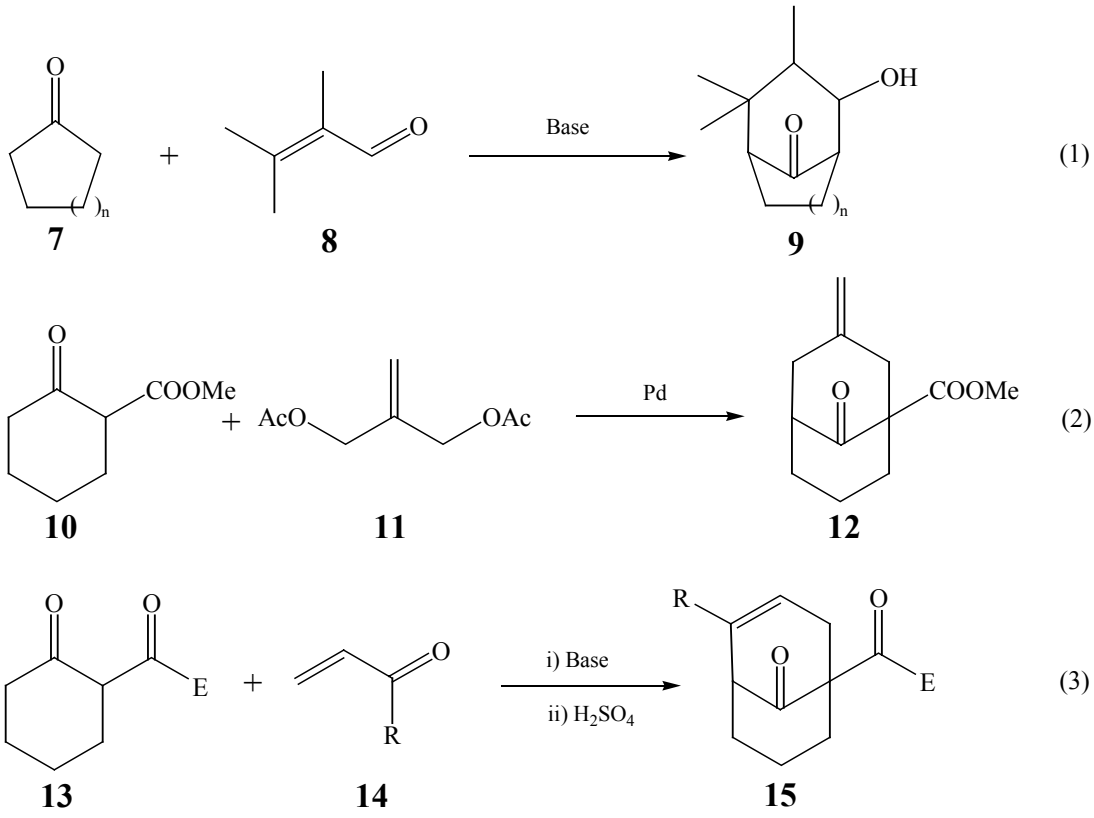


4a **5** **6**

Scheme 2: Mn(III)-based oxidative free-radical cyclization.

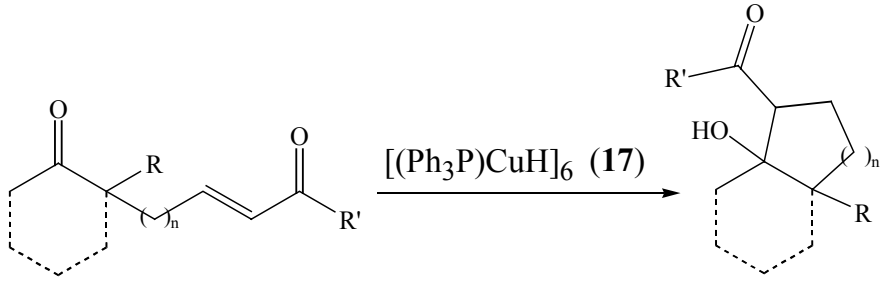
Besides the reactions mentioned so far, a sequential Michael addition-aldol reaction allows the construction of the structural framework of bicyclo[3.3.1]nonane. The syntheses of bicyclic compounds from cycloalkanones were reported (Scheme 3): (1) tandem Michael addition-intramolecular aldolization of ketones with α,β–unsaturated

aldehydes or ketones (eq 1), (2) palladium-catalyzed reaction of cyclic β-keto esters with methallyl diacetate (eq 2), and (3) the annulation of β-keto thiolesters or β-keto sulfones (eq 3). In the previous cases, one of the two fused rings of bicycles compounds comes from the ring system of the starting cyclic ketones[14,15].



Scheme 3: Tandem Michael addition-intramolecular aldolization of ketones with α,β–unsaturated compounds.

Alternatively, the formation of fused skeletons is accomplished by conjugate reduction by Stryker's reagent (**17**) to form copper enolates followed by intramolecular aldol cyclization (Scheme 4), generating five and six-membered carbocycles of type **18** in one-pot[16].

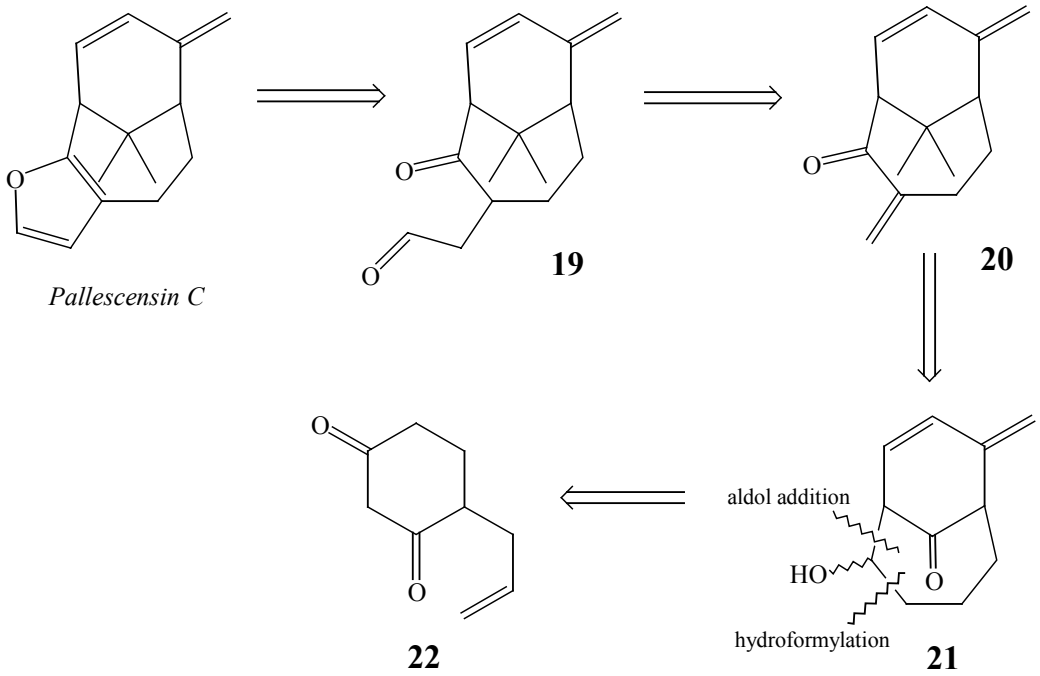


16 (n = 1, 2) **18**

Scheme 4: Fused bicyclic systems synthesis by Stryker's reagent (**17**).

As previously described, numerous synthetic methods towards the formation of bicyclic system exist; however, straightforward cyclization routes often are too difficult and too expensive for large-scale purposes. Therefore, it is important to develop and to study the synthesis of bicyclic systems from simple starting materials with low costs and in high selectivity.

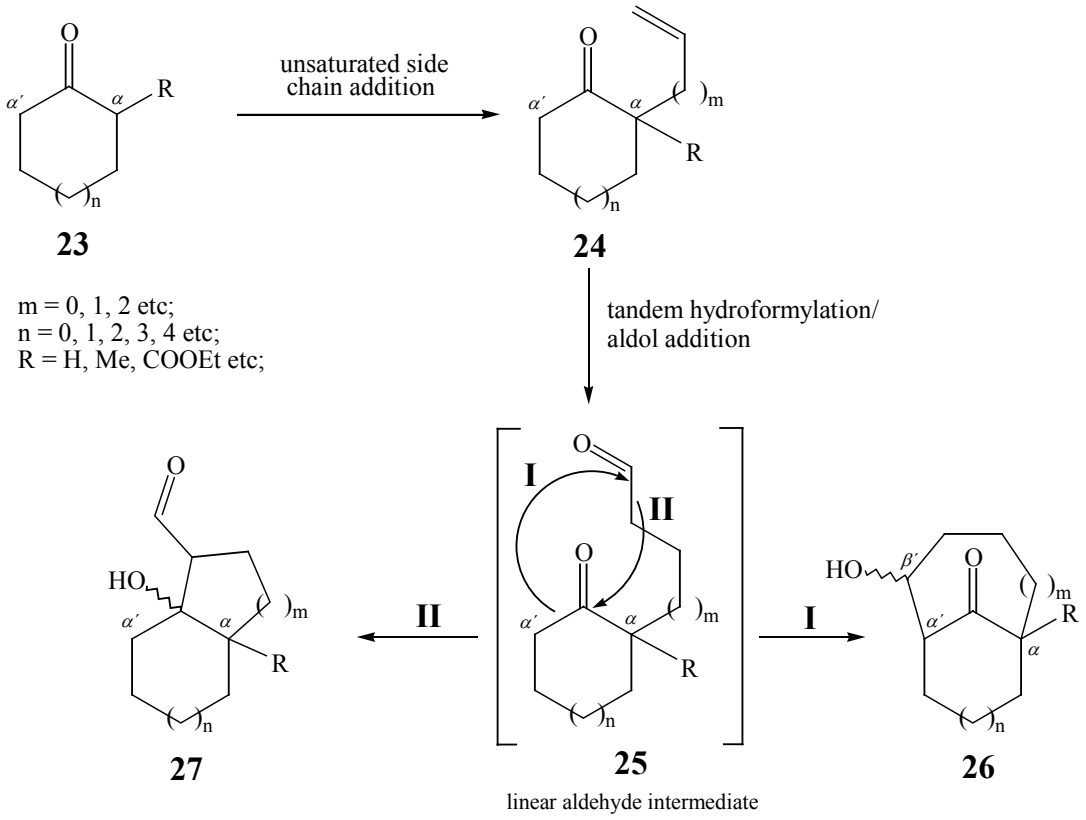
Retrosynthetic analysis of *Pallescensin-C* e.g. (Scheme 5), shows a bicyclo[4.3.1] bridged intermediates of type **21**, which could be obtained by a sequential hydroformylation/ aldol addition.



Scheme 5: Retrosynthetical analysis of *Pallescensin-C*.

Some examples of tandem hydroformylation/ aldol cyclization have already been reported in the context of natural products or their intermediates synthesis by Eilbracht and Hollmann[17]. Then, to accomplish the synthesis of key bicycles intermediates of compounds depicted in Figure 1, containing 5-membered rings or larger, an application of this one-pot procedure reaction could be investigated (Scheme 6).

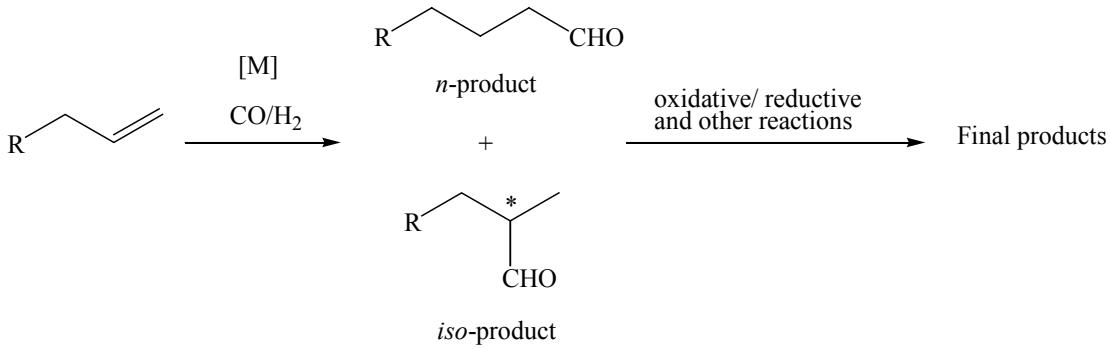
As depicted in Scheme 6, the aim of this project is to investigate further possibilities for the synthesis of bicyclic systems [bridged or fused structures of type **26** or **27** respectively] starting from unsaturated cycloalkanones of type **24** bearing side chains with different length.



Scheme 6: Theoretical cyclisation of ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates of type **23** by tandem hydroformylation/ aldol addition reaction.

Reaction sequences combining hydroformylation with various subsequent transformations of the oxo-aldehydes in one-pot procedures are gaining growing interest[17]. Aldol reactions are often observed as side products under hydroformylation conditions[18]. Then, following earlier investigations in the tandem hydroformylation/ aldol addition[17] different conditions are used allowing the aldol product formation directly under the hydroformylation conditions. The attractive aspects of

hydroformylation reaction are found to be its compatibility with various sensitive and reactive functional groups such as aldehydes, free alcohols, carboxylic acids, allyl halides and tosylates[19,20,21,22]. The hydroformylation reaction, discovered in 1938 by Roelen[23,24] and named later by Adkins[25] could be a valid synthetic approach towards the synthesis of complex carbon skeleton from the appropriate inexpensive starting materials[18,26]. It consists of a reaction between an olefinic double bond and synthesis gas (a mixture of H_2 and CO) leading to linear and branched aldehydes as products which can be converted via reduction, oxidation or other reactions to give alcohols, carboxylic acids, amines or aldol condensations products (Scheme 7).



Scheme 7: Hydroformylation reaction and transformation of the aldehyde function.

The reaction is catalyzed by transition metal complexes of Rhodium, Cobalt, Ruthenium or others[18b] it can also be catalyzed by other homogeneous catalysts including heterogenized modifications[27,28,29].

Rhodium-catalyzed hydroformylation is one of the most prominent applications of homogeneous catalysis in industry[35] and the generally accepted mechanism for rhodium-catalyzed hydroformylation was proposed by Wilkinson in 1968[30]. Numerous investigation on mechanistic[18f,31,32] and asymmetric/enantioselective[33] aspects of hydroformylation are available. Moreover, chemo- and regio-stereoselectivity problems are involved[34] and therefore metal complexes are modified by phosphorous or phosphine ligands[35] which are able to increase the reaction performances.

The very efficient modern rhodium-phosphine catalysts are first developed by Wilkinson[30,36,37] and first employed by Union Carbide[38,39]. This kind of catalyst, compared to older cobalt hydroformylation catalysts, offer the advantages of enhanced rates, lower operating temperatures and pressures, and higher selectivity for straight-

chain aldehydes[39] in the low to medium range (5-100 bar)[34] but these ligands are sensitive towards oxidation[40]. Bryant and co-workers first[41] at Union Carbide Corp. (UCC) and successively Pruett and Smith[42] observed that certain bulky phosphites lead to high selectivities in the rhodium-catalyzed hydroformylation of terminal and internal alkenes. Moreover, Van Leeuwen has reported a variety of diphosphite and diphosphine ligands that give high *n*:*i* regioselectivity[40,43,44], Buchwald[21] and Wink[45] have obtained high regioselectivities in hydroformylation of functionalized alkenes using rhodium diphosphite systems[46]. These ligands are considered too sensitive to hydrolysis and alcoholysis; however, phosphites are less sensitive toward oxidation than phosphines and they show, besides lower σ-donor capacities, better π-acceptor properties. The use of bulky phosphites in the rhodium-catalyzed hydroformylation has been a field of interest[47,48,49], these ligands show a high reactivity in the hydroformylation of otherwise unreactive olefins[50,51,52]. It was noted that both the length of the bridge of the diphosphite[41] and its steric bulk[41,53] determined the preferred bite angle[54] of the bidentate ligands stabilizing the "catalytic" species[54].

The highest selectivities are achieved using bisphenol bridges. Along these lines, in 1988, a catalytic system derived from bis-organophosphite rhodium complex **29a**, which gives high *n*:*iso* ratio and operates under mild conditions[55], has been found to affect the regioselectivity in the hydrormylation of terminal olefins producing a variety of ω–functionalized aldehydes[21]. This catalyst system notably demonstrates increased regioselectivity, and it is tolerant of a variety of potentially reactive functional groups. The active hydroformylation catalyst, presumably **29a**, is generated in situ, in the presence of the substrate, by addition of the bis-organophosphite ligand[56,57] BIPHEPHOS (**29**) to dicarbonylacetylacetonate rhodium at 60 °C. Then, the catalyst species chosen was the rhodium (I) complexes such as $Rh(acac)(CO)_2$ (**28**) (Figure 2) modified by a diphosphite ligand such as BIPHEPHOS (**29**) (Figure 3).

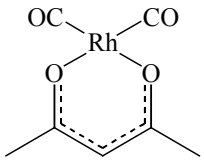


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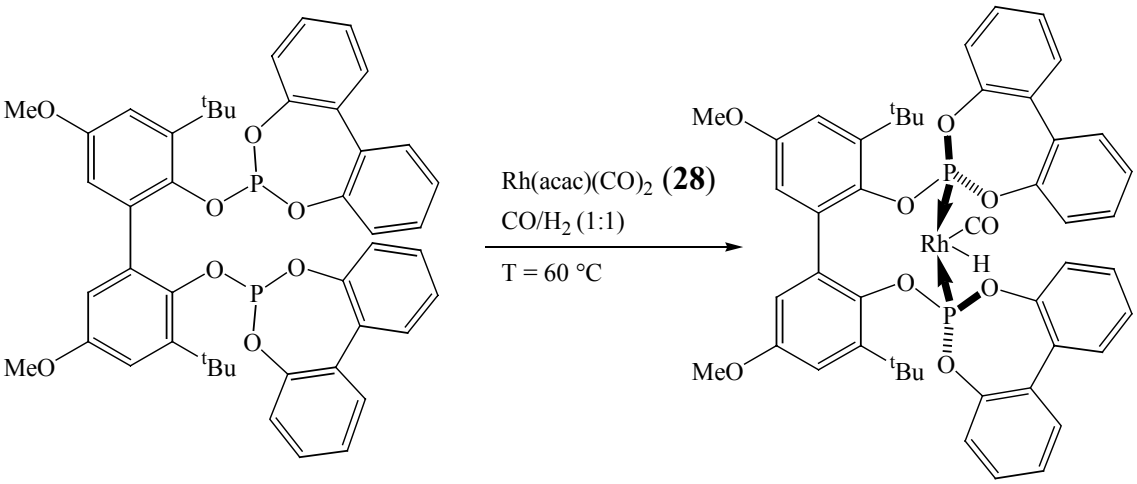
Figure 2: $Rh(acac)(CO)_2$ (**28**) molecular structure.

The diphosphite ligand BIPHEPHOS (**29**) (Figure 3) shows the bite angle and the steric bulk compatible with the $Rh(acac)(CO)_2$ (**28**) structure[35], and its reactive species with the coordination of the heteroatom to the metal centre is represented in **29a**[21] (Figure 3). This system BIPHEPHOS/Rh-catalyst introduced by Union Carbide[58] has proven to be a reliable catalyst for *n*-selective hydroformylation of a wide variety of different alkenes under mild reaction conditions[21].

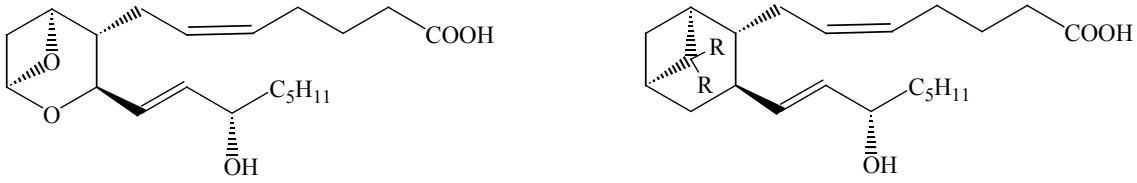


29 **29a**

Figure 3: BIPHEPHOS (**29**) structure and Rh-BIPHEPHOS (**29a**) as active species.

The aldol condensation[59] is one of the most important reactions in synthetic organic chemistry[60], apparently first reported by Chiozza[59a] in 1856 and later by Wurtz[59b] and Perkin[59c]. The advantage is the construction of a relatively complex carbon skeleton from simple precursors.

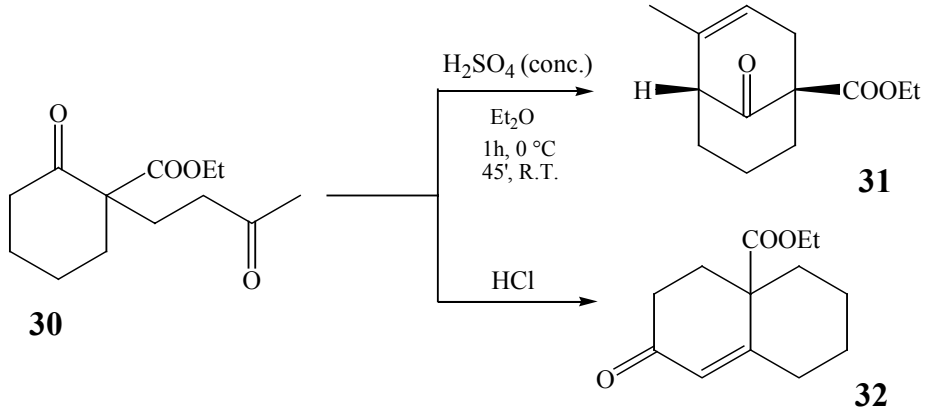
In a study towards the synthesis of analogs of *Tromboxane* A_2 (TXA_2)[61] (Figure 4), an extremely potent compound which promotes the aggregation of blood platelets, via bicyclic ketones produced by aldol condensation, Evans and al.[62] observed how the chemoselectivity of the intramolecular aldol addition would be influenced by an acid employed.



TXA_2 TXA_2 analog compounds (R = H, Me)

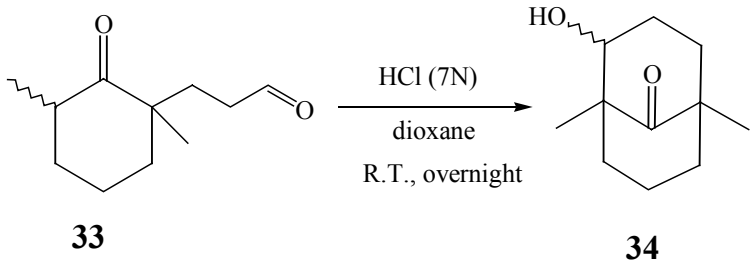
Figure 4: *Tromboxane A_2* (TXA_2) molecular structure and its analog compounds

In fact, the 1,5-diketone **30** is converted to bridged compound **31** (Scheme 8) on treatment with concentrated sulphuric acid while the use of concentrated hydrochloric acid, acetic acid, stannic chloride and boron trifluoride, furnished only the ”Robinson annulation” product **32**.



Scheme 8: Example of chemoselective aldol condensation under acidic conditions

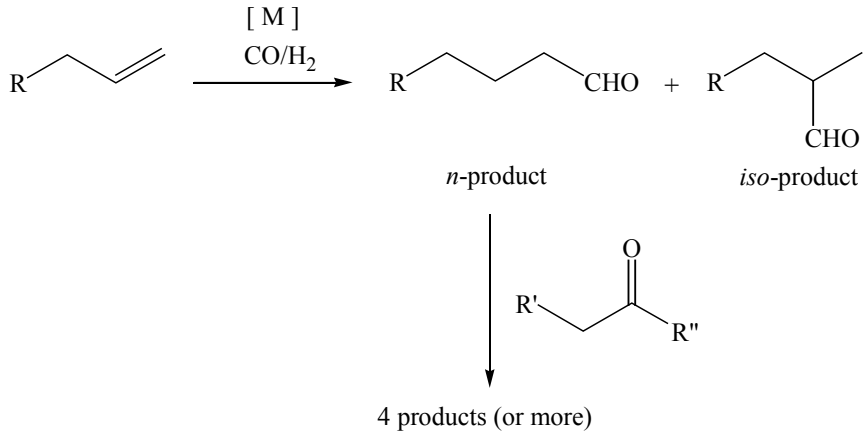
Gambacorta et al.[63] during their studies about the Pinguisane terpenoids synthesis[64], applied the acid catalyzed intramolecular aldol condensation by HCl. Starting from the 6-membered cycloalkanone **33**, bearing a remote aldehyde function (Scheme 9), the *β*-hydroxy ketone afforded **34** as an *endo-exo* mixture of epimers.



33 **34**

Scheme 9: Example of acid catalyzed intramolecular aldol addition carried out on a cyclohexanone derivative **33**.

However, the fixed length of the chain to only three carbon atoms makes the Michael reaction a procedure useful only to the synthesis of [n.3.m] bridged compounds.
Aldol reactions in some cases are observed under hydroformylation conditions as products of the oxo-aldehydes leading to higher boiling side products[65]. On the other hand, however, mixed aldol reactions of oxo-aldehydes with other carbonyl compounds can be used for the synthesis of new open-chained and cyclic carbon skeletons. Combining hydroformylation and aldol addition of the oxo aldehyde to a second carbonyl compound poses the usual selectivity problems of hydroformylation and of mixed aldol condensation with the additional problem, that the aldol step has to proceed under the hydroformylation conditions (Scheme 10).



Scheme 10: General procedure of the hydroformylation reaction with subsequent aldol addition.

Therefore, numerous efforts have been made to combine hydroformylation with a consecutive aldol reaction in a one-pot reaction sequence on[17,66]. Selective conversions

of this type, starting from simple olefins would allow for a convenient straightforward access to complex carbon skeletons.

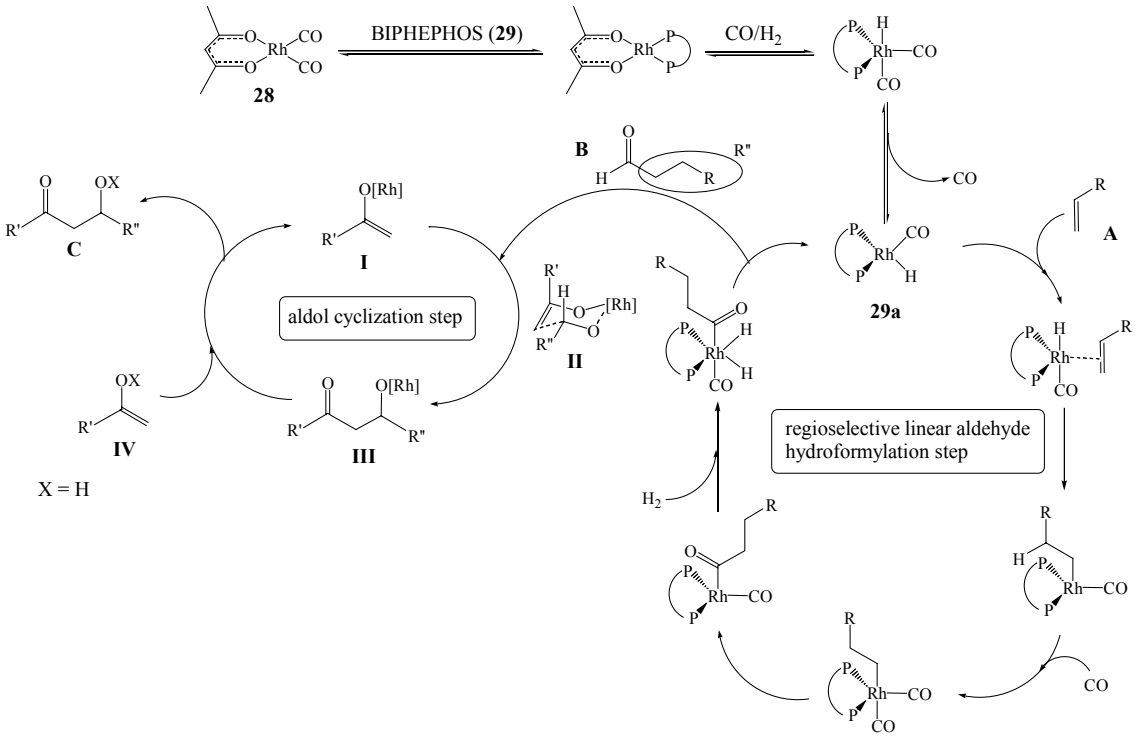
Thus, if converting a terminal olefin under hydroformylation conditions in the presence of a second carbonyl compound, first, *n*- and *iso*-selectivity of the hydroformylation step and second, the chemo- and regio-selectivity of the aldol condensation step has to be controlled. Since the metal catalyzed hydroformylation occurs under reductive conditions and the aldol addition step requires acid or base catalysis numerous side reactions are possible.

As reported from Bergman and Heathcock[67] in order that the catalyst was compatible under aldol reaction conditions, four important features must be incorporated into this catalytic process. Thus: (1) the rhodium enolate must be sufficiently nucleophilic to condense with aldehydes, (2) the rhodium aldolate complexes must be resistant to significant competing irreversible decomposition under the reaction conditions, (3) the rhodium-oxygen bond in the rhodium complexes must be reactive towards the organic enol derivatives, (4) the enol source and the aldehyde must not condense without the catalyst[68].

Moreover, the aldol addition combined with the hydroformylation does not proceed in the presence of transition metals such as rhodium in strongly coordinating solvents such as THF, acetonitrile or methanol. Indeed, they are able to form Lewis acid/ Lewis base adducts with the rhodium catalysts[69], therefore apolar solvents need to be used.

If connecting the Wilkinson[30] hydroformylation studies with the Bergman and Heathcock[67] investigations concerning the aldol reaction by means of rhodium enolate, the complete tandem hydroformylation/ aldol addition process could be represented as shown in Scheme 11.

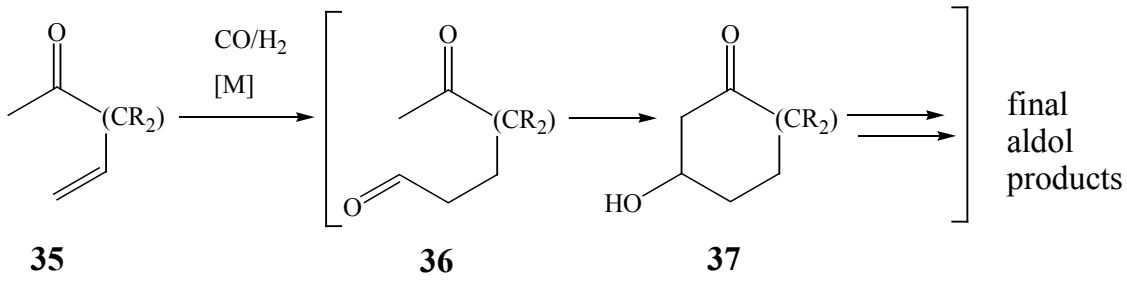
At first, the precursor catalyst complex $Rh(acac)(CO)_2$ (**28**) reacts immediately with the BIPHEPHOS ligand (**29**), two CO ligands are substituted with the least sterically hindered phosphorus atoms[40] of the ligand and the equilibrium with **29a** in Scheme 11 exists in the catalyst system.



Scheme 11: Rhodium catalyzed tandem hydroformylation/ aldol addition of alkenes substrates.

The second part of the process involves the *n*-regioselective hydroformylation catalytic cycle[34] of the alkene substrate **A** (such as the cycloalkanone **24** in Scheme 6), the linear aldehyde of type **B** so formed (corresponding to the **25** in Scheme 6) undergo the catalytic aldol addition step. In this latter cycle, the rhodium enolate **I** formed[67] reacts to the aldehyde **B** resulting in the formation of a rhodium aldolate **III** via the Zimmerman-Traxler[70] transition state **II**. A transfer of the hydrogen (X = H) from another enol compound **IV** results in the formation of the final adduct **C** (corresponding to **26** and/or **27** in Scheme 6) and the reactive rhodium enolate **I** is regenerated.

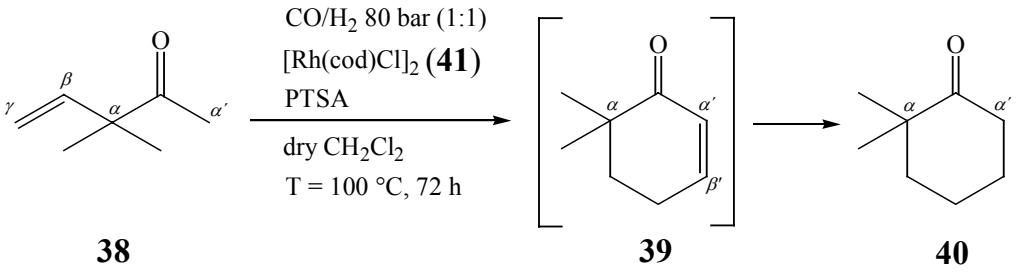
In order to reduce the multitude of selectivity problems, first studies of tandem hydroformylation/ aldol condensation were carried out with unsaturated ketones of type **35** leading to cyclic products of type **37** and derivatives thereof (Scheme 12)[17,66,71].



Scheme 12: General tandem hydroformylation/ aldol addition and condensation procedure.

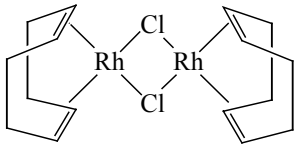
As outlined in Scheme 12 unsaturated ketones of type **35** can undergo hydroformylation at the olefinic double bond followed by a mixed aldol type cyclisation. According to earlier investigations[71] in intramolecular aldol reactions of keto aldehydes **36** the ketone moiety usually reacts as the enolate equivalent and undergoes nucleophilic addition to the aldehyde function and a cyclization of type **37** is obtained.

For a detailed study of a combination of hydroformylation and aldol addition both steps in a tandem procedure the β,γ-unsaturated ketone 3,3-dimethyl-4-penten-2-one (**38**)[71] (Scheme 13) was chosen as the substrate.



Scheme 13: Tandem hydroformylation/ aldol condensation of 3,3-dimethyl-4-penten-2-one (**38**).

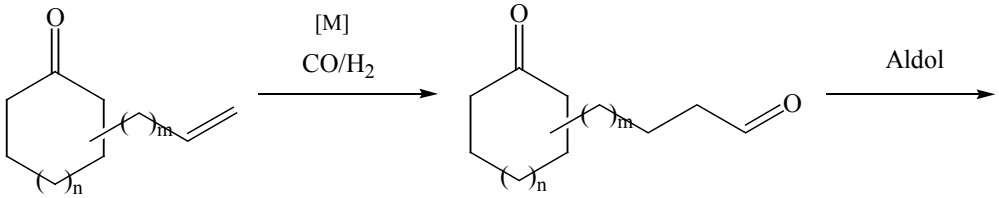
The β,γ-unsaturated ketone **38** undergoes tandem hydroformylation/ aldol condensation, making use of $[Rh(cod)Cl]_2$[65,72] as catalyst (**41**) (Figure 5) and PTSA as cocatalyst to give the α',β'-unsatured cyclic compound **39** which after hydrogenation of the double bond in α'-position generates the substituted cyclohexanone **40** (Scheme 13).



41

Figure 5: $[Rh(cod)Cl]_2$ (**41**) molecular structural.

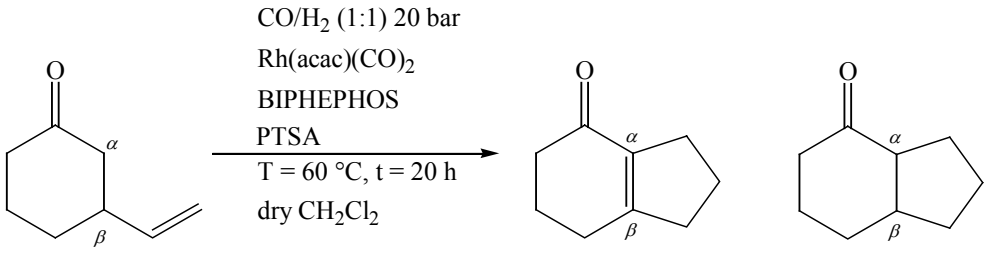
More complicated is the application of the same procedure to unsaturated carbonyl compounds to form bicyclic products. Here cyclic ketones with unsaturated side chains in various positions of the ring are required as starting materials (Scheme 14)[73].



m = 0, 1, 2 etc
n = 0, 1, 2, 3, 4 etc.

Scheme 14: Tandem hydroformylation/ aldol cyclization on cyclic ketones with unsaturated side chains in various positions of the ring.

If running the reaction with 3-vinyl-cyclohexanone (**42**) a bicyclo[4.3.0]nonane skeleton is generated in the ring-annulation's step. Successively to the aldol condensation a double bond isomerisation to form the higher substituted enone **43** takes place. Further hydrogenation of the intermediate enone generates the saturated hydroindanone[73] **44** (Scheme 15).



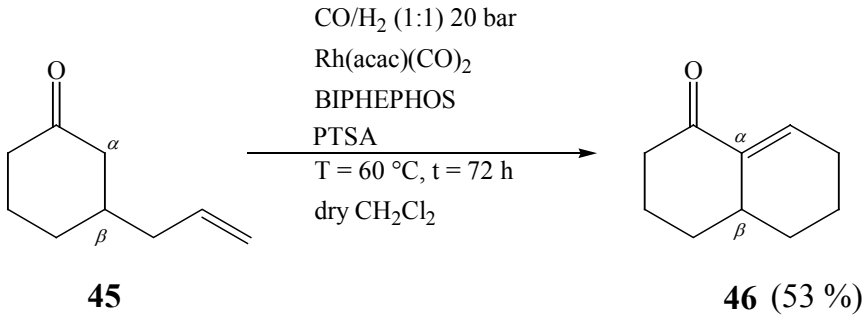
42 **43** (49 %) **44** (29 %)

cis:trans = 3:1

Scheme 15: Tandem hydroformylation/ aldol condensation reaction starting from 3-vinyl-cyclohexanone (**42**).

In summary, the tandem reaction of 3-vinyl substituted cycloalkanones offers an access to the synthesis of hydropentalene and hydroindene derivatives that represent common substructures in many terpenoid compounds.

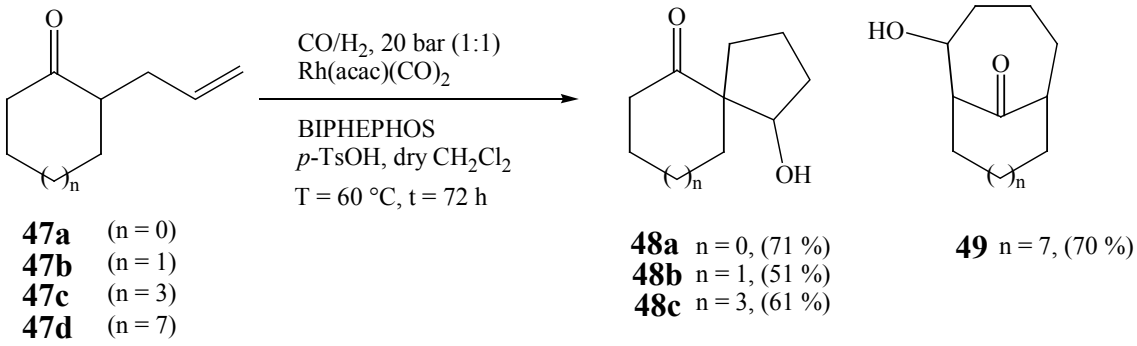
Annulation of six-membered rings can be achieved if starting from 3-allylsubstituted cycloalkanones. Hydroformylation of **45** then leads to the fused bicycles, α,β-unsaturated ketone **46**, similar to Quassinoids structure[74], in satisfying yield (Scheme 16).



45 **46** (53 %)

Scheme 16: Tandem hydroformylation/ aldol condensation of 3-allyl-cyclohexanone (**45**).

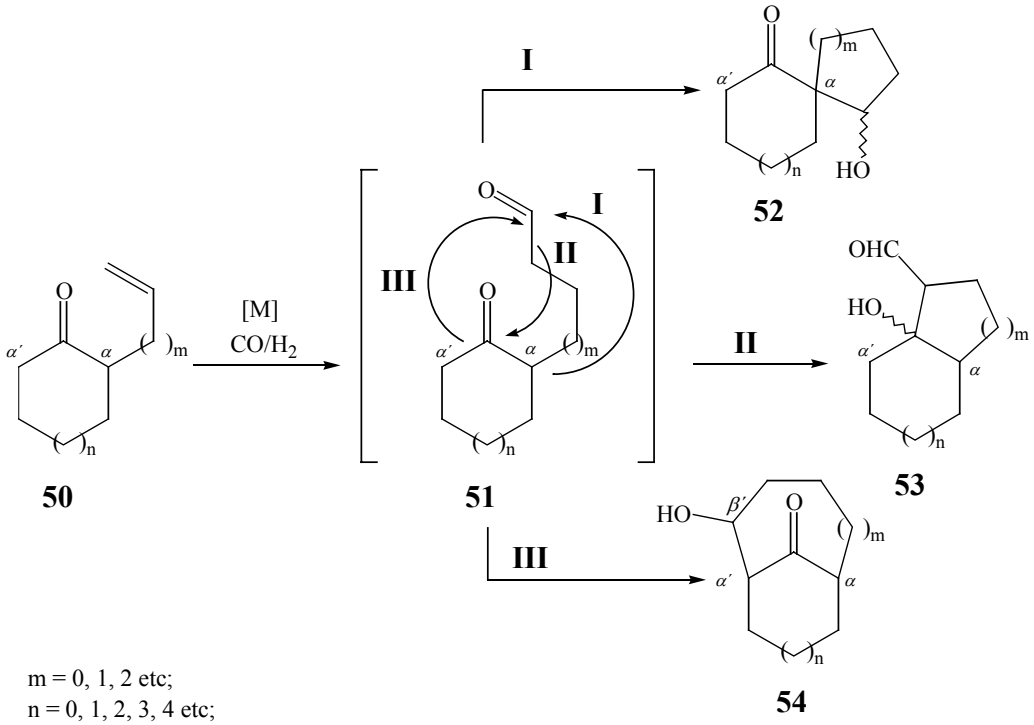
Besides the synthesis of annulated carbocycles the method also offers an access to spiro-cyclic compounds. In order to obtain spiro-annulated aldol products as well, the sequence has to be started from allyl substituted cycloalkanones[73]. Indeed, the conversions of 2-allyl-cyclopentanone (**47a**), -cyclohexanone (**47b**) and -cyclooctanone (**47c**) give the spirocyclic β-hydroxy-ketones **48a-c** in medium to good yields (Scheme 17). The cyclisations proceed regioselectively via the keto enols of the intermediate ε-keto aldehydes that generate the five-membered rings[73].



Scheme 17: Tandem hydroformylation/ aldol addition of 2-allyl-cycloalkanones (**47a-d**).

In contrast, starting with 2-allylcyclododecanone (**47d**) the tandem reaction does not lead to the spirocyclic aldol adduct in analogy to **47a-c**. Here, the hydroformylation equally proceeds with high *n*-regioselectivity but the cyclization gives the bicyclo [9.4.1]hexadecanone derivative (**49**) (Scheme 17)[73].

The present research project concentrates on the conversion of 2-alkenyl-cycloalkanones derivatives of type **50** as first model substrates (Scheme 18) and in further investigations the ring size, chain length and substitution pattern will be varied.



Scheme 18: Theoretical pathways of tandem hydroformylation/ aldol addition reaction.

The unsaturated chain allows hydroformylation of the olefinic function in the terminal position, according to Scheme 12, and a subsequent aldol addition of the hydroformylation product of type **51** under the same reaction conditions with varying selectivity (Scheme 18).

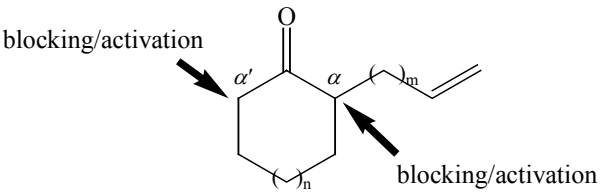
If assuming regioselective *n*-hydroformylation, a linear aldehyde chain as in **51** is generated and by the presence of the ketone functionality, an intramolecular crossed aldol condensation can occur in three different ways (Scheme 18).

I) If the α-carbon, to which the aliphatic chain is attached, reacts (as enol or enolate) with the linear aldehyde, a second ring is formed and a spiro compound of type **52** is obtained as previously reported in Scheme 17.

II) If the ketone plays the role of the carbonyl function and the aldehyde is the methylene function, fused ring-systems of type **53** are formed (Scheme 18).

III) If the aldehyde function reacts with its α'-carbon, a bridged bicyclic system of type **54** is formed as obtained if the reaction is performed starting from 2-allyl-cyclododecanone (**47d**) as reported in Scheme 17.

For mixed crossed aldol addition procedures, various methods of activation and blocking of specific positions are available and applicable to tandem hydroformylation/ aldol addition[66,71] (Scheme 19).



m = n = 0, 1, 2, etc

Scheme 19: Regio-control of tandem hydroformylation/ aldol condensation conditions.

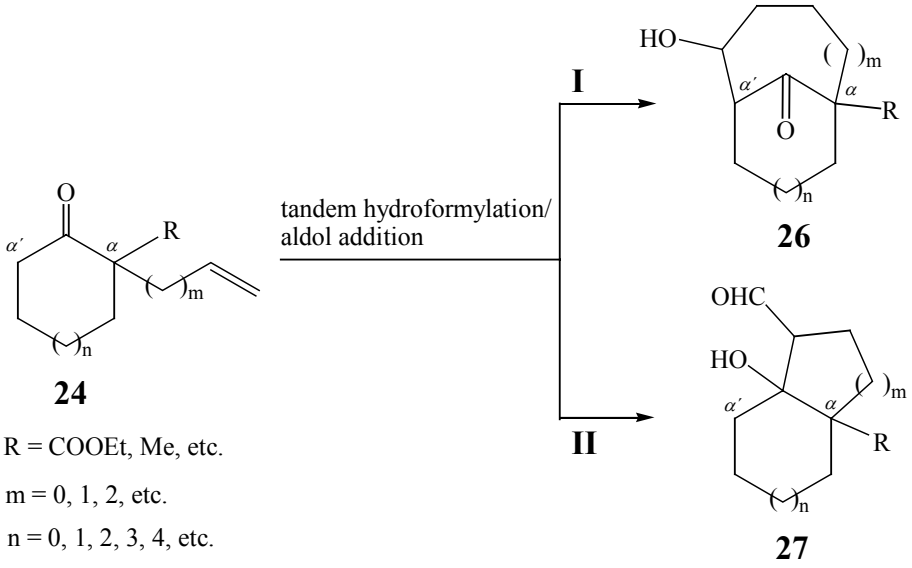
In the following several possible strategies towards selective control of hydroformylation/ aldol addition reactions in various directions are discussed.

General list types of control:

- Blocking with removable or no-removable groups
- Activating with electron withdrawing group (EWG)
- Activating via enol equivalents

- Strategy 1: removable (or no-removable) blocking group in α–position.

It is possible to introduce a removable blocking group, such as an ester function, to avoid the cyclization in the α-position, thus two different pathways are possible leading to the bicyclic product of type **26** (Scheme 20, path I) cyclisation in α'-position whereas the fused aldol adduct of type **27** (path II) can be obtained if the tandem hydroformylation/ aldol condensation occurs on the keto-function.

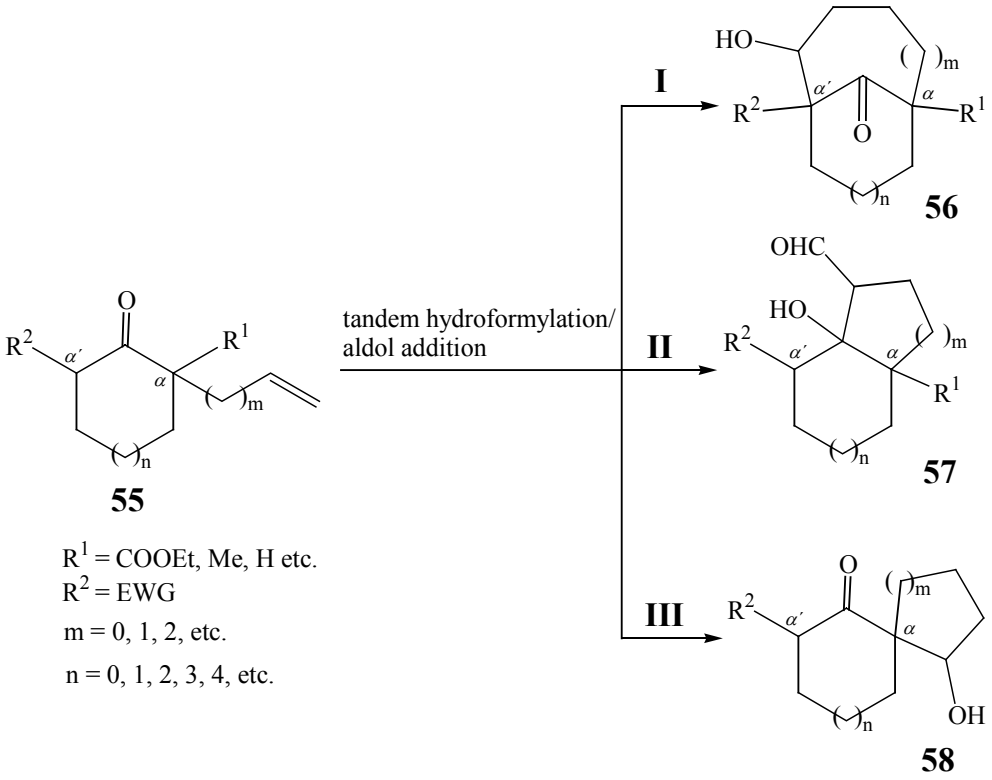


Scheme 20: Removable blocking group in α-position.

- Strategy 2: activating with EWG (electron withdrawing group)

For the activation of the α'-position a model starting material is the keto ester **55**. When inserting an activating group EWG (like COOEt) in the α'-position the reactivity of this carbon increases (Scheme 21). The activating group (EWG) should force the reaction

towards the cyclization in the α'-position to form a bicyclic compound **56** (path I) whereas products **57** (path II) or **58** (path III) are less favourable.



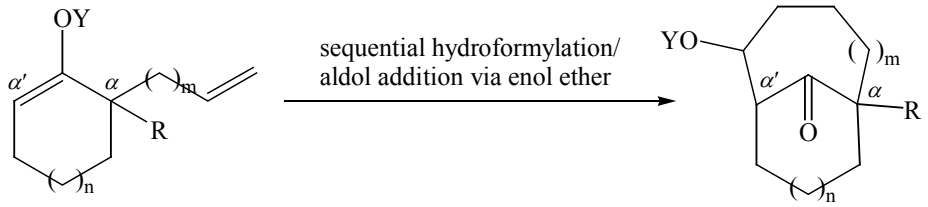
Scheme 21**:** Activating with EWG (electron withdrawing group) in α'-position.

- Strategy 3: activation with enol ethers.

Various other methods have been developed for the directed coupling of two different carbonyl compounds (or carbonyl equivalents) to give a specific carbon-carbon bond formation between the α–C atom of one carbonyl compound component and the carbonyl group of the other.

Silyl enol ethers of type **59** (Scheme 22, Y = -SiR_3) are highly versatile enol derivates that can be regioselectively prepared from various ketones. Mukaiyama´s method using the trimethyl silyl enol ether of one carbonyl compound and stoichiometric amounts of Lewis acid, offers access to directed crossed aldol reaction[75]. This procedure can be useful to generate bicyclic compounds of type **60**.

Alternatively, instead of silylated enol ethers various other enol equivalents (including borane) can be used (Scheme 22, Y = -BR_2).



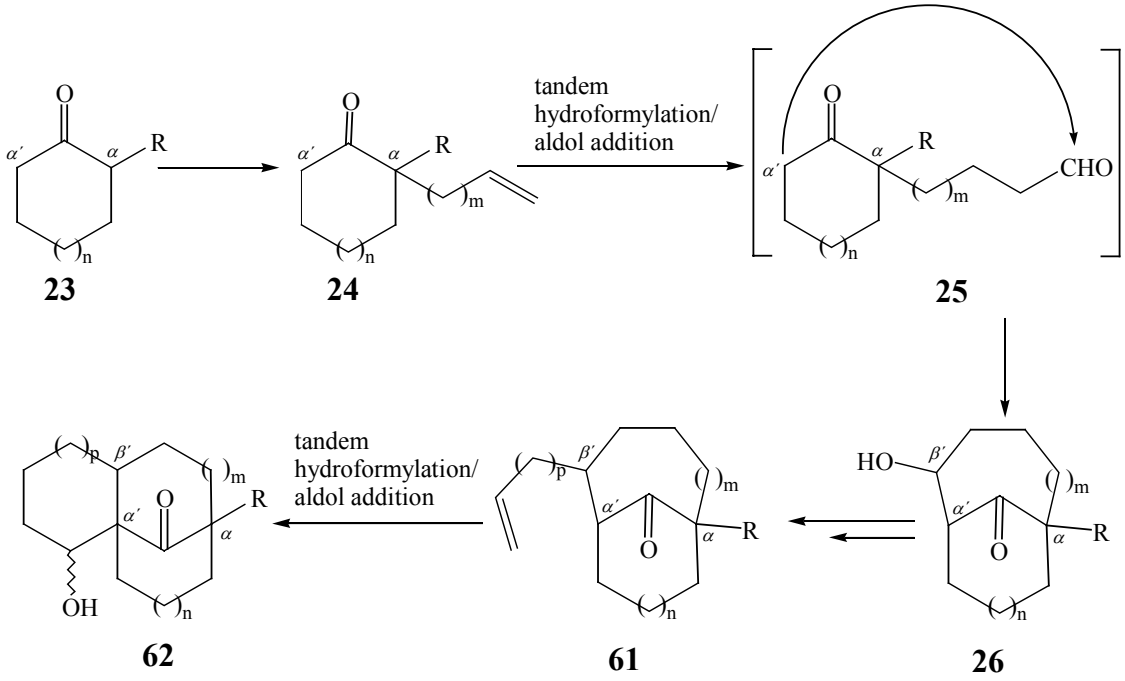
59 **60**

m = 0, 1, 2, etc; n = 0, 1, 2, etc;

R = H, Me, COOEt, etc; Y = -SiR_3, -BR_2 or other enol equivalents

Scheme 22: Activation with enol ethers.

Combining all the possible pathways in Scheme 18 and the results from Scheme 16, the number of molecular target increases and a new application of the tandem hydroformylation/ aldol addition is shown in Scheme 23. Cycloalkanones of type **23**, after introducing the unsaturated side chain in α-position, could undergo immediate aldol addition or condensation of the intermediate δ-keto aldehyde **25** at α'-position and a bicyclic-bridged compound of type **26** should be obtained (Scheme 23).



23 **24** **25** **26** **61** **62**

R = H, COOEt, Me, etc.

m = 0, 1, 2, etc.; n = 0, 1, 2, 3, 4, etc.; p = 0, 1, 2 etc

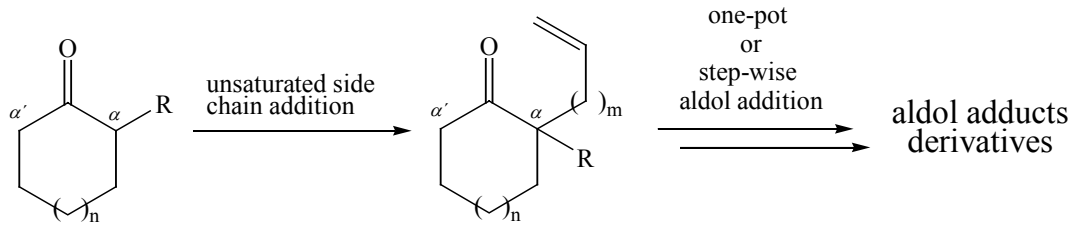
Scheme 23: Preparation of tri-cyclic compounds of type **62** by tandem hydroformylation/ aldol addition reaction via a bicyclic product of type **26**.

After the introduction of the new vinyl group or a longer unsaturated side chain (m = 0, 1, 2 etc.) in β'-position of **26** to get a compound like **61**, a new tandem hydroformylation/ aldol condensation could be applied and, as well as shown in Scheme 16, and the reaction should yield a condensed tricyclic compound of type **62** (Scheme 23).

2 Theoretical part

2.1 Preparation of starting materials

The appropriate precursor compounds with which to begin a study of methods of sequential hydroformylation/ aldol addition as depicted in Scheme 6 can be synthesized via a variety of methods. Thus, those compounds of type **24** can be synthesized starting from cycloalkanones of type **23** (R = COOEt) by introducing in α-position an allylic or homoallylic unsaturated side chain (Scheme 24).



23 **24**

m = 1, 2; n = 0, 1, 2 etc

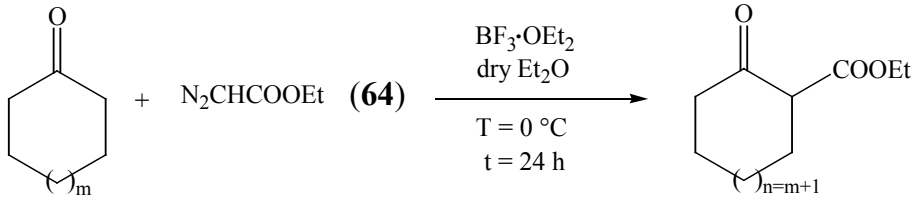
R=COOEt, H, Me

Scheme 24: General strategy for sequential hydroformylation/ aldol addition.

a. Synthesis of ethyl 2-oxo-cycloalkane carboxylates (65c-e)

While the cyclic β-ketoesters of type **23** with 5- and 6-membered rings (Scheme 24, **65a** with n = 0 and **65b** with n = 1) are commercially available, the preparation of the larger ones (**65c-e**, n = 2, 3 and 4) could be accomplished under mild conditions, through the ring expansion of cycloalkanones via W. L. Mock's procedure[76] as show in Scheme 25. These investigations furnish an excellent method to obtain homologated cycloalkanones by $BF_3{\cdot}OEt_2$ catalyzed[77,78] alkyl diazoacetate[79] insertion into a carbonyl-alkyl bond[80]. Aliphatic diazoalkanes react with carbonyl compounds by virtue of their nucleophilic properties, forming homologous carbonyl compounds by elimination of nitrogen. In the case of cycloalkanones this procedure leads to the formation of cycloalkanones which are ring enlarged by one C-atom. Using the general procedure reported by H.-J. Liu[81], the reaction of cyclohexanone (**63a**), cycloheptanone (**63b**) or cyclooctanone (**63c**) in

the presence of $BF_3{\cdot}OEt_2$ and ethyl diazoacetate (**64**), proceeded selectively in high yields as shown in Table 1.



63a-c (m = 1, 2, 3) **65c-e** (n = 2, 3 ,4)

Scheme 25: Preparation of ethyl 2-oxo-cycloalkane carboxylates (**65c-e**) by ring expansion reaction.

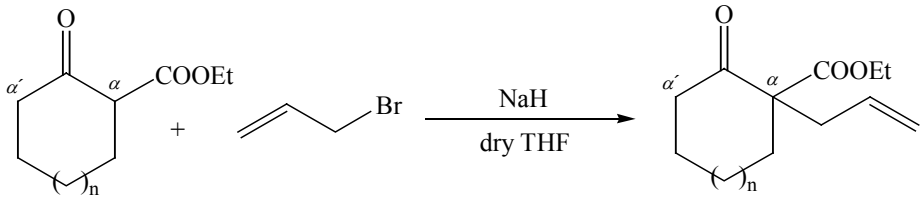
Table 1: Preparation of ethyl 2-oxo-cycloalkane carboxylates (**65c-e**)[a]

Reaction	m	Starting Mat.	Product	n	Yields (%)
R 1	1	**63a**	**65c**	2	74
R 2	2	**63b**	**65d**	3	98
R 3	3	**63c**	**65e**	4	91

a) The smaller ones 5-, and 6-membered *β*-keto ester rings labeled as **65a,b** are commercially available.

b. Preparation of ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a-e)

Ethyl 1-alkenyl 2-oxo-cycloalkane carboxylates of type **24** (Scheme 24, R = COOEt, m = 1; n = 0-4) can be obtained by alkylation of the corresponding cycloalkanones **65a-e** (from Scheme 25) in the presence of 1 eq. of NaH[82,83] and 1 eq. of allylbromide (**66**) as alkylating agent (Scheme 26). The *β*-ketoesters **65a-e** react smoothly, furnishing the unsaturated derivatives **4a-e** in high yield (over 90 %) with exception of the reaction carried out starting from ethyl 2-oxo-cycloheptane carboxylate (**65c**) which is converted into compound **4c** in about 80 % yield (Table 2, R 6).



65a-e (n = 0-4) **66** **4a-e** (n = 0-4)

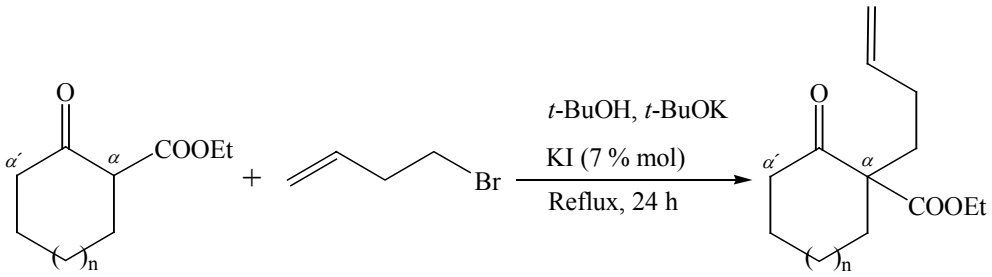
Scheme 26: Synthesis of ethyl 1-allyl-2-oxo-cycloalkane carboxylates (**4a-e**).

Table 2: Allylation in α position of ethyl 2-oxo-cycloalkane carboxylates (**65a-e**)

Reaction	n	Starting Mat.	Product	Yields (%)
R 4	0	**65a**	**4a**	93
R 5	1	**65b**	**4b**	91
R 6	2	**65c**	**4c**	80
R 7	3	**65d**	**4d**	96
R 8	4	**65e**	**4e**	92

c. Preparation of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (68a-c,e)

Proceeding with the preparation of starting materials that could be used in one-pot reactions, compounds of type **24** bearing an homoallylic side chain in α-position (Scheme 24, R = COOEt, m = 2) are prepared. The alkylation reaction is performed starting from **65a-c,e** (n = 0-2,4) and in the presence of *t*-BuOK as base with catalytic amounts of KI[84,85] and addition of 4-bromo-1-butene (**67**). The reaction proceeds with formation of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates **68a-c,e** (Scheme 27) in good yields with exception of the reaction carried out with ethyl 2-oxo-cycloheptane carboxylate (**65e**) which is converted into compound in **68e** in 47 % yield (Table 3, R 12).



65a-c,e (n = 0-2, 4) **67** **68a-c,e**

Scheme 27: Synthesis of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**)

Table 3: Synthesis of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**)

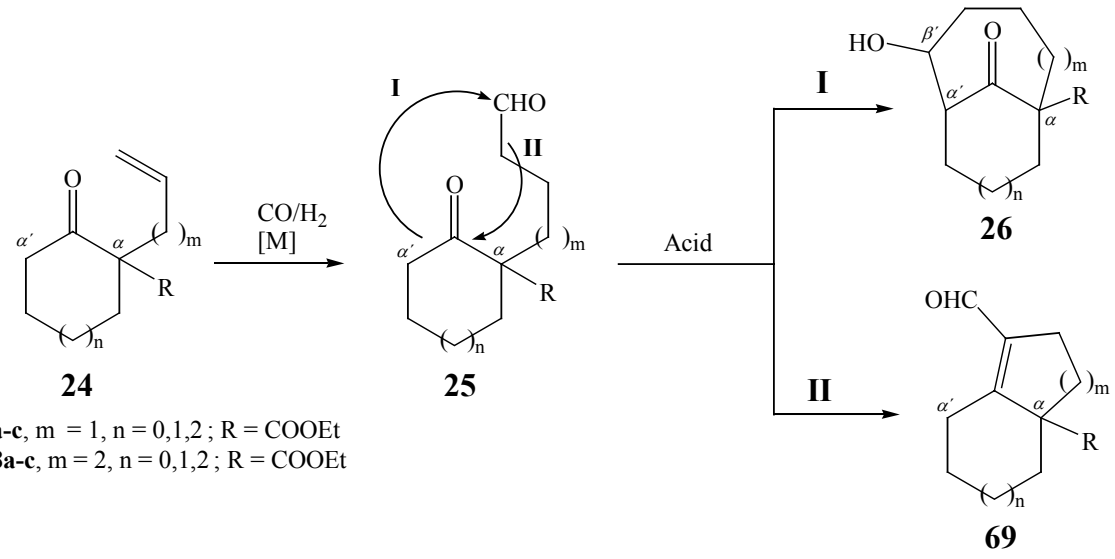
Reaction	**n**	**Starting Mat.**	**Product**	**Yields (%)**
R 9	0	**65a**	**68a**	85
R 10	1	**65b**	**68b**	85
R 11	2	**65c**	**68c**	81
R 12	4	**65e**	**68e**	47

2.2 Stepwise hydroformylation/ aldol addition under acidic conditions

2.2.1 Introduction

Taking into account the aldol condensation results obtained from Evans et al.[62] under acidic conditions as depicted in Scheme 8, studies were performed in order to find out how the reaction parameters (co-catalyst, solvent, temperature, reaction time) could influence the chemoselectivity of the intramolecular aldol addition[86,87] of compounds of type **24** (Scheme 28, **4a-c** and **68a-c**).

Intramolecular aldol addition will be investigated in the presence of both strong mineral acids (H_2SO_4 and HCl). As depicted in the Scheme 28 two different intramolecular aldol additions, due to the presence of two sites of enolization, could be possible: one resulting from the attack of the ketoester enolate on the aldehyde (**26**, path I), while the second one, the aldol adduct of type **69** is formed from the aldehyde-enolate with reversed chemoselectivity (path II).

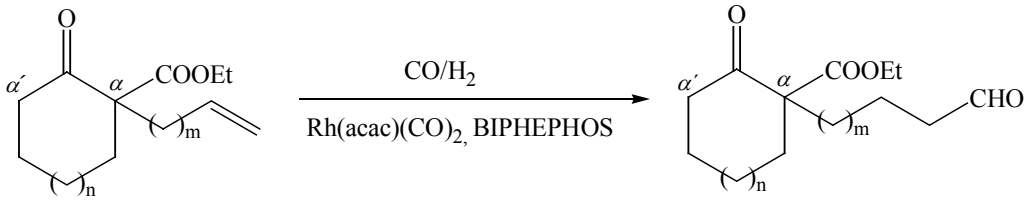


Scheme 28: Chemoselectivity in the intramolecular aldol addition of keto-aldehydes of type **24**.

a Preparation of ethyl 2-oxo-(*n*-oxo-alkenyl)cycloalkane carboxylates (*n* = 4, 5).

The first logical step is to perform the hydroformylation reaction of unsaturated *β*-ketoesters **4a-c** and **68a-c** under regiocontrol in the presence of BIPHEPHOS (**29**) as ligand.

As it has been observed that the hydroformylation could be performed under mild conditions when the ligand BIPHEPHOS (**29**) is employed[21], hydroformylation reactions are carried out in the presence of 4 % mol of ligand and 1 % mol of $Rh(acac)(CO)_2$ (**28**), using 20 bar of CO/ H_2, 60 °C for three days (Scheme 29). All results are compiled in Table 4.



4a-c (m = 1, n = 0, 1, 2)
68a-c (m = 2, n = 0, 1, 2)

70a-c (m = 1, n = 0, 1, 2)
71a-c (m = 2, n = 0, 1, 2)

Scheme 29: Hydroformylation of ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates **4a-c** and **68a-c**.

Table 4**:** Hydroformylation of unsaturated *β*-ketoester (**4a-c** and **68a-c**)

Reaction	m	n	Starting Mat.	Product	Yields (%)
R 13	1	0	**4a**	**70a**	82
R 14	1	1	**4b**	**70b**	98
R 15	1	2	**4c**	**70c**	97
R 16	2	0	**68a**	**71a**	61
R 17	2	1	**68b**	**71b**	35
R 18	2	2	**68c**	**71c**	40

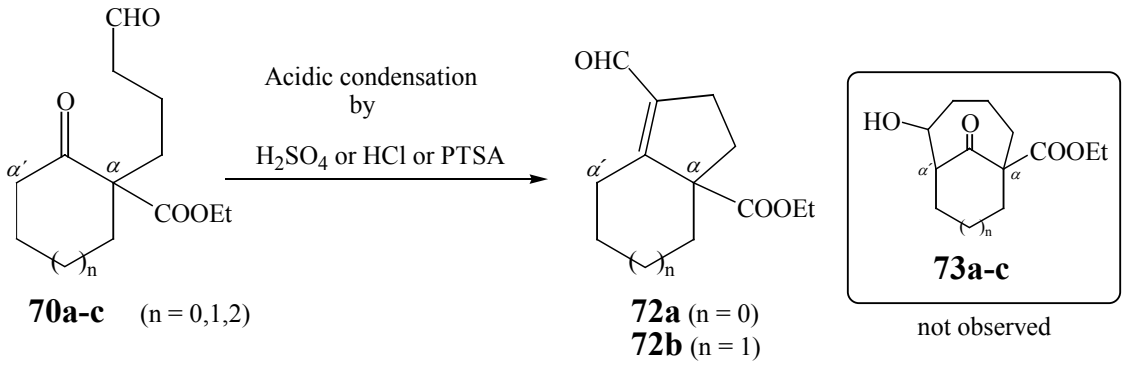
Conditions: 1 % mol - $Rh(acac)(CO)_2$, 4 % mol - BIPHEPHOS, dry DCM, T = 60 °C, t = 72 h.

In contrast to the results obtained in hydroformylation of ethyl 2-allyl-cycloalkane carboxylates (**4a-c**) (Table 4, R 13-15) the compounds **68a-c**, with a longer side chain, when hydroformylated under the same reactions conditions, react with lower yields to form compounds **71a-c** (Table 4, R 16-18).

2.2.2 Intramolecular aldol addition of ethyl 2-oxo-1-(*n*-oxo-butyl)cycloalkane carboxylates (*n* = 4, 5).

a. Aldol addition tests on ethyl 2-oxo-1-(4-oxo-butyl)-cycloalkane carboxylates (70a-c)

As alluded to in the introduction, several parameters could influence the chemoselectivity of the aldol addition. Then, the intramolecular aldol addition of the 1,6 dicarbonyl compound **70a-c** has been carried out under acidic conditions (H_2SO_4[62] and HCl[63]) using DCM and dioxane as solvent (Scheme 30). All investigations are listed in Table 5.



70a-c (n = 0,1,2)

72a (n = 0)
72b (n = 1)

Scheme 30: Intramolecular aldol condensations of ethyl 2-oxo-1-(4-oxo-butyl)-cycloalkane carboxylates **70a-c** under acidic conditions.

When ethyl 2-oxo-1-(4-oxo-butyl)-cycloalkane carboxylates (**70a-c**) are treated under acidic conditions at room temperature, no aldol addition products like **73a-c** are observed (Scheme 30). From the results in Table 5, it can be assumed that the chemoselectivity of the reaction should be influenced by the ring size. Indeed, the replacement of seven-membered **70c** by five-, six-membered ring such as **70a,b** leads to conversions into the fused aldol compounds **72a,b** involving an intramolecular aldol condensation.

Table 5: Intramolecular aldol condensations of compounds **70a-c** under acidic conditions

[a]React.	n	Starting Mat.	Acid	Solvent	Product	Yields (%)
R 19	0	**70a**	HCl	DCM	**72a**	99
R 20	0	**70a**	H_2SO_4	DCM	**72a**	99
R 21	0	**70a**	HCl	dioxane	**72a**	61
R 22	0	**70a**	H_2SO_4	dioxane	**72a**	99
R 23[b]	0	**70a**	PTSA	DCM	**72a**	99
R 24	1	**70b**	HCl	DCM	**72b**	99
R 25	1	**70b**	H_2SO_4	DCM	**72b**	98
R 26	1	**70b**	HCl	dioxane	**72b**	52
R 27	1	**70b**	H_2SO_4	dioxane	**72b**	98
R 28[b]	1	**70b**	PTSA	DCM	**72b**	97
R 29	2	**70c**	HCl	DCM	**70c**	--
R 30	2	**70c**	HCl	dioxane	**70c**	--

a) Unless otherwise noted, all reactions are performed at room temperature for a period of 24 h; b) T = 60 °C, t = 72 h.

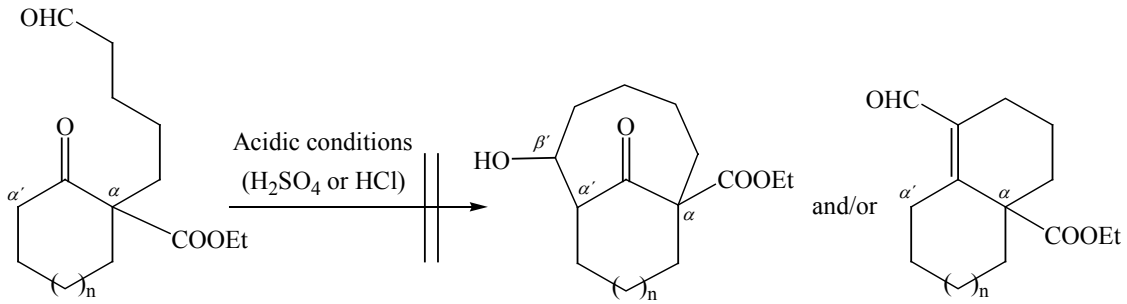
As summarized in Table 5, keto-aldehydes **70a,b** in the presence of different acids and solvents, undergo aldol condensation to form the corresponding fused aldol adducts **72a,b** in good to excellent yield. Strong mineral acids H_2SO_4 and HCl as well as PTSA[25,71] could satisfactorily be employed in DCM or dioxane.

If, however HCl in dioxane (R 21 and R 26) at room temperature for 24 hours are used in the reaction, the aldol adducts are obtained in lower yield, whereas the corresponding reactions in the presence of H_2SO_4 in dioxane proceeds with high yields (R 22 and R 27).

From these results it can be concluded that while the chemoselectivity of the reaction is neither affected by the polarity of the acids, nor the temperature or reaction time, lower yield are observed by changing of the acid (H_2SO_4 and HCl) and solvent (dioxane vs. DCM).

b. Attempts of aldol addition on ethyl 2-oxo-1-(5-oxo-pentyl)cycloalkane carboxylates (71a-c)

Proceeding with 1,7-ketoaldehyde of type **71a-c** (Scheme 29) the reactions are performed under the same conditions as described above. Failure of the aldol addition promoted by acid catalysis is observed (Scheme 31).



71a-c (n = 0, 1, 2) **74a-c** **75a-c**

Scheme 31: Attempted intramolecular aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cycloalkane carboxylates (**71a-c**).

Finally, an investigation of the starting material **71c** in dichloromethane at 60 °C for 72 hours in the presence of HCl (Table 6, R 35) results, once again, in failure of the aldol addition.

Table 6: Attempts of aldol cyclization of ethyl 2-oxo-1-(5-oxo-pentyl)cycloalkane carboxylates (**71a-c**)

[a]Reaction	n	Starting Mat.	Acid	Product
R 31	0	**71a**	HCl	Start. Mat.
R 32	0	**71a**	H_2SO_4	Start. Mat.
R 33	1	**71b**	HCl	Start. Mat.
R 34	1	**71b**	H_2SO_4	Start. Mat.
R 35[b]	2	**71c**	HCl	Start. Mat.

a) Unless otherwise noted, all reactions are performed at room temperature in DCM for a period of 24 h; b) T = 60 °C, t = 72 h.

Several interesting conclusion can be drawn from the results reported above. Under acidic conditions only the allyl ketoaldehydes **70a,b** reacted to give only the corresponding fused bicyclic products **72a,b** when 5- and 6-membered ring compounds are used (Scheme 30).

However, while the step-wise reactions subsequent to the generation of the aldehyde have been performed in the presence of strong mineral acids such as H_2SO_4 and HCl, these catalysts are too aggressive for performing the reaction in an autoclave.

Then, according the results observed above, the PTSA in amounts ranging 5-10 mol % is the suitable catalyst in DCM for accomplishing these reactions in a one-pot hydroformylation/ aldol addition.

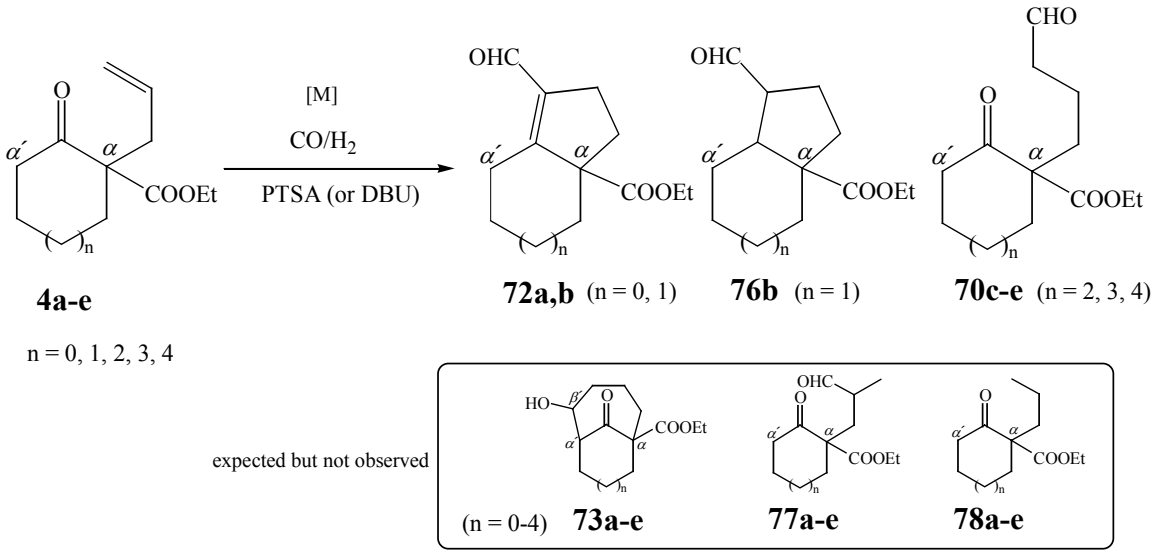
2.3 One-pot tandem hydroformylation/ aldol addition

2.3.1 Tandem hydroformylation/ aldol addition of ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates

a. Use of ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a-e)

Earlier investigations concerning the acid catalyzed tandem hydroformylation/ aldol condensation under harsh conditions[73] of 3,3-dimethyl-4-penten-2-one (**38**) (Scheme 13) and under milder conditions[73] of 3-allyl-cyclohexanone (**45**) (Scheme 16), suggest that using the same latter reaction conditions, even monocycles like ethyl 1-allyl-2-oxo-cycloalkane carboxylates **4a-e** could form the aldol adducts of type **26** and/or **27** (Scheme 6). Thus, the compounds **4a-e** are hydroformylated with $Rh(acac)(CO)_2$ (**28**) as catalyst[88,89,90,91,92] (1 mol %), BIPHEPHOS (**29**) as ligand[21,91] (4 mol %) in the presence of PTSA as co-catalyst[71,25] (5 mol %), under 20 bar of syn-gas pressure (CO/H_2 in a ratio of 1:1), temperatures around 60 °C for 3 days (Scheme 32).

However, in order to verify the possible cyclization under basic conditions, the six-membered compound **4b** was submitted to the similar reaction conditions by replacing PTSA with DBU as co-catalyst.



Scheme 32: Attempts of tandem hydroformylation/ aldol addition on ethyl 1-allyl-2-oxo-cycloalkane carboxylates (**4a-e**) under acidic or basic conditions.

The results, obtained when the ethyl 1-allyl-2-oxo-cycloalkane carboxylates (**4a-e**) were submitted to the tandem hydroformylation/ aldol addition conditions, are shown in Table 7. The one-pot hydroformylation/ aldol addition procedure carried out on 5-, 6-membered compounds **4a,b** proceeds with aldol condensation, derived from enolate of aldehyde on the ketone, resulting in a fused bicycle formation like **72a,b** (Scheme 32). Moreover, while the ethyl 1-allyl-2-oxo-cyclopentane carboxylate **4a** is found to yield the **72a** (n = 0) as the only product (Table 7, R 36), the compound **72b** (n = 1) is accompanied by small amounts of the subsequently hydrogenated system **76b** (Table 7, R 37). In contrast to the previous results, the size of the cycloalkanone ring seems to have a significant effect on the chemoselectivity of the reaction. Then, the same reaction conditions applied on the larger 7-, 8-, 9-membered compounds **4c-e** gave exclusively the *n*-products of hydroformylation **70c-e** (Scheme 32) and none of the aldol adducts of type **73** or **72** is detected (Table 7, R 38-40). Anyway, branched aldehydes of type **77** and double bond hydrogenated compound of type **78** have never detected (Scheme 32). Finally, to the results obtained when PTSA was used, the reaction of the 6-membered compound **4b** carried out in the presence of DBU (5 % mol) as co-catalyst, forms a mixture of linear aldehyde **70b** accompanied by small amounts of the fused bicycle **72b** in a ratio of 11:1 (Table 7, R 41).

Table 7**:** One-pot reaction conditions applied on ethyl 1-allyl-2-oxo-cycloalkane carboxylates (**4a-e**)

Reaction	**n**	**Starting Mat.**	**Products**		**Yields (%)**
R 36[a]	0	**4a**	**72a**	--	65
R 37[a]	1	**4b**	**72b** (3)[c]	**76b** (1)[c]	79[d]
R 38[a]	2	**4c**	**70c**	--	98
R 39[a]	3	**4d**	**70d**	--	37
R 40[a]	4	**4e**	**70e**	--	40
R 41[b]	1	**4b**	**72b** (1)[c]	**70b** (11)[c]	98[d]

a) 1 mol % - $Rh(acac)(CO)_2$, 4 mol % - BIPHEPHOS, 5 mol % - PTSA, dry DCM, T = 60 °C, t = 72 h; b) 1 mol % - $Rh(acac)(CO)_2$, 4 mol % - BIPHEPHOS, 5 mol % - DBU, dry DCM, T = 60 °C, t = 72 h; c) ratio by ^{1}H-NMR analysis; d) calculated by GC-analysis.

Again, as observed in the step-wise procedure, the different outcome of these reactions could be explained by the ring forming Baldwin's rules[93]. Appling these rules on the 5-, and 6-membered cycloalkanones **4a,b**, both the intramolecular aldol addition via 7-*enol-endo-exo-trig* annulation in α*'*-position to give compounds **73a,b** (deriving from the

keto-enolate) and the 5-*enol-exo-exo-trig* condensation at the ketone moiety to furnish compounds **72a,b** (deriving from the aldehyde-enolate) can occur (Scheme 32). Nevertheless from the results reported above, the formation of **72a,b** appears to be favored under these conditions. This chemoselectivity could be explained if considering besides the Baldwin's rules[93a,b] also the Bürgi-Dunitz trajectory theory[94]. In fact, it could be supposed that the aldehyde enolate intermediate of the compounds **4a,b** is able to attack the ketone with a preferred angle of approach about 109° (Figure 6).

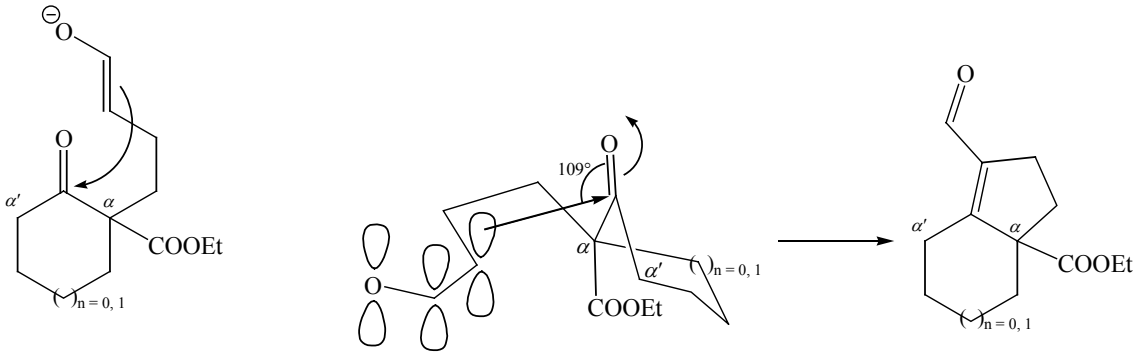


Figure 6 : Mechanism of 5-*enol-exo-exo-trig* intramolecular aldol condensation on 5-, 6-membered compounds **4a** (n = 0) and **4b** (n = 1) respectively.

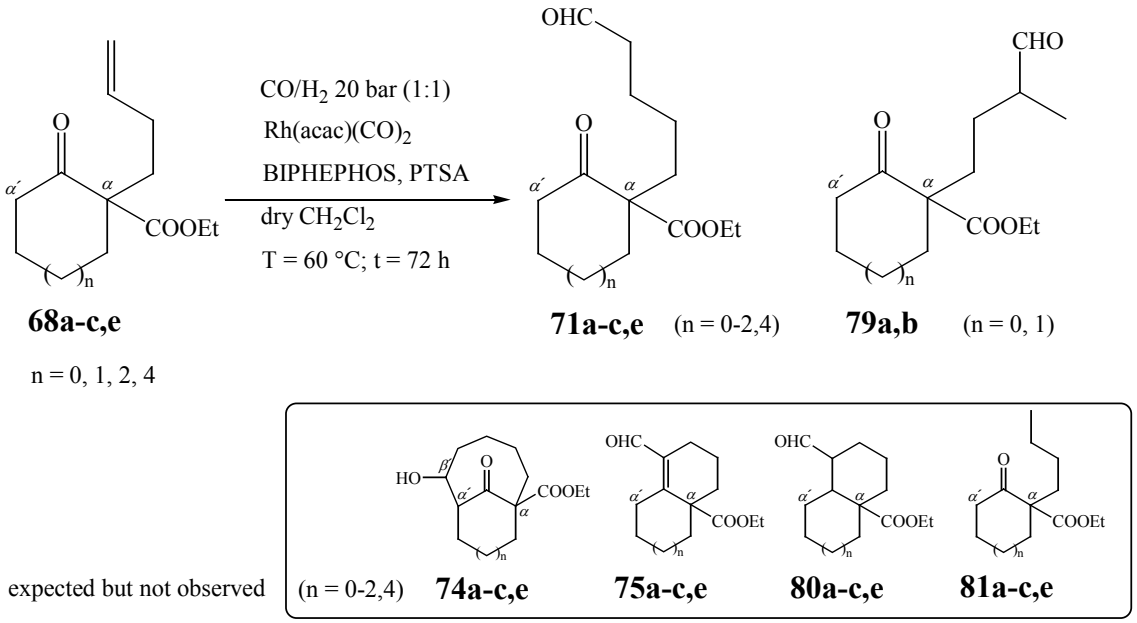
The absence of intramolecular aldol condensation regarding the larger rings **4c-e** could be due to the conformation of the rings. In fact, if the 7-, 8-, 9-membered rings are considered, a combination of angle strain (Baeyer strain)[95,96] and bond opposition strain (Pitzer strain)[95,96] with cross ring interaction (transannular strain) lead to a disfavored conformation for the favored angle of approach.

In order to test the suitability of the one-pot procedure, further sequential hydroformylation/ aldol addition investigations will be also carried out on cycloalkanones bearing a longer side chain.

b. Use of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (68a-c,e)

To provide further information about the role of ring size and tethers under the same previous tandem hydroformylation/ aldol addition conditions (Scheme 32)

cycloalkanones bearing a longer side chain used so far, such as ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**), were examined (Scheme 33).



Scheme 33: Attempts of tandem hydroformylation/ aldol addition on ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**).

Table 8: Tandem hydroformylation/ aldol cyclization applied on ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**)

Reaction	n	Start. Mat.	Products		Yields (%)
R 42	0	**68a**	**71a** (5)[a]	**79a** (1)[a]	78
R 43	1	**68b**	**71b** (33)[a]	**79b** (1)[a]	86
R 44	2	**68c**	**71c**	--	40
R 45	4	**68e**	**71e**	--	26

Reaction conditions: 1 mol % - $Rh(acac)(CO)_2$, 4 mol % - BIPHEPHOS, 5 mol % - PTSA, dry DCM, T = 60 °C, t = 72 h; a) ratio by ^{1}H-NMR analysis.

As listed in Table 8 (R 42-43) the ethyl 1-(but-3-enyl)-2-oxo-cyclopentane-, -hexane carboxylates (**68a** and **68b** respectively) react under tandem hydroformylation/ aldol addition conditions to form a mixture of linear aldehyde products **71a** and **71b** accompanied by small amounts of the corresponding branched aldehydic compounds **79a** and **79b**. The reaction occurred exclusively with formation of linear aldehyde derivatives **71c,e** when seven-, and nine-membered cyclic compounds **68c,e** respectively

are used (Table 8, R 44-45). It seems that the regioselectivity of the hydroformylation process is directly dependent on the size of the cycloalkanone.

These results show that both the 6-*enol-exo-exo-trig* annulations like **75** (condensation at keto group) and the 8-*enol-endo-exo-trig* as **74** are disfavored. Besides the Baldwin's rules[93a,b] and the Bürgi-Dunitz trajectory theory[94], the activation energy for ring closure should be considered. The strain energy involved in the formation of the bridged or fused rings should be a critical factor in this annulation due to the length of the chain. As the chain length increases the probability of the chain approaching the cycloalkanone decreases (negative entropy due to less freedom of internal rotation around the single bonds of the chain backbone when the open-chain precursor is converted into the ring shaped transition state[95,97]. Moreover the results could be explained, if bond opposition forces due to imperfect staggering (Pitzer strain[95,96]), deformation of ring bond angles (Baeyer strain[95,96]) and transannular strain due to repulsive interactions between atoms across the ring when they are forced close to each other[95] are considered.

In conclusion, all the results obtained under tandem hydroformylation/ aldol addition conditions can be collected in Table 9.

Scheme 34: Ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates (**4a-e** and **68a-c,e**) under tandem hydroformylation/ aldol addition conditions.

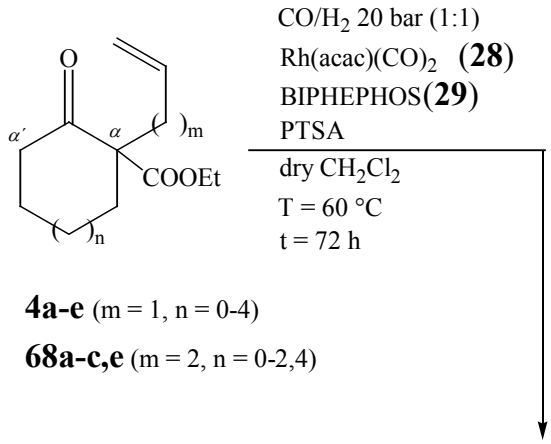
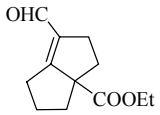
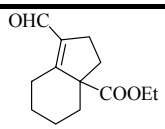
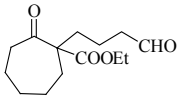
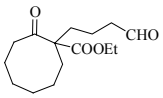
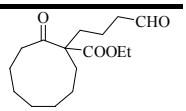
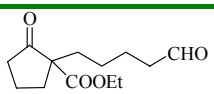
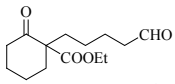
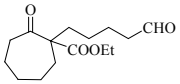
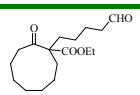


Table 9: Main results by sequential hydroformylation/ aldol addition conditions carried out on ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates (**4a-e** and **68a-c,e**).

m	n	0	1	2	3	4
1		 **72a** (65%)	 **72b** (79 %)[a]	 **70c** (98 %)	 **70d** (37 %)	 **70e** (40 %)
2		 **71a** (78 %)[b]	 **71b** (86 %)[b]	 **71c** (40 %)	--	 **71e** (26 %)

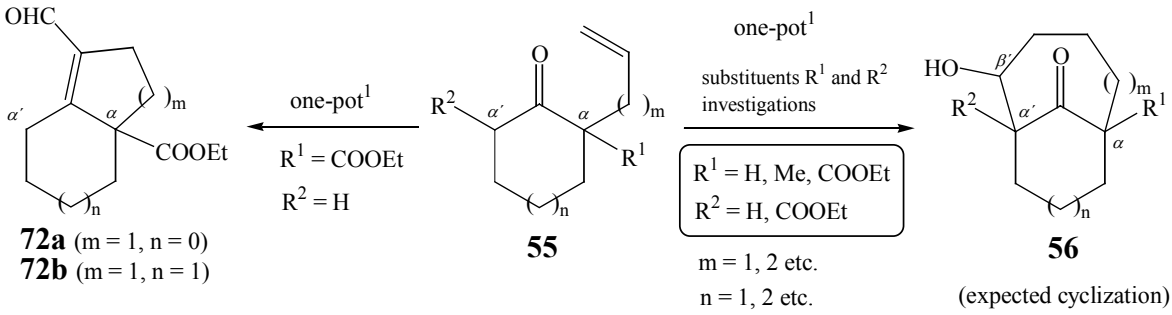
( ) = Yield; a) Including amounts of the corresponding hydrogenated compound **76b**; b) Including amounts of the corresponding branched aldehydes **79a** (m = 2; n = 0) and **79b** (m = 2; n = 1) respectively.

- Although bicyclic compounds of type **73** (Scheme 32) or **74** (Scheme 33) have never been observed, the tandem hydroformylation/ aldol addition acid catalyzed by PTSA is an efficient method to transform 5-, 6-membered allyl cycloalkanones like **4a,b** directly into the corresponding bicyclic pentalene or indene skeletons **72a,b** respectively (Scheme 32).
- The larger 7-, 8-, 9-membered allyl cycloalkanones **4c-e** gave linear aldehydes **70c-e** (m = 1; n = 2-4) as main products (Scheme 32).
- No cyclization has been observed regardless the ring size when homoallylated compounds of type **68** are used. Only linear aldehydes **71a-c,e** and traces of branched ones **79a** (m = 2; n = 0) and **79b** (m = 2; n = 1) have been detected (Scheme 33).

2.4 Study of the substituent effects in the 2-oxo-2-alkenyl-cycloalkanes under sequential hydroformylation/ aldol addition reactions

2.4.1 Introduction

As the unsaturated β-ketoesters with 5-, 6-membered rings of type **55** (**4a** with R^1 = COOEt, R^2 = H, m = 1; n = 0 and **4b** with R^1 = COOEt, R^2 = H, m = 1; n = 1) via sequential hydroformylation/ aldol addition afford the fused aldol adducts **72a,b**, further studies are performed for the construction of bridged system of type **56** (Scheme 35). Investigations are conducted in order to find out how the aldol reaction succeeding hydroformylation is influenced by the presence of further substituents in the unsaturated ketones of type **55**.



72a (m = 1, n = 0)
72b (m = 1, n = 1)

55

56

1) $Rh(acac)(CO)_2$, CO/H_2 10 bar (1:1), PTSA, BIPHEPHOS, dry DCM, 60 °C, 72h.

Scheme 35: Possible pathway in tandem hydroformylation/ aldol addition of activated cycloalkanones of type **55**.

Thus, it could be expected that kinetic or thermodynamic control should be effective if:

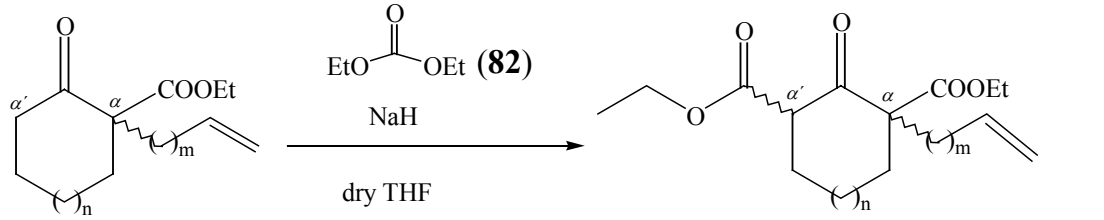
- the α'-position reactivity could be increased by replacing R^2 with an activating group such as ester, CN etc.,
- steric influence in the α'-position is lowed by using substituents such as a methyl group or hydrogen.

2.4.2 Tandem hydroformylation/ aldol addition investigations with diethyl 1-alkenyl-2-oxo-cycloalkane-1,3-dicarboxylates.

In the context of compounds useful in the formation of bridged systems of type **56**, the compound with which to begin is the 1,3-dicarboxylate of type **55** where the α'-position is activated by introducing an electron-withdrawing function such as an ester (Scheme 35). In this way, the enolate of a 1,3-dicarbonyl derivative should be more reactive towards the intramolecular cyclization under the tandem hydroformylation/ aldol addition reaction conditions.

a. Preparation of the diethyl 1-alkenyl-2-oxo-cycloalkane dicarboxylates (83b,c and 84).

The preparation of unsaturated ketones bearing an ester function in α'-position is conducted using the procedure reported by Marshall et al.[98] in which starting materials are added to a refluxing mixture of NaH and diethylcarbonate (**82**) in dry THF. Thus, starting from the allylated compounds **4b** (n = 1) and **4c** (n = 2) and the homoallylated 7-membered ring compound **68c**, after distillation, corresponding 1,3-dicarboxylates **83b,c** and **84** (Scheme 36) are obtained in good yields as compiled in Table 10.



4b,c (m = 1; n = 1, 2)
68c (m = 2; n = 2)

83b,c (m = 1; n = 1, 2)
84 (m = 2; n = 2)

Scheme 36: Synthesis of diethyl 1-alkenyl-2-oxo-cycloalkane-1,3-dicarboxylates **83b,c** and **84**.

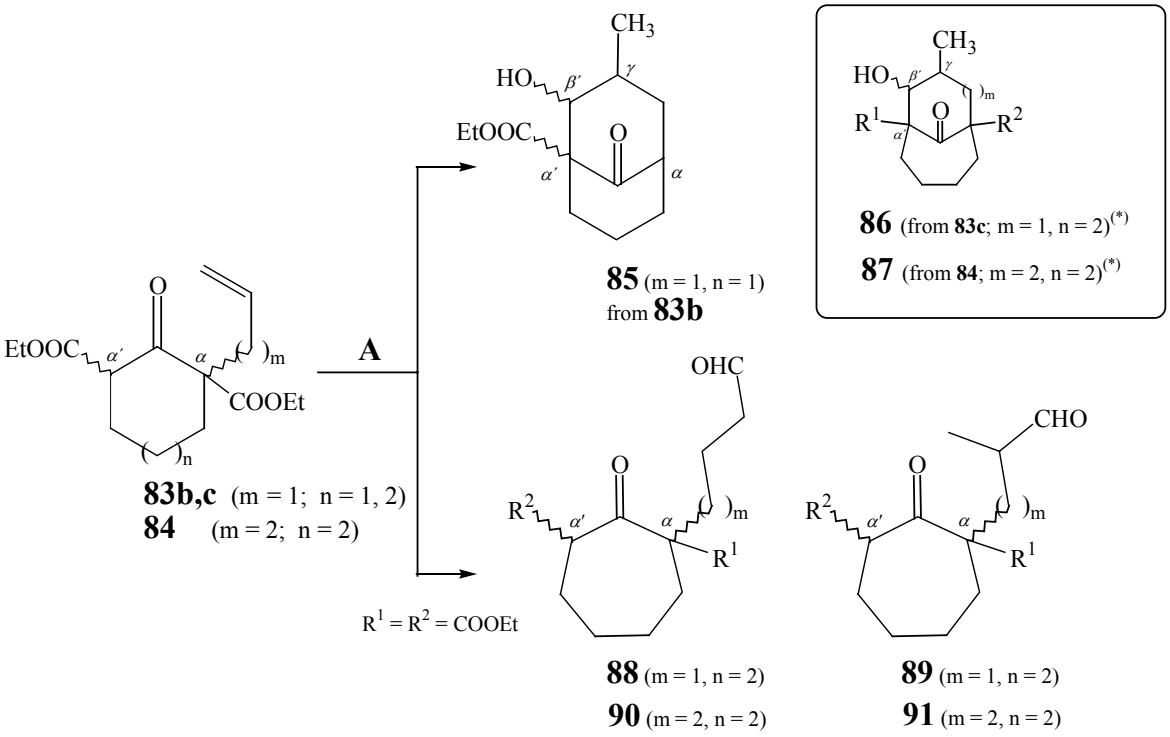
Table 10: Preparation of diethyl 1-alkenyl-2-oxo-cycloalkane-1,3-dicarboxylates **83b,c** and **84c**

Reaction	m	n	Starting Mat.	Product	dr[a]	Yields (%)
R 46	1	1	**4b**	**83b**	1:1	90
R 47	1	2	**4c**	**83c**	1:1	82
R 48	2	2	**68c**	**84**	--	83

a) Calculated by NMR analysis.

b. Reactivity of diethyl 1-alkenyl-2-oxo-cycloalkane-1,3-dicarboxylates (83b,c and 84c) under tandem hydroformylation/ aldol addition reaction conditions.

Preliminary investigations are conducted starting from the substituted six-membered ring compound **83b** (Scheme 37, m = 1, n = 1) subjected to the sequential hydroformylation/ aldol conditions under mild conditions (CO/H_2 20 bar, 60 °C for 72 h) in the presence of 1 mol % of $Rh(acac)(CO)_2$ (**28**) catalyst and 4 mol % of *p*-TsOH. An interesting feature emerged from the analysis of this result as shown in Scheme 37 (Table 11, R 49). A cyclization in α'-position to form the bicyclo[3.3.1]octane ring system **85** is resulting from the attack of the enolate of the ketoester to the *iso*-aldehyde which is formed in spite of the presence of the BIPHEPHOS (**29**) ligand. Moreover, loss of the ester group in α-position is observed.



A: $Rh(acac)(CO)_2$; CO/H_2 20 bar (1:1); 4 mol % - BIPHEPHOS; 5 mol % - PTSA; dry CH_2Cl_2; T = 60 °C; t = 72 h

(*) expected but not observed

Scheme 37: Attempt of tandem hydroformylation/ aldol addition of diethyl 1-alkenyl-2-oxo-cycloalkane dicarboxylates (**83b,c** and **84**).

Table 11: Tandem hydrformylation/ aldol addition of diethyl 1-alkenyl-2-oxo-cycloalkane dicarboxylates (**83b,c** and **68c**)

Reaction	m	n	Starting Mat.	Product		Yields (%)
R 49	1	1	**83b**	**85**	--	37
R 50	1	2	**83c**	**88** (5)[a]	**89** (1)[a]	98
R 51	2	2	**84**	**90** (2)[a]	**91** (1)[a]	90

Reaction conditions: 1 mol % - $Rh(acac)(CO)_2$, 4 mol % - BIPHEPHOS, 5 mol % - PTSA, dry DCM, T = 60 °C, t = 72 h; a) calculated by ^{1}H-NMR analysis.

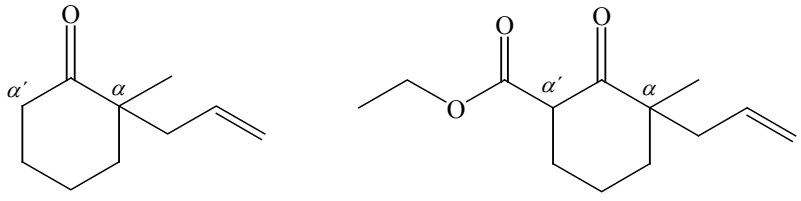
Proceeding the investigations by using larger rings, the allylated ketoester **83c** (Scheme 37, m = 1, n = 2) is also considered. As it has previously been observed the unsaturated mono-ketoester **4c** (Scheme 32) when submitted to tandem hydroformylation/ aldol addition conditions, the **83c** is not observed to react to the aldol adduct and only the *n*-aldehyde is isolated.

In contrast to the results previously reported about bicycles like **85**, the 1,3-dicarboxylate **83c** reacted to give a mixture of *n-iso*-aldehyde in a ratio of 5:1 as

observed by ^{1}H-NMR and no aldol adduct of type 86 is detected (Scheme 37). Again, in spite of the presence of BIPHEPHOS (**29**), the loss of regioselectivity of the hydroformylation reaction is observed. As the mixture of the aldehydes **88** and **89** is isolated in excellent yields, the failure to observe the intramolecular aldol adducts is again explained in terms of ring-size influence, as reported in the reaction of β-ketoester **4c** (Scheme 32). Under the mild conditions applied for compound **83c**, the ketoester **84c** reacts with a moderate regioselectivity with 2:1 preference for the *n*-product **90** as listed in Table 11 (R 51). According with the results above, no cyclization is observed.

2.4.3 Tandem hydroformylation/ aldol addition investigations with ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93) and 2-allyl-2-methyl-cyclohexanone (92).

Proceeding with investigations to find out how the substitution pattern in unsaturated cycloalkanones could influence the sequential hydroformylation/ aldol addition, systems of type **55** (Scheme 35) such as the 2-allyl-2-methyl-cyclohexanone (**92**) and the ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**), are tested (Figure 7). The compound **92** is employed in order to suppress the electronic or sterical effect of the ester nearby the allyl chain; thus, a methyl group is installed in α-position. Furthermore as in the previous case (Scheme 37) an ester function in α'-position could be introduced like **93** (Figure 7).

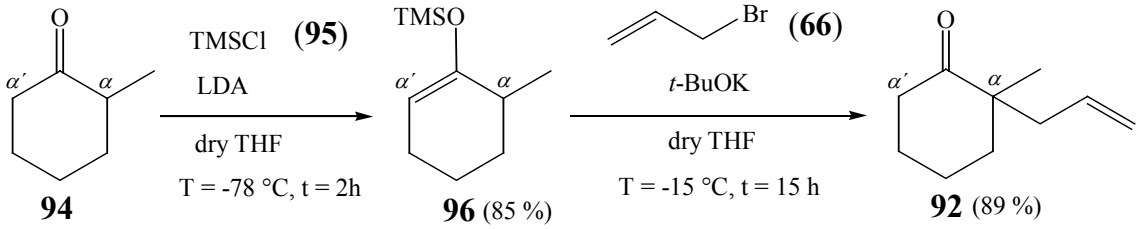


92 **93**

Figure 7: 2-allyl-2-methyl-cyclohexanone (**92**) and ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**).

a. Synthesis of 2-allyl-2-methyl-cyclohexanone (92)

While the alkylation reaction of β-ketoesters is easily performed without any further activation of the carbonyl group, the alkylation at the more hindered α-site of unsymmetrical cycloalkanones such as the 2-methyl-cyclohexanone (**94**) could require the generation of enolates as intermediates. Silyl enol ethers[99] are introduced as precursors of specific enolates. They have several advantages over other enol derivatives, not the least being the ease with which specific silyl enol ethers can be prepared from unsymmetrical ketones[100,101]. Making use of quoted procedures recommended by House and co-workers[100] for the preparation of the silyl-enol ether under kinetic control, the compound **96** is selectively formed from **94** by using first lithium diisopropyl-amide[102], to generate the lithium enolate, and then O-silylating with chlorotrimethylsilane (**95**). Moreover as indicated by Fleming and Paterson[103], high conversion and regioselectivity can be achieved into the lithium enolate formation if the reaction is carried out at -78 °C. Thus, in only 2 h the silyl enol ether **96** is obtained in 85 % of yield (whereas the 'thermodynamic' silyl-enol ethers is formed after 5 days)[103] using TMSCl (**95**) and LDA as base[104] (Scheme 38, R 52).

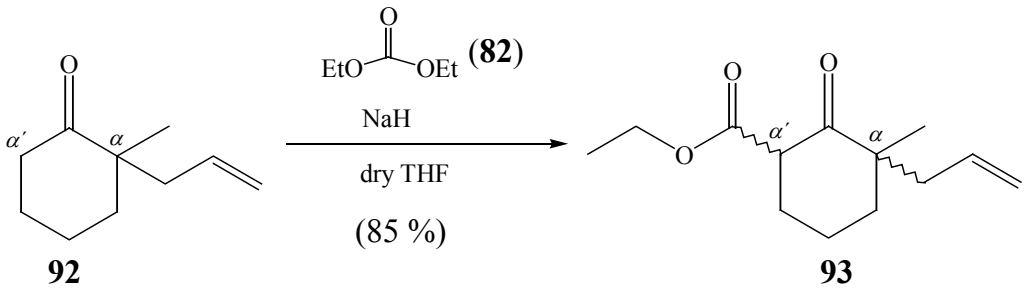


Scheme 38: Synthesis of 2-allyl-2-methyl-cyclohexanone (**92**).

The alkylation on more substituted α-position takes place if the silyl enol ether **96** is treated with allylbromide **66** as alkylating agent and *t*-BuOK[105]. The reaction proceeds via alkali-enolates[104] (R 53) which can be easily generated from **96** by cleavage of the oxygen-silicon bond with alkali-potassium enolate (Scheme 38). Thus, the alkylated product 2-allyl-2-methylcyclohexanone (**92**) is synthesized in 89 % yields.

b. Preparation ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

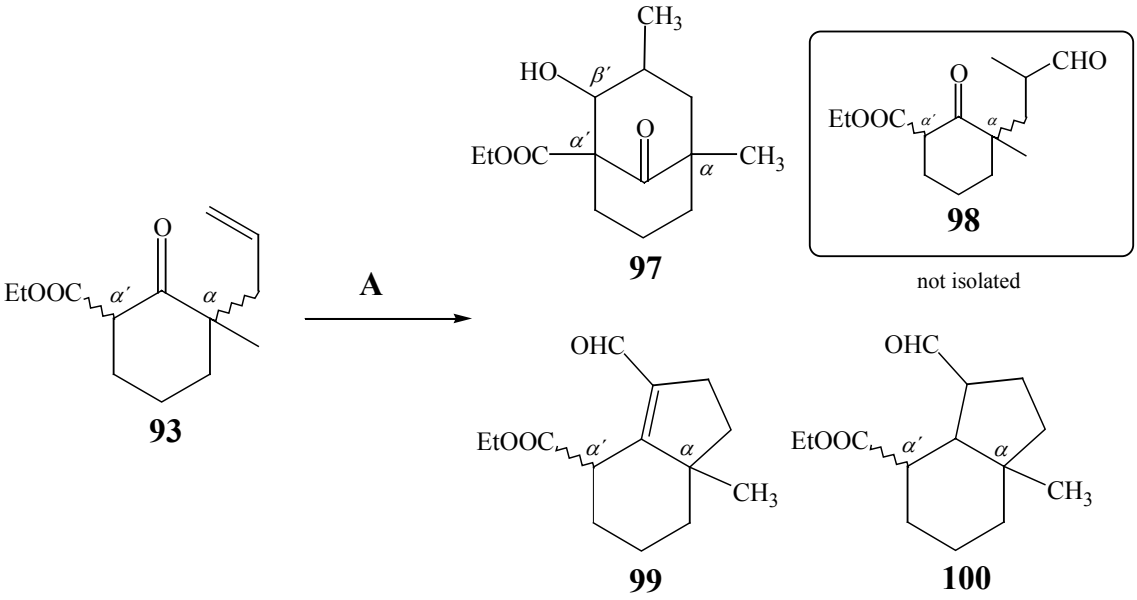
As previously described, the electron-withdrawing ester function could be introduced in α'-position of the 2-allyl-2-methyl-cyclohexanone (**92**) via a procedure analogously performed for the preparation of 1,3-dicarboxylates as depicted in Scheme 37. Then, ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**) is synthesized in 85 % yield by adding on **92** of diethylcarbonate (**82**) and NaH as base[98] (Scheme 39, R 54).



Scheme 39: Synthesis of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**).

c. Tandem hydroformylation/ aldol addition of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

Starting with the ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**) bearing a α-allyl substituent the sequential hydroformylation/ aldol addition is carried out in the presence of *p*-TsOH under mild conditions of 20 bar, 60 °C and for 3 days (Scheme 40). The reaction proceeds with formation of three products **97**, **99** and **100** in a ratio of 7.2:1:5 (detected by ^{1}H-NMR analysis) respectively, where, the major component is the bridged compound **97** isolated in 32 % yield (R 55).



A: Rh(acac)$(CO)_2$, CO/H_2 20 bar (1:1), 5 mol % - BIPHEPHOS, 4 mol % - PTSA, dry CH_2Cl_2, T = 60°C, t = 72 h

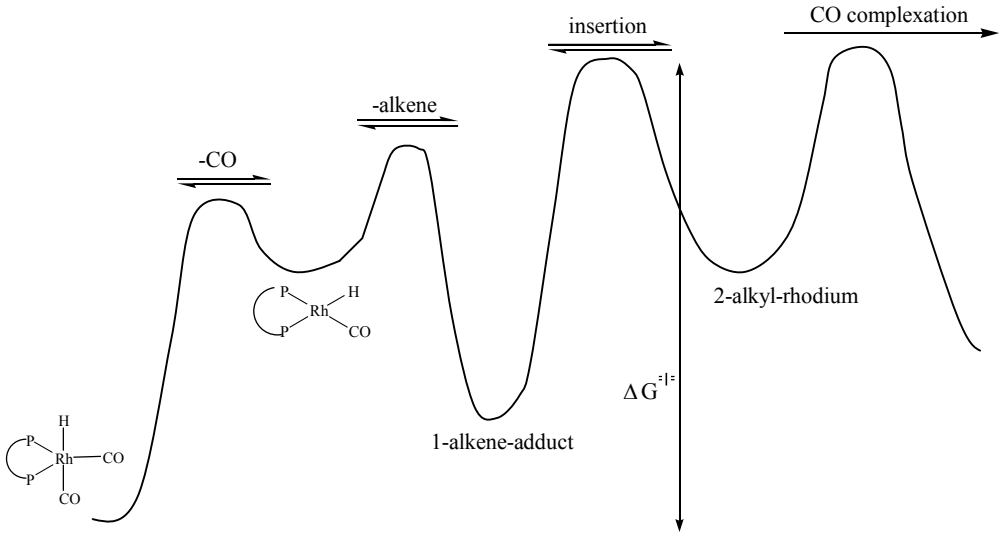
Scheme 40: Tandem hydroformylation/ aldol addition of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**).

In analogy to the one-pot hydroformylation/ aldol addition of 1,3-di-ester **83b** (Scheme 37), predominately the *iso*-isomer ethyl-3-methyl-3-(2-methyl-3-oxo-propyl)-2-oxo-cyclohexane carboxylate (**98**) is generated, which could readily undergo cyclization to form ethyl 2-hydroxy-3,5-dimethyl-9-oxo-bicyclo[3.3.1]nonane-1-carboxylate (**97**) (Scheme 40). Once again, in the presence of ester function in α'-position the formation of *iso*-aldehyde could be explained if considering the kinetics and energetics of the hydroformylation sequence. As side products the fused bicyclic adducts ethyl-3-formyl-7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (**99**) and ethyl-3-formyl-7a-methyl octahydro-1*H*-indene-4-carboxylate (**100**), resulting from the reaction of *n*-aldehyde, are detected.

For the formation of branched aldehyde **98** (Scheme 40) as predominant intermediate the insertion step should be considered as reversible, dependent on reaction conditions. A potential scheme showing the competition between the backward reaction and the complexation of CO reaction is shown in Scheme 41. At low temperatures and sufficiently high pressures the formation of 2-alkyl species from 1-alkenes **93** (Scheme 40) or **83b** (Scheme 37) can also be irreversible. The barriers for the backwards reaction (β-elimination) and forward reaction (CO complexation) drawn at about the same height

indicate the competition between the two steps. β-elimination may lead to 2-alkene, which forms a less stable complex than 1-alkene (not shown).

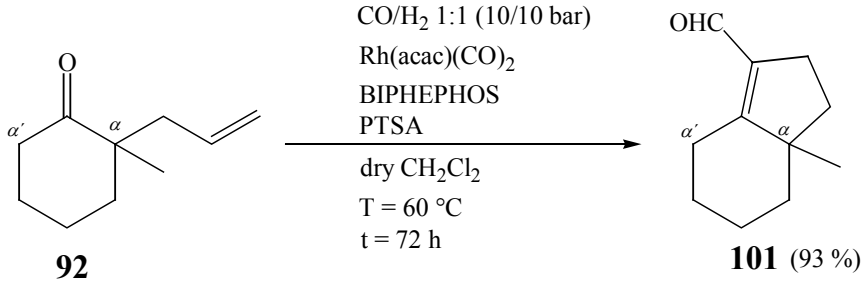
Clearly, energy differences are very small and entropy and concentrations will have large influence on the actual kinetics[106].



Scheme 41: Reversible migratory insertion of alkenes to 2-alkyl-rhodium species.

d. Tandem hydroformylation/ aldol addition of 2-allyl-2-methyl-cyclohexanone (92).

If the 2-allyl-2-methyl-cyclohexanone (**92**) is investigated the reaction proceeds exclusively with *n*-selectivity leading to 3a-methyl-3,3a,4,5,6,7-hexahydro-2H-indene-1-carbaldehyde (**101**) in 93 % yield (Scheme 42, R 56).



Scheme 42: Tandem hydroformylation/ aldol addition of 2-allyl-2-methyl-cyclohexanone (**92**).

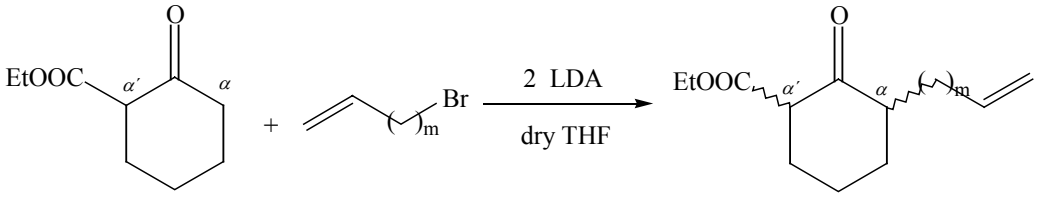
Again, according to the results observed with unsaturated β-ketoesters **4a,b** (Scheme 32), an aldol condensation on the ketone function occurs resulting in the formation of the "kinetic" aldol adduct regardless the functional group (ester or methyl groups) in the α-position.

2.4.4 Tandem hydroformylation/ aldol addition of ethyl 3-alkenyl 2-oxo-cyclohexane carboxylates.

As previously reported a low tendency of the α'-position to the intramolecular condensation is observed when the substituent R^2 = H (Scheme 32 and Scheme 40). On the other hand, activating groups such as an ester function installed in such position, resulting in the formation of *iso*-product. All attempts to influence the chemoselectivity of the aldol addition by introduction of activating or blocking groups (Me, COOEt) in α- or α'-position, towards the synthesis of bicyclic compounds of type **56** (Scheme 35) failed. Further studies in order to find out if the substituents in α-position combined with the α'-position one could influence the outcomes of the reaction have been conducted. Then, in absence of such blocking group, β-ketoester of type **55** (R^1 = H, R^1 = COOEt, Scheme 35) bearing an olefinic chain in α-position seems to be the available starting material.

2.4.5 Preparation of ethyl 3-alkenyl-2-oxo-cyclohexane carboxylates.

Hauser and al.[107] reported that treatment of β-ketoesters with 2 eq. of a strong base followed by the appropriate alkylating agent[108] furnished the alkylation of the more reactive enolate. Following this procedure starting from **65b**, the 1,3-dianion generated by LDA[109] could readily react with alkylating agents (Scheme 43) such as allylbromide (**66**) or homoallybromide (**67**). According to the results compiled in Table 12 (R 57), the ethyl 3-allyl-2-oxo-cyclohexane carboxylate (**102**) is obtained in high yield, whereas the reaction to form the corresponding homoallyl product **103** proceeds with considerably lower yields (24 %) (R 58).



65b **66** (m = 1) **67** (m = 2) **102** (m = 1) **103** (m = 2)

Scheme 43: Synthesis of ethyl 3-alkenyl-2-oxo-cyclohexane carboxylates (**102** and **103**).

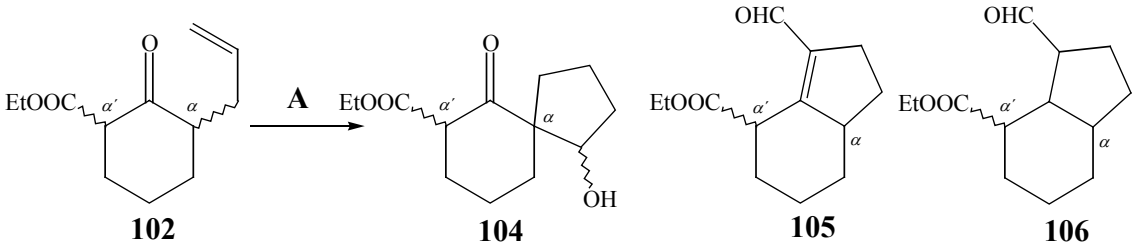
Table 12: Synthesis of ethyl 3-alkenyl-2-oxo-cyclohexane carboxylates (**102b** and **103b**)

Reaction	Starting Mat.	Length chain (m)	Product	dr[a]	Yields (%)
R 57	**65b**	**66** (m = 1)	**102**	2.5:1	82
R 58	**65b**	**67** (m = 2)	**103**	3:1	24

a) By NMR analysis.

a. Tandem hydroformylation/ aldol addition of ethyl 3-allyl-2-oxo-cyclohexane carboxylate (102)

Beginning with compound **102** the tandem hydroformylation/ aldol addition is performed under mild conditions (CO/H_2 20 bar, 60 °C for 3 days) (Scheme 44, R 59). The reaction proceeds through an aldol addition resulting in the formation of inseparable mixture of spiro compound **104**, the fused aldol adducts like **105** and its hydrogenated derivative **106** are observed in a ratio of 20:3.2:1 as determined by NMR.



102 **104** **105** **106**

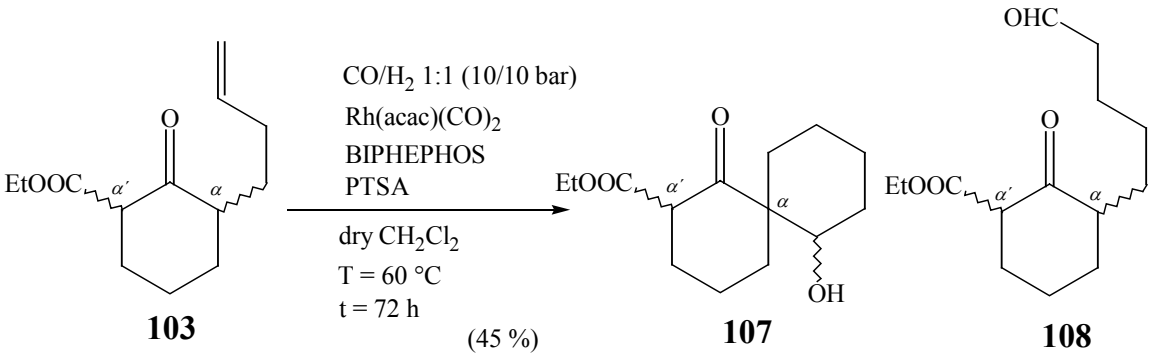
A: CO/H_2 20 bar (1:1), $Rh(acac)(CO)_2$, BIPHEPHOS, PTSA, dry CH_2Cl_2, T = 60 °C, t = 72 h

Scheme 44: Tandem hydroformylation/ aldol addition on ethyl 3-allyl-2-oxo-cyclohexane carboxylate (**102**).

Several interesting conclusion could be drawn from the results depicted in Scheme 44. Cycloalkanones bearing an ester function in α'-position and monosubstituted in α-position with an olefinic chain undergo intramolecular aldol addition to give the spiro compound **104**. As side products, minor amounts of fused compounds **105** and **106** are observed. Then, according to Hollmann's results[73], the α-position appears to be the most reactive if such site of the cycloalkanone is monosubstituted. Moreover, in contrast to the results obtained with the unsaturated 1,3-diester cycloalkanone **83b** (Scheme 37) and unsaturated α'-ester cycloalkanone **93** (Scheme 40), where only the aldol adduct is formed by the *iso*-isomer, regiocontrolled reaction towards the formation of *n*-aldehyde is accomplished.

b. Tandem hydroformylation/ aldol addition on ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate (103)

Continuing these investigations ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate (**103**) is hydroformylated in the presence of *p*-TsOH under mild conditions in a yield of 40 %. According to the latter results, the aldol addition occurs in α-position, resulting in the formation of ethyl 7-hydroxy-1-oxo-spiro[5.5]undecan-2-carboxylate (**107**). The formation of the spiro-compound **107** is accompanied by the linear aldehyde **108** as a mixture in a ratio of 1:1 (Scheme 45, R 60).



Scheme 45: Tandem hydroformylation/ aldol addition on ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate (**103**).

All the most significant results obtained under tandem hydroformylation/ aldol addition conditions are compiled in Table 13:

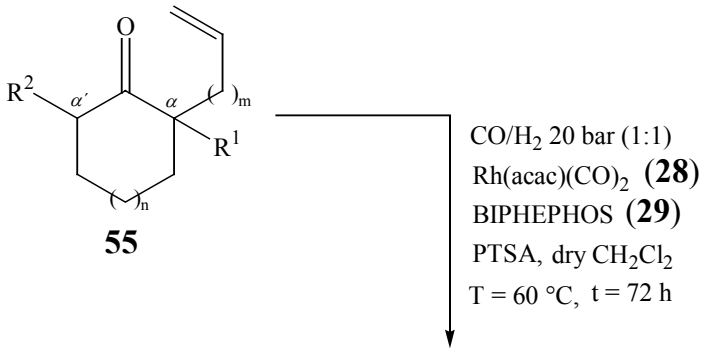
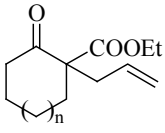
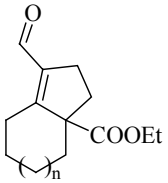
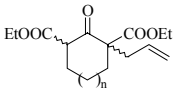
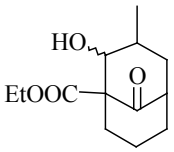
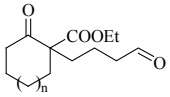
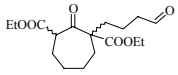
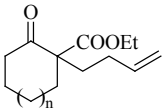
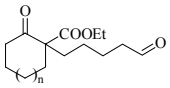
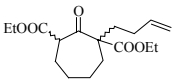
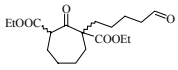
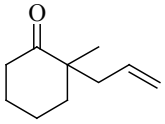
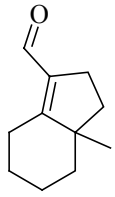
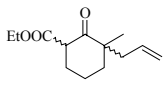
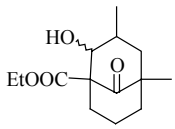
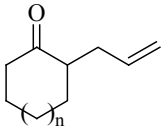
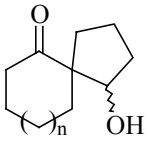
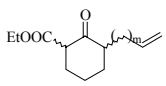
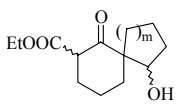


Table 13: Summary of tandem hydroformylation/ aldol addition results

R1	R2 = H				R2 = COOEt			
	m	n	Starting material	Product	m	n	Starting material	Product
COOEt	1	0 1	 **4a-e**	 **72a** (65 %) **72b** (79 %)[a]	1	1	 **83b,c**	 **85** (37 %)
		2 3 4		 **70c-d**		2		 **88** (98 %)
	2	0 1 2 4	 **68a-c,e**	 **71a-c,e**	2	2	 **84**	 **90** (90 %)
Me	1	1	 **92**	 **101** (93 %)	1	1	 **93**	 **97** (32 %)
H	1	0 1 3	 **47a-c**[c]	 **48a** (71%)[c] **48b** (51 %)[c] **48c** (61 %)[c]	1 2	1	 **102** **103**	 **104** (45 %) **107** (40 %)

( ) = Yield; a) Including amounts of the corresponding hydrogenated compound **76b**; b) Including amounts of the corresponding branched aldehydes **79a** (m = 2; n = 0) and **79b** (m = 2; n = 1) respectively; c) C. Hollmann results[73].

As it can be seen from Table 13 the results obtained under sequential hydroformylation/ aldol addition conditions could be ordered with regard to the substituent in α'- position:

1. When in α'- position R^2 = H:

- Fused aldol bicycles **72a,b** are formed when five-, six-membered rings bearing an allyl side chain are used, whereas larger rings proceed with high *n*-regioselectivity in the hydroformylation step, towards the formation of *n*-aldehydes **70c,d**.
- Increasing the chain length, no aldol adduct is observed regardless of the ring size; only linear aldehydes are isolated **71a-c,e**.
- Less bulky substituent in α-position such as a methyl group does not influence the chemoselectivity of the aldol reaction and again a fused aldol product like **101** is formed if 2-allyl-2-methyl-cyclohexanone is used.
- Cycloalkanones mono-substituted in α-position (Scheme 17), react through an aldol addition resulting in the formation of spiro-compounds **48a-c**.

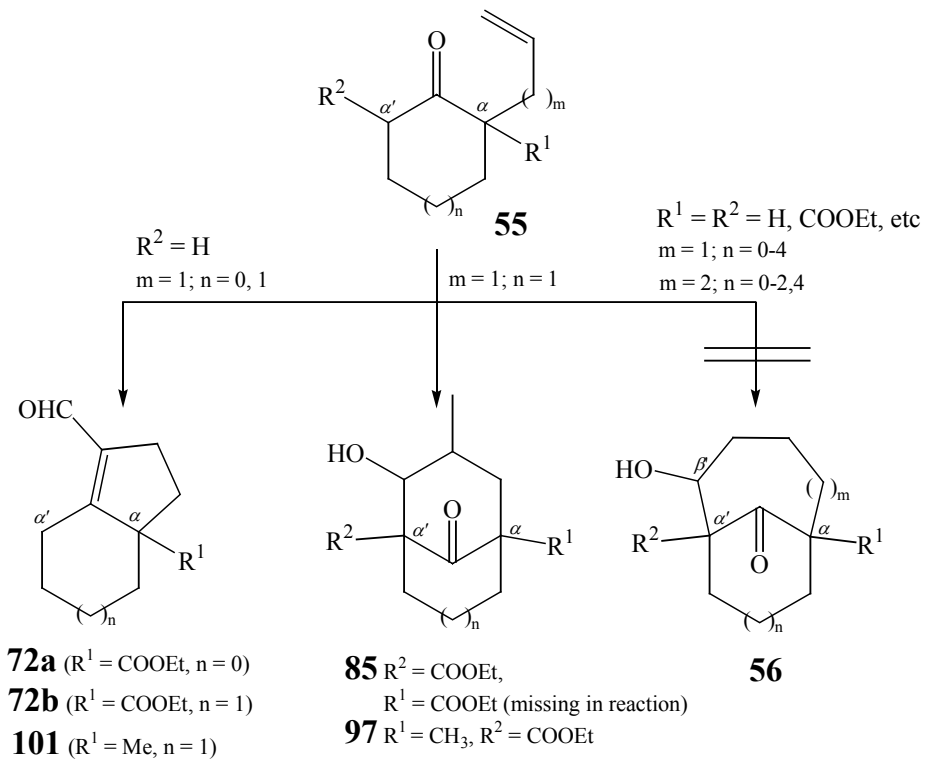
2. When in α'-position R^2 = COOEt:

- As the bridged bicyclo[3.3.1]nonane systems **85** and **97**, are formed regardless of the substituent in α-position (CH_3, COOEt) of the six-membered ring used; a loss of regioselectivity is observed in the hydroformylation step.
- No aldol adduct is formed starting from larger rings, instead, only linear aldehyde derivatives **88** and **90** are obtained.
- Spiro compounds **104** and **107** are formed if monosubstituted α-position cycloalkanones are converted[73].

2.5 Attempts of sequential hydroformylation/ Mukaiyama aldol addition of silyl enol ethers

2.5.1 Introduction

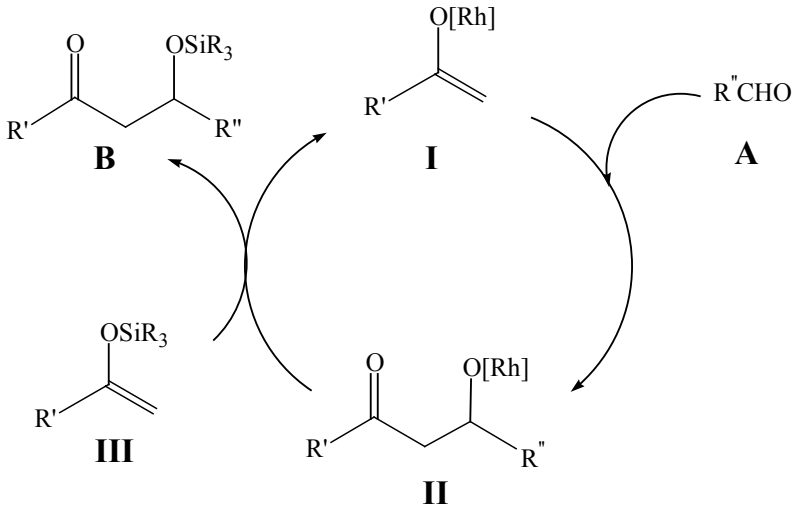
As it has been concluded from the results reported in the last section and depicted in Scheme 46, the sequential hydroformylation and acid–catalyzed aldol addition appears to be an effective method towards the preparation of fused aldol adducts like **72a,b** and **101** (Schemes 32 and 42) or bicycles such as **85** (Scheme 37) and **97** (Scheme 40). On the other hand, the procedure has proved to be less useful when the construction of bicyclic alkanones of type **56** is required. Therefore, investigations have to be conducted by performing an alternative activation of the carbonyl group.



Scheme 46: Cyclization obtained by tandem hydroformylation/ aldol addition.

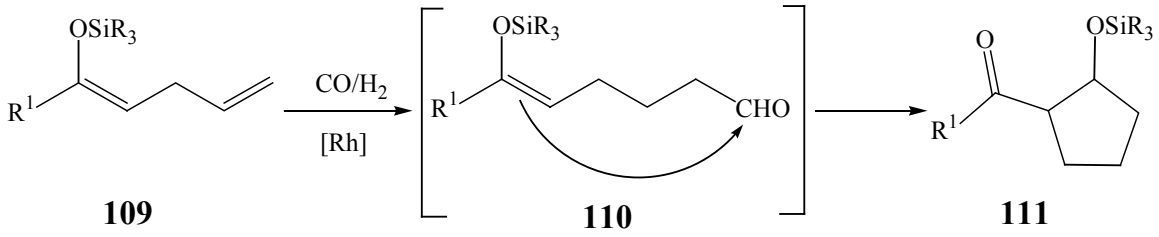
House and Mukaiyama published a general method to accomplish cross-aldol additions starting from silyl enol ethers of various carbonyl compounds, which react with aldehydes and ketones in the presence of titanium tetrachloride under mild conditions. Such silyl enol ethers possess significant nucleophilic character owing to electron

donation to the alkene π-system derived from resonance interaction with the oxygen ion pairs[110,111] and a high degree of chemoselectivity[112] could be achieved. Silyl enol ethers on one hand are reported to be stable against hydroformylation conditions[20] and directed aldol addition[113] can be catalyzed by a large number of transition metal complexes[71]. Rhodium (I) complex catalyzed reactions of enol-silanes **III** and aldehydes **A**, are investigated by Matsuda[88,114,115], Reetz[69] and Heathcock[67]; the latter showed in detail the catalytic mechanism using a rhodium complex (Scheme 47).



Scheme 47: Catalytic cyclic in the Rh-catalyzed aldol addition.

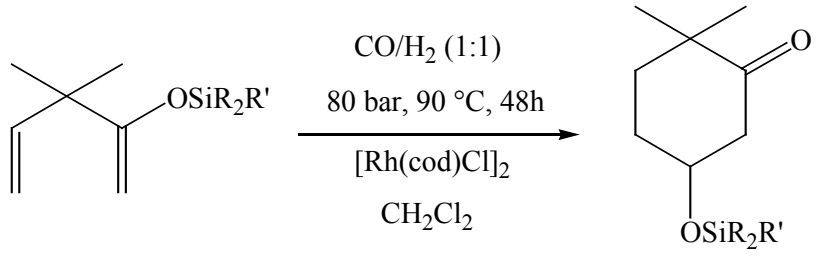
The aldehyde **A** reacts with the rhodium enolate **I** giving the rhodium aldolate **II**, successively through silyl transfer from the enolsilane **III** the final adduct **B** is formed. Following these observations, Eilbracht et al.[66] accomplished an intramolecular aldol addition of unsaturated silyl enol ethers under hydroformylation conditions in a one-pot procedure catalyzed by a rhodium (I) complex (Scheme 48). Sequential hydroformylation and intramolecular aldol addition of silyl enol ethers of type **109** bearing remote olefinic functionalities give β-silyloxy substituted cyclic ketones of type **111** (Scheme 48).



109 **110** **111**

Scheme 48: Tandem hydroformylation/ Mukaiyama aldol reaction of silyl enol ethers.

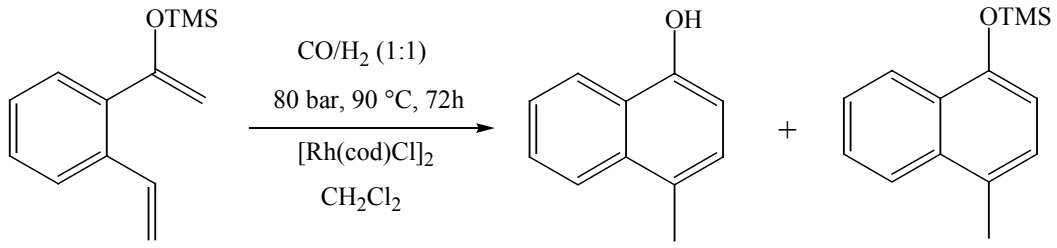
In previous investigations using $[Rh(cod)Cl]_2$ (**41**) as catalyst[66], starting from unsaturated silyl enol ethers of type **112** six-membered rings of type **113**, as depicted in Scheme 49, by converting only one of the two different double bonds are obtained.



112 **113**

Scheme 49: Silyl enol ether in intramolecular aldol addition.

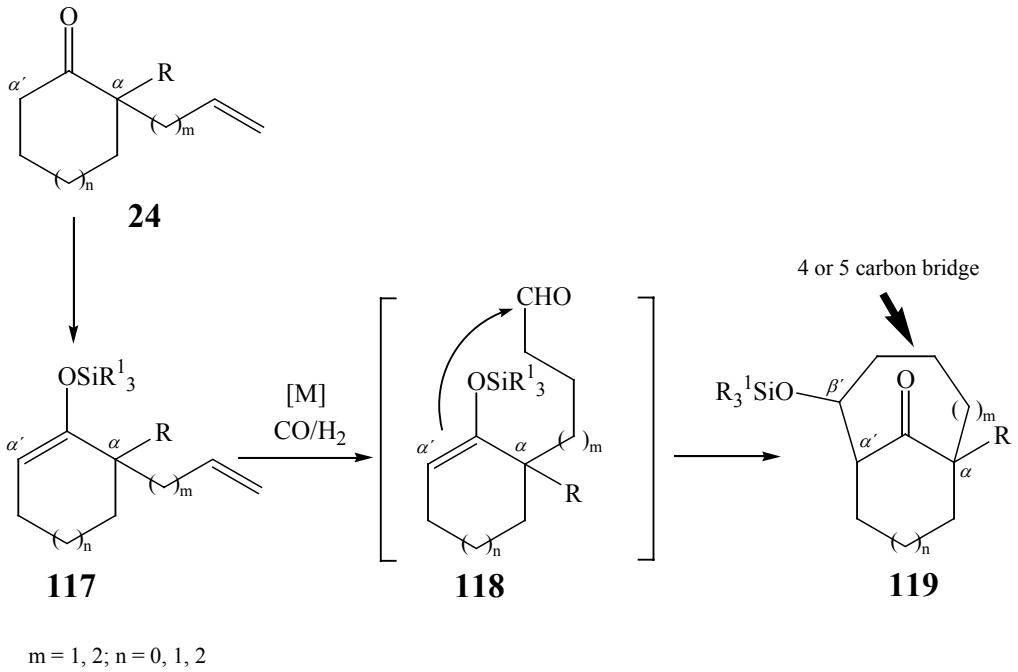
The overall procedure described above can be used for completely different substrates such as the unsaturated enol silane **114** to give naphthol derivatives **115** and **116** (Scheme 50). In this case the intermediate product undergoes desilylation and dehydration followed by tautomerisation of the enone form to the more stable derivatives **115** and **116**.



114 **115** (37 %) **116** (17 %)

Scheme 50: Intramolecular aldol addition of trimethylsilyl enol ether **114**.

To investigate this procedure a number of enolsilane of cycloalkanones of type **24** (**4a,b** with R = COOEt; m = 1; n = 0, 1; or **68a-c** with R = COOEt; m = 2; n = 0, 1, 2) were used to study the one-pot hydroformylation/ aldol addition have been prepared and exposed to the hydroformylation conditions (Scheme 51).



Scheme 51: Tandem hydroformylation/ aldol addition of silyl enol ether compounds of type **117**.

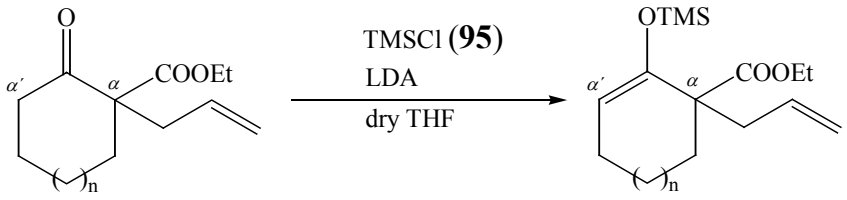
2.5.2 Attempts of rhodium-catalyzed Mukaiyama aldol addition

a. Preparation of TMSilyl enol ethers of ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a,b)

Denmark's investigations[116] showed the high efficiency of the aldol addition chemistry of trichlorosilyl enolates and trimethylsilyl enolates derived from ketones. They are effective aldol reagents in the absence of additives, reacting with aldehydes at ambient temperature to provide high yields of aldol adduct. A general preparative method for the synthesis of silyl enol ethers involved preliminary treatment of ketones with bases of sufficient strength to convert the ketones completely into their enolate anions. Subsequent reaction of the enolate anion(s) with excess of trimethylsilyl chloride produces the O-silylated product. The preparation of enolates of unsymmetrical ketones

of type **117** (Scheme 51) could be achieved by controlling the reaction conditions. House and co-workers[100] report silyl-enol ethers, under kinetic control, are very selectively formed from ketones by using first lithium diisopropylamide to generate the lithium enolate and then O-silylating with chlorotrimethylsilane. Paterson and al.[103] found that the method could be improved by generating the lithium enolate at -78 °C and by avoiding the aqueous work-up giving high yields and regioselectivities. House et al. found that silyl enol ethers, under thermodynamic control, are best prepared by equilibrating the mixture of silyl enolates formed by treating the ketone with triethylamine and chlorotrimethylsilane in dimethylformamide. The equilibration is done simply by heating the reaction mixture under reflux for hours or days.

Following these observations and taking into account the investigations proposed here, applying House's procedure[100] silyl enol ethers **120a,b** (Scheme 52) of type **117** (Scheme 51) are synthesized in the presence of trialkylsilane such as chloro trimethylsilane (TMSCl) (**95**) under kinetic control at -78 °C for 4 hours. The results are listed in Table 14.



4a,b (n = 0, 1) **120a,b**

Scheme 52: Preparation of trimethylsilyl enol ethers **120a,b** from ethyl 1-allyl-2-oxo-cycloalkane carboxylates (**4a,b**).

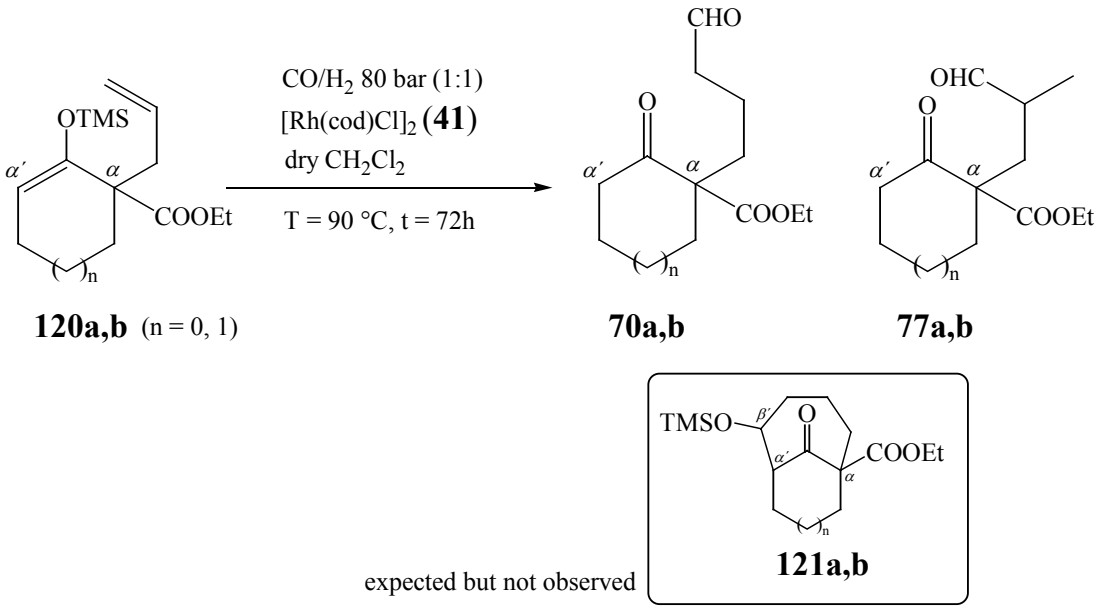
Table 14**:** Preparation of trimethylsilyl enol ethers **120a,b**

Reaction	n	Starting Mat.	Product	Yields %
R 61	0	**4a**	**120a**	96
R 62	1	**4b**	**120b**	91

Both the compounds are obtained in high yield after filtration of LiCl salts through a short pad of neutral alumina (R 61 and R 62).

b Hydroformylation of α´,β- unsaturated silyl enol ethers (120a,b)

In order to evaluate the behavior of these silyl enol ethers towards the Mukaiyama aldol addition, the compounds **120a,b** are subjected to the standard conditions, previously optimized[66] (Scheme 49 and 50). The reactions are carried out in the presence of $[Rh(cod)Cl]_2$[117] (**41**) as catalyst species under 80 bar of syn-gas pressure CO/H_2 (1:1) at 90 °C for 3 days (Scheme 53). After filtration on a short pad of alumina, which is used as standard neutral work up which can avoid any type of decomposition such as desilylation or retro-aldol reaction, the crude reaction mixture is analyzed. In contrast to the preliminary results upon these conditions, the aldol addition does not take place and a mixture of linear aldehydes **70a,b** and branched ones **77a,b** is obtained in high yield (Table 15, R 63 and R 64).



Scheme 53: Tandem hydroformylation/ Mukaiyama addition on **120a,b**.

Table 15: Tandem hydrofromylation/ aldol addition of silyl enol ethers **120a,b**

Reaction	n	Starting Mat.	Product		Yields %
R 63	0	**120a**	**70a** (22)[a]	**77a** (1)[a]	95
R 64	1	**120b**	**70b** (8)[a]	**77b** (1)[a]	90

Conditions: 1 % - mol $[Rh(cod)Cl]_2$, DCM, T = 90 °C, t = 72 h a) by ^{1}H-NMR analysis.

The results show that the trimethylsilyl enol ether is too labile under these hydroformylation conditions and consequentially the formation of rhodium enolate

cannot take place. The King and Iqbal[118] infrared spectroscopic investigations on the alkylrhodium tetracarbonyl derivatives could be useful to explain the loss of the TMSilyl group: here at elevated pressures the $[Rh(CO)_2Cl_2]$ and the ethene, HCl is formed (Scheme 54).

$$[Rh(CO)_2Cl]_2 + 4CO + 2H_2 + 2C_2H_4 \longrightarrow 2C_2H_5Rh(CO)_4 + 2HCl$$

Scheme 54: King and Iqbal investigations on the alkylrhodium tetracarbonyl derivatives.

Similarly, $[Rh(cod)Cl]_2$ (**41**) under the sequential hydroformylation/ Mukaiyama addition conditions could generate the tetracarbonylrhodium hydride (**123**) (Scheme 55) species with formation of HCl, as well as the previous $[Rh(CO)_2Cl_2]$, which is able to remove the trimethylsilyloxy function.

$$\underset{\mathbf{41}}{[Rh(cod)Cl]_2} \xrightarrow[-(cod)]{CO} \underset{\mathbf{122}}{[Rh(CO)_2Cl]_2} \xrightarrow[-HCl]{CO/H_2} \underset{\mathbf{123}}{HRh(CO)_4}$$

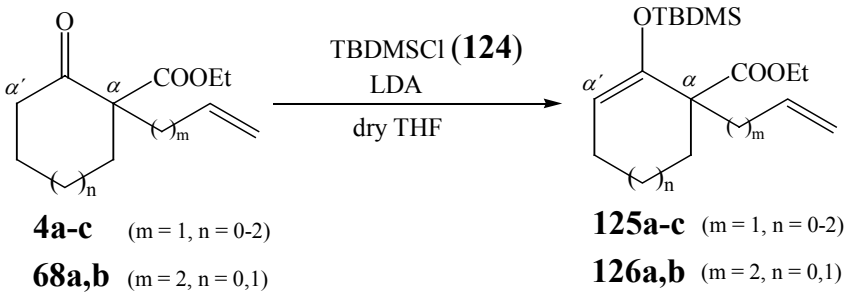
Scheme 55: Generation of the tetracarbonylrhodium hydride (**123**).

From these observations, it could be concluded that a preparation of more stable silyl enol ether or the change of the catalyst species has to be accomplished.

b. Preparation of TBDMSilyl enol ethers of ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates (125a-c and 126a,b)

To overcome the problems described above, more stable silyl ethers[119] such as *tert*-butyldimethylsilyl enol ethers are found to be more stable to hydrolysis than trimethylsilyl enol ethers by a rate factor of 10^4 and they are compatible with a much wider range of reagents used in organic synthesis. Therefore, under the conditions applied for the preparation of TMSilyl-enol the reactions of compounds **4a-c** with chloro *tert*-butyldimethlysilane (**124**) (TBDMSCl) proceeds with good yields (Scheme 56) into the silyl compounds **125a,c** (Table 16, R 65-67). Besides these allyl silyl-enol

ethers, homoallyl cycloalkanones **68a,b** were used to form the corresponding TBDMSilyl enol ethers **126a,b** in high yields (Table 16, R 68-69).



4a-c (m = 1, n = 0-2)
68a,b (m = 2, n = 0,1)

125a-c (m = 1, n = 0-2)
126a,b (m = 2, n = 0,1)

Scheme 56: Preparation of *tert*-butyldimethylsilyl enol ethers from ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates (**4a-c**) and (**68a,b**).

Table 16**:** Preparation of *tert*-butyldimethylsilyl enol ethers **125a-c** and **126a,b**

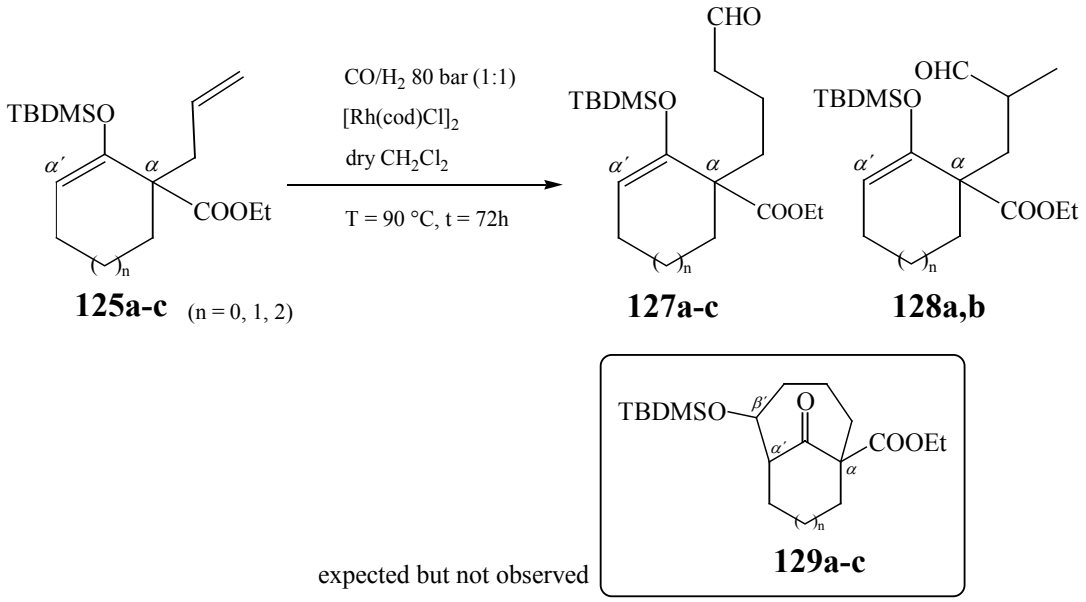
Reaction	m	n	Starting Mat.	Product	Yields %
R 65	1	0	**4a**	**125a**	90
R 66	1	1	**4b**	**125b**	73
R 67	1	2	**4c**	**125c**	85
R 68	2	0	**68a**	**126a**	98
R 69	2	1	**68b**	**126b**	96

c. Attempts of tandem hydroformylation/ Mukaiyama aldol addition of allylated TBDMSilyl enol ethers (125a-c)

All these silyl enol ethers **125a-c** and **126a,b** (from Scheme 56) have to be hydroformylated under standard conditions to evaluate the behavior of these compounds towards the Mukaiyama aldol addition.

Similar results to TMSilyl-enol ethers (Scheme 53) are observed upon filtration of the crude reaction mixture through a small pad of alumina. Indeed, if compounds **125a-c** (Scheme 57) are treated with 1 mol % of $[Rh(cod)Cl]_2$ under 80 bar of CO/H_2 at 90 °C for 2 days. Only a mixture of linear aldehyde **127a,b** and branched isomers **128a,b** is obtained in high yield (Table 17, R 70 and 71), whereas the reaction starting from compound **125c** proceeds with high regioselectivity towards the *n*-aldehyde **127c** but

with drastically lower yield (Table 17, R 72). Again no Mukaiyama aldol adducts (**129a-c**) are obtained but here the TBDMSilyl function is maintained whereas the TMS group is lost as shown in Scheme 53.



Scheme 57: Tandem hydroformylation/ Mukaiyama cyclization of TBDMSilyl enol ethers **125a-c**.

Table 17: Tandem hydroformylation/ Mukaiyama addition of silyl enol ethers **125a-c**

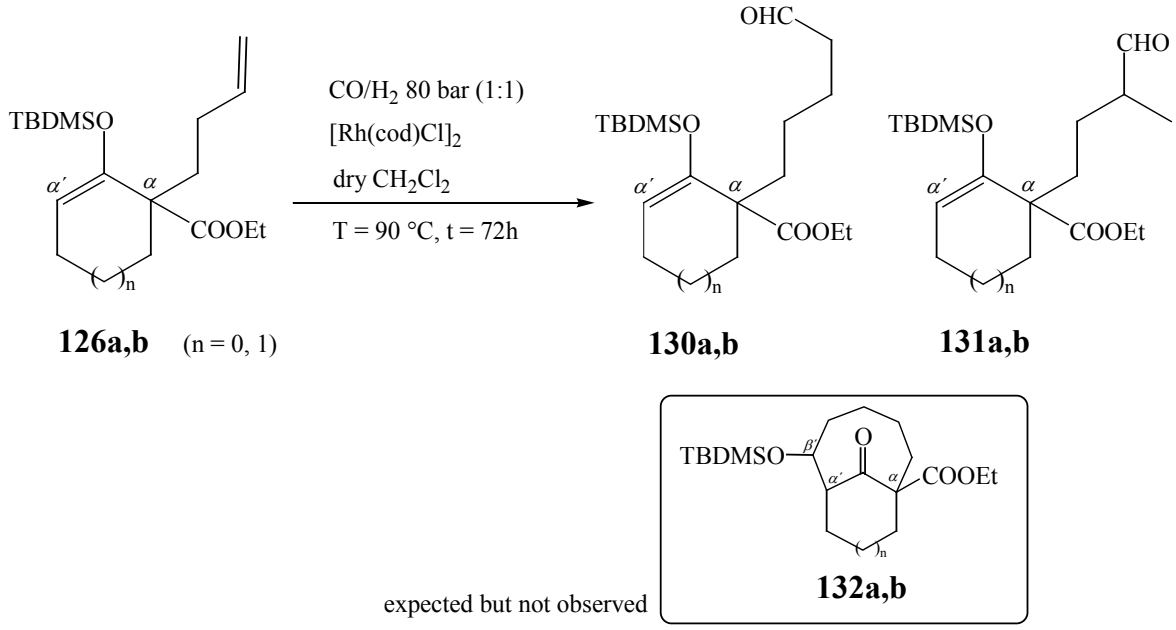
Reaction	n	Starting Mat.	Product		Yields %
R 70	0	**125a**	**127a** (1.2)[a]	**128a** (1)[a]	94
R 71	1	**125b**	**127b** (1.5)[a]	**128b** (1)[a]	92
R 72	2	**125c**	**127c**	--	23

Reaction conditions: 1 % - mol $[Rh(cod)Cl]_2$, CO/H_2 80 bar (1:1), dry DCM, T = 90 °C, t = 72 h; a) by ^{1}H-NMR analysis.

d. Attempt of tandem hydroformylation/ Mukaiyama aldol addition of homoallylated TBDMSilyl enol ethers (126a,b).

Upon the previous reaction conditions, the homoallylated TBDMSilyl enol ethers **126a,b** with 5 and 6 membered ring are tested. Although a more stable silyloxy function is employed under these reaction conditions, again no Mukaiyama aldol adduct products like **132a,b** are detected. The **126a,b** do not undergo aldol addition and again a mixture of *n*-aldehydes **130a,b** and *iso*-isomers **131a,b** of the remote double

bond is generated in the hydroformylation step (Scheme 58). The results are summarized in Table 18.



Scheme 58: Attempted tandem hydroformylation/ aldol addition, under Mukaiyama conditions, of compounds **126a,b**.

Table 18: Attempted tandem hydroformylation/ aldol addition of compounds **126a,b** under Mukaiyama conditions

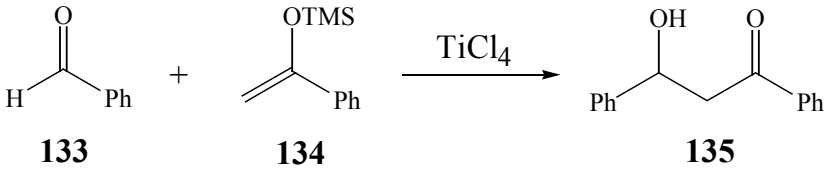
Reaction	n	Starting Mat.	Product		Yields %
R 73	0	**126a**	**130a** (7)[a]	**131a** (1)[a]	75
R 74	1	**126b**	**130b** (4.5)[a]	**131b** (1)[a]	85

Reaction conditions: 1 % - mol $[Rh(cod)Cl]_2$, CO/H_2 80 bar (1:1), dry DCM, T = 90 °C, t = 72 h; a) ^{1}H-NMR analysis.

Based on all these negative results, the cyclization via silyl-enol ether should be performed via stepwise procedure by the use of Lewis acids[120].

2.5.3 Enol ethers in the stepwise hydroformylation/ aldol cyclization under Mukaiyama conditions

As mentioned in the introduction, Mukaiyama[115,121] and shortly thereafter House[122], published a general method to accomplish cross-aldol addition starting from silyl enol ethers of various carbonyl compounds which could react with aldehydes and ketones in the presence of titanium tetrachloride under mild conditions. Titanium tetrachloride is found to generate the active eletrophilic species as results of its strong interaction with carbonyl compounds, and the complex thus formed would react easily even with relatively weak carbon nucleophiles (such as enol ethers)[123].

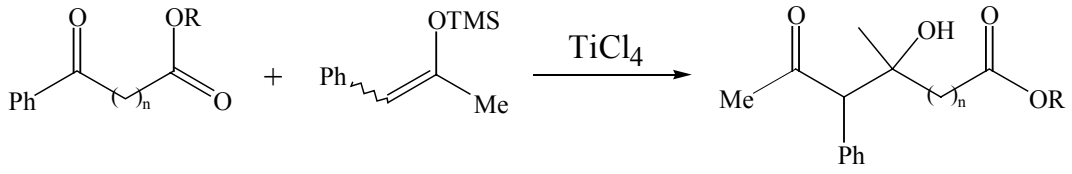


133 **134** **135**

Scheme 59: Aldol addition in the presence of $TiCl_4$.

As depicted in Scheme 59, the aldol reaction between silyl enol ether of acetophenone **134** and benzaldehyde **133** in the presence of titanium(IV)tetrachloride afforded the aldol product **135** in high yields[115,121]. Further studies of this reaction reveal a number of advantages over conventional methods. First, it not only gives a variety of aldol adducts in high yield but also a regioselective aldol adduct when the silyl enol ether of an unsymmetrical ketone is used. That is, the aldol reaction proceeds with retention of the regiochemical integrity of the starting silyl enol ethers to afford the corresponding aldol regiospecifically. Starting silyl enol ethers **136** can be conventionally prepared regioselectively under kinetical or thermodynamical control. Second, functional group selectivity is observed i.e. reactions with aldehydes proceeds at -78 °C whereas those with ketones proceed at elevated temperatures (ca 0 °C). Chemoselectivity is observed with acceptors having two different kinds of carbonyl function, for example aldehyde and ketone or ester, in the same molecule.

Ketoester **136** and silyl enol ether **137** give the hydroxyketoester **138** as sole product[124] (Scheme 60).

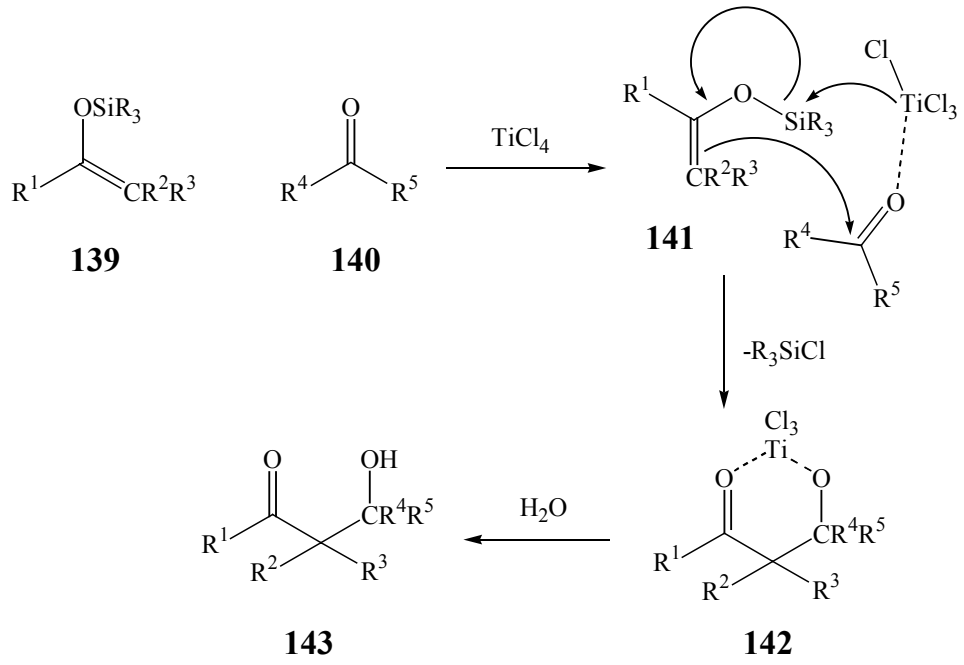


136 **137** **138**

n = 0, 2, 3
R = Me, Et

Scheme 60: Chemoselectivity of aldol addition when keto esters of type **136** and $TiCl_4$ are used.

A direct aldol reaction between two ketones affords thermodynamically unfavourable aldols in high yields due to of stabilization of the aldol adducts intramolecular chelation of type **142** with titanium (Scheme 61).

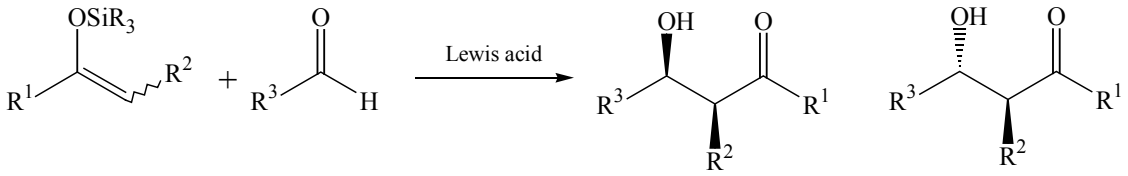


139 **140** **141** **142** **143**

Scheme 61: The step-wise Mukaiyama aldol addition reaction of enolsilanes of type **139** with aldehydes or ketones.

From mechanistic aspects, silyl enol ethers of type **139** could readily attack a carbonyl compound like **140** activated by titanium tetrachloride in a nucleophilic fashion to form trimethylsilyl chloride and an intermediate chelate of type **142.** Hydrolysis of this intermediate should then afford aldol of type **143**. Despite its remarkable power as a

method for carbon-carbon bond formation, the level and sense of its stereoselectivity often vary. The *syn*/*anti* ratio for the aldol products **146** and/or **147** (Scheme 62) is affected by the stereochemistry of the aldehyde and silyl enolate, and the character of the Lewis acid catalyst[125]. However the stereochemical observations have been rationalized by considering an acyclic transition state[126].

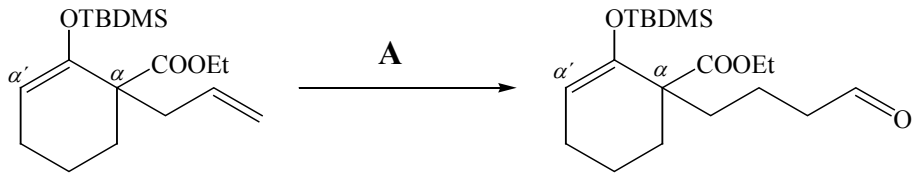


144 **145** **146** (*syn*) **147** (*anti*)

Scheme 62: Lewis acid-catalyzed aldol reaction of silicon enolates.

a. Preparation of ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(4-oxo-butyl)-cyclohex-2-ene-carboxylate (127b)

For initial investigations on the formation of bridged systems, the hydroformylation of the unsaturated silyl enol ether **125b** is performed with a catalytic amount of $Rh(acac)(CO)_2$ (**28**) in CH_2Cl_2 under 20 bar of CO/H_2 at 60 °C. The regioselectivity of the reaction is successfully achieved by use of 5 mol % of BIPHEPHOS (**29**) giving exclusively the *n*-aldehyde **127b** in 88 % of yield (Scheme 63, R 75).



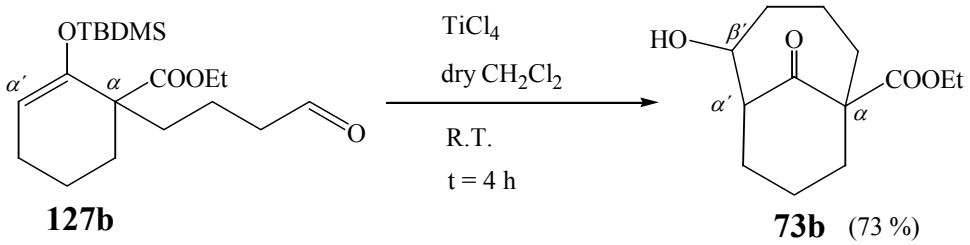
125b **127b** (88%)

A: $Rh(acac)(CO)_2$, CO/H_2 20 bar (1:1), BIPHEPHOS, dry DCM, T = 60 °C, t = 48 h

Scheme 63: Synthesis of ethyl 2-(tert-butyl-dimethyl-silanyloxy)-1-(4-oxo-butyl)-cyclohex-2-ene-carboxylate (**127b**).

b. Intramolecular aldol addition catalyzed by $TiCl_4$: synthesis of ethyl 5-hydroxy-10-oxo-bicyclo[4.3.1]decane-1-carboxylate (73b)

As stated in the introduction under mild conditions ($TiCl_4$, DCM at room temperature) cross-aldol addition could be performed in good yields[121,127]. According to these observations, the reaction on **127b** compound proceeds with retention of regiochemical integrity of the starting silyl enol ethers[121] to afford the corresponding crossed aldol **73b** in 73 % yield (Scheme 64).



127b **73b** (73 %)

Scheme 64: Synthesis of ethyl 5-hydroxy-10-oxo-bicyclo[4.3.1]decane-1-carboxylate (**73b**).

The different outcome of the attempts to perform one-pot hydroformylation/ Mukaiyama aldol additions could be explained according to the Bouillon's investigations[128]. Indeed, in the intramolecular aldol reaction of silyl enol ether of type **127b** (Scheme 64), the Lewis acid could catalyze the reaction decreasing the intermediate energetic barrier.

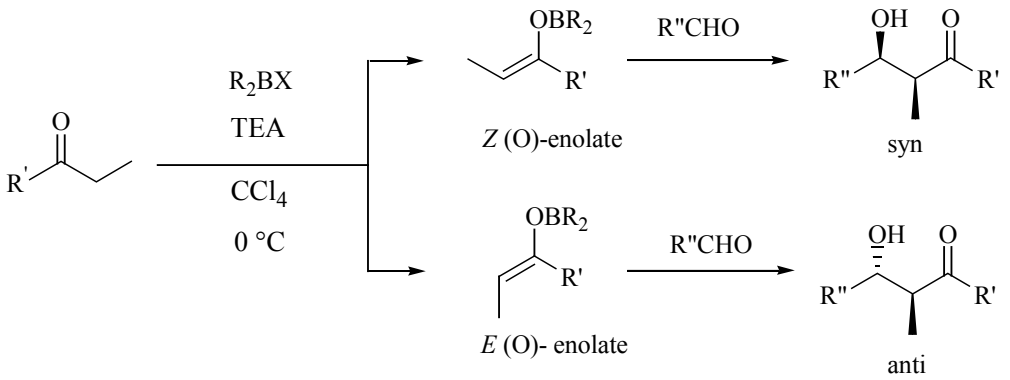
2.6 Sequential enolboration/ hydroformylation/ aldol addition reactions

2.6.1 Introduction

Efforts towards the synthesis of bridged bicycles of type **56** with various ring sizes (Scheme 46) *via* intramolecular regio- and chemoselective aldol processes followed by a regioselective *n*-hydroformylation in a one-pot reaction failed although silyl enol ethers via Mukaiyama conditions were employed (previous chapter). Thus, continuing the investigations of C–C bond forming reactions under the conditions of Rh-catalysed hydroformylation, other methods starting with activated enolates will be considered.

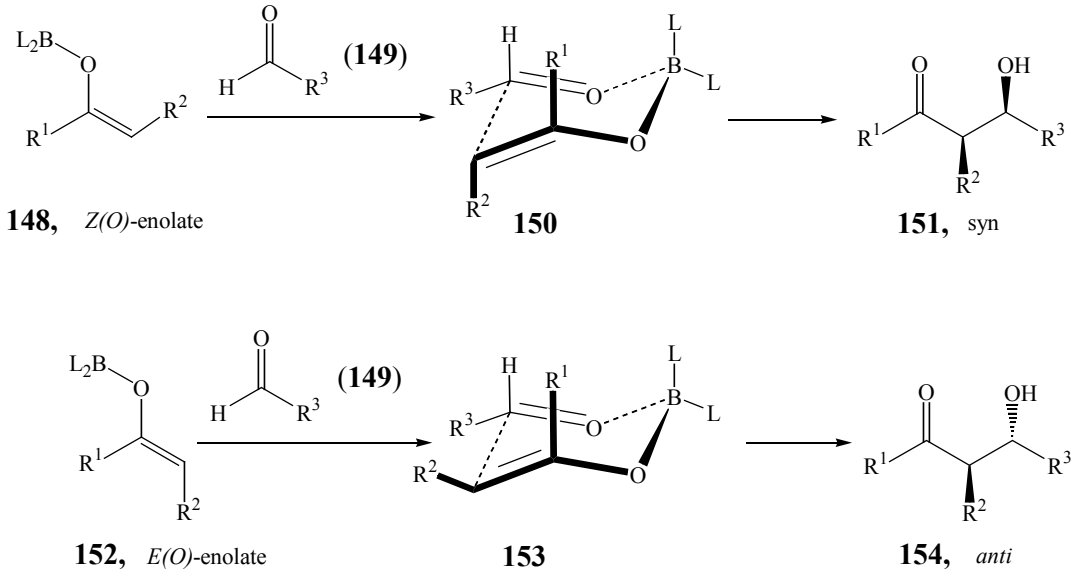
Boron enolates are highly versatile intermediates in organic synthesis[129] and because of their high reactivity they are used as important intermediates in organic synthesis[130,131]. Direct generation of these species from carbonyl compounds could be useful for expanding the synthetic utility of boron enolates–mediated aldol reaction. One of the methodologies towards the preparation of boron enolates involves the reaction of ketones with a suitable organoboron derivative, R_2BX in the presence of a suitable tertiary amine (Scheme 65). It has been thought that increasing the Lewis acidity of boron by introducing an excellent leaving group on the boron would result in an increase in acidity of the carbonyl compounds by coordination of a carbonyl group to the boron compound. The corresponding boron enolate would be formed by abstraction of the α-proton of the carbonyl compound with a weak base such as a tertiary amine of variable steric requirements. Ganesanet et al.[132] in a study of the effects of amine, solvent, concentration, temperature and other reaction parameters controlling the enolate geometry observed the interaction of tertiary amines of variable steric requirements with R_2BX such as dicyclohexylchloroborane (*cy*-hex)$_2$BC1 (**159**) (Figure 8). The results suggest that the smaller amines coordinate strongly with (*cy*-hex)$_2$BC1 while the more bulky amines do not. These amines have also been examined for the enolboration in order to understand the effect of the steric requirements of the amine on the enolate geometry. While the smaller amines favor formation of *E(O)*-boron enolate, the more hindered amines favor formation of the isomeric *Z(O)*-boron enolate. Triethylamine could be chosen as one of the best amines in terms of yield and selectivity. In addition, Evans[133] has systematically studied the aldol stereoselection of

boron enolates and established that *Z(O)*-boron enolates give *syn* aldols and *E(O)*-boron enolates give *anti* aldols stereoselectively (Scheme 65).



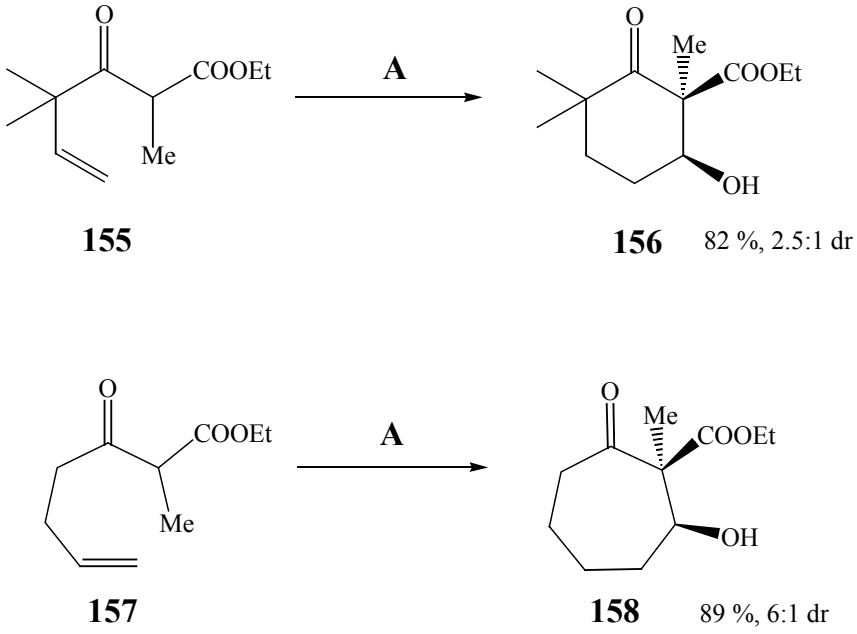
Scheme 65: Aldol stereoselection of boron enolates.

The boron enolate-mediated aldol addition proceeds via a more rigid chair-like six-membered transition state than those of alkali metal enolate, because of a shorter bond length between boron and oxygen (Scheme 66). That is, dialkylboron enolates have relatively short metal-ligand and metal-oxygen bonds, which are suited to maximizing 1,3-diaxal (R^3-L) interaction *syn* the transition state. This facilitates the formation of more stable transition state (**150** and **153**), where R^3 occupies a pseudo equatorial position, when vinyloxyboranes (**148** and **152**) react with aldehydes to afford aldol adducts (**151** and **154**).



Scheme 66: Stereoselection aldol addition of *Z(O)* or *E(O)*-boron enolates and aldehydes.

Keränen's previous investigations[134] concerning the sequential enolboration/ hydroformylation/ aldol addition (Scheme 67) with unsaturated ketoesters suggest that the (*cy*-hex)$_2$BC1 (**159**) (Figure 8) is a an effective enolborane[132,135] precursor and triethylamine (TEA)[132] is a good tertiary amine in the boron enolates formation.



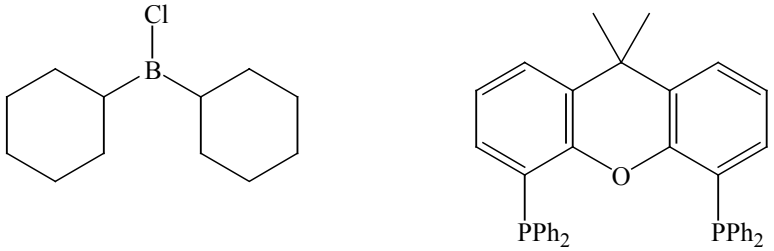
A: 1.05 eq. (cy-hex)$_2$BCl, 1.05 eq. TEA, 0 °C, 0.9 mol % Rh(acac)(CO)$_2$, 1.8 mol % XANTPHOS, 16 h, 60 bar CO/H$_2$

Scheme 67: Synthesis of 6- and 7-membered ring carbocycles **156** and **158** from ketoesters **155** and **157**.

The generation of 6- and 7-membered ring carbocycles like **156** and **158** was attempted by applying the ketoesters **155** and **157**. In the case of **155**, the desired cyclization product ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexane carboxylate (**156**) was obtained in 82 % isolated yield as a 2.5:1 mixture of diastereoisomers. Another encouraging result was obtained when ketoester **157** if subjected to the same conditions, resulting in the formation of the 7-membered ring of methyl 2-hydroxy-1-methyl-7-oxocycloheptane carboxylate (**158**) as the sole product in 89 % yield as a 6:1 mixture of diastereoisomers (Scheme 67). Notably, the boron enolate tolerates the hydroformylation conditions and reacts immediately with the aldehyde group, thus preventing unwanted side reactions.

Moreover, when ligands are required to accomplish a regioselective hydroformylation reaction, the process tends to favor the use of the diphosphine XANTPHOS

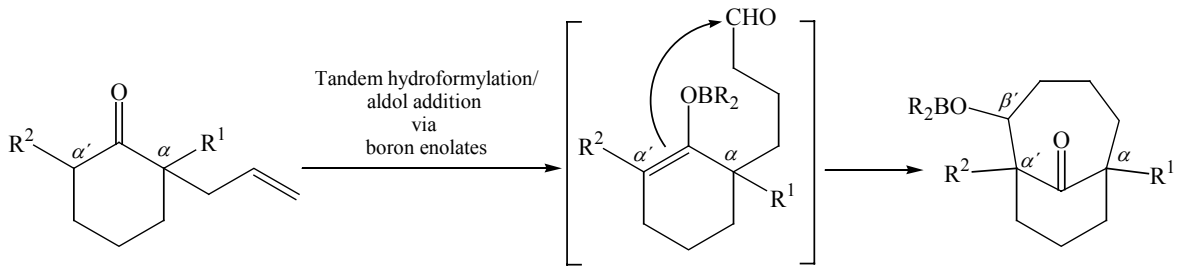
(**160**)[44,136,40] (Figure 8) as bidentate ligand to afford the *n*-aldehyde allowing higher temperatures than those tolerated by BIPHEPHOS (**29**).



159 **160**

Figure 8: (*cy*-hex)$_2$BC1 (**159**) and XANTPHOS (**160**) molecular structures.

The suitability of this method to form functionalized *β*-hydroxycycloalkanones bearing α-quaternary centres in high yields and good diastereoselectivities is particularly attractive in the synthesis of some natural cyclic compounds. Thus, unsaturated cycloalkanones of type **161** (Scheme 68) undergo tandem hydroformylation/ aldol addition via in situ generated boron enolates in the presence of 1 mol % of Rh(acac)(CO)$_2$ (**28**), 1.8 mol % XANTPHOS (**160**), (*cy*-hex)$_2$BCl/ TEA in DCM[134].



161 **162** **163**

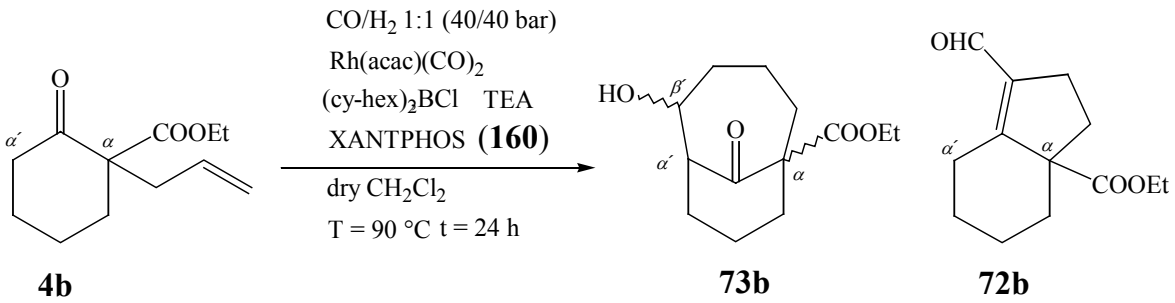
$R^1 = R^2$ = COOEt, Me, H, etc

Scheme 68: Boron enolates of 2-allyl-cyclohexanone derivatives of type **161** towards the formation of bridged compounds of type **163**.

a. Conversion of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (4b)

Starting to test the methodology on the unsaturated cycloalkanones, the ethyl 1-allyl-2-oxo-cyclohexanone carboxylate (**4b**) boron enolate is in situ generated smoothly by treating of cycloalkanone with NEt_3 as base, and (*cy*-hex)$_2$BCl at 0°C, under argon atmosphere (Scheme 69, R 77). After approximately 40 minutes Rh-catalyst is added

and the reaction is carried out under 80 bar of CO/ H_2 (1:1) for 24 hours at 90°C. The oxidative work-up[137] of crude mixture, consistent of boron chelate and ammonium salts and working under neutral conditions, aldol adducts are isolated. The regulation of the pH by using a pH 7 phosphate buffer is necessary to avoid the retro-aldol products. The results showed in a different chemoselectivity observed when the same starting materials undergo one-pot hydroformylation/ aldol addition under acidic conditions (Scheme 32). A mixture of bridged bicycle **73b** and trace of fused unsaturated bicycle **72b** is obtained.

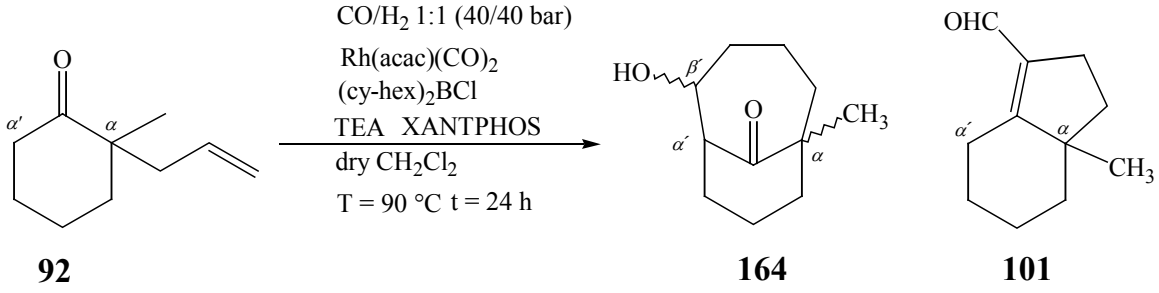


Scheme 69: Tandem hydroformylation/ aldol addition via *in situ* generated boron enol ether of ethyl 1-allyl-2-oxo-cyclohexanone carboxylate (**4b**).

In contrast with the results observed under tandem hydroformylation and acid-catalyzed aldol addition where the fused bridged compound **72b** is the only product (Scheme 32), a bridged system **73b** in the aldol addition is observed. The result confirmed the highly efficient formation of the enol borane of compound **4b** to activate the α'-position in absence of any auxiliary activating group.

b. Conversion of 2-allyl-2-methyl-cyclohexanone (92)

Proceeding with unsaturated cycloalkanones, the 2-allyl-2-methyl-cyclohexanone (**92**) is investigated (Scheme 70, R 78). When exposing **92** to the previous reaction conditions, the compound reacts through an aldol addition resulting in the formation of bridged β-hydroxy ketone **164** (as main product) and **101** in a ratio of 9:1. While via sequential hydroformylation/ aldol addition acid catalyzed (Scheme 42) the formation of the compound **101** was observed as the sole product, under these conditions a reverse of chemoselectivity is obtained.



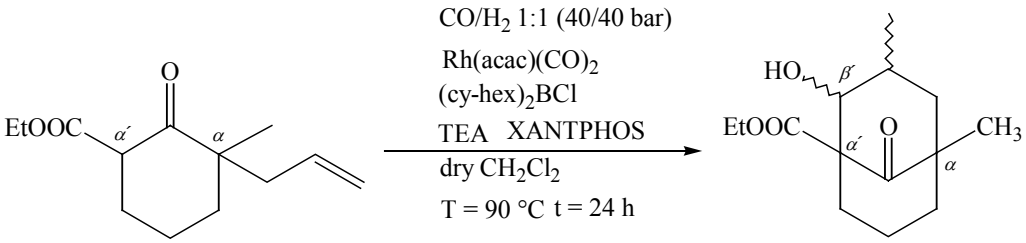
92 **164** **101**

Scheme 70: Tandem hydroformylation/ aldol addition via in situ generated borane-enol ether of 2-allyl-2-methyl-cyclohexanone (**92**).

c. Conversion of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

Next, the generation of bridged system was attempted with the conversion of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**) (Scheme 71, R 79). When subjected to the reaction sequence, bridged *β*-hydroxy ketone **97** as the sole product in 46 % yield is obtained.

As it can be observed, as well as under one-pot acid catalyzed reaction (Scheme 40) once again the regioselectivity of the hydroformylation is influenced of the presence of ester function in *α'*-position and the formation of 6-membered ring is favored.



93 **97**

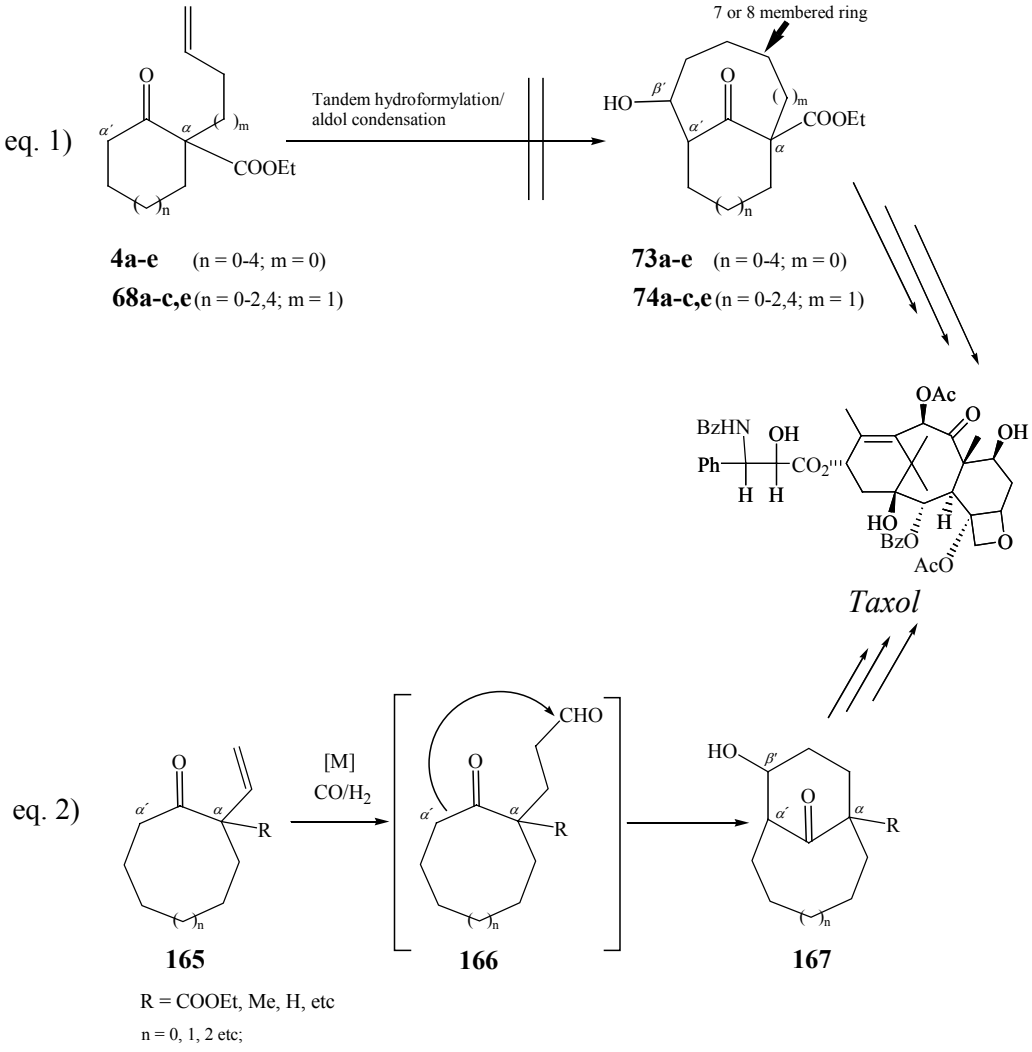
Scheme 71: Tandem hydroformylation/aldol addition via in situ generated borane-enol ether of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**).

Thus, the one-pot enolboration/ hydroformylation/aldol addition reaction demonstrate its utility in the regio- and chemoselective synthesis of bridged bicyclic compounds bearing functionalised substituents starting from easily available cyclolakanones.

2.7 Tricyclic compound via Michael addition/ aldol reactions

2.7.1 Introduction

Many diverse and biologically important natural products like Taxol (Figure 1 or Scheme 72) embody the bicyclo[5.3.1]undecane ring system as the core carbocyclic sub-unit[7]. As reported in the last sections in Scheme 32 and Scheme 33, and summarized here in Scheme 72 (eq. 1), every attempt to accomplish the formation of bicycles like **73a-e** (m = 0; n = 0-4) or **74a-c,e** (m = 1; n = 0-4) failed if the sequential hydroformylation/ aldol addition was performed starting from cycloalkanones bearing an allylic or homoallylic side chain.



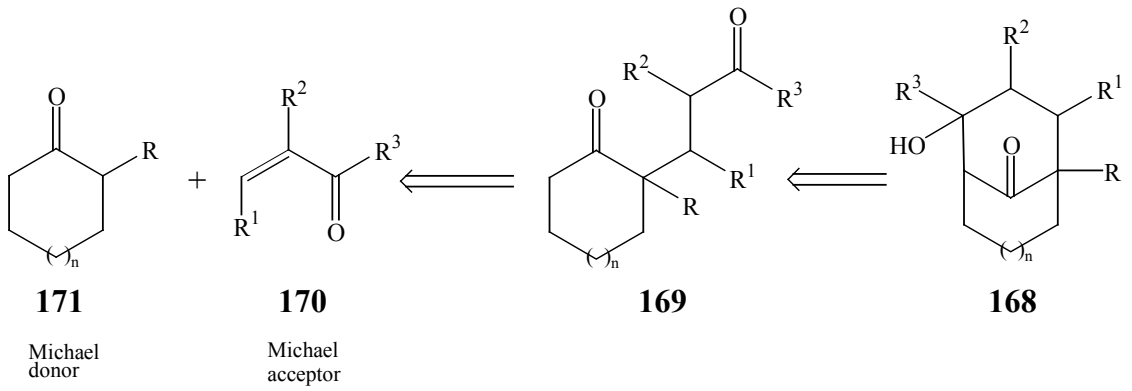
Scheme 72: A new approach to the synthesis of bicyclic[x.3.1] compounds of type **167**.

Alternatively, by analyzing the bond formations needed to construct the desired bridged system, it can be seen that the bicyclo[x.3.1]cycloalkanone systems of type **167** (Scheme 72, eq. 2) similar to **73b** (m = 0, n = 1) or **74b** (m = 1, n = 1) could be accomplished by tandem hydroformylation/ aldol addition of cycloalkanones of type **165** if an unsaturated two-carbon atoms chain is added. The introduction of the required vinyl chain is proposed via several ways, among those, if considering the reactivity of vinyl sulfoxide with certain nucleophiles giving the Michael-adducts[138] and their thermal decomposition to give olefins[139], this reaction could be applied to the introduction of the vinyl group into the β-ketoester[140,141]. These methods are of limited scope in terms of the active methylene compounds applicable. Another limitation is that they provide only ethenylated products not blocking the α-position. It is expected that such compounds can readily isomerizes to the thermodynamically stable conjugated enone.

In order to circumvent these limitations, the preparation of 2-vinyl-cycloalkanones could be accomplished in the preparation of 1,2 divinyl cycloalkanols[142]. In fact, α-chloro-cycloalkanones could react with vinylmagnesium chloride[143,144] affording chlorohydrin which undergo 1,2-migration of the vinyl group smoothly to afford the 2-vinylcycloalkanone when its magnesium salts is heated[143,144,145,146,147].

Recently, Yamaguchi et al.[148] developed an ethenylation reaction of cyclic ketones and β-dicarbonyl compounds with trimethylsilylethyne in the presence of $GaCl_3$[16]. The reaction converts silyl enol ethers to α-ethenylated products in one-step. This novel ethenylation reaction has a wide applicability and provides not only ketones with a quaternary α-carbon but also enolizable products. A limitation of the method, however, is that cyclic ketones with relatively small ring sizes such as cyclohexanones and cycloheptanones give considerable amounts of the conjugated α-enones. Alternatively, Kanematsu's[149] procedure could be considered using the reaction between sulfonylallene and enammines of cyclic ketones but the vinyl cycloalkanones derivatives are present in low yields. Although this method could be a valid alternative vinylation method, costs and safety considerations discourage their use for large-scale synthesis. Finally, Nishino's method[150] seems to be the best one, but many steps are necessary to introduce the vinyl chain starting from an α-chloro cycloalkanone. On the other hand, the 1,5-dicarbonyl compounds of type **169** (Scheme 73) could also be obtained from straightforward routes, in fact, they can be synthesized starting from

cycloalkanones of type **171** or its derivates by a Michael reaction employing the α,β-unsaturated aldehydes[70] of type **170**.



Scheme 73: Synthesis of bridged compounds via Michael reaction.

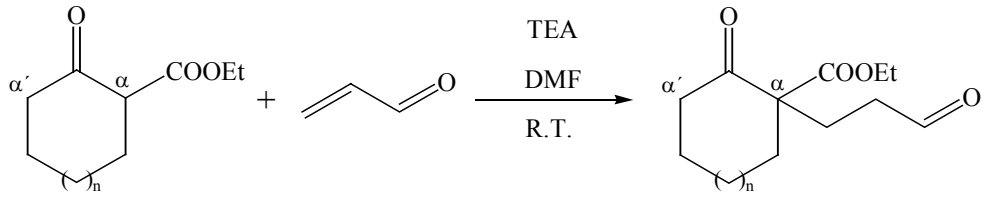
Traditionally, Michael addition reactions of β-keto esters are catalyzed by very strong bases such as alkali metal alkoxides. Several undesirable side reactions can be caused by these strongly basic catalysts[151,152] including rearrangements, secondary condensations, isomerizations, polymerizations, double additions and transesterifications.

In order to circumvent strongly alkaline conditions several alternative methods have been developed in recent years[153,154,155,156] that make use of weak Brønsted bases (e.g. Barium hydroxide, alkali metal fluorides) or some Lewis acids catalyzing the Michael addition reaction, albeit not always with satisfactory efficiency[157].

2.7.2 Synthesis of bicyclo[m.3.1]alkane systems via stepwise Michael addition/ aldol cyclization under acidic conditions (m = 2-5)

a. Conversion of ethyl 2-oxo-cycloalkane carboxylate in the presence of acrolein

To begin the route, the Michael addition is conducted following the procedure reported by Kanaguchi et al.[158] in which acrolein (**172**) (Scheme 74) is added to a solution of ethyl 2-oxo-cycloalkane carboxylates **65a-d** and TEA in DMF at room temperature to give the Michael adducts **173a-d** as listed in Table 19.



65a-d (n = 0-3) **172** **173a-d** (n = 0-3)

Scheme 74: Synthesis of ethyl 2-oxo-1-(3-oxo-propyl)-cycloalkane carboxylates (**173a-d**).

Table 19: Synthesis of ethyl 2-oxo-1-(3-oxo-propyl)-cycloalkane carboxylates (**173a-d**)

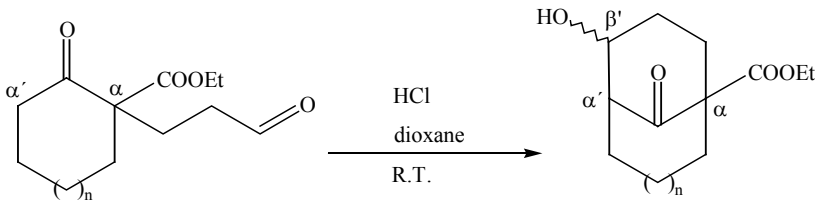
Reaction	n	Starting Mat.	Product	Yields (%)
R 80	0	**65a**	**173a**	90
R 81	1	**65b**	**173b**	50
R 82	2	**65c**	**173c**	68
R 83	3	**65d**	**173d**	75

All reactions proceed with high yield of the 1,5-ketoaldehyde **173a-d** which are readily ready to be employed in the aldol addition reaction.

b. Intramolecular aldol cyclization of ethyl 2-oxo-1-(3-oxo-propyl)-cycloalkane carboxylate (173a-d)

On the base of the results observed in intramolecular aldol addition acid or base – catalyzed of 1,6 keto-aldehyde **70a-c** (Scheme 30), attempts to utilize these reaction conditions methodology to convert the Michael adducts **173a-d** (Scheme 75) into *β*-hydroxy bicyclic compounds of type **167** (Scheme 72, eq. 2) have been conducted. All results are listed in Table 20. When the 5-, 6-membered ring compounds **173a,b** (Scheme 75) are treated with HCl in dioxane[63], the results reveal the formation of bicyclic compounds **174a,b** in good yields. As expected the aldol addition proceeds

with low degree of diastereoselectivity as the aldol adducts are obtained as mixtures of two diastereoisomers.



173a-d **174a-d**

Scheme 75: Preparation of bicyclo[m.3.1] compounds (m = 2-5) of **173a-d** under acidic conditions.

Table 20: Intramolecular aldol addition of the compounds **173a-d**

Reaction	n	Starting Mat.	Product	dr[a]	Yields (%)
R 84	0	**173a**	**174a**	3.8:1	78
R 85	1	**173b**	**174b**	1.6:1	87
R 86	2	**173c**	**174c**	5.4:1	55
R 87	3	**173d**	**174d**	4:1	62

a) Calculated by NMR-analysis

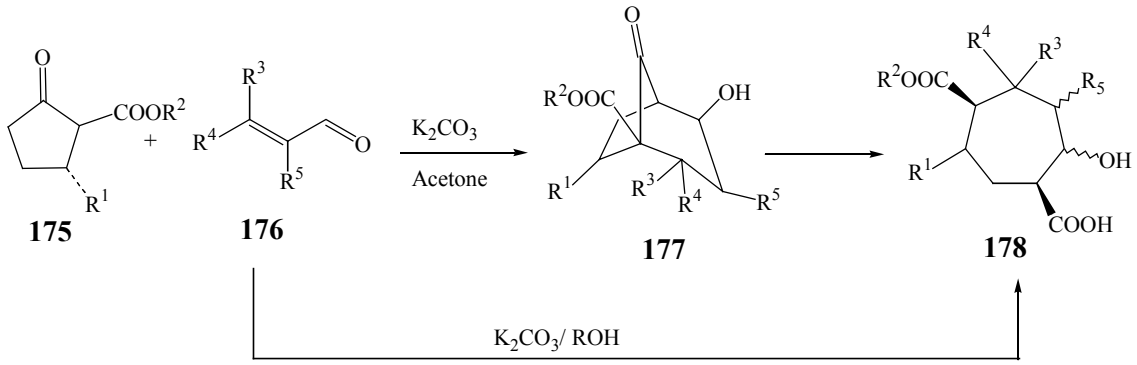
Tests of these conditions on larger cycloalkanones **173c-d** (R 86-R 87) were carried out under the same mild reaction conditions. In contrast to the latter results, lower yields are observed.

Following the interest in tandem reactions which combine multiple transformations in an efficient one-pot procedure in order to move in the direction of *β*-hydroxy cycloalkanones of type **167** (Scheme 72, eq. 2), an one-pot Michael-aldol addition under basic conditions will be investigated.

2.7.3 One-pot Michael addition/ aldol cyclization under basic conditions.

In the course of the study on the stereoselective synthesis of the naturally occurring Prelog-Djerassi lactone, Rodriguez et al.[159] found a very useful base-catalyzed diastereoselective three centre Michael addition of chiral *β*-ketoester (**175**) to *α,β*-

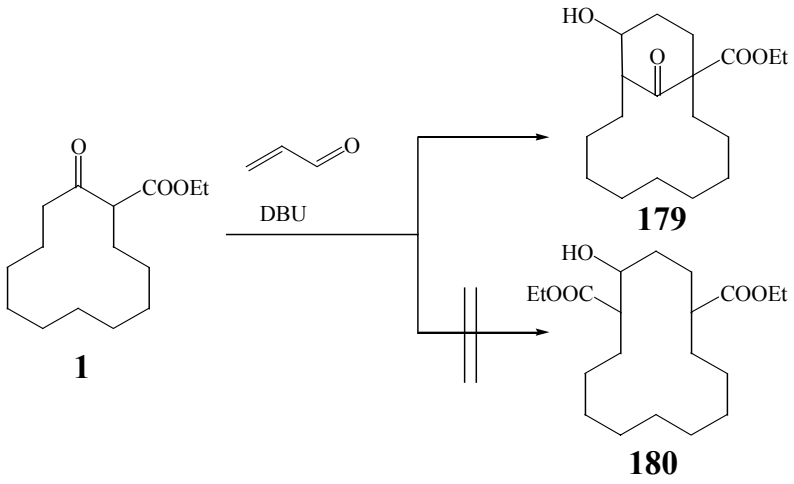
unsaturated carbonyl compounds of type **176** (Scheme 76). In addition to these results, they described a mild and general one-pot high yield preparations of synthetically valuable β-hydroxy bicyclo[3.2.1]octanones of type **177** by a slight modification of their initial conditions for the Michael addition[160]. Furthermore, bicyclic derivatives are involved as intermediates in the ring expansion of cyclopentanones to seven-membered ring[161] such as compound **178**. The one-pot condensation-cyclization takes place under very mild conditions with α, β-unsaturated aldehydes of type **176** in acetone at room temperature in the presence of 1.5 eq. of K_2CO_3. Moreover, if compound **177** is treated with K_2CO_3 in the presence of MeOH or EtOH, they smoothly undergo retro-Dieckmann reaction[162], to the corresponding substituted cycloheptane derivatives **178**[163].



Scheme 76: Base-catalyzed two-carbons ring expansion of cyclopentanone (**175**).

In 1997, Filippini et al.[164] reported a base-induced anionic sequence involving five different reactions starting from the 5-membered ring compound of type **175** by replacing acetone with MeOH or EtOH (Scheme 76). The overall transformation named "MARDi cascade" involved a Michael addition, an intramolecular aldol addition, a retro-Dieckmann reaction followed by dehydration, and chemoselective ester saponification. The results are the facile one-pot diastereoselective formation of highly functionalized and synthetically valuable cycloheptanes **178** (Scheme 76).

In contrast to these results, if the reaction is performed starting with cyclododecanone **1** under same reaction conditions (Scheme 77), bicycle compound **179** is obtained[165] while the expected opened-bridge ring product **180** is not observed.

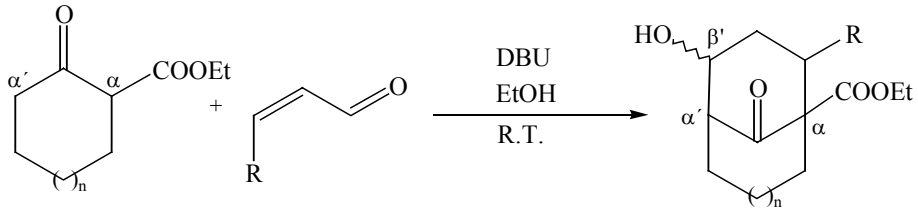


Scheme 77: M.A.R.Di reaction on ethyl 2-oxo-cyclododecanone carboxylate (**1**).

In order to find out how the DBU-EtOH could influence the reaction on membered rings larger than cyclopentanone, investigations starting from 6-membered rings are performed in the presence of α,β-unsaturated enals and base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in EtOH[166].

2.7.4 Preparation of bicyclo[m.3.1]compounds derivatives under acidic conditions via one-pot procedure (m = 3-5).

The sequential Michael addition intramolecular aldolization between 1 eq. of β-ketoesters **65b-d** (with 6-, 7-, 8-membered rings) with 1 eq. of acrolein (**172**) are carried out in the presence of DBU as base in EtOH at room temperature (Scheme 78).
According to the results observed with ethyl 2-oxo-cyclododecanone carboxylate (**1**), the reactions proceed through a sequential Michael addition/ intramolecular aldol reaction resulting in the formation β-hydroxy bicycles **174b-d** in high yield as summarized in Table 21 (R 88-90).
Proceeding into investigations, crotonic aldehyde (**181**) is employed as Michael acceptor (Scheme 78). Thus, 6- and 7-membered rings **65b,c** react in EtOH under Michael addition/ aldol condition to give the aldol adducts **182b,c** as a mixture of diastereoisomers in high yields (Table 21, R 91-92).



65b-d (n = 1, 2, 3) **172** (R = H) **174b-d** (R = H) (n = 1, 2, 3)

65b,c (n = 1, 2) **181** (R = CH_3) **182b,c** (R = CH_3) (n = 1, 2)

Scheme 78: One-pot Michael addition intramolecular aldol cyclization wth acrolein (**172**) and crotonic aldehyde (**181**).

Table 21**:** One-pot Michael addition intramolecular aldol cyclization by DBU

Reaction	n	Starting Mat.	R	Product	dr[a]	Yields (%)
R 88	1	**65b**	H	**174b**	1:1	96
R 89	2	**65c**	H	**174c**	5:1	78
R 90	3	**65d**	H	**174d**	4:1	76
R 91	1	**65b**	CH_3	**182b**	8.3:3.6:1.5:1	86
R 92	2	**65c**	CH_3	**182c**	9:4.7:2:2:1.7:1	80

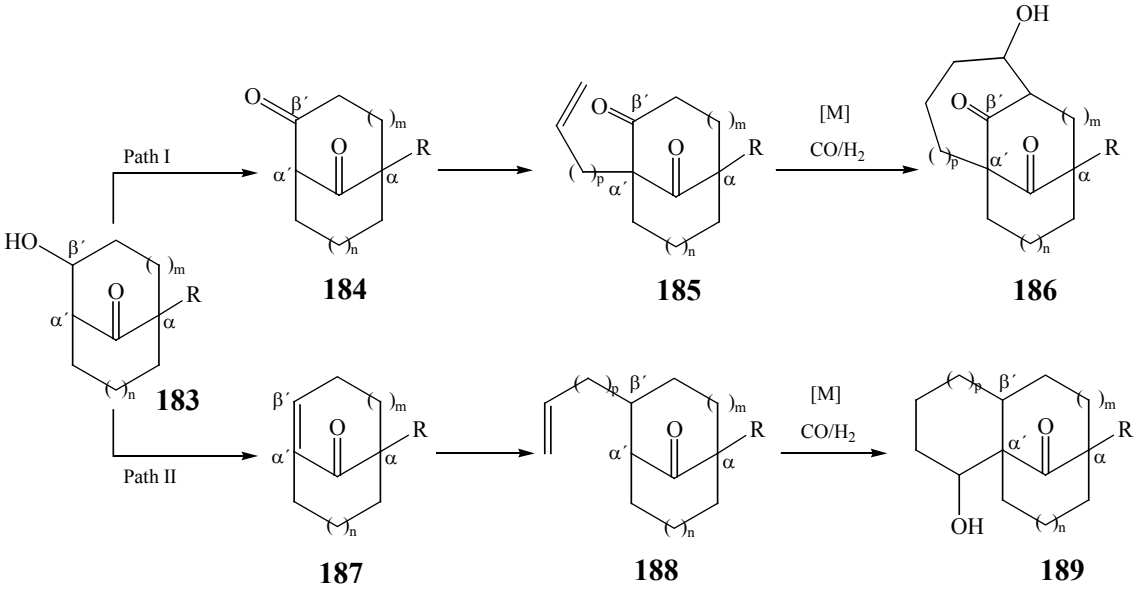
a) by ^{1}H-NMR analysis

From all these results it can be concluded that good to excellent yields of bicycles[3.3.1] and [4.3.1] compounds **182b** and **182c** respectively (R 91-R 92) are obtained regardless the nature of α,β-unsaturated enals (**172** or **181**) and ring sizes. No M.A.R.Di cascade reaction is detected as observed in 5-membered ring[164] (Scheme 76). With the aim to combine the rapid preparation of bridged system **174b-d** (Scheme 78) via one-pot Michael addition with the proven method of ring closure offered by tandem hydroformylation/ aldol addition and enolboration/ hydroformylation/ aldol addition the β-hydroxy bicyclic substrates are chosen as starting materials in the preparation of tricycle compounds.

2.7.5 Preparation of tricyclic compounds via bridged bicyclic systems

2.7.5.1 Introduction

The last part of this work is to establish a general route towards the formation of bridged and fused tricyclic compounds of type **186** or **189** (Scheme 79) combining all the observed results concerning the sequential hydroformylation/ aldol addition or Michael addition/ aldol reactions. This required the synthesis of more complicated substrates than those prepared previously that allow the closure of a three or four carbon atoms aldehydic chain introduced in α'-position, which could be added by a number of methods.



m = 1, 2, etc; n = 0, 1, 2 etc; p = 0, 1, 2, etc; R = COOEt, Me, H etc

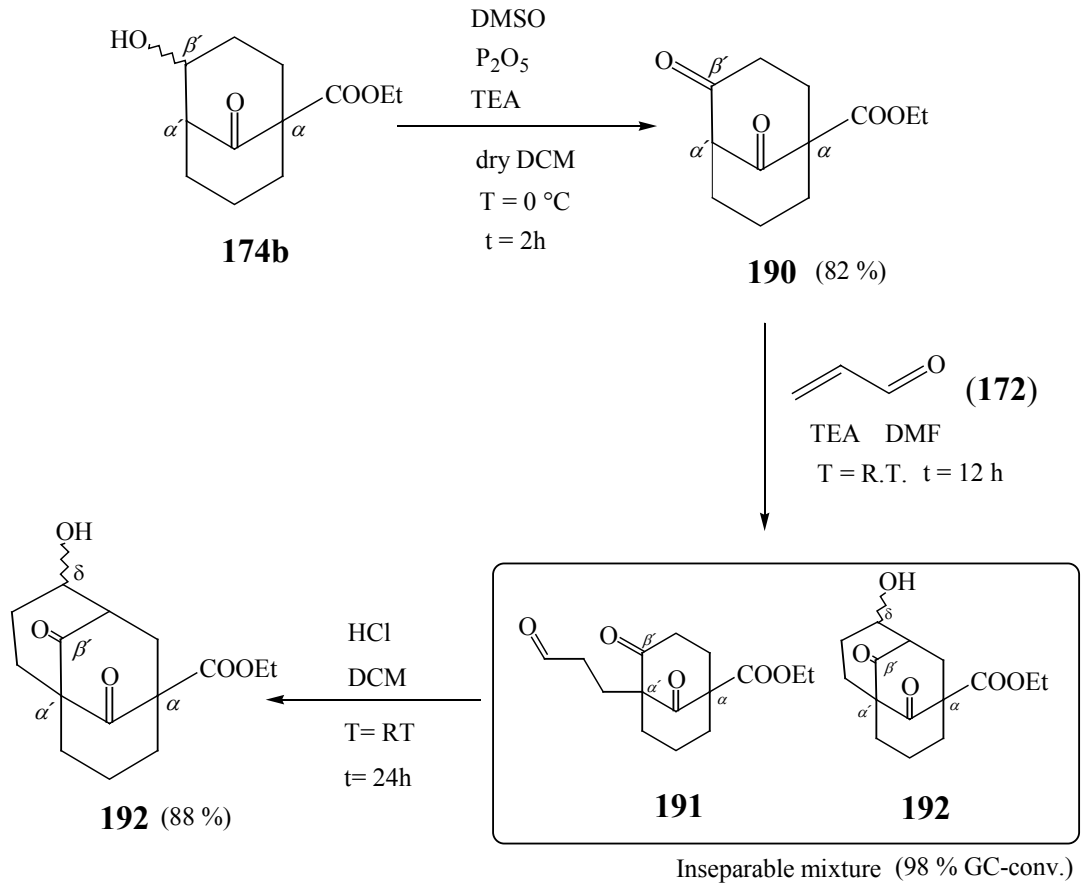
Scheme 79: Hypothetical approach towards the synthesis of multi-ring systems.

First of all, bicyclo[3.3.1]alkanone compound of type **183**, such as **174b** (Scheme 75), is considered as standard starting material to the synthesis of tricyclic compounds with m = n = p = 1. The introduction of this necessary aldehydic chain could be accomplished via two different ways. First, oxidation of β-hydroxy bicycle resulting into the formation of 1,3-diketone of type **184** which may increase the acidity of α'-position needed to construct the bridged compound of type **185** via a further Michael addition/ aldol reaction instead of a vinylic chain addition followed by a one-pot Rh-catalyzed cyclization (Scheme 79, path I). A different strategy towards the synthesis of tricyclic compounds could be carried out to obtain fused aldol adducts of type **189** by

installing a vinyl or allyl group via Sakurai reaction[167,168] which could later undergo a tandem hydroformylation/ aldol addition acid-catalyzed (Scheme 79, path II).

2.7.5.2 Tricyclic bridged compounds of type 186 (Scheme 79, path I)

As illustrated in Scheme 78, the first strategy pursed in the construction of tricyclic systems involves the synthesis of 1,3-diketone of type **184**. To accomplish this in a straightforward fashion, Swern oxidation[169,170,171,172] could be performed starting from the *β*-hydroxy bicycle **174b** (Table 21, R 89), and the ethyl 4,9-dioxo-bicyclo[3.3.1]nonane-1-carboxylate (**190**) is obtained in 82 % of yield (Scheme 80, R 93). This compound **190** is then subjected to Michael addition with acrolein in the presence of TEA and work-up under acidic conditions to afford the corresponding inseparable mixture of keto aldehyde **191** and *β*-hydroxy tricycle **192** (Scheme 80, R 94). Thus, in attempting to perform the aldol addition, the crude mixture is treated with an aqueous solution of HCl and stirred for 24h. The tricyclic compound **192** as a mixture of four diastereoisomers is observed, accounted for by the disappearance of aldehyde in the NMR of the crude mixture and simultaneously the presence of those typical signals belonging to the alcohol function (Scheme 80, R 95).

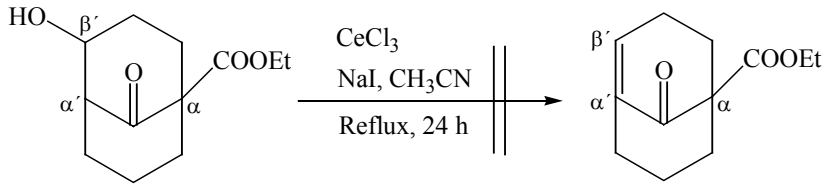


Scheme 80: Preparation of bridged tricyclic compound **192**.

2.7.5.3 Tricyclic fused compounds of type 189 (Scheme 79, path II)

In order to move further in the direction of fused tricyclic systems of type **189** (Scheme 79), compounds of type **188** bearing the required unsaturated chain in *β'*-position could be directly obtained from *α,β*-unsaturated ketone of type **187** by the Sakurai reaction[167,168,173, 75c] and consequently by tandem hydroformylation/ aldol addition.

Proceeding from *β*-hydroxy bicycle **174b**, the preparation of unsaturated ketoester **193** (Scheme 81) could be performed under dehydration conditions using cerium(III)chloride heptahydrate in combination with sodium iodide[174]. Unfortunately, this attempt to carry out the reaction towards the preparation of compound **193** resulted in recovering of starting material (R 96).

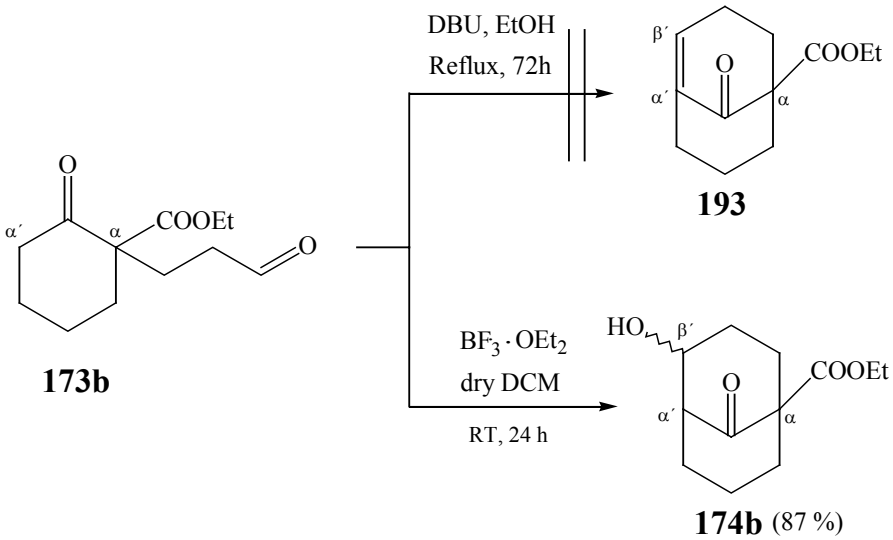


174b **193**

Scheme 81: Attempt condensation in the presence of $CeCl_3$.

A different approach to this compound **193** will be investigated under both acidic and basic conditions. The ketoaldehyde **173b** is treated with DBU in EtOH affording an intractable crude mixture (Scheme 82, R 97).

Alternatively, starting again from **173b** the reaction is performed by $BF_3{\cdot}OEt_2$[141] in abs. DCM. An intramolecular aldol addition is observed to takes place and the bridged system **174b** in isolated in 87 % yields (Scheme 82, R 98), however, in according to the Bredt's rules[175], the intramolecular aldol condensation of **173b** to generate **193** is disfavored.



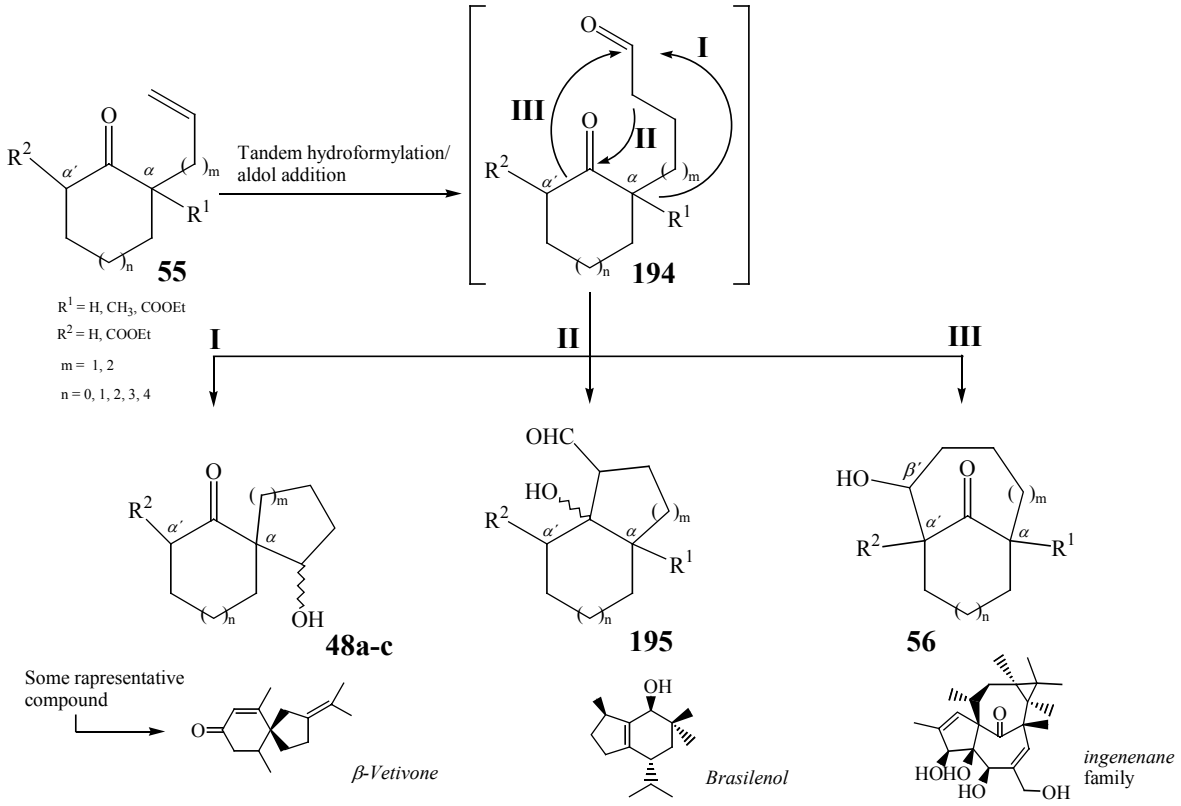
Scheme 82: Attempted intramolecular aldol condensation of **173b** under basic or acidic conditions.

It could be concluded that the use of sequential Michael addition/ aldol reaction gave a preliminary interesting results towards the construction of tricyclic compounds of type **186** (Scheme 79, n = m = p = 1) such as **192** (Scheme 80). In contrast, the combination

of Michael addition/ aldol reaction with tandem hydroformylation/ aldol addition is not successful for obtaining fused tricyclic compounds of type 189 due to the failure of the intramolecular aldol condensation via **187** and **188** intermediates (Scheme 79) as shown in Scheme 81 and 82.

3 Summary

Aim of the present investigations was to find out valid synthetically strategies to get bicyclic skeletons of natural products via one-pot tandem hydroformylation/ aldol addition starting from common and commercially available compounds. Many natural compounds have a framework similar to the spiro-cicylic compounds of type **48a-c**, fused rings **195** or bridged rings **56** and often they have a policyclic skeleton (Scheme 83). Following previous investigations reported by C. Hollmann[73] (Schemes 15, 16 and 17), tandem hydroformylation/ aldol addition are applied on cycloalkanones of type **55** bearing unsaturated side chains and various different substituents R^1 and R^2 (Scheme 83).

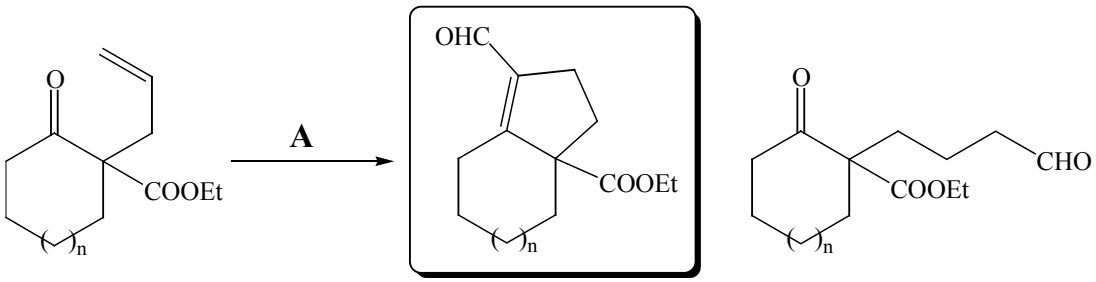


Scheme 83: Synthesis of skeletons of some natural products by tandem hydroformylation/ aldol condensation.

Investigations concerning the acid catalyzed tandem hydroformylation/ aldol condensation under acidic conditions carried out on the ethyl 1-allyl-2-oxo-cycloalkane carboxylates **4a-e** show chemoselectively fused bicyclic compounds like **72a,b** when

the compounds with a 5- or 6-membered ring (**4a** and **4b** respectively) are used (Scheme 84).

In contrast to the above results, the same reaction conditions applied on the larger 7-, 8-, 9-membered compounds **4c-e** gave exclusively the *n*-products of hydroformylation **70c-e**.



4a, n = 0
4b, n = 1
4c, n = 2
4d, n = 3
4e, n = 4

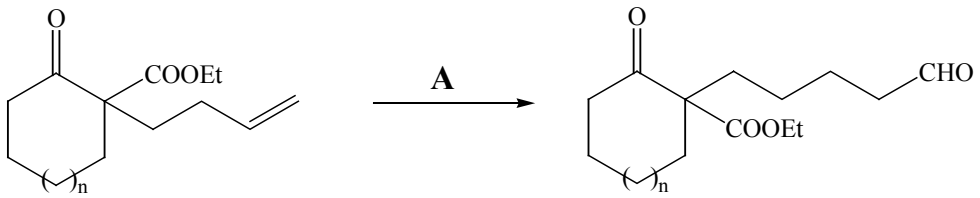
72a, n = 0, (65 %) (from **4a**)
72b, n = 1, (79 %)* (from **4b**)

70c, n = 2, (98 %) (from **4c**)
70d, n = 3, (37 %) (from **4d**)
70e, n = 4, (40 %) (from **4e**)

A: $Rh(acac)(CO)_2$, CO/H_2 20 bar (1:1), 5 mol % - PTSA ,4 mol % - BIPHEPHOS, dry DCM, 60 °C, 72h.
* Including the correspondig hydrogenated product

Scheme 84: Synthesis of fused rings **72a,b** from 5-, 6-membered cycloalkanones **4a,b**.

Cycloalkanones bearing longer side chains such as ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (**68a-c,e**) (Scheme 85), react under tandem hydroformylation/ aldol addition to form mixtures of linear aldehyde products **71a-c,e** accompanied by small amounts of branched aldehyde compounds.



68a, n = 0
68b, n = 1
68c, n = 2
68e, n = 4

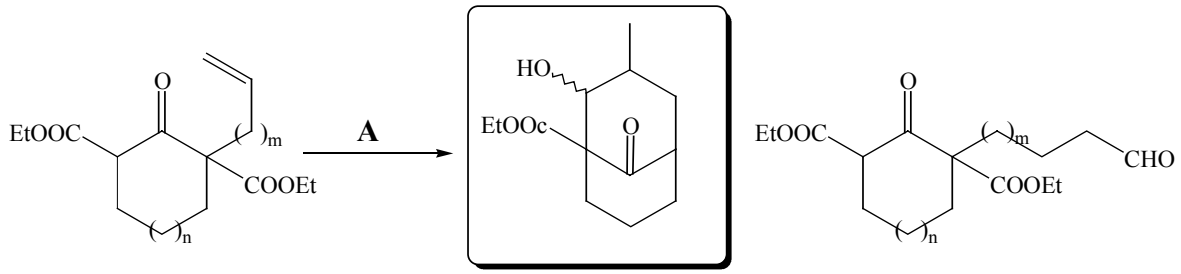
71a, n = 0, *n/iso* 5:1, (78 %) (from **68a**)
71b, n = 1, *n/iso* 33:1, (86 %) (from **68b**)
71c, n = 2, (40 %) (from **68c**)
71e, n = 4, (26 %) (from **68e**)

A: $Rh(acac)(CO)_2$, CO/H_2 20 bar (1:1), 5 mol % - PTSA ,4 mol % - BIPHEPHOS, dry DCM, 60 °C, 72h.

Scheme 85: Attempts of cyclizations from homoallyl cycloalkanones **68a-c,e**.

As the unsaturated β-ketoesters with 5-, 6-membered rings **4a,b** via sequential hydroformylation/ aldol addition are able to afford the fused aldol adducts **72a,b**, further studies were performed using cycloalkanones which would allow the construction of bridged system of type **56** (Scheme 83). The installation of substituents R^1 and R^2 with different electronic or steric effects furnished a valid method to control the regio- and chemoselectivity of the intramolecular cyclization.

First, the compound **83b** with a 6-membered ring submitted to tandem hydroformylation/ aldol addition furnished the bicylic compounds **85** by the cyclization of the branched aldehyde intermediate (Scheme 86). In contrast to the results reported above, the 1,3-dicarboxylate **83c** reacted to give the hydroformylated products **88** as a mixture of *n*-*iso*-aldehydes and no aldol adducts are detected. Proceeding with the homologated ketoester **84**, the sequential hydroformylation/ aldol addition furnished again a mixture of *n*-*iso*-aldehydes **90** (Scheme 86).



83b, m = 1, n = 1
83c, m = 1, n = 2
84, m = 2, n = 2

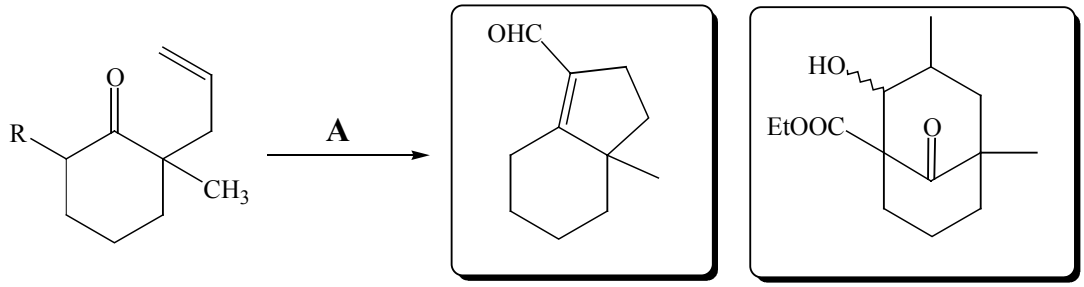
85, (37 %) (from **83b**)

88, m = 1, n = 2, *n/iso* 5:1 (98 %) (from **83c**)
90, m = 2, n = 2, n/iso 2:1 (90 %) (from **84**)

A: $Rh(acac)(CO)_2$, CO/H_2 20 bar (1:1), 5 mol % - PTSA ,4 mol % - BIPHEPHOS, dry DCM, 60 °C, 72h.

Scheme 86: Synthesis of bridged bicyclic[3.3.1] skeleton by tandem hydroformylation/ aldol addition.

Fused bicycle compound of type **195** (Scheme 83) is also obtained when the 2-allyl-2-methyl-cyclohexanone (**92**) is used. The reaction proceeds exclusively with *n*-selectivity leading to 7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-3-carboxylate (**101**) in 93 % yield (Scheme 87). Again, due to steric hindrance of ester function and in analogy to the one-pot of **83b**, the bridged compound **97**, from the branched aldehyde intermediate, is formed when the cycloalkanone **93** is used.



92, R = H
93, R = COOEt

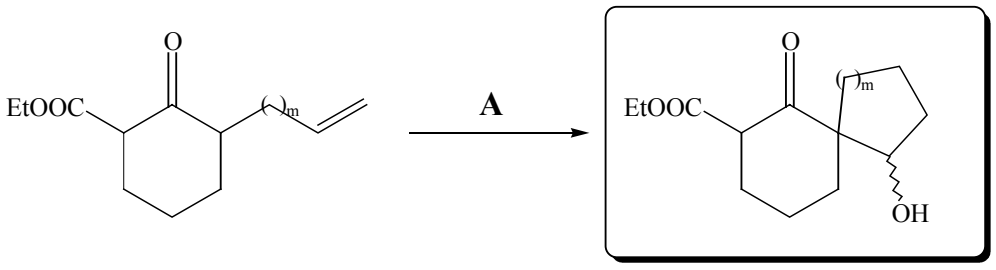
101, (93 %) (from **92**)

97, (32 %) (from **93**)

A: $Rh(acac)(CO)_2$, CO/H_2 20 bar (1:1), 5 mol % - PTSA ,4 mol % - BIPHEPHOS, dry DCM, 60 °C, 72h.

Scheme 87: Synthesis of fused and bridged bicyclic skeletones from substituted cycloalkanones **92** and **93**.

Cycloalkanones bearing an ester function next to the ketone moiety and the olefinic chain in opposite side like the allylic **102** and homoallylic **103** with 6-membered ring (Scheme 88), undergo intramolecular aldol addition to give the spiro compounds such as **104**, as main products of a mixture containing the fused aldol adducts and the product **107**.



102b, m = 1
103b, m = 2

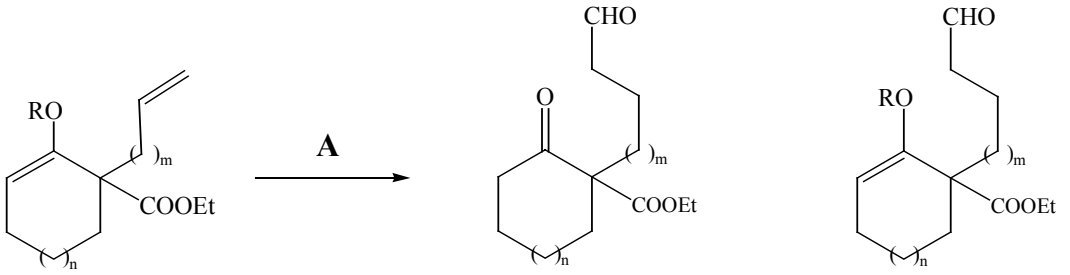
104, m = 1, (45 %)* (from **102b**)
107, m = 2, (40 %)* (from **103b**)

A: CO/H_2 20 bar (1:1), $Rh(acac)(CO)_2$, BIPHEPHOS, PTSA, dry DCM, T = 60 °C, t = 72 h
* mixture of sub-products is present

Scheme 88: Synthesis of spiro-cyclo skeletons **104** and **107**.

Although the tandem hydroformylation/ aldol addition of unsaturated ketoesters are able to furnish different cyclization fashion, as an alternative method, silyl enol ethers like **120a,b**, **125a-c** and **126a,b** were investigated (Scheme 89). In contrast to the

previous results, no cyclization takes place but only a mixture of linear and branched aldehyde is observed.



R = TMS; m = 1;
120a, n = 0; **120b**, n = 1;

R = TBDMS; m = 1
125a, n = 0; **125b**, n = 1; **125c**, n = 2;

R = TBDMS; m = 2;
126a, n = 0; **126b**, n = 1;

70a, m = 1; n = 0, (95 %) (from **120a**)
70b, m = 1; n = 1, (90 %) (from **120b**)

R = TBDMS; m = 1
127a, n = 0, (94 %) (from **125a**)
127b, n = 1, (92 %) (from **125b**)
127c, n = 2, (23 %) (from **125c**)

R = TBDMS; m = 2
130a, n = 0, (75 %) (from **126a**)
130b, n = 1, (85 %) (from **126b**)

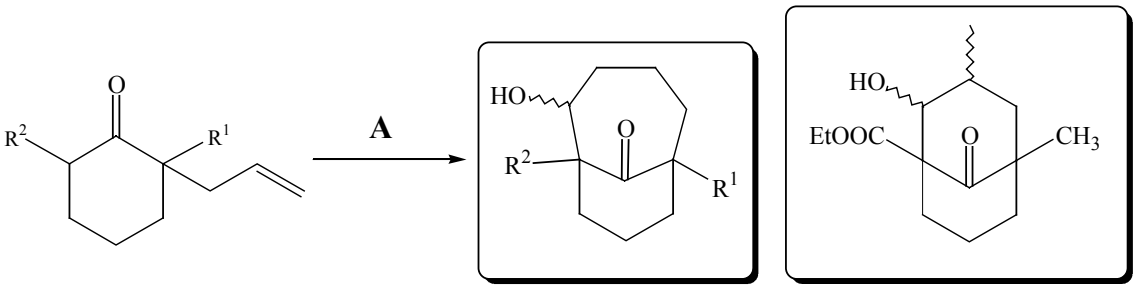
A: CO/H_2 80 bar (1:1), $[Rh(cod)Cl]_2$, dry DCM, T = 90 °C, t = 72h

Scheme 89: Attempts of cyclization by tandem hydroformylation/ Mukaiyama aldol addition.

Finally, proceeding with unsaturated cycloalkanones an enolboration/ hydroformylation/ aldol addition is performed. In contrast to the results observed under tandem hydroformylation/ aldol addition acid-catalyzed conditions, where the fused bridged compounds **72a,b** are the major products (Scheme 84), a reverse of chemoselectivity of the aldol addition is observed under these reaction conditions. Indeed, starting from **4b** and **92** compounds, the reactions proceed with high chemoselectivity and the bridged systems **73b** and **164** are generated respectively (Scheme 90). The result confirmed the highly efficient formation of the enol borane of unsaturated cycloalkanones in absence of any auxiliary activating group.

On the other hand, when ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**) is subjected to this reaction, bridged β-hydroxy ketone **97**, as the sole product in 46 % yield, is obtained.

As can be observed, once again the regioselectivity of the hydroformylation is influenced of the presence of ester function (R^2 = COOEt) and the formation of the 6-membered ring is favored (Scheme 90).



4b, R^1 = COOEt, R^2 = H;

92, R^1 = Me, R^2 = H;

93, R^1 = Me, R^2 = COOEt;

73b, R^1 = COOEt, R^2 = H; (from **4b**)

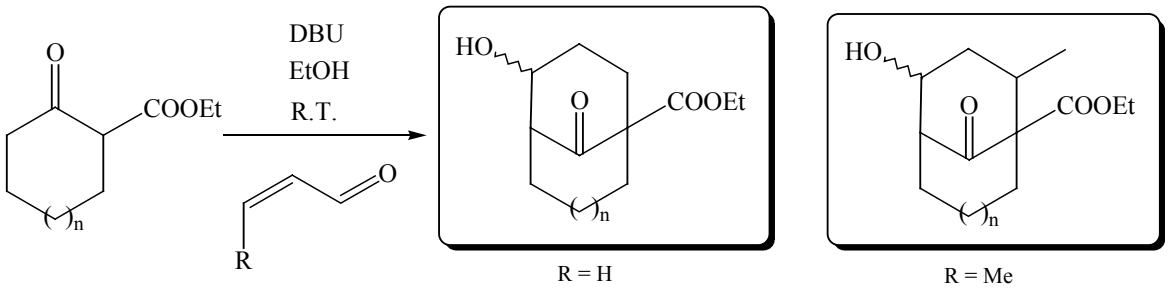
164, R^1 = Me, R^2 = H; (from **92**)

97, (46 %) (from **93**)

A: CO/H_2 80 bar (1:1), 0.9 % mol - $Rh(acac)(CO)_2$, $(cy\text{-hex})_2BCl$, TEA, 1.8 mol % - XANTPHOS, dry DCM, T = 90 °C, t = 24 h

Scheme 90: Synthesis of bridged bicyclic skeletones by enolboration/ hydroformylation/ aldol addition of **4b**, **92** and **93**.

Proceeding with the studies towards the construction the bridged skeletons of type **56** (Scheme 83), one-pot Michael addition/ intramolecular aldol reaction was carried out adding acrolein or crotonic aldehyde to a solution of **65b-d** (6-, 7-, 8-membered rings) in the presence of catalytic amount of DBU. Under these conditions both bridged compounds like **174b-d** or **182b,c** are obtained as a mixture of diastereoisomers (Scheme 91). Mild reaction conditions together with excellent yields turns out the DBU-ethanol mediated Michael addition reaction as an important and superior alternative to the classic base catalysis and other methods, since both side-reactions and subsequent reactions under strong basic conditions are avoided.



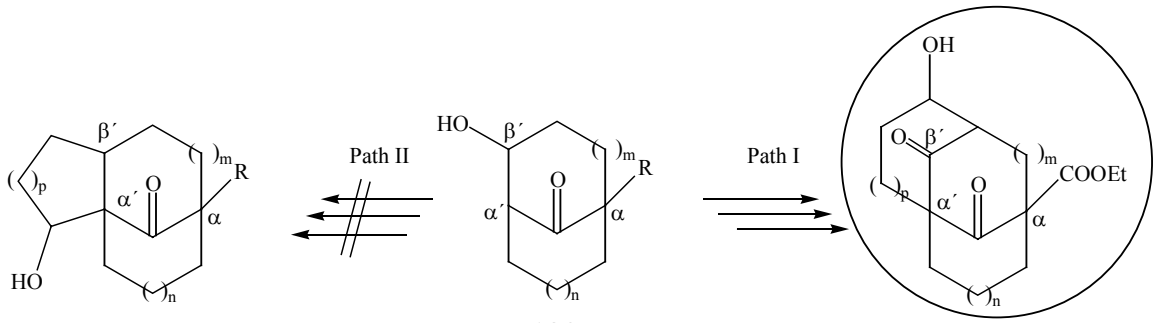
65b, n = 1
65c, n = 2
65d, n = 3

174b, n = 1, (96 %) (from **65b**)
174c, n = 2, (78 %) (from **65c**)
174d, n = 3, (76 %) (from **65d**)

182b, n = 1, (86 %) (from **65b**)
182c, n = 2, (80 %) (from **65c**)

Scheme 91: Synthesis of bridged bicyclic skeletons via Michael addition/ aldol cyclization.

Ultimate goal of this work was the efforts towards the formation of tricyclic systems of type **186** or **189** (Scheme 92) by performing the sequential hydroformylation/ aldol addition two or more times.



189

183
m, n, p = 1, 2 etc

186

Scheme 92: Plan towards the synthesis of tri-cyclic compounds of type **186**.

From these results while sequential Michael addition/ aldol reaction gave preliminary interesting results towards the construction of tricyclic compounds of type **186** combined with the tandem hydroformylation/ aldol addition (path I), attempts for obtaining fused tricyclic compounds of type **189** failed (path II) (Scheme 92).

Further investigations towards the synthesis of polycyclic compounds and about their stereochemistry will be involved in next projects.

4 Experimental part

4.1 General aspects

Reagent, solvents and synthesized catalyst

All reagents were purchased from commercial sources and were used withouth further purification unless otherwise stated. THF and Et_2O were distilled over sodium metal and benzophenone, while CH_2Cl_2 and triethylamine were distilled over CaH_2.
The $[Rh(cod)Cl]_2$ catalyst used in hydroformylation was prepared via the method of Crabtree[72], while the $Rh(CO)_2(acac)$ hydroformylation catalyst and $RhCl{\cdot}3H_2O$ were donated by Degussa AG, Düsseldorf.

Spectroscopic and analytical methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX 400, 500 instruments. $CDC1_3$ was used as the solvent, and both proton and carbon spectra were referenced to $CDCl_3$ (δ 7.25 and δ 77.00). The assignment of the signals in most cases is based on H,H-, C,H- und *long range* C,H-correlation spectroscopy. All 1D-NMR spectra were Fourier transformed using Bruker WINNMR software and plotted using the ACDLABS SpecMan software suite. **IR** spectra were acquired using Nicolet Impact 400 D using neat compounds or thin films in $CDCl_3$ between KBr. High resolution analytical mass spectra **HR-FABMS** and **HR-EIMS** were recorded on JEOLJMS-SX 102 A and Finnigan MS 8200 spectrometers, respectively.

Chromatographic/ purification methods

Analytical gas chromatography was carried out on a Fisons 8130 gas chromatograph with 25 m CP-sil-5(CB) capillaries. Detection was accomplished via a flame-ionization detector. **TLC** was performed exclusively on aluminum-backed Merck F_{254} silica gel 60 plates, with the appropriate running solvents. **Column chromatography** was performed using gel silica 60 (size 0.063-0.200 nm). Filtration subsequent to hydroformylation in order to remove residue were performed with Merck alumina, neutral activity.

Working methods

Reactions are performed in normal laboratory glassware with round glass joints, and reactions requiring an inert atmosphere were run under positive pressure of argon.
Pressure reactions have been carried in autoclaves (250 ml, type A, PTFE-insert) from Berghof, Eningen, Germany, and similar autoclaves (70 ml, stainless steel).

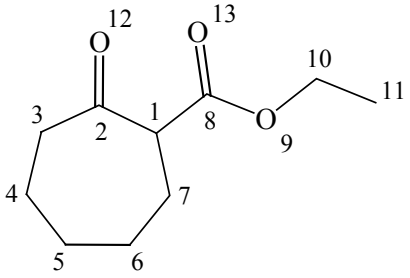
4.2 One-pot sequential hydroformylation/ aldol addition on ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates

4.2.1 Preparation of starting materials

a. Preparation of ethyl 2-oxo-cycloalkane carboxylates (65c-e)[81]

R 1: Synthesis of ethyl 2-oxo-cycloheptane carboxylate (65c)[81]

To a solution of cyclohexanone (**63a**) (2.0 g, 20.0 mmol) in dry Et_2O at 0 °C are added 4.23 g (30.0 mmol) of a solution $BF_3 \cdot OEt_2$ (1M in cyclohexane) in 15 ml dry Et_2O. A solution of ethyl diazoacetate (**64**) (3.4 g, 30.0 mmol) in 10 ml dry Et_2O is then added over a period of 15 min. and the resulting solution is stirred at room temperature under an argon atmosphere. After 24 h, the mixture is cooled to 0 °C and neutralized with saturated aqueous solution of $NaHCO_3$. The resulting mixture is extracted with chloroform (3 x 20 ml). The combined extracts are washed with a saturated solution of NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. Purification by bulb-to-bulb distillation (T = 80 °C, P = 6 x 10^{-2} mbar) gave 2.72 g (14.7 mmol, 74 % yield) of ethyl 2-oxo-cycloheptane carboxylate[81] (**65c**) ($C_{10}H_{16}O_3$, 184.232 g/mol) as a colorless oil.



65c

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 184 (M^+, 52), 156 (99), 138 (75), 110 (75), 82 (90), 55 (65). **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 2890 (s), 2926 (s), 2852 (m), 1744 (s), 1707 (s), 1639 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.21 (t, 3H, ^3J = 7.03 Hz, CH_3-11), 1.38 (m, 2H), 1.56 (m, 1H), 1.79 (m, 3H), 2.03 (m, 1H), 2.37 (m, 1H), 2.54 (m, 2H), 3.48 (dd, 1H, ^3J = 10.3 Hz, ^3J = 4.02 Hz, CH-1), 4.14 (q, 2H, ^3J = 7.03 Hz, CH_2-10). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-11), 24.3, 27.5, 27.9, 29.5, 43.0 (CH_2-3/4/5/6/7), 58.8 (CH, C-1), 60.9 (CH_2, C-10), 170.5 (CO, C-8), 208.9 (CO, C-2).

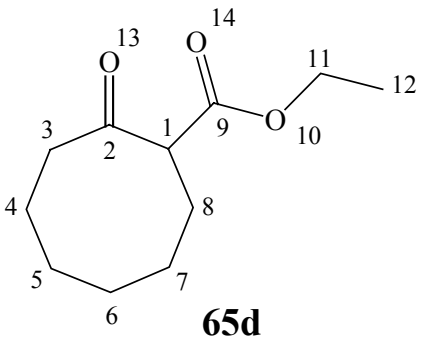
R 2: Synthesis[81] of ethyl 2-oxo-cyclooctane carboxylate (65d)

Amounts:	37.9 g	(267.0 mmol)	$BF_3 \cdot OEt_2$
	20.0 g	(178.0 mmol)	cycloheptanone (**63b**)
	30.43 g	(267.0 mmol)	ethyl diazoacetate (**64**)
	100 ml		abs. Et_2O

Procedure: Analogously to R 1.

Work-up: The combined extracts are washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. Purification by bulb-to-bulb distillation (T = 70 °C, P = 2 x 10^{-2} mbar) furnished 34.53 g (174.0 mmol, 98 % yield) of ethyl 2-oxo-cyclo-octane carboxylate[183] (**65d**) ($C_{11}H_{18}O_3$, 198.259 g/mol) as a colorless oil.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 198 (M^+, 48), 152 (56), 124 (98), 96 (62), 55 (42). **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 2979 (s), 2929 (s), 2856 (s), 1747 (s), 1705 (s), 1644 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.26 (t, 3H, ^3J = 7.03 Hz, CH_3-12), 1.40-1.50 (m, 5H), 1.68 (m, 2H), 1.85 (m, 1H), 2.07 (m, 1H), 2.35 (m, 3H), 3.50 (m, 1H), 4.18 (q, 2H, ^3J = 7.03 Hz, CH_2-11). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.2 (CH_3, C-12), 23.7, 25.9, 26.5, 28.6, 29.8, 32.2 (CH_2-3/4/5/6/7/8), 56.9 (CH, C-1), 60.0 (CH_2, C-11), 175.9 (CO, C-9), 212.2 (CO, C-2).



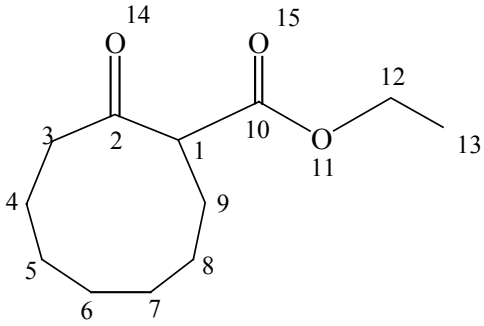
65d

R 3: Synthesis[81] of ethyl 2-oxo-cyclononane carboxylate (65e)

Amounts:	33.6 g	(237.0 mmol)	$BF_3 \cdot OEt_2$
	20.0 g	(158.0 mmol)	cyclo-octanone (**63c**)
	27.0 g	(237.0 mmol)	ethyl diazoacetate (**64**)
	100 ml		abs. Et_2O

Procedure: Analogously to R 1.

Work-up: The combined extracts are washed with brine, dried, and concentrated in vacuum. Purification by bulb-to-bulb distillation T = 70 °C, P = 2.3 x 10^{-2} mbar, gave 30.32 g (142.8 mmol, 91 % yield) of ethyl 2-oxo-cyclononane carboxylate[76] (**65e**) ($C_{12}H_{20}O_3$, 212.285 g/mol) as a colorless oil.



65e

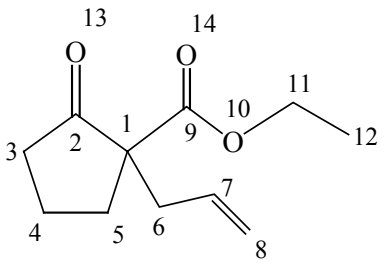
Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 212 (10), 183 (16), 166 (38), 138 (98), 110 (45), 55 (45). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2930 (s), 2873 (s), 2856 (m), 1746 (s), 1708 (s), 1641 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.16 (t, 3H, ^3J = 7.03 Hz, CH_3-13), 1.44 (m, 4H), 1.64 (m, 2H), 1.81 (m, 2H), 2.02 (m, 2H), 2.27 (m, 2H), 2.51 (m, 2H), 3.55 (dd, 1H, ^3J = 8.03 Hz, ^3J = 6.27 Hz, CH-1), 4.05 (q, 2H, ^3J = 7.03 Hz, CH_2-12). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-13), 23.7, 24.2, 24.3, 24.8, 25.7, 26.9, 42.2 (CH_2, C-3/4/5/6/7/8/9), 58.6 (CH, C-1), 61.0 (CH_2, C-12), 175.7 (CO, C-10), 211.6 (CO, C-2).

b. Preparation of ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a-e)

R 4: Synthesis[82] of ethyl 1-allyl-2-oxo-cyclopentane carboxylate (4a)

To an ice-cooled solution of ethyl 2-oxo-cyclopentane carboxylate (**65a**) (10.0 g, 64.0 mmol) in dry THF (100 ml) NaH is added (2.56 g, 64.0 mmol, 60 % dispersion in mineral oil). Allyl bromide (**66**) (7.62 g, 64.0 mmol) in 20 ml of dry THF is added over a period of 1 h, and the mixture is stirred overnight (12 h) at r.t. The reaction mixture is diluted with Et_2O (60 ml), washed with H_2O (3 x 20 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue is distilled bulb-to-bulb (T = 40 °C, 7.0 x 10^{-2} mbar) to give 11.6 g (59.11 mmol, 93 %) of ethyl 1-allyl-2-oxo-cyclopentane carboxylate[83] (**4a**) ($C_{11}H_{16}O_3$, 196.243 g/mol) as a colorless oil.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 197 (M^++1, 100), 168 (30), 123 (30), 105 (25), 94 (38), 55 (12). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3078 (m), 2979 (s), 2908 (s), 1751 (s), 1727 (s), 1640 (s), 1465 (s), 1390 (s), 1295 (s), 958 (s), 860 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.21 (t, 3H, ^3J = 7.03 Hz, CH_3-12), 1.84-2.02 (m, 3H), 2.15-2.43 (m, 4H), 2.65 (m, 1H), 4.13 (q, 2H, ^3J = 7.03 Hz, CH_2-11), 5.06 (ddd, 2H, ^3J = 17.82 Hz, ^3J = 10.79 Hz, ^3J = 7.03 Hz, CH_2-8), 5.7 (dddd, 1H, ^3J =



4a

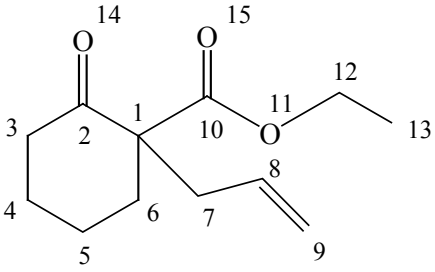
17.82 Hz, ^{3}J = 10.54 Hz, ^{3}J = 7.28 Hz, ^{3}J = 7.28 Hz, CH-7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-12), 19.4, 32.1, 37.7, 38.0 (CH_2, C-3/4/5/6), 59.8 (Cq, C-1), 61.4 (CH_2, C-11), 120.0 (CH_2, C-8), 132.9 (CH, C-7), 170.8 (CO, C-9), 214.6 (CO, C-2).

R 5: Synthesis[82] of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (4b)

Amounts:	10.0 g	(58.0 mmol)	ethyl 2-oxo-cyclohexane carboxylate (**65b**)
	2.32 g	(58.0 mmol)	NaH (60 % dispersion in mineral oil)
	6.96 g	(58.0 mmol)	allyl bromide (**66**)
	100 ml		dry THF

Procedure: Analogously to R 4.

Work-up: The combined organic layer is dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 11.1 g (52.7 mmol, 91 % yield) of ethyl 1-allyl-2-oxo-cyclohexane carboxylate[83] (**4b**) ($C_{12}H_{18}O_3$, 210.270 g/mol) are isolated by bulb-to-bulb distillation (T = 50 °C, 7.0 x 10^{-2} mbar) as a colorless oil.



4b

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 211 (M^++1, 100), 210 (10), 137 (55), 119 (87), 108 (30), 55 (10). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2979 (s), 2941 (s), 2866 (s), 1746 (s), 1726 (s), 1639 (s), 1463 (s), 1387 (s), 1282 (s), 918 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 3H, ^{3}J = 7.03 Hz, CH_3-13), 1.14-1.36 (m, 1H), 1.54-1.73 (m, 3H), 1.93-1.98 (m, 1H), 2.24-2.30 (m, 1H), 2.37-2.44 (m, 3H), 2.52-2.57 (m, 1H), 4.12 (q, 2H, ^{3}J = 7.03 Hz, CH_2-12), 4.96 (ddd, 2H, ^{3}J = 14.56 Hz, ^{2}J = 3.01 Hz, ^{4}J = 0.75 Hz, CH_2-9), 5.66 (dddd, 1H, ^{3}J = 17.32 Hz, ^{3}J = 14.81 Hz, ^{3}J = 7.78 Hz, ^{3}J = 7.28 Hz, CH-8). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-13), 22.3, 27.4, 35.6, 39.2, 41.0 (CH_2, C-3/4/5/6/7), 60.7 (Cq, C-1), 61.1 (CH_2, C-12), 118.1 (CH_2, C-9), 133.2 (CH, C-8), 171.3 (CO, C-10), 207.4 (CO, C-2).

R 6: Synthesis[82] of ethyl 1-allyl-2-oxo-cycloheptane carboxylate (4c)

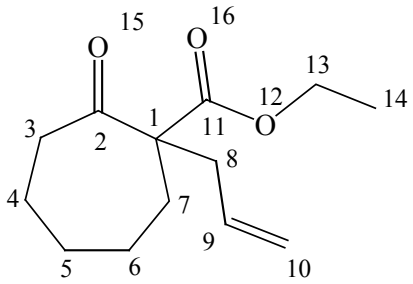
Amounts:	1.0 g	(5.4 mmol)	ethyl 2-oxo-cycloheptane carboxylate (**65c**)

216.0 mg	(5.4 mmol)	NaH (60 % dispersion in mineral oil)
710.0 mg	(6.0 mmol)	allyl bromide (**66**)
30 ml		dry THF

Procedure: Analogously to R 4.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 0.964 g (4.30 mmol, 80 %) of ethyl 1-allyl-2-oxo-cycloheptane carboxylate[83] (**4c**) ($C_{13}H_{20}O_3$, 224.296 g/mol) are isolated by bulb-to-bulb distillation (T = 80 °C, 4.5 x 10^{-2} mbar) as a colorless oil.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 183 (13), 179 (10), 151 (22), 55 (18). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2979 (s), 2861 (s), 1736 (s), 1711 (s), 1639 (s), 1455 (s), 1389 (s), 1293 (s), 938 (s), 859 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.21 (t, 3H, ^3J = 7.23 Hz, CH_3-14), 1.33-1.41 (m, 1H), 1.53-1.60 (m, 3H), 1.63-1.78 (m, 3H), 2.04-2.09 (m, 1H), 2.27-2.32 (m, 1H), 2.39-2.44 (m, 1H), 2.59-2.64 (m, 1H), 2.68-2.72 (m, 1H), 4.13 (q, 2H, ^3J = 7.23 Hz, CH_2-13), 5.03 (dd, 2H, ^3J = 16.46 Hz, ^3J = 10.72 Hz, CH_2-10), 5.68 (ddd, 1H, ^3J = 17.45 Hz, ^3J = 10.47 Hz, ^3J = 6.98 Hz, CH-9). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-14), 24.5, 25.5, 29.8, 32.0, 39.6, 42.0 (CH_2, C-3/4/5/6/7/8), 60.7 (Cq, C-1), 61.1 (CH_2, C-13), 118.5 (CH_2, C-10), 133.5 (CH, C-9), 171.9 (CO, C-11), 209.0 (CO, C-2).



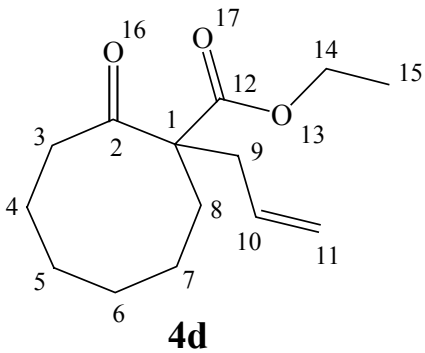
4c

R 7: Synthesis[82] of ethyl 1-allyl-2-oxo-cyclooctane carboxylate (4d)

Amounts:	2.0 g	(20.0 mmol)	ethyl 2-oxo-cyclooctane carboxylate (**65d**)
	0.4 g	(20.0 mmol)	NaH (60 % dispersion in mineral oil)
	1.2 g	(20.0 mmol)	allyl bromide (**66**)
	100 ml		dry THF

Procedure: Analogously to R 4.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 4.56 g (19.2 mmol, 96 %) of ethyl 1-allyl-2-oxo-cyclooctane carboxylate[83] (**4d**) ($C_{14}H_{22}O_3$, 238.323 g/mol) are obtained after purification by bulb-to-bulb distillation (T = 80 °C, 4.5 x 10^{-2} mbar) as a colorless oil.



4d

Spectroscopic data: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.08 (t, 3H, ^{3}J = 7.2 Hz, CH_3-15), 1.2-1.3 (m, 6H), 1.49-1.52 (m, 1H), 1.70-1.82 (m, 2H), 2.02-2.12 (m, 2H), 2.20-2.26 (m, 1H), 2.52-2.66 (m, 2H), 4.02 (q, 2H, ^{3}J = 7.28 Hz, CH_2-14), 4.9 (dd, 2H, $^{3}J_{trans}$ = 17.07 Hz, $^{3}J_{cis}$ = 10.04 Hz, CH_2-11), 5.50 (ddd, 1H, ^{3}J = 16.82 Hz, ^{3}J = 10.04 Hz, ^{3}J = 6.53 Hz, CH-10). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 13.8 (CH_3,C-15), 19.1, 22.4, 23.1, 24.3, 25.0, 35.6 (CH_2, C-3/4/5/6/7/8/9), 60.7 (CH_2, C-14), 63.8 (Cq, C-1), 118.0 (CH_2, C-11), 133.0 (CH, C-10), 171.2 (CO, C-12), 209.7 (CO, C-2).

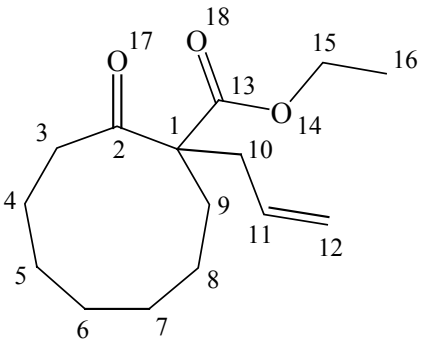
R 8: Synthesis[82] of ethyl 1-allyl-2-oxo-cyclononane carboxylate (4e)

Amounts:	4.0 g	(18.0 mmol)	ethyl 2-oxo-cyclononane carboxylate (**65e**)
	0.72 g	(18.0 mmol)	NaH (60 % dispersion in mineral oil)
	2.16 g	(18.0 mmol)	allyl bromide (**66**)
	100 ml		dry THF

Procedure: Analogously to R 4.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 4.08 g (16.0 mmol, 92 % yield) of ethyl 1-allyl-2-oxo-cyclononane carboxylate (**4e**) ($C_{15}H_{24}O_3$, 252.349 g/mol) are isolated by bulb-to-bulb distillation (T = 80 °C, 4.5 x 10^{-2} mbar) as a colorless oil.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 253 (M^{+}+1, 8), 223 (10), 207 (24), 179 (88), 137 (38), 95 (98), 67 (100), 55 (30).



4e

IR (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2927 (s), 2874 (s), 2853 (s), 1739 (s), 1708 (s) 1640 (s), 1559 (s), 1455 (m), 1388 (s), 1295 (s), 955 (s), 832 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 3H, ^{3}J = 7.03 Hz, CH_3-16), 1.49 (m, 2H), 1.61-1.72 (m, 4H), 1.79-1.84 (m, 2H), 1.89-2.02 (m, 3H), 2.09-2.15 (m, 1H), 2.20-2.24 (m, 2H), 2.45 (m, 1H), 2.68 (m, 1H), 4.12 (q, 2H, ^{3}J = 7.03 Hz, CH_2-15), 4.90 (dd, 1H, $^{3}J_{cis}$ = 10.29 Hz, ^{2}J = 1.25 Hz, CH_2-12), 4.98 (dd, 1H, $^{3}J_{trans}$ = 17.07 Hz, $^{2}J_{gem}$ = 1.25 Hz, CH_2-12), 5.77 (ddd, 1H,

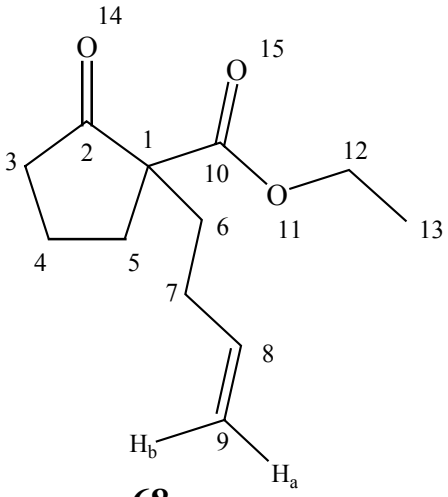
^3J = 17.07 Hz, ^3J = 10.29 Hz, ^3J = 6.53 Hz, CH-11). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-16), 23.1, 24.1, 25.4, 28.3, 28.8, 29.2, 30.0, 38.5, (CH_2, C-3/4/5/6/7/8/9/10), 61.1 (CH_2, C-15), 61.9 (Cq, C-1), 114.7 (CH_2, C-12), 138.0 (CH, C-11), 171.7 (CO, C-13), 212.3 (CO, C-2).

c. Synthesis of ethyl 1-(but-3-enyl)-2-oxo-cycloalkane carboxylates (68a-c,e)

R 9: Synthesis[84] of ethyl 1-(but-3-enyl)-2-oxo-cyclopentane carboxylate (68a)

To a stirred mixture of ethyl 2-oxo-cyclopentane carboxylate (**65a**) (2.0 g, 12.0 mmol) and potassium *t*-butoxide in *t*-butanol (14.1 ml, 1.0 M), potassium iodide (0.12 g, 0.77 mmol) and 4-brom-1-butene (**67**) (2.02 g, 15.0 mol) are added. After being stirred under argon at room temperature for 2 h, the reaction mixture is gently refluxed for 24 hours. The cooled reaction mixture is treated with water (30 ml), extracted with Et_2O (3 x 20 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue is distilled bulb-to-bulb (T = 60 °C, 5.0 x 10^{-2} mbar) giving 2.22 g (10.55 mmol, 85 % yield) of ethyl 1-(but-3-enyl)-2-oxo-cyclopentane carboxylate[176] (**68a**) ($C_{12}H_{18}O_3$, 210.270 g/mol) as a colorless oil.

Spectroscopic data: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.17 (t, 3H, ^3J = 7.23 Hz, CH_3-13), 1.37-1.40 (m, 1H), 1.57-1.62 (m, 1H), 1.83-1.97 (m, 5H), 2.15-2.23 (m, 1H), 2.32-2.37 (m, 1H), 2.46-2.49 (m, 1H), 4.09 (q, 2H, ^3J = 7.23 Hz, CH_2-12), 4.89 (dd, 1H, $^3J_{cis}$ = 10.72 Hz, CH-9a), 4.96 (dd, 1H, $^3J_{trans}$ = 17.2 Hz, CH-9b), 5.71 (dddd, 1H, ^3J = 16.46 Hz, ^3J = 10.22 Hz, ^3J = 7.73 Hz, ^3J = 6.48 Hz, CH-8). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-13), 19.5, 29.0, 32.7, 32.8, 37.7 (CH_2, C-3/4/5/6/7), 60.0 (Cq, C-1), 61.2 (CH_2, C-12), 114.9 (CH_2, C-9), 137.5 (CH, C-8), 170.7 (CO, C-10), 214.5 (CO, C-2).



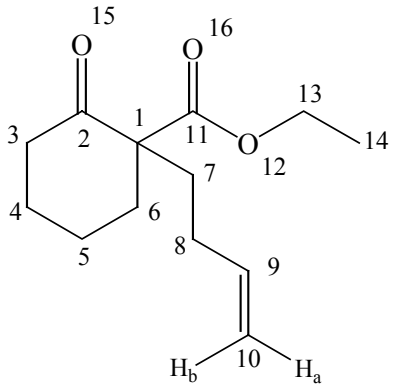
68a

R 10: Synthesis[84] of ethyl 1-(but-3-enyl)-2-oxo-cyclohexane carboxylate (68b)

Amounts:	2.0 g	(11.7 mmol)	ethyl 2-oxo-cyclohexane carboxylate (**65b**)
	1.44 g	(12.8 mmol)	potassium *t*-butoxide (in *t*-BuOH)
	0.117 g	(0.71 mmol)	potassium iodide
	1.9 g	(14.0 mmol)	4-brom-1-butene (**67**)
	50 ml		*t*-BuOH

Procedure: Analogously to R 9.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 2.23 g (9.94 mmol, 85 % yield) of ethyl 1-(but-3-enyl)-2-oxo-cyclohexane carboxylate[84] (**68b**) ($C_{13}H_{20}O_3$, 224.296 g/mol) are isolated by bulb-to-bulb distillation (T = 60 °C, 5.0 x 10^{-2} mbar) as a colorless oil.



68b

Spectroscopic data: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.16 (t, 3H, ^3J = 7.28 Hz, CH_3-14), 1.31-1.38 (m, 1H), 1.50-1.66 (m, 5H), 1.83-1.93 (m, 3H), 2.33-2.43 (m, 3H), 4.10 (q, 2H, ^3J = 7.28 Hz, CH_2-13), 4.82 (d, 1H, ^3J = 10.04 Hz, CH-10a), 4.90 (dd, 1H, ^3J = 17.07 Hz, ^2J = 1.25 Hz, CH-10b), 5.68 (ddd, 1H, ^3J = 16.56 Hz, ^3J = 10.54 Hz, ^3J = 6.27 Hz, CH-9). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 13.8 (CH_3, C-14), 22.3, 27.4, 28.3, 33.6, 35.9, 40.8 (CH_2, C-3/4/5/6/7/8), 60.3 (Cq, C-1), 60.9 (CH_2, C-13), 114.4 (CH_2, C-10), 137.8 (CH, C-9), 171.6 (CO, C-11), 207.4 (CO, C-2).

R 11: Synthesis[84] of ethyl 1-(but-3-enyl)-2-oxo-cycloheptane carboxylate (68c)

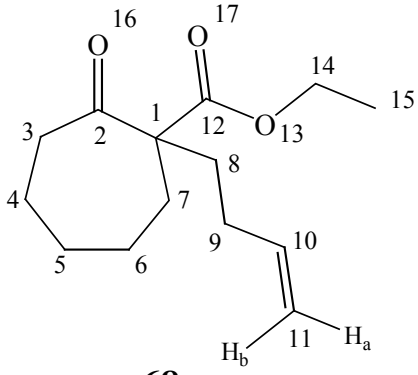
Amounts:	1.00 g	(4.4 mmol)	ethyl 2-oxo-cycloheptane carboxylate (**65c**)
	540.0 mg	(4.4 mmol)	potassium *t*-butoxide (in *t*-BuOH)
	44.0 mg	(0.26 mmol)	potassium iodide
	710.0 mg	(5.28 mmol)	4-brom-1-butene (**67**)
	50 ml		*t*-BuOH

Procedure: Analogously to R 9.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 850.0 mg (3.56 mmol, 81 % yield) of ethyl 1-(but-3-enyl)-

2-oxo-cycloheptane carboxylate[177] (**68c**) are isolated by bulb-to-bulb distillation (T = 60 °C, 5.0 x 10^{-2} mbar) ($C_{14}H_{22}O_3$, 238.323 g/mol) as a colorless oil.

Spectroscopic data: **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2977 (s), 2860 (s), 1736 (s), 1708 (s), 1640 (s), 1454 (s), 1389 (s), 1298 (s), 941 (s), 859 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.20 (t, 3H, ^{3}J = 7.03 Hz, CH_3-15), 1.56-1.70 (m, 8H), 1.94-2.13 (m, 4H), 2.42-2.45 (m, 1H), 2.52-2.61 (m, 1H), 4.13 (q, 2H, ^{3}J = 7.03 Hz, CH_2-14), 4.87 (d, 1H, ^{3}J = 10.29 Hz, CH-11a), 4.95 (dd, 1H, ^{3}J = 17.32 Hz, ^{2}J = 1.51 Hz, CH-11b), 5.69 (ddd, 1H, ^{3}J = 16.82 Hz, ^{3}J = 10.29 Hz, ^{3}J = 6.27 Hz, CH-10). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-15), 24.7, 25.4, 28.8, 29.8, 32.8, 34.5, 41.9 (CH_2, C-3/4/5/6/7/8/9), 60.9 (CH_2, C-14), 62.4 (Cq, C-1), 114.6 (CH_2, C-11), 137.9 (CH, C-10), 172.3 (CO, C-12), 209.2 (CO, C-2).



68c

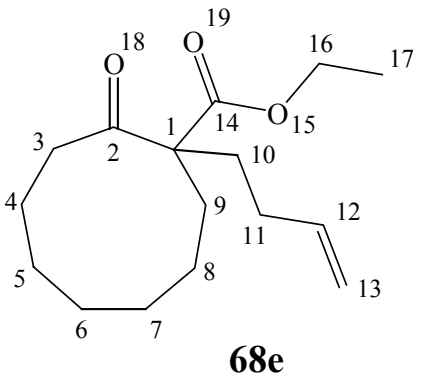
R 12: Synthesis[84] of ethyl 1-(but-3-enyl)-2-oxo-cyclononane carboxylate (68e)

Amounts:	5.0 g	(23.0 mmol)	ethyl 2-oxo-cyclononane carboxylate (**65e**)
	3.13 g	(28.0 mmol)	potassium *t*-butoxide (in *t*-butanol)
	238.0 mg	(1.43 mmol)	potassium iodide
	3.78 g	(28.0 mmol)	4-brom-1-butene (**67**)
	50 ml		*t*-butanol

Procedure: Analogously to R 9.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 2.913 g (10.0 mmol, 47 % yield) of ethyl 1-(but-3-enyl)-2-oxo-cyclononane carboxylate (**68e**) ($C_{16}H_{26}O_3$, 266.376 g/mol) are isolated by bulb-to-bulb distillation (T = 60 °C, 5.0 x 10^{-2} mbar) as a colorless oil.

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 266 (M^+, 4), 225 (34), 212 (30), 193 (6), 138 (21), 81 (77), 67 (75), 55 (92). **High Resolution Mass**: Calculated: 266.1882 Found: 266.1887. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (w), 2929 (vs), 2873 (s), 2854 (s), 1737 (s), 1708 (vs), 1641 (m), 1477 (m), 1467



68e

(s), 1446 (s), 1195 (s), 1130 (s), 1031 (m), 912 (m). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.17 (t, 3H, ^{3}J = 7.03 Hz, CH_3-17), 1.25-1.41 (m, 8H), 1.61-1.68 (m, 2H), 1.76-2.24 (m, 7H), 2.63-2.71 (m, 1H), 4.10 (q, 2H, ^{3}J = 7.03 Hz, CH_2-16), 4.92 (ddd, 2H, $^{3}J_{trans}$ = 17.07 Hz, $^{3}J_{cis}$ = 10.04 Hz, J_{gem} = 1.51 Hz, CH_2-13), 5.77 (ddd, 1H, ^{3}J = 16.56 Hz, ^{3}J = 10.04 Hz, ^{3}J = 6.27 Hz, CH-12). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-17), 19.7, 23.0, 23.5, 24.5, 24.9, 27.3, 28.5, 30.2, 37.4 (CH_2, C-3/4/5/6/7/8/9/10/11), 60.9 (CH_2, C-16), 63.5 (Cq, C-1), 114.6 (CH_2, C-13), 137.6 (CH, C-12), 172.1 (CO, C-14), 210.5 (CO, C-2).

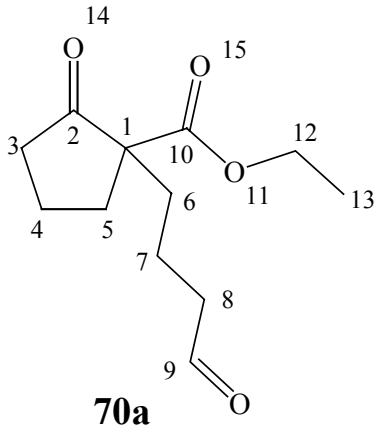
4.3 Stepwise hydroformylation/ intramolecular aldol addition of ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates

4.3.1 First step: hydroformylation reactions

a. Ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a-c) as starting materials

R 13: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (70a)

A solution of ethyl 1-allyl-2-oxo-cyclopentane carboxylate (**4a**) (2.0 g, 10.0 mmol), 313.6 mg (5 mol %) of BIPHEPHOS (**29**), and [Rh(acac)$(CO)_2$] (**28**) (1 mol %) in anhydrous dichloromethane (20 ml) is placed in an autoclave. After flushing with argon the reactor is pressurized with 10 bar carbon monoxide and 10 bar hydrogen, the mixture is magnetically stirred and heated to 60 °C for 3 days. Then the autoclave is allowed to cool to room temperature. After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed evaporation and the residue is analyzed by gas chromatography. The product of the reaction mixture is separated by bulb-to-bulb distillation (T = 85 °C, P = 5 x 10^{-2} mbar) and 1.853 g (8.2 mmol, 82 % yield) of ethyl 2-oxo-1-(4-oxo-pentyl)cyclopentane carboxylate[178] (**70a**) ($C_{12}H_{18}O_4$, 226.269 g/mol) are obtained.



70a

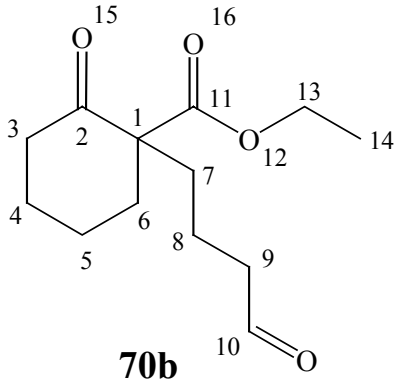
Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 226 (1), 198 (8), 196 (48), 156 (92), 152 (62), 79 (98), 55 (25). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2963 (s), 2832 (s), 2725 (w), 1749 (s), 1723 (s), 1450 (m). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.21 (t, 3H, ^{3}J = 7.23 Hz, CH_3-13), 1.50-1.68 (m, 3H), 1.86-2.01 (m, 4H), 2.22 (m, 1H), 2.35-2.50 (m, 4H), 4.12 (q, 2H, ^{3}J = 7.23 Hz, CH_2-12), 9.7 (br t, 1H, ^{3}J = 1.50 Hz, C*H*O-9). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-13), 17.4, 19.5, 32.7, 33.0, 37.8, 43.8 (CH_2-3/4/5/6/7/8), 60.1 (Cq, C-1), 61.4 (CH_2, C-12), 170.8 (CO, C-10), 201.7 (CO, C-9), 214.6 (CO, C-2).

R 14: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (70b)

Amounts:	2.0 g	(9.5 mmol)	ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**)
	24.0 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	313.0 mg	(5.0 % mol)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously toR 13; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography giving 2.32 g (9.3 mmol, 98 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)[178] ($C_{13}H_{20}O_4$, 240.296 g/mol).



70b

Spectroscopic data: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 3H, ^{3}J = 7.23 Hz, CH_3-14), 1.39-1.95 (m, 10H), 2.36-2.47 (m, 4H), 4.15 (q, 2H, ^{3}J = 7.23 Hz, CH_2-13), 9.68 (br s, 1H, ^{3}J = 1.50 Hz, C*H*O-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-14), 16.9, 22.4, 27.4, 33.9, 35.90, 40.9, 43.8 (CH_2-3/4/5/6/7/8/9), 60.5 (Cq, C-1), 61.1 (CH_2, C-13), 171.6 (CO, C-11), 201.8 (CO, C-10), 207.6 (CO, C-2).

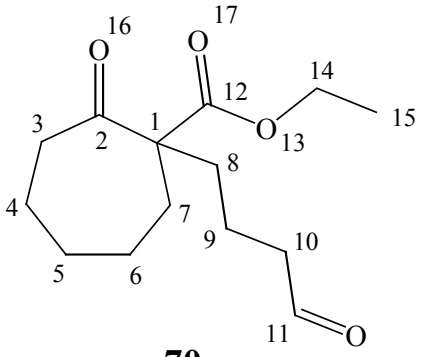
R 15: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (70c)

Amounts:	4.0 g	(17.8 mmol)	ethyl 1-allyl-2-oxo-cycloheptane carboxylate (**4c**)
	46.0 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	550.0 mg	(5.0 % mol)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously to R 13, 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and 4.38 g (17.2 mmol, 97 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (**70c**) ($C_{14}H_{22}O_4$, 254.3221 g/mol) are obtained as a colorless single product without any further purification.

Spectroscopic data: of **70c**: **GC-MS** (EI, 70 eV): m/z (%) = 254 (2), 209 (10), 181 (8), 109 (12), 95 (33), 81 (39), 67 (56), 55 (55). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3428 (m), 2935 (vs), 2863 (s), 2721 (m), 1727 (vs), 1712 (vs), 1455 (s), 1455 (s), 1446 (s), 1224 (s), 1176 (s), 1151 (s), 970 (m). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 3H, ^3J = 7.23 Hz, CH_3-15), 1.35 (m, 2H), 1.51-1.54 (m, 6H), 1.68 (m, 2H), 1.89 (m, 1H), 2.06-2.11 (m, 1H), 2.36-2.42 (m, 3H), 2.56-2.61 (m, 1H), 4.14 (q, 2H, ^3J = 7.23 Hz, CH_2-14), 9.68 (br t, 1H, ^3J = 1.50 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-15), 17.3, 24.7, 25.3, 29.7, 32.7, 34.6, 41.9, 43.8 (CH_2-3/4/5/6/7/8/9/10), 61.0 (CH_2, C-14), 62.5 (Cq, C-1), 172.1 (CO, C-12), 201.8 (CO, C-11), 209.2 (CO, C-2).



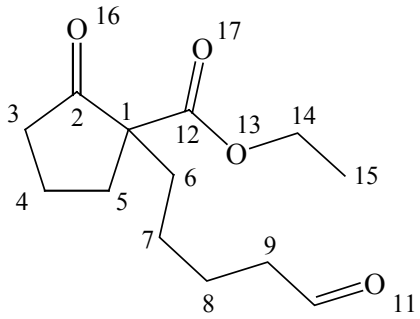
70c

b. Ethyl (1-but-3-enyl)-2-oxo-cycloalkane carboxylates (68a-c) as starting materials

R 16: Synthesis of ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (71a).

A solution of 2.0 g (9.5 mmol) of ethyl 1-(but-3-enyl)-2-oxo-cyclopentane carboxylate (**68a**), 297 mg (5.0 mol %) of BIPHEPHOS (**29**) and 49.0 mg (1.0 mol %) of [Rh(acac)(CO)$_2$] (**28**) in anhydrous dichloromethane (20 ml) is placed in an autoclave. After flushing with argon the reactor is pressurized with 10 bar carbon monoxide and 10 bar hydrogen, the mixture is magnetically stirred and heated to 60 °C for 3 days. Then the autoclave is allowed to cool to room temperature. After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas chromatography. The product is separated by bulb-to-bulb distillation (T = 110 °C, P = 5.5 x 10^{-2} mbar) obtaining 2.057 g (8.57 mmol, 61 % yield) of the linear aldehyde ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (**71a**) ($C_{13}H_{20}O_4$, 240.296 g/mol) as a colorless oil.

Spectroscopic data of **71a**: **GC-MS** (EI, 70 eV): m/z (%) = 241 (M^++1, 4), 212 (5), 195 (5), 166 (10), 83 (40), 55 (40). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2940 (s), 2865 (s), 2721 (w), 1724 (vs), 1720 (vs), 1712 (vs), 1446 (m), 1450 (s), 1218 (s), 1178 (s), 1137 (s), 1097 (s), 1022 (m). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.18 (t, 3H, ^{3}J = 7.03 Hz, CH_3-15), 1.55-2.46 (m, 12H), 4.08 (q, 2H, ^{3}J = 7.03 Hz, CH_2-14), 9.69 (br s, 1H, C*H*O-10). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-15), 19.5, 22.1, 24.2, 32.7, 33.3, 37.8, 43.4 (CH_2, C-3/4/5/6/7/8/9), 60.1 (Cq, C-1), 61.2 (CH_2, C-14), 170.8 (CO, C-12), 202.2 (CO, C-10), 214.7 (CO, C-2).



71a

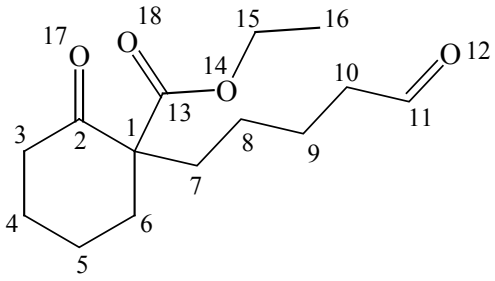
R 17: Synthesis of ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (71b)

Amounts:	2.0 g	(8.9 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cyclohexane carboxylate (**68b**)
	45.9 mg	(1.0 mol %)	[Rh(acac)(CO)$_2$] (**28**)
	279.0 mg	(5.0 mol %)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously to R 13; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: The solvent is removed and the residue is analyzed by gas-chromatography. The product is then separated by bulb-to-bulb distillation, T = 110 °C, P = 5.0 x 10^{-2} mbar, giving 0.79 g (3.0 mmol, 35 % yield) of ethyl 2-oxo-1-(5-oxo-

pentyl)cyclohexane carboxylate (**71b**) as a colorless oil. **Spectroscopic data**: of **71b**: **GC-MS** (EI, 70 eV): m/z (%) = 254 (2), 225 (30), 209 (95), 181 (70), 152 (5), 124 (40), 96 (10), 55 (10). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2940 (s), 2865 (s), 2721 (w), 1724 (vs), 1720 (vs), 1712 (vs), 1463 (s), 1450 (s), 1307 (s), 1241 (s), 1207 (s), 1135 (s), 1097 (s), 1022 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.22 (t, 3H, ^3J = 7.03 Hz, CH_3-16), 1.38 (m, 1H), 1.50 (m, 1H), 1.58 (m, 3H), 1.63-1.71 (m, 3H), 1.82 (m, 1H), 1.95 (m, 1H), 2.38-2.46 (m, 6H), 4.15 (q, 2H, ^3J = 7.03 Hz, CH_2-15), 9.7 (t, 1H, ^3J = 1.75 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-16), 22.3, 22.5, 23.8, 27.5, 34.3, 36.1, 41.0, 43.5 (CH_2, C-3/4/5/6/7/8/9/10), 60.6 (Cq, C-1), 61.1 (CH_2, C-15), 170.8 (CO, C-13), 202.3 (CO, C-11), 207.9 (CO, C-2).



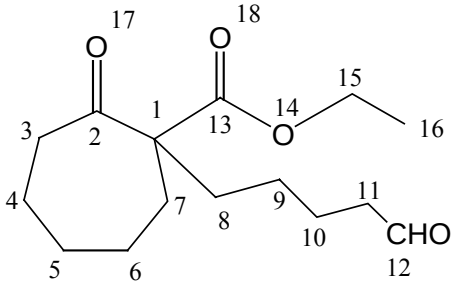
71b

R 18: Synthesis of ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (71c)

Amounts:	0.40 g	(1.6 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cycloheptane carboxylate (**68c**)
	4.1 mg	(1.0 mol %)	$[Rh(acac)(CO)_2]$ (**28**)
	50.0 mg	(5.0 mol %)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously to R 13, 20 bar [$p(CO):p(H_2)$ = 1:1]; T = 60 °C, 72 h.

Work-up: The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. The product is then separated by column chromatography with a mixture of cyclohexane-MTBE (3:1), and 0.171 g (0.6 mmol, 40 % yield) of ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (**71c**) are obtained as a colorless oil.



71c

Spectroscopic data of **71c**: **GC-MS** (EI, 70 eV): m/z (%) = 268 (M^+, 1), 223 (6), 195 (7), 111 (8), 55 (41). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2935 (vs), 2863 (s), 2721 (m), 1731 (vs), 1727 (vs), 1712 (vs), 1455 (s), 1446 (s), 1417 (m), 1367 (m), 1309 (m), 1251 (s), 1224 (s), 1176 (s), 1151 (s), 1097 (s), 1025 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] =

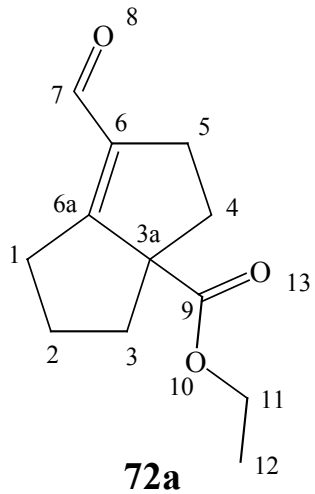
1.21 (t, 3H, ^{3}J = 6.27 Hz, CH_3-16), 1.35 (m, 2H), 1.50-1.69 (m, 10H), 1.92 (m, 1H), 2.08 (m, 1H), 2.39 (m, 3H), 2.58 (m, 1H), 4.11 (q, 2H, ^{3}J = 7.03 Hz, CH_2-15), 9.70 (br s, 1H, C*H*O-12). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-16), 22.3, 24.1, 24.7, 25.4, 29.7, 32.8, 35.0, 42.0, 43.5 (CH_2, C-3/4/5/6/7/8/9/10/11), 61.0 (CH_2, C-15), 62.5 (Cq, C-1), 172.3 (CO, C-13), 202.3 (CO, C-12), 209.5 (CO, C-2).

4.3.2 Second step: Step-wise intramolecular aldol addition under acidic conditions

a. Ethyl 2-oxo-1-(4-oxo-butyl)cycloalkane carboxylates (70a-c)

R 19: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

To a solution of ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (**70a**) (1.0 g, 4.4 mmol) in 20 ml of DCM is added HCl 7N (14.0 ml) and the mixture is stirred for 18h at room temperature. Then, the solution is cautiously neutralized with $NaHCO_3$ and the aqueous layer is extracted with ether (3 x 20 ml). The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 905 mg (4.3 mmol, 99 % yield) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained as a colorless oil.



72a

Spectroscopic data of **72a**: **GC-MS** (EI, 70 eV): m/z (%) = 209 (M^{+}+1, 67), 208 (22), 179 (2), 163 (7), 135 (100), 107 (45), 79 (68), 65 (15). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2938 (s), 2868 (w), 1725 (s), 1683 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.20 (t, 3H, ^{3}J = 7.03 Hz, CH_3-12), 1.30 (m, 1H), 1.44 (m, 1H), 1.65-1.73 (m, 2H), 1.88-1.93 (m, 1H), 2.19 (m, 2H), 2.49-2.57 (m, 2H), 3.18 (m, 1H), 4.12 (q, 2H, ^{3}J = 7.03 Hz, CH_2-11), 10.0 (s, 1H, C*H*O-7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-12), 23.5, 25.4, 28.2, 35.3, 38.2 (CH_2, C-1/2/3/4/5), 60.9 (CH_2, C-11), 137.7 (Cq, C-6), 163.7 (Cq, C-6a), 174.4 (CO, C-9), 188.0 (CO, C-7).

R 20: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

To a solution of ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (**70a**) (1.0 g, 4.4 mmol) in 20 ml of DCM is added H_2SO_4 conc. (98 %) 1.05 ml (16.0 mmol) and the mixture is stirred for 3 hours at T = 0 °C and for other 21 hours at room temperature. Then, the solution is cautiously neutralized with $NaHCO_3$ and the aqueous layer is extracted with ether and washed with brine. The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum obtaining 906 mg (4.3 mmol, 99 % yield) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained as a colorless oil. **Spectroscopic data** of **72a** are consistent with those reported in R 19.

R 21: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

Amounts:	1.0 g	(4.4 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (**70a**)
	14.0 ml		HCl (7N)
	20 ml		dioxane

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 560 mg (2.6 mmol, 61 %) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained. **Spectroscopic data** of **72a** are consistent with those reported in R 19.

R 22: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

Amounts:	1.0 g	(4.4 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (**70a**)
	1.05 ml		H_2SO_4 conc. (98 %)
	20 ml		dioxane

Procedure: Analogously to R 20.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 906 mg (4.3 mmol, 99 % yield) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained. **Spectroscopic data** of **72a** are consistent with those reported in R 19.

R 23: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

To a solution of ethyl 2-oxo-1-(4-oxo-butyl)cyclopentane carboxylate (**70a**) 1.0 g (4.4 mmol), in 20 ml of DCM is added PTSA 42.0 mg (5.0 % mol) and the mixture is stirred for 72 h at reflux. Then, the solution is extracted with Et_2O, the combined organic phases are washed with water and dried over anhydrous $MgSO_4$. After evaporation of solvent under reduced pressure, the residue is analyzed by gas-chromatography. 906 mg (4.3 mmol, 99 % yield) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained. **Spectroscopic data** of **72a** are consistent with those reported in R 19.

R 24: Synthesis of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (72b)

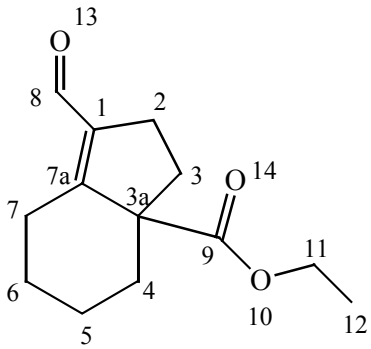
Amounts:	1.0 g	(4.1 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)
	13.1 ml		HCl (7N)
	20 ml		DCM

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 0.891 g (4.01 mmol, 99 % yield) of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) is obtained.

Spectroscopic data of **72b**: **GC-MS** (EI, 70 eV): m/z (%) = 222 (M^+, 7), 149 (30), 121 (28), 29 (100). **High Resolution Mass**: Calculated: 222.1256; Found: 222.1256. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3307 (w), 2938 (vs), 2859 (s), 2730 (s), 1727 (vs), 1668 (vs, 1446 (s), 1390 (m), 1224 (s), 1176 (s), 1027 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm]

= 1.19 (t, 3H, ^3J = 6.98 Hz, CH_3-12), 1.29-1.43 (m, 3H), 1.67 (m, 2H), 1.89 (m, 1H), 2.19 (m, 2H), 2.48-2.56 (m, 3H), 3.17 (m, 1H), 4.11 (q, 2H, ^3J = 6.98 Hz, CH_2-11), 9.99 (s, 1H, C*H*O-8). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-12), 23.5, 25.4, 26.9, 28.2, 35.3, 38.1 (CH_2, C-2/3/4/5/6/7), 60.6 (Cq, C-3a), 60.8 (CH_2, C-11), 137.6 (Cq, C-1), 163.9 (Cq, C-7a), 174.4 (CO, C-9), 188.0 (CO, C-8).



72b

R 25: Synthesis of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (72b)

Amounts:	0.5 g	(2.0 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)
	0.9 ml		H_2SO_4 conc. (98 %)
	15 ml		DCM

Procedure: Analogously to R 20.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum obtaining 0.435 g (1.96 mmol, 98 % yield) of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) is obtained. **Spectroscopic data** of **72b** are consistent with those reported in R 24.

R 26: Synthesis of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (72b)

Amounts:	1.0 g	(4.1 mmol)	2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)
	13.1 ml		HCl (7N)
	20 ml		dioxane

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 473 mg (2.1 mmol, 52 % yield) of ethyl 1-formyl-

2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) is obtained.

Spectroscopic data of **72b** are consistent with those reported in R 24.

R 27: Synthesis of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (72b)

Amounts:	0.5 g	(2.0 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)
	0.90 ml		H_2SO_4 conc. (98 %)
	20 ml		dioxane

Procedure: Analogously to R 20.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum giving 0.435 g (1.96 mmol, 98 % yield) of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) is obtained. **Spectroscopic data** of **72b** are consistent with those reported in R 24.

R 28: Synthesis of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (72b)

Amounts:	1.0 g	(4.1 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**)
	40.0 mg	(5.0 % mol)	PTSA
	20 ml		DCM

Procedure: Analogously to R 23.

Work-up: Then, the solution is extracted with Et_2O, the combined organic phases are washed with water and dried over anhydrous $MgSO_4$.. After evaporation of solvent under reduced pressure, the residue is analyzed by gas-chromatography. 0.88 g (3.96 mmol, 97 % yield) of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) is obtained.

Spectroscopic data of **72b** are consistent with those reported in R 24.

R 29: Attempt to synthesize ethyl 1-formyl-2,4,5,6,7,8,-hexahydro-azulene-3a(3*H*) carboxylate (72c)

Amounts:	0.15 g	(0.6 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (**70c**)
	2.0 ml		HCl (7N)
	10 ml		DCM

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. Starting material is recovered.

R 30: Attempt to aldol addition of ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (70c)

Amounts:	0.15 g	(0.6 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (**70c**)
	2.00 ml		HCl (7N)
	10 ml		dioxane

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. Starting material is recovered.

b. Ethyl 2-oxo-1-(5-oxo-pentyl)cycloalkane carboxylates (71a-c)

R 31: Attempted aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (71a)

Amounts:	0.3 g	(0.6 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (**71a**)
	4.0 ml		HCl (7N)
	10 ml		DCM

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. After removal of solvent, no products are obtained: starting material is recovered.

R 32: Attempted aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (71a)

Amounts:	0.3 g	(0.6 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (**71a**)
	0.90 ml		H_2SO_4 conc. (98 %)
	10 ml		DCM

Procedure: Analogously to R 20.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. After removal of solvent no products are obtained starting material is recovered.

R 33: Attempted aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (71b)

Amounts:	0.3 g	(0.6 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (**71b**)
	4.0 ml		HCl (7N)
	10 ml		DCM

Procedure: Analogously to R 19.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. After removal of the solvent, no products are obtained starting material is recovered.

R 34: Attempted aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (71b)

Amounts:	0.3 g	(0.6 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (**71b**)
		0.90 ml	H_2SO_4 conc. (98 %)
		10 ml	DCM

Procedure: Analogously to R 20.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. After removal of the solvent no products are obtained starting material is recovered.

R 35: Attempted aldol addition of ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (71c)

Amounts:	0.2 g	(0.74 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (**71c**)
	2.0 ml		HCl (7N)
	10 ml		DCM

Procedure: Analogously to R 23; T = 60 °C, t = 72 h.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. After removal of the solvent no products are obtained starting material is recovered.

4.3.3 Attempts of tandem hydroformylation/ aldol addition on ethyl 1-alkenyl-2-oxo-cycloalkane carboxylates.

a. Ethyl 1-allyl-2-oxo-cycloalkane carboxylates (4a-e)

R 36: Synthesis of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (72a)

A solution of ethyl 1-allyl-2-oxo-cyclopentane carboxylate (**4a**) (1.0 g, 5.1 mmol), 150 mg (4.0 mol %) of BIPHEPHOS (**29**), 49.2 mg (5.0 mol %) of PTSA and 13.1 mg (1.0 mol %) of [Rh(acac)$(CO)_2$] (**28**) in anhydrous dichloromethane (20 ml) is placed in an autoclave. After flushing with argon the reactor is pressurized with 10 bar carbon monoxide and 10 bar hydrogen, the mixture is magnetically stirred and heated to 60 °C for 3 days. Then the autoclave is allowed to cool to room temperature. After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas chromatography. The mixture is separated by column chromatography using a mixture of cyclohexane and MTBE (8:1) as eluent 698.0 mg (3.35 mmol, 65 % yield) of ethyl 6-formyl-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate (**72a**) ($C_{12}H_{16}O_3$, 208.254 g/mol) are obtained as a colorless oil. **Spectroscopic data** of **72a** are consistent with those reported in R 19.

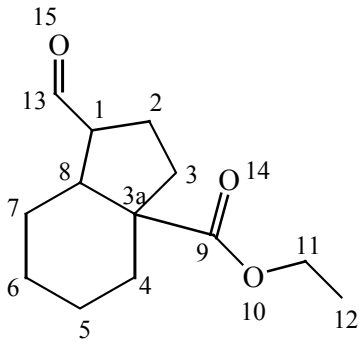
R 37: Conversion of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (4b)

Amounts:	1.0 g	(4.7 mmol)	ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**)
	24.0 mg	(1.0 mol %)	[Rh(acac)$(CO)_2$] (**28**)
	147.0 mg	(4.0 mol %)	BIPHEPHOS (**29**)
	45.0 mg	(5.0 mol %)	PTSA
	20 ml		abs. DCM

Procedure: Analogously to R 36; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas chromatography. By bulb-to-bulb distillation (T = 75 °C, 7.0 x 10^{-2} mbar) are obtained 0.712 g (79 % by G.C-analysis) as a colorless mixture of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) and ethyl 1-formyl-octahydro-3a*H*-indene-3a-carboxylate (**76b**) ($C_{13}H_{20}O_3$, 224.280 g/mol) in a ratio of 3:1 detected by ^{1}H-NNR analysis. The ethyl 1-formyl-octahydro-3a*H*-indene-3a-carboxylate (**76b**) is present as a mixture of 2 diastereoisomers in a ratio of 1:1.3 calculated by ^{1}H-NNR analysis. **Spectroscopic data** of **72b** are consistent with those reported in R 24.

The presence of the ethyl 1-formyl-octahydro-3a*H*-indene-3a-carboxylate (**76b**) is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 9.54 (d, 1H, ^{3}J = 2.76 Hz, C*H*O-13, DS1/DS2), 9.72 (d, 1H, ^{3}J = 1.76 Hz, C*H*O-13, DS2/DS1). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 41.5 (CH, C-8, DS1/DS2), 42.0 (CH, C-8, DS2/DS1), 54.3 (CH, C-1, DS1/DS2), 54.4 (CH, C-1, DS2/DS1), 203.0 (CO, C-13, DS-1/2), 203.5 (CO, C-13, DS-2/1).



76b

R 38: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (70c)

Amounts:	812.0 mg	(3.6 mmol)	ethyl 1-allyl-2-oxo-cycloheptane carboxylate (**4c**)
	2.00 mg	(1.0 mol %)	$[Rh(acac)(CO)_2]$ (**28**)
	111.0 mg	(4.0 mol %)	BIPHEPHOS (**29**)
	34.0 mg	(5.0 mol %)	PTSA
	20 ml		dry DCM

Procedure: Analogously to R 36; 20 bar [$p(CO):p(H_2)$ = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 0.916 g (3.6 mmol, 98 %) of ethyl 2-oxo-1-(4-oxo-butyl)cycloheptane carboxylate (**70c**) ($C_{14}H_{22}O_4$, 254.3221 g/mol) are isolated as a colorless single product without any further purification.

Spectroscopic data of **70c** are consistent with those reported in R 15.

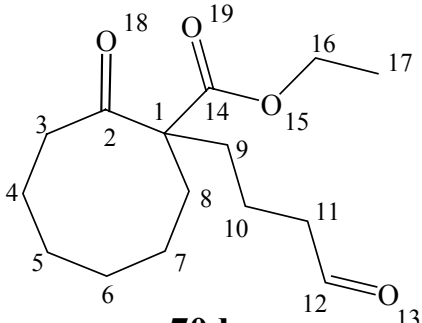
R 39: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cyclooctane carboxylate (70d)

Amounts:	1.00 g	(4.2 mmol)	ethyl 1-allyl-2-oxo-cyclooctane carboxylate (**4d**)
	10.0 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	132.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	40.0 mg	(5.0 % mol)	PTSA

20 ml		dry DCM

Procedure: Analogously to R 36; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 419.0 mg (3.7 mmol, 37 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)cyclo-octane carboxylate (**70d**) ($C_{15}H_{24}O_4$ 268.349 g/mol) are isolated as a colorless single product without any further purification.



70d

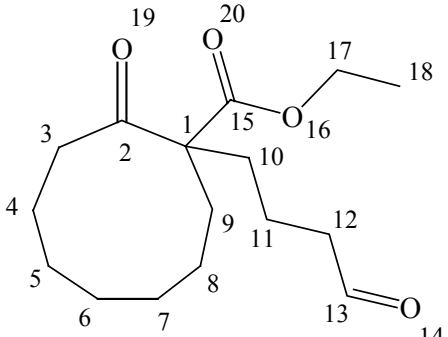
Spectroscopic data: **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3434 (w), 2929 (s), 2873 (m), 2854 (m), 2721 (w), 1737 (vs), 1725 (vs), 1708 (vs), 1643 (m), 1477 (m), 1446 (s), 1232 (s), 1193 (s), 1025 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.22 (t, 3H, ^{3}J = 6.98 Hz, CH_3-17), 1.30-1.50 (m, 10H), 1.65 (m, 1H), 1.86-1.91 (m, 3H), 2.20-2.44 (m, 3H), 2.70 (m, 1H), 4.15 (q, 2H, ^{3}J = 6.98 Hz, CH_2-16), 9.7 (br s, 1H, C*H*O-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-17), 19.7, 22.7, 23.5, 23.9, 24.6, 25.2, 28.5, 37.8, 39.3 (CH_2, C-3/4/5/6/7/8/9/10/11), 61.1 (Cq, C-1), 61.4 (CH_2, C-16), 170.9 (CO, C-14), 201.2 (CO, C-12), 213.8 (CO, C-2).

R 40: Synthesis of ethyl 2-oxo-1-(4-oxo-butyl)cyclononane carboxylate (70e)

Amounts:	1.00 g	(4.0 mmol)	ethyl 1-allyl-2-oxo-cyclononane carboxylate (**4e**)
	10.0 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	120.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	38.0 mg	(5.0 % mol)	PTSA
	20 ml		dry DCM

Procedure: Analogously to R 36; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 451.0 mg (1.6 mmol, 40 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)cyclononane carboxylate (**70e**) ($C_{16}H_{26}O_4$, 282.375 g/mol) are isolated as a colorless single product without any further purification.



70e

Spectroscopic data: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.18 (t, 3H, ^{3}J = 7.03 Hz, CH_3-18), 1.5 (m, 10H), 1.7 (m, 2H), 1.8 (m, 2H), 2.2 (m, 2H), 2.4 (m, 2H), 2.7 (m, 2H), 4.16 (q, 2H, ^{3}J = 7.03 Hz, CH_2-17), 9.7 (m, 1H, C*H*O-13). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.2 (CH_3, C-18), 17.1, 19.9, 23.2, 23.8, 24.7, 25.1, 27.5, 30.7, 37.7, 44.1 (CH_2, C-3/4/5/6/7/8/9/10/11/12), 61.3 (Cq, C-1), 63.8 (CH_2, C-17), 172.1 (CO, C-15), 201.8 (CO, C-13), 210.0 (CO, C-2).

R 41: Conversion of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (4b)

Amounts:	1.0 g	(4.7 mmol)	ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**)
	12.0 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	147 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	36.0 mg	(5.0 % mol)	DBU
	20 ml		dry DCM

Procedure: Analogously to R 36; 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed; the residue is analyzed by gas-chromatography. 1.105 g of the crude products is formed of a mixture of ethyl 1-formyl-2,3,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{12}H_{16}O_3$, 208.254 g/mol) and ethyl 2-oxo-1-(4-oxo-butyl)-cyclohexane carboxylate (**70b**) ($C_{13}H_{20}O_4$, 240.296 g/mol) in a ratio of 11:1 detected by ^{1}H-NMR analysis.

Spectroscopic data: of **72b** are consistent with those reported in R 37.

Spectroscopic data: of **70b**[178] are consistent with those reported in R 14.

b. Ethyl (1-but-3-enyl)-2-oxo-cycloalkane carboxylates (68a-c,e)

R 42: **Synthesis of ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (71a)**

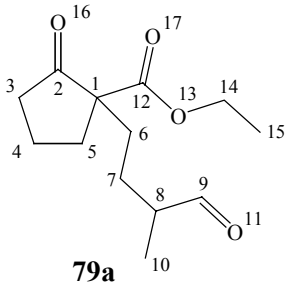
Amounts:	0.2 g	(0.95 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cyclopentane carboxylate (**68a**)
	4.9 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	29.7 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	9.1 mg	(5.0 % mol)	PTSA
	20 ml		dry DCM

Procedure: Analogously to R 36, 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 131.0 mg (0.57 mmol, 78 %) as a colorless mixture of ethyl 2-oxo-1-(5-oxo-pentyl)cyclopentane carboxylate (**71a**) ($C_{13}H_{20}O_4$, 240.296 g/mol) and ethyl 2-oxo-1-(4-methyl-3-oxo-butyl)cyclopentane carboxylate (**79a**) in a ratio of 5:1 (detected by ^{1}H-NMR analysis) are obtained without any further purification.

Spectroscopic data: of **71a** are consistent with those reported in R 16.

The presence of the ethyl 2-oxo-1-(4-methyl-3-oxo-butyl)cyclopentane carboxylate (**79a**) is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.53 (m, 1H, C*H*O-9); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 204.4 (CO, C-9).



79a

R 43: Preparation of ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (71b)

Amounts:	2.0 g	(8.9 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cyclohexane carboxylate (**68b**)
	45.9 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	279.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	90.1 mg	(5.0 % mol)	PTSA
	20 ml		dry DCM

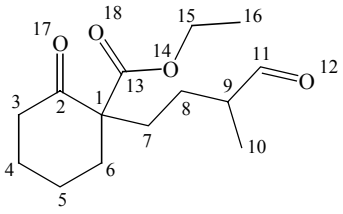
Procedure: Analogously to R 36, 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 0.747 g (3.11 mmol, 86 %) as a colorless mixture of

ethyl 2-oxo-1-(5-oxo-pentyl)cyclohexane carboxylate (**71b**) ($C_{14}H_{22}O_4$, 254.322 g/mol) and its branched isomers ethyl 2-oxo-1-(4-methyl-3-oxo-butyl)cyclohexane carboxylate (**79b**) in a ratio of 33:1, detected by ^{1}H-NMR analysis, are obtained without any further purification.

Spectroscopic data: of **71b** are consistent with those reported in R 17.

The presence of the ethyl 2-oxo-1-(4-methyl-3-oxo-butyl)cyclohexane carboxylate (**79b**) is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 9.58 (m, 1H, C*H*O-11); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 203.9 (CO, C-11).



79b

R 44: Preparation of ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (71c)

Amounts:	0.4 g	(4.0 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cycloheptane carboxylate (**68c**)
	4.0 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	50.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	14.0 mg	(5.0 % mol)	PTSA
	20 ml		dry DCM

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 171.0 mg (0.6 mmol, 40 % yield) of the colorless linear aldehyde ethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane carboxylate (**71c**) ($C_{15}H_{24}O_4$, 268.349 g/mol) are furnished without any further purification.

Spectroscopic data: of **71c** are consistent with those reported in R 18.

R45: Preparation of ethyl 2-oxo-1-(5-oxo-pentyl)cyclononane carboxylate (71e)

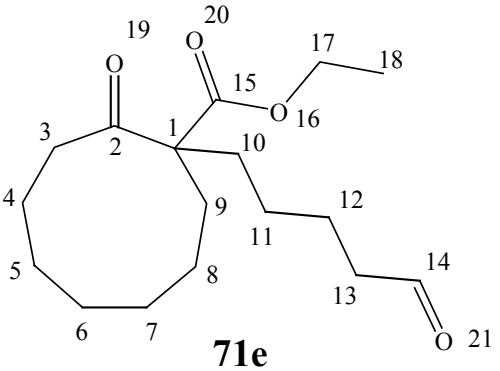
Amounts:	0.4 g	(1.5 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cyclononane carboxylate (**68e**)

4.0 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
50.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
14.0 mg	(5.0 % mol)	PTSA
20 ml		dry DCM

Procedure: Analogously to R 36, 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed and the residue is analyzed by gas-chromatography. 115.0 mg (0.39 mmol, 26 % yield) of the colorless linear aldehyde ethyl 2-oxo-1-(5-oxo-pentyl)cyclononane carboxylate (**71e**) ($C_{17}H_{28}O_4$ (296.402 g/mol) are obtained without any further purification.

Spectroscopic data: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.18 (t, 3H, ^3J = 6.27 Hz, CH_3-18), 1.37-1.69 (m, 16H), 1.92 (m, 1H), 2.08 (m, 1H), 2.37-2.44 (m, 3H), 2.57 (m, 1H), 4.11 (q, 2H, ^3J = 7.03 Hz, CH_2-17), 9.7 (t, 1H, ^3J = 1.51 Hz, C*H*O-14). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.5 (CH_3, C-18), 22.8, 23.6, 24.5, 24.6, 25.9, 28.8, 29.7, 30.9, 38.9, 39.0, 43.9 (CH_2, C-3/4/5/6/7/8/9/10/11/12/13), 61.6 (CH_2, C-17), 62.5 (Cq, C-1), 172.2 (CO, C-15), 202.8 (CO, C-14), 213.0 (CO, C-2).



71e

4.4 Study of substituent effects in the 2-oxo-2-alkenyl-cycloalkanes under sequential hydroformylation/ aldol addition conditions

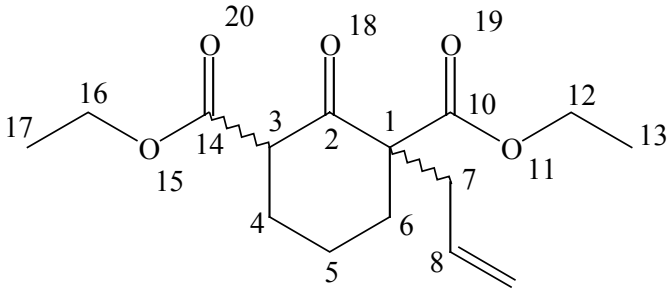
4.4.1 Diethyl 1-alkenyl-2-oxo-cycloalkane-1,3-dicarboxylates

a. Preparation of starting materials

R 46: Preparation[98] of diethyl 1-allyl-2-oxo-cyclohexane-1,3-dicarboxylate (83b)

In a 250 ml three-necked flask, equipped with a reflux condenser and dropping funnel, is placed a suspension of NaH (0.88 g, 22.0 mmol, 60% in mineral oil) in dry THF (60 ml). A solution of diethyl carbonate (**82**) (2.12 g, 2.2 ml, 18.0 mmol) in 20 ml of dry THF is added dropwise under stirring. Then, a solution of ethyl 1-allyl 2-oxo-

cyclohexane carboxylate (**4b**) (2.0 g, 9.5 mmol) in 15 ml dry THF is added dropwise with stirring under reflux over a period of 5 h. After the addition is completed, the reaction mixture is refluxed for an additional 1 h. Then the mixture is cooled to 0 °C. A solution of acetic acid and water (1:1) is added carefully. The organic layer is separated, and the aqueous layer is extracted with MTBE. The combined organic layers are washed with 40 ml of a solution of $NaHCO_3$ and (3 x 20 ml) of brine, then dried over anhydrous $MgSO_4$ and filtered. After removal of the solvent, the residual oil is distilled bulb-to-bulb, T = 70 °C (P = 4.5 x 10^{-2} mbar), to give 2.41 g (8.5 mmol, 90 % yield) of diethyl 1-allyl-2-oxo-cyclohexane-1,3-dicarboxylate (**83b**) ($C_{15}H_{22}O_5$, 282.340 g/mol) as a colorless mixture of 2 diastereoisomers in a ratio of 1:1 detected by NMR analysis.



83b

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 282 (M^+, 8), 241 (19), 237 (23), 209 (38), 195 (100), 136 (6), 55 (22). **High Resolution Mass**: Calculated: 282.1467, Found: 282.1467. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3076 (w), 2928 (vs), 2856 (s), 1737 (s), 1725 (s), 1716 (s), 1651 (m), 1614 (m), 1448 (s), 1219 (s), 1258 (s), 1218 (s), 1023 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.21 (m, 6H, CH_3-13/17), 1.55-2.70 (approx. 8H), 3.50 (dd, 1H, $^3J_{aa}$ = 10.47 Hz, $^3J_{ae}$ = 5.24 Hz, CH-3), 4.07 (q, 2H, ^3J = 6.48 Hz, CH_2-12/16), 4.15 (q, 2H, ^3J = 6.98 Hz, CH_2-16/12), 5.03 (m, 2H, CH_2-9), 5.67 (m, 1H, CH-8). Mixture of two diastereoisomers DS1/DS2 **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-13/17), 14.1 (CH_3, C-17/13), 18.7, 21.3, 22.6, 30.2, 31.1, 36.0, 39.2, 39.4 (CH_2, C-4/5/6/7, DS1 and DS2), 45.0 (CH, C-3, DS1/DS2), 56.4 (CH, C-3, DS2/DS1), 60.0 (Cq, C-1), 60.4, 61.0, 61.1, 61.4 (CH_2, C-12/16, DS1 and DS2), 118.4, 118.5 (CH_2, C-9, DS1 and DS2), 132.8, 133.8 (CH, C-8, DS1 and DS2), 169.6 (CO, C-10/14), 172.7 (CO, C-14/10), 208.0 (CO, C-2).

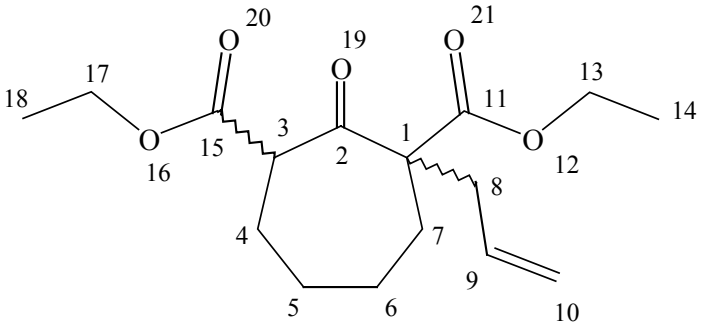
R 47: Synthesis[98] of diethyl 1-allyl-2-oxo-cycloheptane-1,3-dicarboxylate (83c)

Amounts: 4.6 g (20.0 mmol) ethyl 1-allyl 2-oxo-cycloheptane carboxylate (**4c**)

1.89 g	(47.0 mmol)	NaH (60 % in mineral oil)
4.72 g	(40.0 mmol)	diethyl carbonate (**82**)
50 ml		dry THF

Procedure: Analogously to R 46.

Work-up: After removal of the solvent, the residual oil is distilled bulb-to-bulb (T = 70 °C, P = 4.5 x 10^{-2} mbar) to give 4.85 g (16.0 mmol, 82 % yield) of diethyl 1-allyl-2-oxo-cycloheptane-1,3-dicarboxylate (**83c**) ($C_{16}H_{24}O_5$, 296.367 g/mol) as a colorless oil mixture of 2 diastereoisomers in a ratio of 1:1 detected by NMR analysis.



83c

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 297 (M^+ +1, 36), 251 (84), 223 (25), 194 (96), 178 (12), 149 (100), 55 (20). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2954 (vs), 2925 (vs), 2854 (vs), 1754 (m), 1737 (s), 1644 (w), 1463 (s), 1376 (s), 1301 (m), 1259 (m), 1178 (m), 1153 (m). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.19 (t, 6H, ^3J = 7.48 Hz, CH_3-14/18), 1.25 (m, 2H), 1.44 (m, 3H), 1.80 (m, 2H), 2.20 (m, 2H), 2.30 (m, 1H), 3.22 (m, 1H, CH-3), 4.05 (q, 2H, ^3J = 7.48 Hz, CH_2-13/17), 4.13 (q, approx. 2H, ^3J = 7.23 Hz, CH_2-17/13), 4.95 (ddd, 2H, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^2J = 1.5 Hz, CH_2-10), 5.76 (ddd, 1H, ^3J = 16.95 Hz, ^3J = 10.2 Hz, ^3J = 6.73 Hz, CH-9). Mixture of two diastereoisomers DS1/DS2 **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-14/18), 14.1 (CH_3, C-18/14), 26.7, 27.0, 28.4, 31.8, 36.3 (CH_2, C-4/5/6/7/8), 45.0, 51.7 (CH, C-3, DS1/DS2), 59.5 (CH_2, C-13/17), 61.0 (CH_2, C-17/13), 61.1 (Cq, C-1), 116.5 (CH_2, C-10), 135.3 (CH, C-9), 169.2 (CO, C-11/15), 175.2 (CO, C-15/11), 203.0 (CO, C-2).

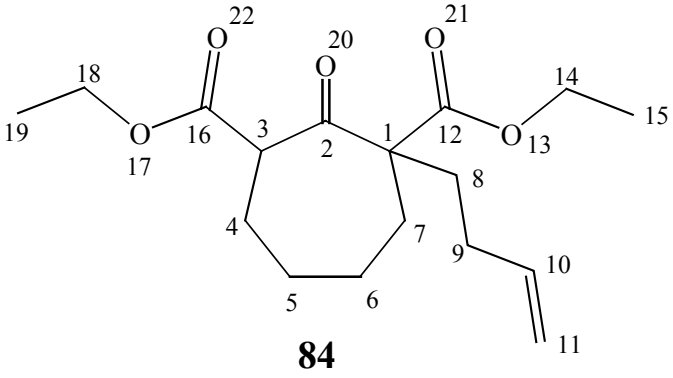
R 48: Preparation[98] of diethyl 1-(but-3-enyl)-2-oxo-cycloheptane-1,3-dicarboxylate (84)

Amounts:	3.4 g	(14.0 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cycloheptane carboxylate (**68c**)
	1.32 g	(32.0 mmol)	NaH (60 % in mineral oil)
	3.30 g	(28.0 mmol)	diethyl carbonate (**82**)
	50 ml		dry THF

Procedure: Analogously to R 46.

Work-up: The solvent is removed in vacuum and residue is analyzed by gas chromatography. The product is separated by bulb-to-bulb distillation, T = 70 °C (P = 3.0 x 10^{-2} mbar) giving 3.6 g (11.0 mmol, 83 %) of diethyl 1-(but-3-enyl)-2-oxo-cycloheptane-1,3-dicarboxylate (**84**) ($C_{17}H_{26}O_5$, 310.394 g/mol) as a colorless oil.

Spectroscopic data: IR (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2977 (s), 2929 (s), 2857 (s), 1733 (vs), 1641 (m), 1463 (m), 1455 (m), 1374 (m), 1261 (m), 1176 (s), 1031 (s), 912 (m). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.17 (t, 3H, ^{3}J = 6.98 Hz, CH_3-15/19), 1.22 (t, 3H, ^{3}J = 6.98 Hz, CH_3-19/15), 1.36-1.67 (approx. 8H), 1.95 (m, 2H), 2.19 (m, 1H), 2.26 (m, 1H), 3.35 (m, 1H, CH-3), 4.04 (q, 2H, ^{3}J = 7.23 Hz, CH_2-14/18), 4.10 (q, 2H, ^{3}J = 7.23 Hz, CH_2-18/14), 4.90 (ddd, 2H, $^3J_{trans}$ = 17.2 Hz, $^3J_{cis}$ = 10.2 Hz, $^2J_{gem}$ = 1.5 Hz, CH_2-11), 5.69 (ddd, 1H, $^3J_{trans}$ = 16.95 Hz, $^3J_{cis}$ = 10.2 Hz, ^{3}J = 6.73 Hz, CH-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-15/19), 14.1 (CH_3, C-19/15), 24.6, 26.8, 28.8, 31.4, 32.0, 34.0 (CH_2, C-4/5/6/7/8/9), 44.7 (CH, C-3), 59.8 (CH_2, C-14/18), 59.9 (CH_2, C-18/14), 63.5 (Cq, C-1), 114.8 (CH_2, C-11), 137.7 (CH, C-10), 173.5 (CO, C-12/16), 175.9 (CO, C-16/12), 207.3 (CO, C-2).



84

b. Tandem hydroformylation/ aldol addition

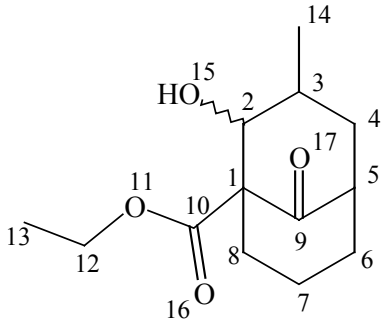
R 49: Tandem hydroformylation/ aldol addition of diethyl 1-allyl-2-oxo-cyclohexane-1,3-dicarboxylate (83b)

Amounts:	2.12 g	(7.1 mmol)	diethyl 1-allyl-2-oxo-cyclohexane -1,3-dicarboxylate (**83b**)
	0.8	(1.0 mol %)	[Rh(acac)$(CO)_2$] (**28**)
	0.22 g	(4.0 mol %)	BIPHEPHOS (**29**)
	68.0 mg	(5.0 mol %)	PTSA
	100 ml		dry THF

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syn-gas, the remaining solution is filtered through alumina N (III) and using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 0.63 g (2.6 mmol, 37 %) of ethyl 2-hydroxy-3-methyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (**85**) ($C_{13}H_{20}O_4$, 240.296 g/mol) are isolated as a colorless oil.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 240 (M^+, 7), 222 (46), 195 (54), 170 (77), 167 (10), 97 (18), 55 (34). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3450 (s), 2962 (vs), 2871 (s), 1731 (s), 1714 (s), 1413 (s), 1261 (vs), 1093 (vs), 1020 (vs). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.07 (d, 3H, ^3J = 6.27 Hz, CH_3-14), 1.28 (t, 3H, ^3J = 6.98 Hz, CH_3-13), 1.38-1.47 (m, 1H), 1.58-1.78 (m, 3H), 1.91-2.15 (m, 3H), 2.33-2.49 (m, 3H), 3.95 (d, 1H, $^3J_{aa}$ = 10.72 Hz, CH-2), 4.24 (m, 2H, CH_2-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-13), 19.8 (CH_3, C-14), 20.2, 29.5, 40.8, 45.0 (CH_2, C-4/6/7/8), 32.8 (CH, C-3), 46.0 (CH, C-5), 60.5 (Cq, C-1), 61.5 (CH_2, C-12), 79.6 (CH, C-2), 172.7 (CO, C-10), 212.7 (CO, C-9).



85

R 50: Attempt of tandem hydroformylation/ aldol addition of diethyl 1-allyl-2-oxo-cycloheptane-1,3-dicarboxylate (83c)

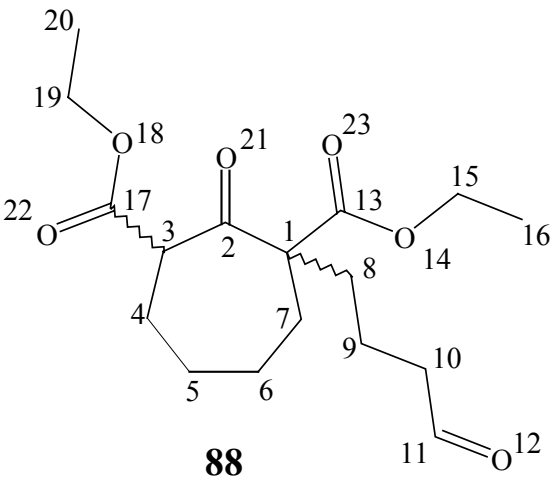
Amounts:	2.12 g	(7.1 mmol)	diethyl 1-allyl-2-oxo-cycloheptane-1,3-dicarboxylate (**83c**)
	0.8	(1.0 mol %)	[Rh(acac)$(CO)_2$] (**28**)
	0.22 g	(4.0 mol %)	BIPHEPHOS (**29**)
	68.0 mg	(5.0 mol %)	PTSA
	100 ml		dry THF

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

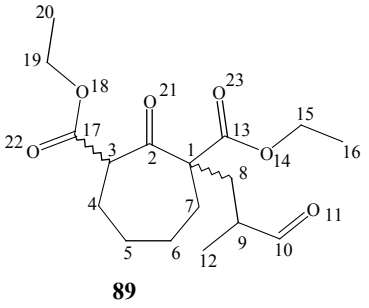
Work-up: The solvent is removed in vacuum and residue is analyzed by gas chromatography. 2.279 g (6.9 mmol, 98 % yield) as a colorless oil mixture of compounds **88** and **89** ($C_{17}H_{26}O_6$, 326.385 g/mol) in a ratio of 5:1, calculated by ^{1}H-

NMR, are obtained. The branched aldehyde **89** is present as a mixture of two diastereoisomers in a ratio of 1:1 calculated by ^{1}H-NMR analysis.

Spectroscopic data of diethyl 2-oxo-1-(4-oxo-butyl)cycloheptane-1,3-dicarboxylate (**88**): **GC-MS** (EI, 70 eV): m/z (%) = 327 (M^{+}+1, 5), 281 (55), 269 (20), 237 (5), 95 (20), 81 (20), 67 (20), 55 (20). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3436 (w), 2979 (s), 2937 (vs), 2861 (s), 2721 (w), 1747 (vs), 1745 (vs), 1735 (vs), 1731 (vs), 1592 (w), 1463 (s), 1369 (s), 1338 (s), 1299 (s), 1259 (s), 1234 (s), 1178 (vs), 1157 (vs), 1095 (s), 1029 (s), 860 (m), 794 (w). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.18 (t, 6H, ^{3}J = 7.48 Hz, CH_3-16/20), 1.30-2.40 (approx. 14H), 3.21 (dd, 1H, $^{3}J_{aa}$ = 7.48 Hz, $^{3}J_{ae}$ = 2.49 Hz, CH-3), 4.05 (q, 2H, ^{3}J = 7.23 Hz, CH_2-15/19), 4.10 (q, 2H, ^{3}J = 7.23 Hz, CH_2-19/15), 9.66 (t, 1H, ^{3}J = 1.25 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-16/20), 14.1 (CH_3, C-20/16), 19.7, 26.7, 26.9, 28.3, 31.5, 31.8, 43.4 (CH_2, C-4/5/6/7/8/9/10), 51.7 (CH, C-3), 60.0 (CH_2, C-15/19), 61.1 (CH_2, C-19/15), 169.2 (CO, C-13/17), 175.6 (CO, C-17/13), 201.8 (CO, C-11).



88



89

The presence of the diethyl 1-(2-methyl-3-oxo-propyl)-2-oxo-cycloheptane-1,3-dicarboxylate (**89**), as a mixture of two diastereoisomers, is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] 9.49 (d, 1H, ^{3}J = 1.5 Hz, C*H*O-10, DS1/DS2), 9.52 (d, 1H, ^{3}J = 1.5 Hz, C*H*O-10, DS2/DS1). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 45.1 (CH, C-9), 205.8 (CO, C-10).

R 51: Attempt of tandem hydroformylation/ aldol addition of diethyl 1-(but-3-enyl)-2-oxo-cycloheptane-1,3-dicarboxylate (84)

Amounts:	2.12 g	(7.1 mmol)	diethyl 1-(but-3-enyl)-2-oxo-cycloheptane-1,3-dicarboxylate (**84**)
	0.8	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	0.22 g	(4.0 % mol)	BIPHEPHOS (**29**)

68.0 mg	(5.0 % mol)	PTSA
100 ml		dry THF

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h

Work-up: The solvent is removed in vacuum and the residue is analyzed by gas chromatography. 2.170 g (6.4 mmol, 90 % yield) as a colorless oil mixture of compounds **90** and **91** ($C_{18}H_{28}O_6$, 340.411 g/mol), in a ratio of 2:1 calculated by ^{1}H-NMR, are obtained.

Spectroscopic data of diethyl 2-oxo-1-(5-oxo-pentyl)cycloheptane-1,3-dicarboxylate (**90**): **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3436 (w), 2979 (s), 2937 (vs), 2861 (s), 2721 (w), 1747 (vs), 1745 (vs), 1735 (vs), 1731 (vs), 1592 (w), 1463 (s), 1369 (s), 1338 (s), 1299 (s), 1259 (s), 1234 (s), 1178 (vs), 1157 (vs), 1095 (s), 1029 (s), 860 (m), 794 (w). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.16 (t, 6H, ^{3}J = 6.75 Hz, CH_3-16/20), 1.20-1.52 (approx. 12H), 2.17-2.35 (approx, 4H), 4.05 (m, 4H, CH_2-15/19), 9.66 (dd, 1H, ^{3}J = 1.25 Hz, C*H*O-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.0 (CH_3, C-16/20), 14.1 (CH_3, C-20/16), 21.7, 24.6, 26.7, 28.7, 31.9, 32.0, 34.0, 43.5 (CH_2, C-4/5/6/7/8/9/10/11), 45.2 (CH, C-3), 59.9 (CH_2, C-15/19), 61.1 (CH_2, C-19/15), 173.5 (CO, C-13/17), 175.6 (CO, C-17/13), 201.1 (CO, C-12), 215.8 (CO, C-2).

90

The presence of the diethyl 1-(2-methyl-4-oxo-butyl)-2-oxo-cycloheptane-1,3-dicarboxylate (**91**) is detected from the most significant peaks identified by NMR analysis:

91

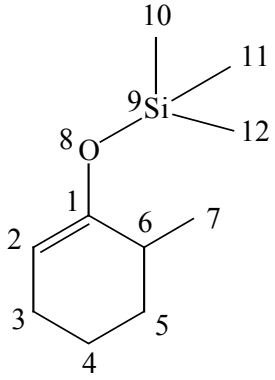
Spectroscopic data of diethyl 1-(2-methyl-4-oxo-butyl)-2-oxo-cycloheptane-1,3-dicarboxylate (**91**): **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 9.50 (m, C*H*O-12), **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.6 (CH_3, C-11), 47.5 (CH, C-10), 204.3 (CO, C-12).

4.4.2 Tandem hydroformylation/ aldol addition of 2-allyl-2-methyl-cyclohexanone (92) and ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

a. Preparation of starting materials

R 52: Synthesis[103] of 6-methyl-1-trimethylsiloxy-cyclohex-1-ene (96)

A solution of 2-methylcyclohexanone (**94**) (20.0 g, 178.0 mmol) in 50 ml of dry THF is added to a stirred solution of lithium diisopropylamide [prepared *in situ* by addition of *n*-butyllithium (75.2 ml of a 2.5 molar solution in hexane, 0.188 mol) to diisopropylamide 29.80 ml (213.0 mmol) in dry THF at -78 °C under argon], over 10 min. The solution is stirred for a further 1 h, then a solution of chlorotrimethylsilane (**95**) (32.68 g, 300.0 mmol) in 30 ml is added over 5 min. The solution is allowed to warm to room temperature and, after stirring for 1 h, the solvent is evaporated in vacuum. Dry pentane (30 ml) is added and the lithium chloride removed by filtration through a short pad of alumina N (III) using *n*-pentane as eluent. Evaporation in vacuum of the filtrate and distillation of the crude mixture gives 27.31 g (14.8 mmol, 85 % yield) of 6-methyl-1-trimethylsiloxycyclohex-1-ene[100] (**96**) ($C_{10}H_{20}OSi$, 184.351 g/mol) as a colorless liquid.



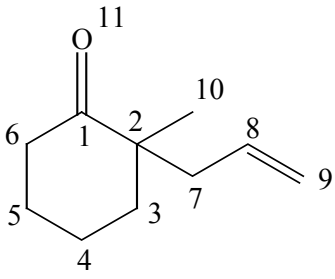
96

Spectroscopic data: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.16 (s, 9H, CH_3-10/11/12), 1.02 (d, 3H, ^3J = 7.03 Hz, CH_3-7), 1.30-1.81 (m, 4H), 1.97 (m, 2H), 2.09-2.14 (m, 1H), 4.78 (dd, 1H, ^3J = 4.02 Hz, ^3J = 1.0 Hz, CH-2). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 0.3 (CH_3, C-10/11/12), 18.6 (CH_3, C-7), 20.3, 24.3, 31.6 (CH_2, C-3/4/5), 33.6 (CH, C-6), 103.4 (CH, C-2), 154.2 (Cq, C-1).

R 53: Synthesis[104] of 2-allyl-2-methyl-cyclohexanone (92)

To a solution of 6-methyl-1-trimethylsiloxy-cyclohex-1-ene (**96**) (27.3 g, 148.0 mmol) in 40 ml dry THF under argon is added at –15 °C a solution of potassium *tert*-butoxide (16.6 g, 148.0 mmol) in 40 ml dry THF and then stirred for 45 min. Then, 17.76 g

(148.0 mmol) of allylbromide (**66**) in 35 ml of dry THF is added and stirred for 15 h at this temperature. The mixture is quenched with 30 ml of water at –78 °C and extracted (3 x 30 ml) with Et_2O. The organic layers are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 19.91 g (13.1 mmol, 89 % yield) of 2-allyl-2-methyl-cyclohexanone[179] (**92**) ($C_{10}H_{16}O$, 152.233 g/mol) are isolated by bulb-to-bulb distillation T = 50 °C (P = 5 x 10^{-2} mbar) as a colorless liquid.



92

Spectroscopic data: **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (s), 2933 (vs), 2865 (vs), 1707 (vs), 1639 (s), 1451 (s), 1376 (s), 1124 (m), 913 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.91 (s, 3H, CH_3-10), 1.42-1.46 (m, 1H), 1.59-1.70 (m, 5H), 2.05-2.24 (m, 4H), 4.88 (dd, 2H, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 12.5 Hz, CH_2-9), 5.54 (ddd, 1H, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 12.5 Hz, ^3J = 7.28 Hz, CH-8). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 22.3 (CH_3, C-10), 20.7, 27.1, 38.2, 38.4, 41.6 (CH_2, C-3/4/5/6/7), 49.5 (Cq, C-2), 117.5 (CH_2, C-9), 133.4 (CH, C-8), 214.6 (CO, C-1).

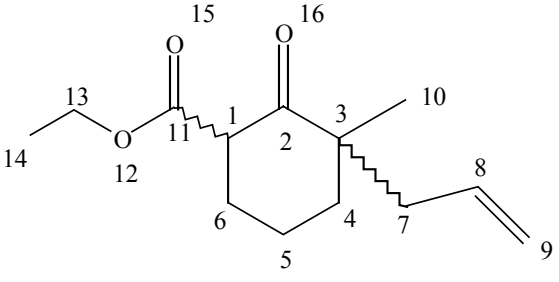
R 54: Synthesis[98] of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

Amounts:	5.0 g	(32.0 mmol)	2-allyl-2-methyl-cyclohexanone (**92**)
	2.94 g	(736.0 mmol)	NaH (60 % in mineral oil)
	7.55 g	(64.0 mmol)	diethylcarbonate (**82**)
	50 ml		dry THF

Procedure: Analogously to R 46.

Work-up: The solvent is removed in vacuum and residue is analyzed by gas chromatography. The product is separated by bulb-to-bulb distillation (T = 70 °C, P = 3.0 x 10^{-2} mbar) giving 6.04 g (27.0 mmol, 85 % yield) of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**) ($C_{13}H_{20}O_3$, 224.296 g/mol) as a colorless liquid.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 224 (M^+, 2), 151 (6), 110 (6), 97 (19), 95 (33), 83 (21), 81 (58), 69 (81), 67 (52), 55 (77). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (s), 2977 (vs), 2935 (vs), 2865 (s), 1743 (vs), 1710 (vs), 1647 (vs), 1610 (vs),



93

1452 (m), 1397 (vs), 1375 (vs), 1260 (vs), 1192 (s), 1032 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.12 (s, 3H, CH_3-10), 1.25 (t, 3H, ^{3}J = 7.28 Hz, CH_3-14), 1.27-1.68 (m, 5H), 2.06-2.25 (m, 3H), 3.41 (dd, 1H, $^{3}J_{ae}$ = 5.77 Hz, $^{3}J_{ee}$ = 2.26 Hz, CH-1), 4.14 (q, 2H, ^{3}J = 7.28 Hz, CH_2-13), 4.98 (d, 2H, ^{3}J = 12.3 Hz, CH-9), 5.70 (ddd, 1H, ^{3}J = 17.82 Hz, ^{3}J = 10.30 Hz, ^{3}J = 7.28 Hz, CH-8). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.3 (CH_3, C-14), 18.3, 23.3, 34.2, 42.9 (CH_2, C-4/5/6/7), 25.3 (CH_3, C-10), 43.6 (Cq, C-3), 57.7 (CH, C-1), 60.3 (CH_2, C-13), 117.7 (CH_2, C-9), 134.7 (CH, C-8), 177.0 (CO, C-11), 210.9 (CO, C-2).

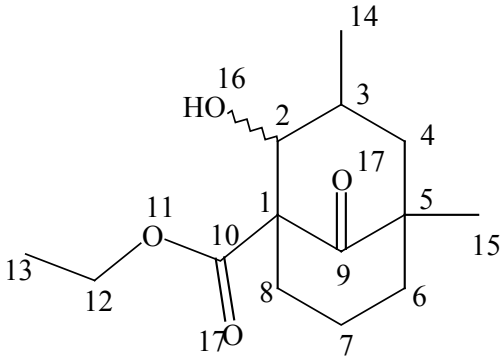
b. Tandem hydroformylation/ aldol addition

R 55: Conversion of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (93)

Amounts:	1.0 g	(4.4 mmol)	ethyl 3-allyl-3-methyl-2-oxo-cyclohexane carboxylate (**93**)
	11.0 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	68.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	42.0 mg	(5.0 % mol)	PTSA
	100 ml		dry THF

Procedure: Analogously to R 36; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

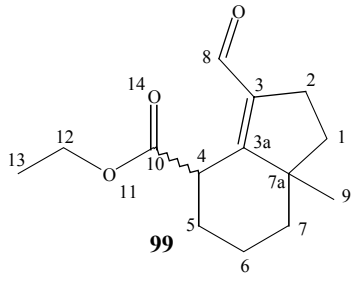
Work-up: After expanding the syn-gas, the remaining solution is filtered through alumina N (III) and using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. A mixture of ethyl 2-hydroxy-3,5-dimethyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (**97**), ethyl-3-formyl-7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (**99**) and ethyl-3-formyl-7a-methyl octahydro-1*H*-indene-4-carboxylate (**100**) is obtained in a ratio of 7.2:1:5 (by ^{1}H-NMR analysis) respectively. After bulb-to-bulb distillation of the crude mixture (T = 90 °C, P = 4.0 x 10^{-2} mbar) 0.350 g (1.4 mmol, 32 % yield) of **97** ($C_{14}H_{22}O_4$, 254.329 g/mol) are obtained as a colorless oil.



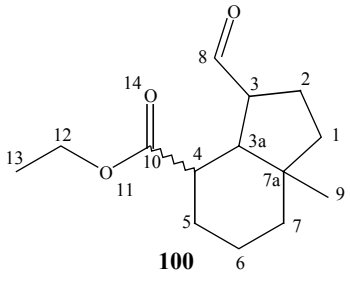
97

Spectroscopic data: ethyl 2-hydroxy-3,5-dimethyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (**97**): **GC-MS** (EI, 70 eV): m/z (%) = 254 (M^+, 1), 236 (1), 109 (5), 95 (8), 81 (11), 67 (13), 55 (16). **HRMS-FAB**: calculated: for $C_{14}H_{23}O_4$ $[M+H]^+$: 255.1596, observed: 255.1596. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3450 (s), 2964 (vs), 2857 (s), 1735 (s), 1714 (s), 1650 (s), 1610 (m), 1450 (s), 1261 (vs), 1097 (vs), 1022 (vs), 800 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.97 (s, 3H, CH_3-15), 1.04 (d, 3H, ^3J = 5.98 Hz, CH_3-14), 1.17 (m, 1H), 1.29 (t, 3H, ^3J = 6.98 Hz, CH_3-13), 1.57 (m, 1H), 1.85-1.99 (m, 3H), 2.11-2.15 (m, 1H), 2.36-2.51 (m, 3H), 3.95 (d, 1H, ^3J = 10.72 Hz, CH-2), 4.24 (q, 2H, ^3J = 6.98 Hz, CH_2-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-13), 19.8 (CH_3, C-14), 20.2, 29.5, 40.8, 45.0 (CH_2, C-4/6/7/8), 24.1 (CH_3, C-15), 32.8 (CH, C-3), 46.3 (Cq, C-5), 61.5 (CH_2, C-12), 79.6 (CH, C-2), 172.7 (CO, C-10), 212.8 (CO, C-9).

The presence of the compounds **99** and **100** is detected from the most significant peaks identified by NMR analysis; the compound **100** is present as a mixture of two diastereoisomers in a ratio of 3:1: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.98 (s, 1H, C*H*O-8, **99**), 9.64 (d, 1H, ^3J = 1.25 Hz, C*H*O-8, **100**, DS1/DS2), 9.48 (d, 1H, ^3J = 3.01 Hz, C*H*O-8, **100**, DS2/DS1). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 44.9, 45.0 (CH, C-4, **99**/**100**), 47.1 (CH, C-3a, **100**), 56.7 (CH, C-3, **100**), 188.8 (CO, C-8, **99**), 204.1 (CO, C-8, **100**).



99



100

R 56: Synthesis of 3a-methyl-3,3a,4,5,6,7-hexahydro-2*H*-indene-1-carbaldehyde (101)

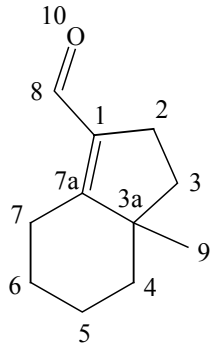
Amounts:	0.5 g	(6.5 mmol)	2-allyl-2-methyl-cyclohexanone (**92**)
	8.3 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)

0.101g	(4.0 % mol)	BIPHEPHOS (**29**)
31.0 mg	(5.0 % mol)	PTSA
20 ml		DCM

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: After expanding the syn-gas, the remaining solution is filtered through alumina N (III) and using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 0.498 g (3.03 mmol, 93 % yield) of 3a-methyl-3,3a,4,5,6,7-hexahydro-2*H*-indene-1-carbaldehyde (**101**) ($C_{11}H_{16}O$, 164.250 g/mol) are obtained as a colorless oil.

Spectroscopic data: 3a-methyl-3,3a,4,5,6,7-hexahydro-2*H*-indene-1-carbaldehyde (**101**)



101

GC-MS (EI, 70 eV): m/z (%) = 164 (M^+, 55), 135 (48), 93 (25), 79 (26), 45 (100), 29 (11). **HRMS-EI**: calculated: 164.1201, observed: 164.1177. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 2935 (vs), 2861 (vs), 2724 (m), 1705 (vs), 1666 (vs), 1455 (s), 1261 (s), 1095 (s), 978 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.05 (s, 3H, CH_3-9), 1.25-3.13 (approx. 12H), 9.99 (s, 1H, C*H*O-8). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 22.6 (CH_3, C-9), 22.1, 23.7, 26.9, 27.1, 38.6, 41.2 (CH_2, C-2/3/4/5/6/7), 50.8 (Cq, C-3a), 134.3 (Cq, C-1), 163.9 (Cq, C-7a), 188.1 (CO, C-8).

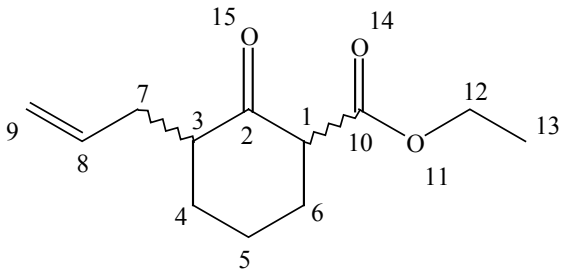
4.4.3 Ethyl 3-alkenyl-2-oxo-cycloalkane carboxylate

a. Preparation of starting materials

R 57: Synthesis[109] of ethyl 3-allyl-2-oxo-cyclohexane carboxylate (102)

A solution of ethyl 2-oxo-cyclohexane carboxylate (**65b**) (5.0 g, 29.0 mmol) in 25 ml of dry THF is added to a stirred solution of lithium diisopropylamide [prepared *in situ* by addition of *n*-butyllithium 23.2 ml (58.0 mmol, a 2.5 M solution in hexane) to diisopropylamine 8.11 ml (58.0 mmol) in dry THF at –78 °C] under argon at –78 °C, over 30 min. The solution is stirred for a further 1 h, then a solution of 2.52 ml (29.0 mmol) allyl-bromide (**66**) is added over 5 min. The solution is allowed to warm to room

temperature and, after stirring for 1 h, the reaction is neutralized with HCl (5 %) and extracted (3 x 30 ml) with MTBE. The organic extracts are washed with 40 ml of saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue is distilled by bulb-to-bulb T = 50 °C (P = 5.0 x 10^{-2} mbar), to give 4.99 g (24.0 mmol, 82 %) of ethyl 3-allyl-2-oxo-cyclohexane carboxylate[180] (**102**) ($C_{12}H_{18}O_3$, 210.275 g/mol) as a colorless oil mixture of 2 diastereoisomers in a ratio of 2.5:1 detected by NMR analysis.



102

Spectroscopic data: **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3076 (w), 2979 (s), 2938 (s), 2861 (s), 1744 (vs), 1715 (vs), 1650 (vs), 1637 (s), 1448 (m), 1301 (s), 1253 (s), 1217 (s), 1096 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.28 (t, 3H, ^3J = 7.28 Hz, CH_3-13), 1.30 (m, 1H), 1.46-1.50 (m, 1H), 1.70 (m, 2H), 1.96 (m, 1H), 2.19 (m, 2H), 2.38 (m, 1H), 2.50 (m, 1H), 3.35-3.40 (dd, 1H, $^3J_{ae}$ = 5.52 Hz, $^3J_{ee}$ = 1.0 Hz, CH-1), 4.18 (q, 2H, ^3J = 7.28 Hz, CH_2-12), 5.03 (dd, 2H, ^3J = 16.81 Hz, ^3J = 10.54 Hz, CH-9), 5.75 (ddd, 1H, ^3J = 16.82 Hz, ^3J = 10.29 Hz, ^3J = 6.53 Hz, CH-8). Mixture of two diastereoisomers DS1/DS2 **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.1, 14.2 (CH_3, C-13, DS1/DS2), 19.9, 27.8, 24.0, 26.6, 30.7, 33.4, 33.7, 36.2 (CH_2, C-4/5/6/7, DS1 and DS2), 48.9, 50.5 (CH, C-3, DS1/DS2), 56.2, 57.8 (CH, C-1, DS1/DS2), 60.2, 60.8 (CH_2, C-12, DS1/DS2), 116.4, 116.6 (CH_2, C-9, DS1/DS2), 135.9, 136.4 (CH, C-8, DS1/DS2), 172.9, 173.7 (CO, C-10, DS1/DS2), 206.8, 207.4 (CO, C-2, DS1/DS2).

R 58: Synthesis[109] of ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate (103)

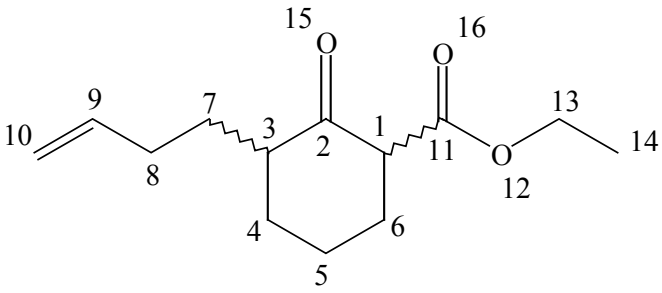
Amounts:	2.0 g	(11.7 mmol)	ethyl 2-oxo-cyclohexane carboxylate (**65b**)
	14.97 g	(23.0 mmol)	*n*-butyllithium (2.5 M in hexane)
	2.37 g	(23.0 mmol)	diisopropylamine
	1.57 g	(23.0 mmol)	4-bromo-1-butene (**67**)
	50.0 ml		dry THF

Procedure: Analogously to R 57.

Work-up: The reaction mixture is maintained at –78 °C for 45 min and gradually warmed to room temperature; neutralized with a solution of HCl (5 %) is added, and

the aqueous layer is extracted three times with 50 ml portions of Et_2O and once with 40 ml of brine and dried over anhydrous $MgSO_4$. The solvent is removed in vacuum and residue is analyzed by gas chromatography. The product, as a colorless oil, is obtained by bulb-to-bulb distillation T = 50 °C (P = 4.0 x 10^{-2} mbar) giving 0.618 g (2.75 mmol, 24 % yield) of ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate[181] (**103**) ($C_{13}H_{20}O_3$, 224.296 g/mol) as a mixture of 2 diastereoisomers in a ratio of 3:1 detected by NMR analysis.

Spectroscopic data: mixture of two diastereoisomers **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.22 (t, 3H, ^3J = 7.03 Hz, CH_3-14), 1.38 (m, 2H), 1.61-2.31 (approx. 10H), 2.49 (m, 1H), 3.37 (m, 1H, CH-1), 4.16 (q, 2H, ^3J = 7.03 Hz, CH_2-13), 5.07 (d, 2H, $^3J_{trans}$ = 17.07 Hz, $^3J_{cis}$ = 10.29 Hz, CH_2-10), 5.75 (dd, 1H, $^3J_{trans}$ = 16.82 Hz, $^3J_{cis}$ = 10.29 Hz, CH-9). Mixture of two diastereoisomers DS1/DS2 **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0, 14.3 (CH_3, C-14, DS1/DS2), 19.9, 22.6, 24.0, 26.9, 27.9, 30.7, 31.0, 31.1, 33.5, 34.1 (CH_2, C-4/5/6/7/8, DS1 and DS2), 48.5, 49.9 (CH, C-3, DS1/DS2), 56.0, 57.7 (CH, C-1, DS1/DS2), 60.0, 60.7 (CH_2, C-13, DS1/DS2), 114.5, 114.7 (CH_2, C-10, DS1/DS2), 138.1, 138.3 (CH, C-9, DS1/DS2), 172.8, 174.5 (CO, C-11, DS1/DS2), 207.2, 207.8 (CO, C-2, DS1/DS2).



103

b. Tandem hydroformylation/ aldol addition

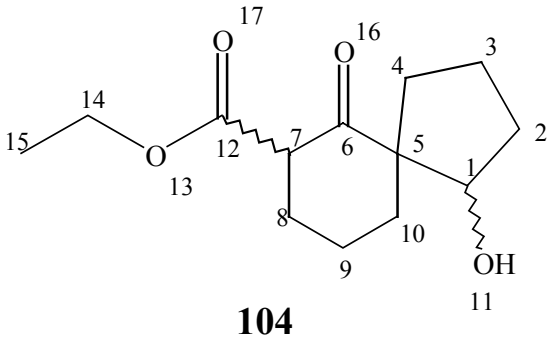
R 59: Synthesis of ethyl 1-hydroxy-6-oxo-spiro[4.5]decane-7-carboxylate (104)

Amounts:	1.0 g	(4.7 mmol)	ethyl 3-allyl-2-oxo-cyclohexane carboxylate (**102**)
	12.0 mg	(1.0 % mol)	$[Rh(acac)(CO)_2]$ (**28**)
	147.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
	46.0 g	(5.0 % mol)	PTSA
	100 ml		dry THF

Procedure: Analogously to R 36, 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: The solvent is removed in vacuum and residue is analyzed by gas chromatography. 0.51 g (45 % by G.C. analysis) as a colorless oil mixture of products ethyl 1-hydroxy-6-oxo-spiro[4.5]decane-7-carboxylate (**104**) ($C_{13}H_{20}O_4$, 240.302 g/mol) and the sub-products ethyl 3-formyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-4-carboxylate (**105**) and ethyl 3-formyl-octahydro-1*H*-indene-4-carboxylate (**106**) in a ratio of 20:3.2:1, detected by ^{1}H-NMR, is observed.

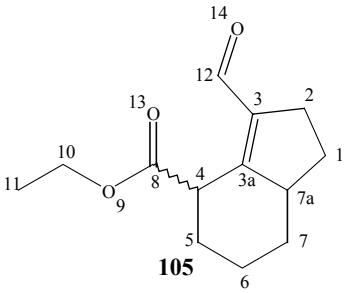
Spectroscopic data: ethyl 1-hydroxy-6-oxo-spiro[4.5]decane-7-carboxylate (**104**)



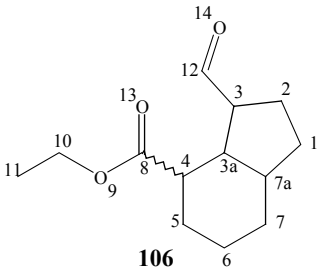
104

GC-MS (EI, 70 eV): m/z (%) = 240 (M^+, 2), 222 (12), 168 (17), 98 (29), 95 (22), 83 (17), 55 (66), 18 (59). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3467 (s), 2937 (vs), 2866 (s), 2728 (s), 1731 (s), 1665 (s), 1611 (w), 1574 (w), 1398 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.24 (m, 3H, CH_3-15), 1.39-2.66 (approx. 12H), 3.44 (dd, 1H, ^{3}J = 7.28 Hz, ^{3}J = 3.76 Hz, CH-7), 4.15 (m, 2H, CH_2-14), 4.70 (dd, 1H, ^{3}J = 9.29 Hz, ^{3}J = 7.03 Hz, CH-1). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3-15) 19.0, 20.1, 29.1, 33.3, 35.4, 41.4 (CH_2-2/3/4/8/9/10), 55.5 (CH, C-7), 61.0 (CH_2, C-14), 86.7 (CH, C-1), 171.2 (CO, C-12), 206.2 (CO, C-6).

The presence of the compounds **105** and **106** is detected from the most significant peaks identified by NMR analysis: **Spectroscopic data** of **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.57 (d, 1H, ^{3}J = 3.01 Hz, C*H*O-12, **106**), 9.99 (s, 1H, C*H*O-12, **105**). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 188.3 (CO, C-12, **105**), 201.2 (CO, C-12, **106**).



105



106

R 60: Synthesis of ethyl 7-hydroxy-1-oxo-spiro[5.5]undecane-2-carboxylate (107)

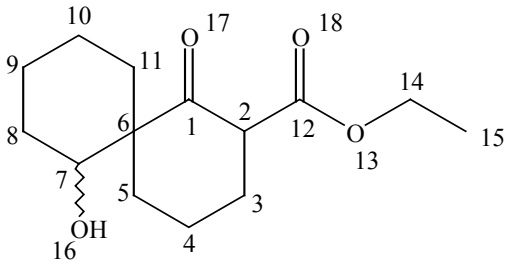
Amounts:	0.2 g	(0.9 mmol)	ethyl 3-(but-3-enyl)-2-oxo-cyclohexane carboxylate (**103**)
	2.3 mg	(1.0 % mol)	[Rh(acac)(CO)$_2$] (**28**)

28.0 mg	(4.0 % mol)	BIPHEPHOS (**29**)
8.6 g	(5.0 % mol)	PTSA
100 ml		dry THF

Procedure: Analogously to R 36; 20 bar [p(CO):p(H_2) = 1:1]; T = 60 °C, 72 h.

Work-up: The solvent is removed in vacuum and the residue is analyzed by gas chromatography. 0.1 g (0.36 mmol, 40 %) as a colorless oil mixture of ethyl 7-hydroxy-1-oxo-spiro[5.5]undecane-2-carboxylate (**107**) $C_{14}H_{22}O_4$ (254.329 g/mol) and ethyl 2-oxo-3-(5-oxo-pentyl)cyclohexane carboxylate (**108**) in a ratio of 1:1 calculated by ^{1}H-NMR.

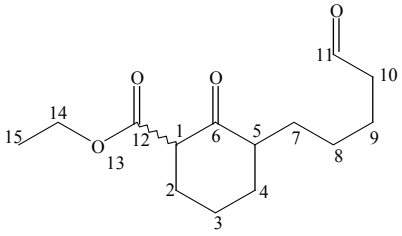
Spectroscopic data: ethyl 7-hydroxy-1-oxo-spiro[5.5]undecane-2-carboxylate (**107**).



107

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.16 (m, 3H, CH_3-15), 1.50-2.50 (approx. 14H), 2.42 (dd, 1H, ^3J = 7.03 Hz, ^3J = 3.51 Hz, CH-2), 3.44 (q, 2H, ^3J = 7.03 Hz, CH_2-14), 3.71 (d, 1H, ^3J = 6.53 Hz, O*H*-16), 4.32-4.36 (dd, 1H, $^3J_{aa}$ = 12.30 Hz, $^3J_{ae}$ = 4.52 Hz, CH-7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 15.2 (CH_3-15), 20.2, 21.1, 23.8, 32.4, 34.1, 37.1, 44.5 (CH_2-3/4/5/8/9/10/11), 57.0 (CH, C-2), 65.8 (CH_2-14), 67.9 (Cq, C-6), 84.3 (CH, C-7), 171.0 (CO, C-12), 207.4 (CO, C-1).

The presence of the compounds **108** is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 10.01 (br s, 1H, C*H*O-11). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 48.1 (CH, C-5), 57.9 (CH, C-1), 173.0 (CO, C-12), 206.1 (CO, C-11).



108

4.5 Enolsilylation tandem hydroformylation/ aldol addition

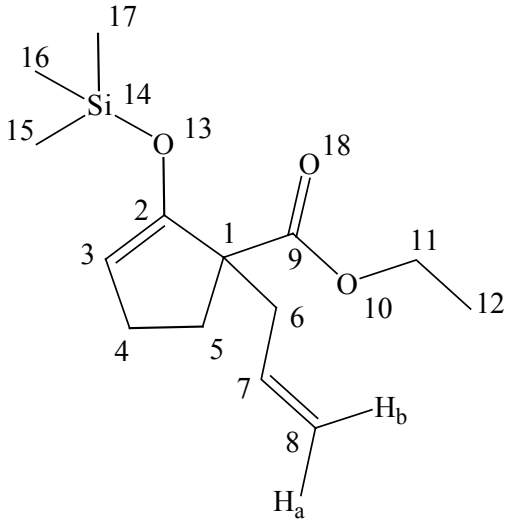
4.5.1 Trimethylsilyl enol ethers

a. Preparation of starting materials (using TMSCl)

R 61: **Synthesis[100] of ethyl 1-allyl-2-trimethylsilanyloxy-cyclopent-2-ene carboxylate (120a)**

To a a stirred solution of lithium diisopropylamide [prepared *in situ* by addition of *n*-butyllithium (4.4 ml of a 2.5 molar solution in hexane, 11.0 mmol) to diisopropylamine, freshly distilled, (1.67 ml, 12.0 mmol)] in dry THF (30 ml), a solution of ethyl 1-allyl-2-oxo-cyclopentane carboxylate (**4a**) (2.0 g, 10.0 mmol) in 15 ml of THF is added at – 78 °C under argon, over 10 min. The solution is stirred for a further 1 h, then 1.836 g (17.0 mmol) of chlorotrimethylsilane (**95**) in 15 ml of abs. THF is added over 5 min. The solution is allowed to warm to room temperature and, after stirring for 1 h, the solvent is evaporated in vacuum. Dry pentane (30 ml) is added and the lithium chloride removed by filtration through a short pad of alumina N (III). Evaporation of the solvent of the filtrate under reduced pressure followed by bulb-to-bulb distillation of the crude mixture (T = 25 °C, P = 4.0 x 10^{-2} mbar) gives 2.568 g (9.56 mmol, 96 % yield) of ethyl 1-allyl-2-trimethylsilanyloxy-cyclopent-2-ene carboxylate (**120a**) ($C_{14}H_{24}O_3Si$, 268.424 g/mol) as a colorless liquid.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 269 (M^++1, 20), 227 (20), 196 (48), 167 (5), 154 (5), 73 (98), 55 (12). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (w), 2978 (s), 2961 (s), 2906 (m), 2859 (s), 1752 (vs), 1649 (s), 1443 (m), 1365 (w), 1266 (s), 1166 (w), 847 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.16 (s, 9H, CH_3-15/16/17), 1.20 (t, 3H, ^3J = 7.03 Hz, CH_3-12), 1.80 (m, 1H), 2.10-2.37 (m, 4H), 2.52 (m, 1H), 4.09 (q, 2H, ^3J = 7.03 Hz, CH_2-11), 4.64 (t, 1H, ^3J = 2.26 Hz, CH-3), 4.99 (dd, 1H, ^2J = 2.01 Hz, $^3J_{cis}$ = 10.04 Hz, C*H*H-8a), 5.05 (dd, 1H, ^2J = 2.01 Hz, $^3J_{trans}$ = 16.56 Hz, CH*H*-8b), 5.73 (ddd, 1H, $^3J_{trans}$ = 17.07 Hz, $^3J_{cis}$ = 10.04 Hz, ^3J = 6.78 Hz, CH-7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 0.3 (CH_3, C-15/16/17), 14.1 (CH_3, C-12), 26.4, 31.1,



120a

38.6 (CH_2, C-4/5/6), 57.8 (Cq, C-1), 60.4 (CH_2, C-11), 102.8 (CH, C-3), 117.5 (CH_2, C-8), 134.7 (CH, C-7), 154.3 (Cq, C-2), 175.0 (CO, C-9).

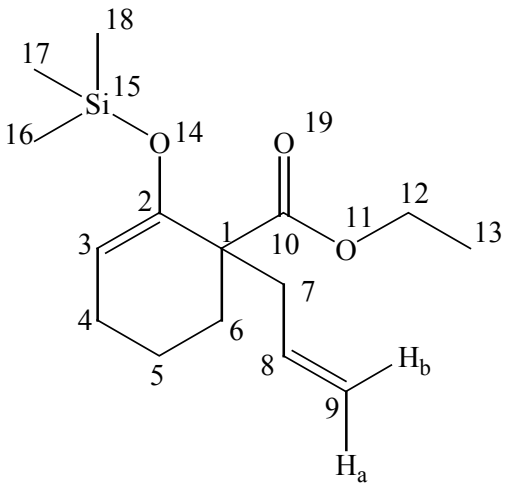
R 62: Synthesis[100] of ethyl 1-allyl-2-trimethylsilanyloxy-cyclohex-2-ene carboxylate (120b)

Amounts:	2.0 g	(95.0 mmol)	ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**)
	4.0 ml	(10.0 mmol)	*n*-butyllithium (2.5 M in hexane)
	1.6 mg	(11.4 mmol)	diisopropylamine
	1.74 g	(16.0 mmol)	chlorotrimethylsilane (TMSCl) (**94**)
	50 ml		dry THF

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum of the filtrate and bulb-to-bulb distillation (T = 70 °C, P = 1.7 x 10^{-1} mbar) gives 2.43 g (8.60 mmol, 91 % yield) of ethyl 1-allyl-2-trimethylsilanyloxy-cyclohex-2-ene carboxylate (**120b**) ($C_{15}H_{26}O_3Si$, 282.451 g/mol) as a colorless liquid.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 282 (M^+, 5), 241 (15), 209 (45), 167 (10), 91 (75), 73 (80). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.14 (s, 9H, CH_3-16/17/18), 1.21 (t, 3H, ^3J = 7.28 Hz, CH_3-13), 1.51-1.65 (m, 4H), 1.90 (m, 1H), 2.01 (m, 1H), 2.48 (m, 2H), 4.09 (q, 2H, ^3J = 7.28 Hz, CH_2-12), 4.81 (dd, 1H, ^3J = 4.27 Hz, ^3J = 3.76 Hz, CH-3), 4.99 (dd, 1H, ^3J = 10.29 Hz, ^2J = 2.01 Hz, C*H*H-9a), 5.03 (dd, 1H, ^3J = 17.32 Hz, ^2J = 2.01 Hz, CH*H*-9b), 5.73 (ddd, 1H, ^3J = 17.32 Hz, ^3J = 10.29 Hz, ^3J = 7.28 Hz, CH-8). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 0.2 (CH_3, C-16/17/18), 14.2 (CH_3, C-13), 19.0, 23.8, 31.6, 39.4 (CH_2, C-4/5/6/7), 50.4 (Cq, C-1), 60.4 (CH_2, C-12), 104.3 (CH, C-3), 117.3 (CH_2, C-9), 135.2 (CH, C-8), 149.6 (Cq, C-2), 175.3 (CO, C-10).



120b

b. Attempted of one-pot tandem hydroformylation/ aldol addition

R 63: Conversion of ethyl 1-allyl-2-trimethylsilanyloxy-cyclopent-2-ene carboxylate (120a)

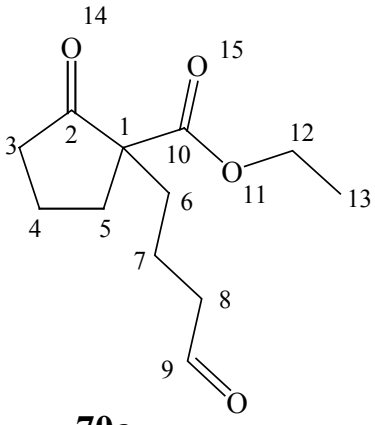
Amounts:	1.0 g	(3.7 mmol)	ethyl 1-allyl-2-trimethylsilanyloxy-cyclopent-2-ene carboxylate (**120a**)
	9.5 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	116.0 mg	(4.0 mol %)	BIPHEPHOS (**29**)
	20 ml		dry dichloromethane

Procedure: Analogously to R 13; 80 bar [$p(CO):p(H_2) = 1:1$]; T = 90 °C, 48 h.

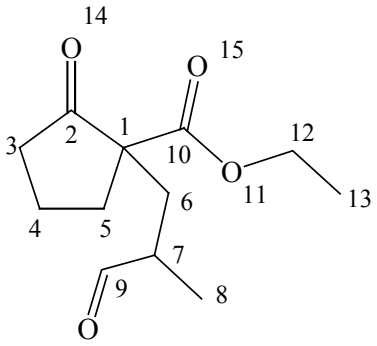
Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 794 mg (3.5 mmol, 95 % yield) as a colorless oil mixture of ethyl 2-oxo-1-(4-oxo-butyl)-cyclopentane carboxylate (**70a**) ($C_{12}H_{18}O_4$, 226.269 g/mol) and ethyl 1-(2-methyl-3-oxo-propyl)-2-oxo-cyclopentane carboxylate (**77a**) in a ratio of 22:1, detected by ^{1}H-NMR, are obtained.

Spectroscopic data of **70a** are consistent with those reported in R 13.

The presence of the compounds **77a** is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.68 (d, 1H, ^3J = 2.01 Hz, C*H*O-9). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 201.7 (CO, C-9).



70a



77a

R 64: Conversion of ethyl 1-allyl-2-trimethylsilanyloxy-cyclohex-2-ene carboxylate (120b)

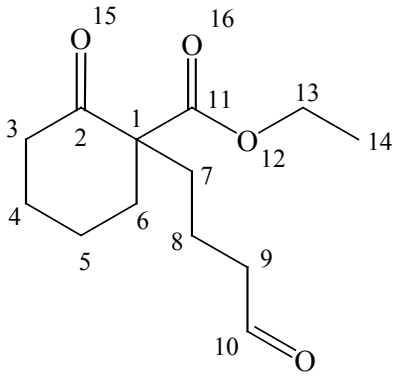
Amounts:	0.5 g	(1.8 mmol)	ethyl 1-allyl-2-trimethylsilanyloxy-cyclohex-2-ene carboxylate (**120b**)
	4.6 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	56.0 mg	(4.0 mol %)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously to R 13, 80 bar [$p(CO):p(H_2) = 1:1$]; T = 90 °C, 48 h.

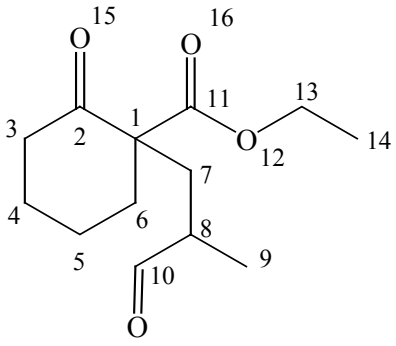
Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 388 mg (1.62 mmol, 90 % yield) as a colorless oil mixture of ethyl 2-oxo-1-(4-oxo-butyl)cyclohexane carboxylate (**70b**) ($C_{13}H_{20}O_4$, 240.296 g/mol) and ethyl 1-(2-methyl-3-oxo-propyl)-2-oxo-cyclohexane carboxylate (**77b**) in a ratio of 8:1, detected by ^{1}H-NMR, are obtained.

Spectroscopic data of **70b** are consistent with those reported in R 14.

The presence of the compounds **77b** is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.49 (d, 1H, ^{3}J = 2.01 Hz, C*H*O-10). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-14), 42.0 (CH_3, C-9), 55.0 (CH, C-8), 202.0 (CO, C-10).



70b



77b

4.5.2 Tert-butyl-dimethylsilyl enol ethers

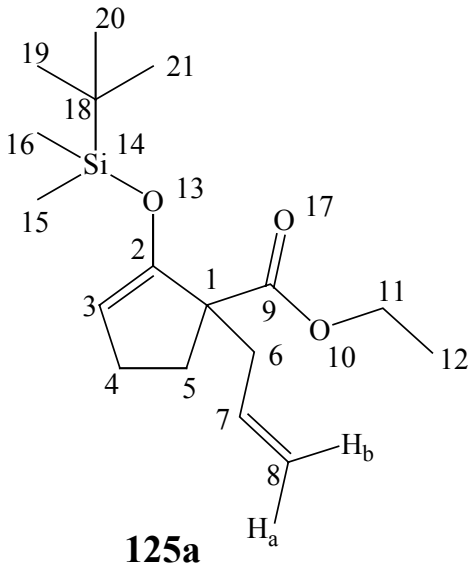
a. Preparation of starting materials

R 65: Synthesis[100] of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclopent-2-ene-carboxylate (125a)

Amounts:	2.0 g	(10.0 mol)	ethyl 1-allyl-2-oxo-cyclopentane carboxylate (**4a**)
	4.4 ml	(11.0 mmol)	*n*-butyllithium (2.5 M in hexane)
	1.67 ml	(12.0 mmol)	diisopropylamine
	2.60 g	(17.0 mmol)	chloro *tert*-butyldimethylsilane (**124**)
	50 ml		dry THF

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum of the filtrate and without any purification gives 2.8 g (8.91 mmol, 90 % yield) of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclopent-2-ene carboxylate (**125a**) ($C_{17}H_{30}O_3Si$, 310.504 g/mol) as a colorless liquid.



125a

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 311 (M^++1, 35), 253 (98), 255 (85), 184 (48), 179 (5), 73 (75). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3076 (m), 2957 (s), 2931 (s), 2903 (s), 2858 (s), 1730 (vs), 1649 (s), 1443 (s), 1363 (s), 1253 (w), 1167 (m), 856 (w). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.11 (s, 3H, CH_3-16/15), 0.13 (s, 3H, CH_3-15/16), 0.88 (s, 9H, CH_3-19/20/21), 1.21 (t, 3H, ^3J = 7.03 Hz, CH_3-12), 1.80 (m, 1H), 2.13 (m, 1H), 2.23 (m, 2H), 2.37 (dd, 1H, ^2J = 13.80 Hz, ^3J = 6.78 Hz), 2.51 (dd, 1H, ^2J = 13.80 Hz, ^3J = 7.78 Hz), 4.09 (q, 2H, ^3J = 7.03 Hz, CH_2-11), 4.77 (dd, 1H, ^3J = 4.77 Hz, ^3J = 2.51 Hz, CH-3), 4.99 (ddd, 1H, ^4J = 1.25 Hz, ^3J = 10.04 Hz, ^2J = 1.0 Hz, C*H*H-8a), 5.06 (ddd, 1H, ^4J = 1.25 Hz, ^3J = 17.32 Hz, ^2J = 1.0 Hz, CH*H*-8b), 5.70 (ddd, 1H, ^3J = 17.07 Hz, ^3J = 10.04 Hz, ^3J = 7.03 Hz, CH-7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = -5.0 (CH_3, C-15/16), -4.9 (CH_3, C-16/15), 14.2 (CH_3, C-12), 17.9

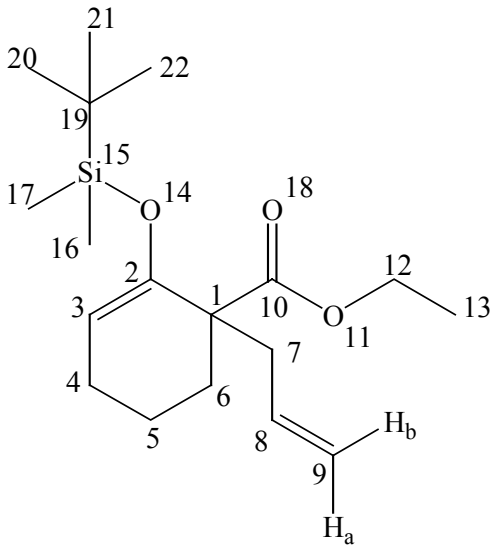
(Cq, C18-Si), 25.4 (CH_3, C-19/20/21), 26.4, 31.0, 38.6 (CH_2, C-4/5/6), 57.9 (Cq, C-1), 60.4 (CH_2, C-11), 102.2 (CH, C-3), 117.5 (CH_2, C-8), 134.7 (CH, C-7), 154.0 (Cq, C-2), 175.1 (CO, C-9).

R 66: Synthesis[100] of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclohex-2-ene carboxylate (125b)

Amounts:	2.0 g	(95.0 mmol)	ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**)
	4.0 ml	(10.0 mmol)	*n*-butyllithium (2.5 M in hexane)
	1.6 ml	(11.4 mmol)	diisopropylamine
	2.42 g	(16.0 mmol)	chloro *tert*-butyldimethylsilane (**124**)
	50 ml		dry THF

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum and without any purification gives 2.25 g (6.93 mmol, 73 % yield) of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclohex-2-ene carboxylate (**125b**) ($C_{18}H_{32}O_3Si$, 324.530 g/mol) as a colorless liquid.



125b

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 325 (M^++1, 20), 279 (20), 267 (98), 251 (10), 239 (55), 195 (5), 153 (5), 73 (85). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (s), 3049 (s), 2977 (s), 2954 (s), 2931 (w), 2899 (s), 2886 (s), 2858 (s), 1730 (s), 1690 (s), 1446 (m), 1362 (m), 1252 (w), 1159 (w), 862 (w). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.13 (s, 3H, CH_3-16/17), 0.15 (s, 3H, CH_3-17/16), 0.87 (s, 9H, CH-20/21/22), 1.23 (t, 3H, ^3J = 7.28 Hz, CH_3-13), 1.53 (m, 2H), 1.67 (m, 1H), 1.80 (m, 1H), 2.01 (m, 2H), 2.45 (dd, 1H, ^2J = 13.80 Hz, ^3J = 8.03 Hz), 2.57 (dd, 1H, ^2J = 13.80 Hz, ^3J = 6.27 Hz), 4.10 (q, 2H, ^3J = 7.28 Hz, CH_2-12), 4.81 (dd, 1H, ^3J = 4.52 Hz, ^3J = 3.51 Hz, CH-3), 5.03 (dd, 1H, ^3J = 10.54 Hz, ^2J = 2.26 Hz, C*H*H-9a), 5.07 (dd, 1H, ^3J = 17.07 Hz, ^2J = 2.26 Hz, CH*H*-9b), 5.74 (dddd, 1H, ^3J = 16.82 Hz, ^3J = 10.29 Hz, ^3J = 6.53 Hz, ^3J = 6.27 Hz, CH-8). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = -4.5 (CH_3, C-16/17), -4.4

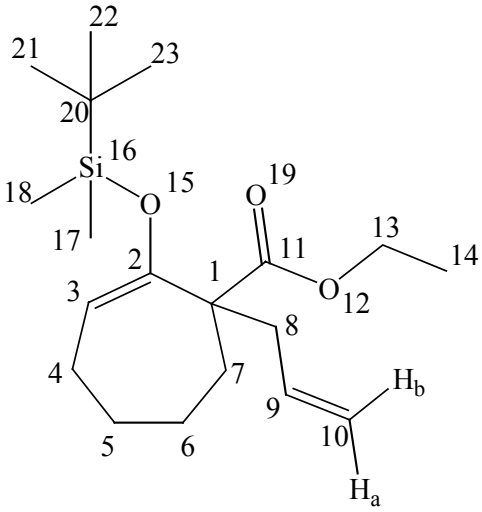
(CH_3, C-17/16), 14.2 (CH_3, C-13), 18.2 (Cq, C19-Si), 25.6 (CH_3, C-20/21/22), 19.0, 23.9, 31.6, 39.4 (CH_2, C-4/5/6/7), 50.5 (Cq, C-1), 60.5 (CH_2, C-12), 103.9 (CH, C-3), 117.5 (CH_2, C-9), 135.1 (CH, C-8), 149.5 (Cq, C-2), 175.5 (CO, C-10).

R 67: Synthesis[100] of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclohept-2-ene carboxylate (125c)

Amounts:	2.0 g	(8.9 mmol)	ethyl 1-allyl-2-oxo-cycloheptane carboxylate (**4c**)
	0.64 g	(9.7 mmol)	*n*-butyllithium (2.5 M in hexane)
	1.07 g	(10.0 mmol)	diisopropylamine
	1.735 g	(11.5 mmol)	chloro *tert*-butyldimethylsilane (**124**)
	50 ml	dry THF	

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum and without any purification gives 2.55 g (7.56 mmol, 85 % yield) of ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclohept-2-ene carboxylate (**125c**) ($C_{19}H_{34}O_3Si$, 338.557 g/mol) as a colorless liquid.



125c

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 339 (M^++1, 10), 323 (98), 309 (5), 293 (5), 265 (5), 208 (15), 73 (20). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3075 (w), 2958 (s), 2929 (s), 2857 (s), 1731 (s), 1652 (m), 1471 (m), 1450 (m), 1361 (m), 1259 (vs), 1193 (s), 1172 (s), 1143 (s), 1092 (vs), 1027 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.15 (s, 3H, CH_3-17/18), 0.16 (s, 3H, CH_3-18/17), 0.86 (s, 9H, CH-21/22/23), 1.25 (t, 3H, ^3J = 7.03 Hz, CH_3-14), 1.59-1.67 (m, 5H), 1.85 (m, 1H), 2.04 (m, 2H), 2.44 (m, 1H), 2.67 (m, 1H), 4.12 (q, 2H, ^3J = 7.03 Hz, CH_2-13), 4.95-4.98 (dd, 1H, ^3J = 7.28 Hz, ^3J = 5.52 Hz, CH-3), 5.02-5.10 (dd, 1H, ^3J = 10.04 Hz, ^2J = 1.25 Hz, C*H*H-10a), 5.06 (dd, 1H, ^3J = 17.07 Hz, ^2J = 1.25 Hz, CH*H*-10b), 5.82 (ddd, 1H, ^3J = 17.07 Hz, ^3J = 10.04 Hz, ^3J = 6.27 Hz, CH-9). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = -4.4 (CH_3, C-17/18), -4.5 (CH_3, C-18/17), 14.1 (CH_3, C-14), 22.6 (Cq, C20-Si), 25.7

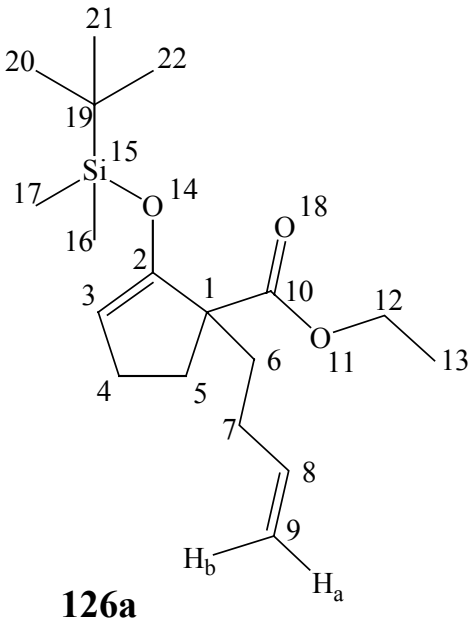
(CH_3, C-21/22/23), 22.8, 23.5, 31.9, 32.0, 41.2 (CH_2, C-4/5/6/7/8), 55.8 (Cq, C-1), 60.4 (CH_2, C-13), 108.5 (CH, C-3), 117.4 (CH_2, C-10), 135.3 (CH, C-9), 152.6 (Cq, C-2), 174.9 (CO, C-11).

R 68: Synthesis[100] of ethyl 1-(3-but-4-yl)-2-(tert-butyl-dimethylsilanyloxy)cyclopent-2-ene carboxylate (126a)

Amounts:	5.0 g	(24.0 mmol)	ethyl (1-but-3-enyl)-2-oxo-cyclopentane carboxylate (**68a**)
	1.53 g	(24.7 mmol)	*n*-butyllithium (2.5 M in hexane)
	2.90 g	(28.8 mmol)	diisopropylamine
	6.12 g	(40.8 mmol)	chloro *tert*-butyldimethylsilane (**124**)
	80 ml		dry THF

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum of the solvent and without any purification gives 7.62 g (23.52 mmol, 98 % yield) of ethyl 1-(3-buten-4-yl)-2-(tert-butyl-dimethylsilanyloxy)cyclopent-2-ene carboxylate (**126a**) ($C_{18}H_{32}O_3Si$, 324.530 g/mol) as a colorless liquid.



126a

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 325 (M^++1, 10), 267 (98), 239 (10), 183 (30), 154 (5), 139 (10), 73 (80). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (m), 2956 (s), 2931 (s), 2902 (s), 2858 (s), 1727 (s), 1643 (m), 1448 (m), 1363 (m), 1252 (vs), 1162 (s), 858 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): [ppm] = 0.06 (s, 3H, CH_3-16/17), 0.16 (s, 3H, CH_3-17/16), 0.88 (s, 9H, CH_3-20/21/22), 1.21 (t, 3H, ^3J = 7.03 Hz, CH_3-13), 1.70 (m, 2H), 1.87-2.02 (m, 4H), 2.20 (m, 2H), 4.10 (q, 2H, ^3J = 7.03 Hz, CH_2-12), 4.62 (dd, 1H, ^3J = 4.52 Hz, ^3J = 2.26 Hz, CH-3), 4.90 (dd, 1H, ^3J = 10.29 Hz, ^2J = 1.76 Hz, C*H*H-9a), 4.98 (dd, 1H, ^3J = 17.32 Hz, ^2J = 1.76 Hz, CH*H*-9b), 5.79 (ddd, 1H, ^3J = 16.56 Hz, ^3J = 10.04 Hz, ^3J = 6.27 Hz, CH-8).**^{13}C-NMR** (100 MHz, $CDCl_3$): [ppm] = -3.8 (CH_3, C-16/17), -3.6 (CH_3, C-17/16), 14.2 (CH_3, C-13), 22.8 (Cq, C19-Si), 25.4 (CH_3, C-20/21/22), 26.4, 29.0, 31.7, 33.7 (CH_2, C-4/5/6/7),

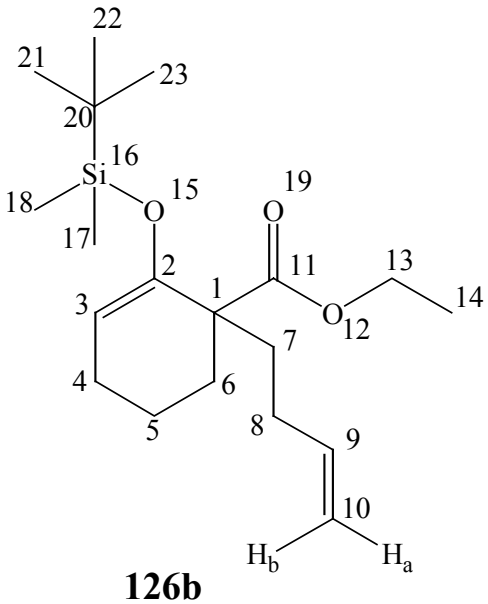
58.0 (Cq, C-1), 60.4 (CH_2, C-12), 102.1 (CH, C-3), 114.1 (CH_2, C-9), 138.9 (CH, C-8), 154.1 (Cq, C-2), 175.3 (CO, C-10).

R 69: Synthesis[100] of ethyl 1-(3-buten-1-yl)-2-(tert-butyl-dimethylsilanyloxy)cyclohex-2-ene carboxylate (126b)

Amounts:	5.0 g	(22.3 mmol)	ethyl (1-but-3-enyl)-2-oxo-cyclohexane carboxylate (**68b**)
	1.56 g	(24.5 mmol)	*n*-butyllithium (2.5 M in hexane)
	2.70 g	(26.7 mmol)	diisopropylamine
	5.68 g	(37.9 mmol)	chloro *tert*-butyldimethylsilane (**74**)
	80 ml		dry THF

Procedure: Analogously to R 61.

Work-up: Evaporation in vacuum of the solvent and without any purification gives 7.28 g (21.5 mmol, 96 % yield) of ethyl 1-(3-buten-1-yl)-2-(tert-butyl-dimethylsilanyloxy)cyclohex-2-ene carboxylate (**126b**) ($C_{19}H_{34}O_3Si$, 338.557 g/mol) as a colorless liquid.



126b

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 339 (M^++1, 30), 281 (85), 266 (15), 210 (5), 73 (60). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3077 (w), 2954 (s), 2932 (s), 2904 (s), 2858 (s), 1729 (s), 1641 (m), 1448 (m), 1363 (m), 1257 (vs), 1157 (s), 860 (s). **^{1}H-NMR** (400 MHz, $CDCl_3$): [ppm] = 0.12 (s, 3H, CH_3-17/18), 0.15 (s, 3H, CH_3-18/17), 0.86 (s, 9H, CH-21/22/23), 1.21 (t, 3H, ^3J = 7.28 Hz, CH_3-14), 1.54–2.03 (approx. 10H), 4.09 (q, 2H, ^3J = 7.28 Hz, CH_2-13), 4.81-4.83 (dd, 1H, ^3J = 4.52 Hz, ^3J = 3.51 Hz, CH-3), 4.89 (dd, 1H, ^3J = 10.29 Hz, ^2J = 1.76 Hz, C*H*H-10a), 4.98 (dd, 1H, ^3J = 17.07 Hz, ^2J = 1.76 Hz, CH*H*-10b), 5.78 (ddd, 1H, ^3J = 16.82, ^3J = 10.29 Hz, ^3J = 6.53 Hz, CH-9). **^{13}C-NMR** (100 MHz, $CDCl_3$): [ppm] = -4.5 (CH_3, C-17/18), -4.4 (CH_3, C-18/17), 14.2 (CH_3, C-14), 25.5 (CH_3, C-21/22/23), 24.0, 24.1, 28.9, 31.8, 34.1 (CH_2, C-4/5/6/7/8), 50.7 (Cq, C-1), 60.4 (CH_2, C-13), 103.9 (CH, C-3), 114.0 (CH_2, C-10), 139.0 (CH, C-9), 149.6 (Cq, C-2), 175.8 (CO, C-11).

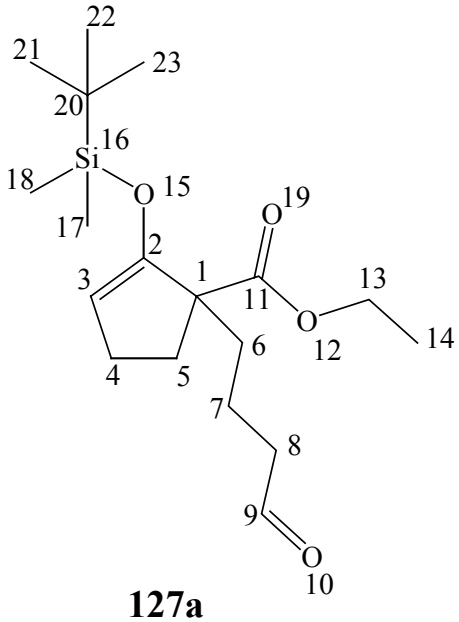
b. Attempted tandem hydroformylation/ aldol addition of silyl enol ethers

R 70: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)-cyclopent-2-ene carboxylate (127a)

Amounts:	1.00 g	(3.0 mmol)	ethyl 1-allyl-2-(tert-butyl-dimethylsilanyloxy)-cyclopent-2-ene carboxylate (**125a**)
	63.0 mg	(2.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	20 ml		dry DCM

Procedure: Analogously toR 13; 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 48 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 2.05 g (6.0 mmol, 94 % yield) as a colorless oil mixture of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)-cyclopent-2-ene carboxylate (**127a**) ($C_{18}H_{32}O_4Si$, 340.539 g/mol) and ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(2-methtyl-3-oxo-propyl)cyclopent-2-ene carboxylate (**128a**) are obtained in a ratio of 1.2:1 identified by ^{1}H-NMR analysis; the branched aldehyde **128a** is present as mixture of two diastereoisomers in a ratio of 1:1 identified by ^{1}H-NMR analysis.

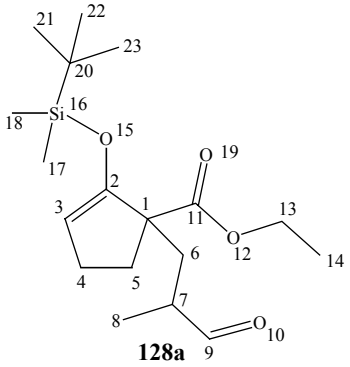


127a

Spectroscopic data: ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclopent-2-ene carboxylate (**127a**). **GC-MS** (EI, 70 eV): m/z (%) = 341 (M^++1, 30), 340 (19), 283 (45), 209 (75), 73 (82). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3479 (w), 2956 (s), 2931 (s), 2903 (w), 2858 (s), 1727 (s), 1647 (s), 1447 (m), 1363 (m), 1253 (w), 1135 (w), 938 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.13 (s, 6H, CH_3-17/18), 0.82 (s, 9H, CH-21/22/23), 1.21 (t, 3H, ^{3}J = 7.03 Hz, CH_3-14), 1.50-2.50 (approx. 10H), 4.07 (q, 2H, ^{3}J = 7.03 Hz, CH_2-13), 4.80 (dd, 1H, ^{3}J = 4.52 Hz, ^{3}J = 2.01 Hz, CH-3), 9.73 (t, 1H, ^{3}J = 1.25 Hz, C*H*O-9). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = -5.5 (CH_3, C-17/18), -4.5 (CH_3, C-18/17), 14.2 (CH_3, C-14), 25.4

(CH_3, C-21/22/23), 17.3, 26.5, 31.7, 33.8, 44.2 (CH_2, C-4/5/6/7/8), 58.1 (Cq, C-1), 60.4 (CH_2, C-13), 102.3 (CH, C-3), 153.9 (Cq, C-2), 174.9 (CO, C-11), 202.5 (CO, C-9).

The presence of the compound ethyl 2-(*tert*-butyldimethyl-silanyloxy)-1-(2-methtyl-3-oxo-propyl)-cyclopent-2-ene carboxylate (**128a**) as mixture of two diastereoisomers in a ratio of 1:1 identified by ^{1}H-NMR analysis, is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm]: 1.08 (d, 3H, ^3J = 7.28 Hz, CH_3-8), 9.50 (d, 1H, ^3J = 2.72 Hz, C*H*O-9, DS1), 9.55 (d, 1H, ^3J = 1.76 Hz, C*H*O-9, DS2). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm]: 15.8, 15.9 (CH_3, C-8, DS1/DS2), 43.0, 43.1 (CH, C-7, DS1/DS2), 102.8, 103.5 (CH, C-3, DS1/DS2), 204.6, 204.9 (CO, C-9, DS1/DS2).



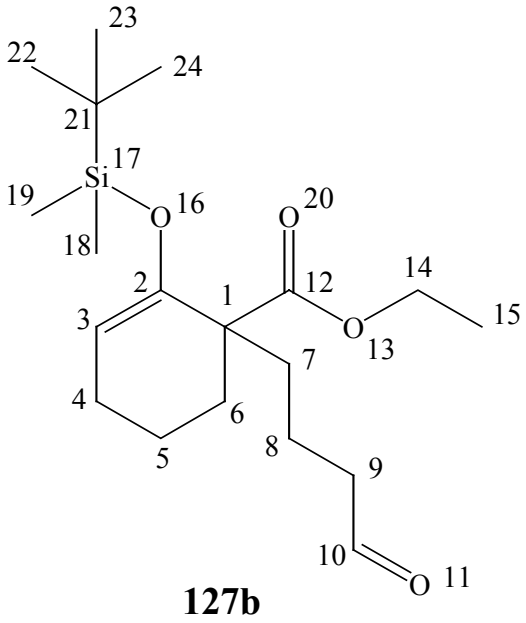
128a

R 71: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclohex-2- ene carboxylate (127b)

Amounts:	1.00 g	(3.0 mmol)	ethyl 1-allyl-2-(tert-butyl-dimethyl silanyloxy)cyclohex-2-ene carboxylate (**125b**)
	60.0 mg	(2.0 mol %)	$[Rh(cod)Cl]_2$ (**9**)
	20 ml		dry dichloromethane

Procedure: Analogously to R 13; 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 48 h.

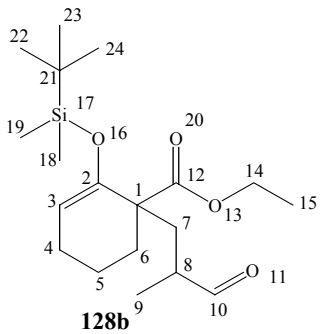
Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. Removal of the solvent furnishes 1.980 g (5.6 mmol, 92 % yield) as a colorless oil mixture of linear aldehyde ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(4-oxo-butyl)cyclohex-2-ene carboxylate (**127b**) and branched aldehyde ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(2-methtyl-3-oxo-propyl)cyclohex-2-ene carboxylate (**128b**) ($C_{19}H_{34}O_4Si$, 354.566 g/mol) in a ratio of (1.5:1) identified by ^{1}H-NMR analysis; the branched aldehyde **128b** is present as a mixture of two diastereoisomers in a ratio of 1:1.4 identified by ^{1}H-NMR analysis.



127b

Spectroscopic data: ethyl 2-(*tert*-butyldimethyl silanyloxy)-1-(4-oxo-butyl)cyclohex-2-ene-carboxylate (**127b**). **GC-MS** (EI, 70 eV): m/z (%) = 355 (M^++1, 25), 354 (5), 298 (10), 281 (25), 223 (55), 73 (60), 57 (25). **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3478 (w), 2954 (s), 2931 (w), 2903 (s), 2886 (s), 2858 (s), 1724 (s), 1662 (s), 1447 (m), 1363 (m), 1253 (w), 1158 (w), 934 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.09 (s, 6H, CH_3-18/19), 0.82 (s, 9H, CH-22/23/24), 1.19 (t, 3H, ^3J = 6.98 Hz, CH_3-15), 1.53-2.42 (approx. 12H), 4.1 (q, 2H, ^3J = 6.98 Hz, CH_2-14), 4.80 (dd, 1H, $^3J_{aa}$ = 7.73 Hz, $^3J_{ae}$ = 4.24 Hz, CH-3), 9.70 (t, 1H, ^3J = 1.75 Hz, C*H*O-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = -5.4 (CH_3, C-18/19), -4.5 (CH_3, C-19/18), 14.1 (CH_3, C-15), 25.5 (CH_3, C-22/23/24), 17.2, 19.2, 23.8, 31.7, 34.4, 44.3 (CH_2, C-4/5/6/7/8/9), 50.7 (Cq, C-1), 60.4 (CH_2, C-14), 104.1 (CH, C-3), 149.4 (Cq, C-2), 175.5 (CO, C-12), 202.4 (CO, C-10).

The presence of the compound ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(2-methtyl-3-oxo-propyl)cyclohex-2-ene carboxylate (**128b**) is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.08 (d, 3H, ^3J = 7.28 Hz, CH_3-9), 9.51 (d, 1H, ^3J = 2.74 Hz, C*H*O-10, DS1/DS2), 9.59 (d, 1H, ^3J = 2.24 Hz, C*H*O-10, DS2/DS1). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 16.1, 16.4 (CH_3, C-9, DS1/DS2), 42.8, 42.9 (CH, C-8, DS1/DS2), 104.6, 105.4 (CH, C-3, DS1/DS2), 204.8, 204.9 (CO, C-10, DS1/DS2).



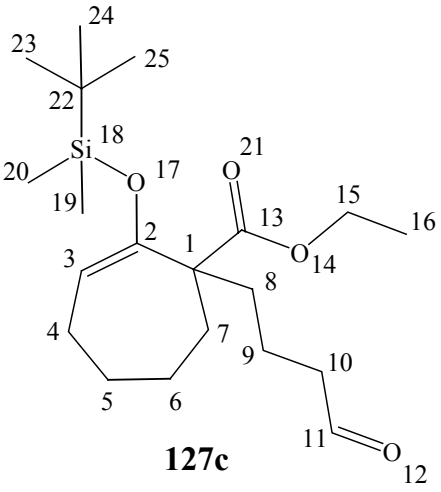
128b

R 72: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclohept-2-ene carboxylate (127c)

Amounts:	2.0 g	(5.9 mmol)	ethyl 1-allyl-2-(tert-butyldimethylsilanyloxy)cyclohept-2-ene carboxylate (**125c**)
	14.0 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	20 ml		dry DCM

Procedure: Analogously toR 13; 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is purified by bulb-to-bulb distillation (T = 125 °C, P = 5.5 x 10^{-2} mbar) to give 0.5 g (1.35 mmol, 23 % yield of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclohept-2-ene carboxylate (**127c**) ($C_{20}H_{36}O_4Si$, 368.583 g/mol) as a colorless liquid.



127c

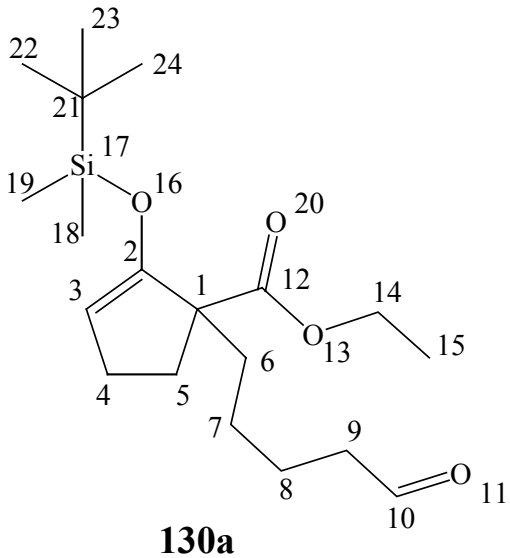
Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 369 (M^++1, 25), 368 (5), 295 (18), 237 (65), 73 (80), 57 (15). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.12 (s, 3H, CH_3-19/20), 0.13 (s, 3H, CH_3-20/19), 0.84 (s, 9H, CH-23/24/25), 1.23 (t, 3H, ^3J = 7.03 Hz, CH_3-16), 1.57-1.66 (m, 6H), 1.73 (m, 2H), 1.82 (m, 2H), 1.91 (m, 2H), 2.40 (m, 2H), 4.16 (m, 2H, CH_2-15), 4.95 (dd, 1H, $^3J_{aa}$ = 7.28 Hz, $^3J_{ae}$ = 5.27 Hz, CH-3), 9.73 (t, 1H, ^3J = 1.76 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = -5.1 (CH_3, C-19/20), -4.5 (CH_3, C-20/19), 14.2 (CH_3, C-16), 25.6 (CH_3, C-23/24/25), 17.4, 22.8, 23.6, 26.4, 31.5, 35.9, 44.4 (CH_2, C-4/5/6/7/8/9/10), 56.1 (Cq, C-1), 60.4 (CH_2, C-15), 108.7 (CH, C-3), 152.7 (Cq, C-2), 174.9 (CO, C-13), 202.7 (CO, C-11).

R 73: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(5-oxo-pentyl)cyclopent-2-ene carboxylate (130a)

Amounts:	2.0 g	(6.1 mmol)	ethyl 1-(3-buten-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)cyclopent-2-ene carboxylate (**126a**)
	31.4 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	20 ml		dry DCM

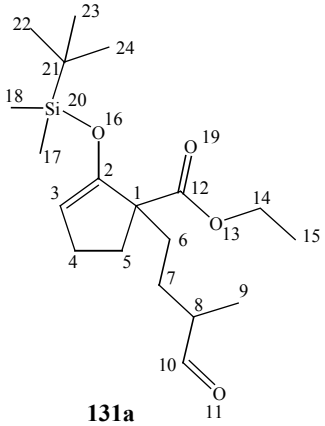
Procedure: Analogously toR 13; 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 1.619 g (4.6 mmol, 75 % yield) as a colorless oil mixture of linear aldehyde ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(5-oxo-pentyl)cyclopent-2-ene carboxylate (**130a**) and branched aldehyde ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(methyl-oxo-butyl)cyclopent-2-ene carboxylate (**131a**) ($C_{19}H_{34}O_4Si$, 354.556 g/mol) in a ratio of 7:1 identified by ^{1}H-NMR analysis.



130a

Spectroscopic data of **130a**: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.05 (s, 6H, CH_3-18/19), 0.88 (s, 9H, CH-22/23/24), 1.21 (t, 3H, ^3J = 7.23 Hz, CH_3-15), 1.38-2.50 (approx. 12H), 4.16 (m, 2H, CH_2-14), 4.95 (dd, 1H, $^3J_{ae}$ = 5.79 Hz, $^3J_{ee}$ = 5.49 Hz, CH-3), 9.72 (br s, 1H, C*H*O-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = -5.7 (CH_3, C-18/19), -3.7 (CH_3, C-19/18), 14.0 (CH_3, C-15), 25.6 (CH_3, C-22/23/24), 22.2 (Cq, C21-Si), 19.5, 24.6, 32.1, 32.7, 33.6, 37.9 (CH_2, C-4/5/6/7/8/9), 50.1 (Cq, C-1), 61.3 (CH_2, C-14), 104.3 (CH, C-3), 152.7 (Cq, C-2), 173.6 (CO, C-12), 203.8 (CO, C-10).



131a

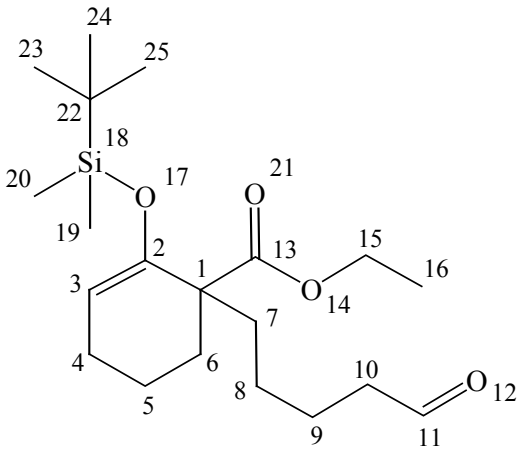
The presence of the compounds **131a** is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.95 (d, 3H, ^3J = 7.28 Hz, CH_3-9), 9.58 (d, 1H, ^3J = 1.0 Hz, C*H*O-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.8 (CH_3, C-9), 25.8 (CH_3, C-22/23/24), 52.6 (CH-8), 106.6 (CH, C-3), 203.8 (CO, C-10).

R 74: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(5-oxo-pentyl)cyclohex-2-ene carboxylate (130b)

Amounts:	2.00 g	(5.9 mmol)	ethyl 2-(3-buten-4-yl)-(2-*tert*-butyl-dimethyl-silanyloxy)cyclohex-2-ene carboxylate (**126b**)
	30.0 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$ (**41**)
	20 ml		dry dichloromethane

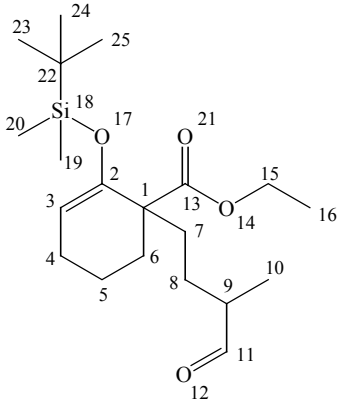
Procedure: Analogously to R 13, 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 72 h.

Work-up: After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 1.84 g (5.0 mmol, 85 % yield) as a mixture of linear aldehyde ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(5-oxo-pentyl)-cyclohex-2-ene carboxylate (**130b**) ($C_{20}H_{36}O_4Si$, 368.583 g/mol) and branched aldehyde ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(methyl-oxo-butyl)cyclohex-2-ene carboxylate (**131b**) in a ratio of 4.5:1, identified by ^{1}H-NMR analysis, are obtained. The branched aldehyde **131b** is present as a mixture of two diastereoisomers in a ratio of 1:2.1 identified by ^{1}H-NMR analysis.



130b

Spectroscopic data of **130b**: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 0.13 (s, 3H, CH_3-19/20), 0.14 (s, 3H, CH_3-20/19), 0.84 (s, 9H, CH-23/24/25), 1.23 (t, 3H, ^3J = 7.03 Hz, CH_3-16), 1.59-2.44 (approx. 14H), 4.12 (m, 2H, CH_2-15), 4.79 (dd, 1H, $^3J_{aa}$ = 7.28 Hz, $^3J_{ae}$ = 5.27 Hz, CH-3), 9.71 (t, 1H, ^3J = 1.75 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = -5.0 (CH_3, C-19/20), -3.5 (CH_3, C-20/19), 14.2 (CH_3, C-16), 25.6 (CH_3, C-23/24/25), 19.0, 22.6, 25.4, 31.5, 34.7, 38.9, 43.7 (CH_2, C-4/5/6/7/8/9/10), 59.6 (Cq, C-1), 61.4 (CH_2, C-16), 103.8 (CH, C-3), 157.9 (Cq, C-2), 175.7 (CO, C-13), 202.2 (CO, C-11).



131b

The presence of the compounds **131b** is detected from the most significant peaks identified by NMR analysis: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 9.57 (d, 1H, ^3J = 1.75 Hz, C*H*O-11, DS1/DS2), 9.59 (d, 1H, ^3J = 1.75 Hz, C*H*O-11, DS2/DS1). **^{13}C-NMR** (125 MHz,

$CDCl_3$): δ [ppm] = 13.8 (CH_3, C-9), 25.8 (CH_3, C-22/23/24), 44.6 (CH-9), 103.8 (CH, C-3), 202.2 (CO, C-11).

4.5.3 Stepwise hydroformylation/ aldol addition of preformed silyl enol ethers

a. Preparation of starting materials

R 75: Synthesis of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclohex-2-ene carboxylate (127b)

Amounts:	1.00 g	(3.0 mmol)	ethyl 1-allyl-2-(*tert*-butyl-dimethylsilanyloxy)cyclohex-2-ene carboxylate (**125b**)
	7.96 mg	(1.0 mol %)	$[Rh(acac)(CO)_2]$ (**28**)
	96.8 mg	(5.0 mol %)	BIPHEPHOS (**29**)
	20 ml		dry DCM

Procedure: Analogously to R 13, 20 bar [$p(CO):p(H_2) = 1:1$]; T = 60 °C, 72 h.

Work-up: The solvent is removed by rotary evaporation and the residue is analyzed by gas chromatography. 0.96 g (2.72 mmol, 88 % yield) of ethyl 2-(*tert*-butyl-dimethyl-silanyloxy)-1-(4-oxo-butyl)cyclohex-2-ene carboxylate (**127b**) are obtained, as a colorless liquid, by column chromatography on alumina N (III) using as eluent a mixture of cyclohexane-Et_2O (3:1).

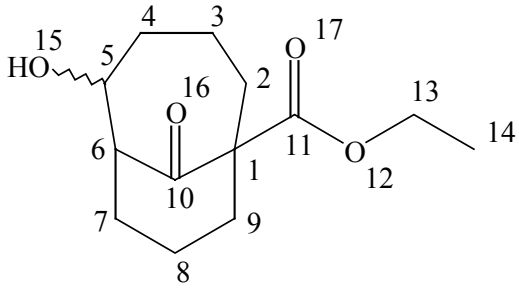
Spectroscopic data of **127b** are consistent with those reported in R 71.

b. Intramolecular aldol addition catalyzed by $TiCl_4$

R 76: Synthesis of ethyl 5-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (73b)

A solution of ethyl 2-(*tert*-butyl-dimethylsilanyloxy)-1-(4-oxo-butyl)cyclohex-2-ene carboxylate (**127b**) (3.0 g, 8.4 mmol) is added to 1.34 ml (2.28 g, 12.0 mmol) of $TiCl_4$

in 40 ml of CH_2Cl_2 at room temperature under an argon atmosphere. This mixture is stirred for 2 hours. After hydrolysis, the resulting organic layer extracted with diethylether is washed (3 x 30 ml) with a solution $NaHCO_3$. The combined extracts are dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The product, as a colorless oil, is obtained by column chromatography on alumina N (III) using as eluent a mixture of cyclohexane and Et_2O (3:1) giving 1.47 g (6.13 mmol, 73 % yield) of ethyl 5-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (**73b**) ($C_{13}H_{20}O_4$, 240.296 g/mol) as a single diastereoisomer.



73b

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 240 (M^+, 4), 222 (14), 194 (14), 149 (63), 79 (42), 55 (25). **High Resolution Mass**: Calculated: 240.1362; Found: 240.1362. **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3469 (s), 2934 (s), 2864 (s), 1737 (s), 1732 (s), 1454 (s), 1367 (s), 1255 (s), 1075 (s), 1027 (s). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.26 (t, 3H, ^3J = 7.23 Hz, CH_3-14), 1.51-2.18 (approx. 10H), 2.40 (m, 1H), 2.65 (m, 1H), 2.78 (m, 1H), 3.87 (m, 1H, CH-5), 4.20 (q, 2H, ^3J = 7.23 Hz, CH_2-13). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-14), 18.0, 19.6, 28.2, 31.7, 34.7, 35.1 (CH_2, C-2/3/4/7/8/9), 56.3 (CH, C-6), 61.0 (Cq, C-1), 61.4 (CH_2, C-13), 71.3 (CH, C-5), 175.1 (CO, C-11), 212.5 (CO, C-10).

4.6 Sequential tandem hydrofromylation/ aldol addition via in situ generated borane enolate

R 77: Conversion of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (4b)

A solution of ethyl 1-allyl-2-oxo-cyclohexane carboxylate (**4b**) 0.5 g (2.3 mmol), 230.0 mg (2.3 mmol) of TEA, 6.0 mg (1.0 mol %) of [Rh(acac)$(CO)_2$] (**28**) in dry DCM is stirred for 15 min. at T = 0 °C, then 0.487 mg (2.3 mmol) of dicyclohexylchloroborane (*cy*-hex)$_2$BCl (**159**) is added and stirred for 30 min. Finally, 23.0 mg (1.8 % mol) of XANTPHOS (**160**) is added, and the reaction mixture is placed in an autoclave. After flushing with argon the reactor is pressurized with 40 bar of carbon monoxide and 40 bar of hydrogen; the mixture is magnetically stirred and heated to 90 °C for 1 day. Then, the autoclave is allowed to cool to room temperature. After expanding the syngas, the remaining solution is filtered through alumina N (III) using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is dissolved in 15 ml of methanol, buffered at pH = 7, added H_2O_2 and stirred at room temperature for 1 h. Then, the mixture is extracted with MTBE (3 x 30 ml), the organic phase dried by $MgSO_4$, concentrated in vacuum and analyzed by gas chromatography. 0.412 g of ethyl 5-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (**73b**) ($C_{13}H_{20}O_4$, 240.296 g/mol) and ethyl 1-formyl-2,4,5,6,7-hexahydro-3a*H*-indene-3a-carboxylate (**72b**) ($C_{13}H_{18}O_3$, 222.280 g/mol) areobtained as a colorless oil. The products **73b** and **72b** are identified by comparison to those spectroscopic data reported in R 76 and R 24 respectively.

Spectroscopic data of **73b** are consistent with those reported in R 76.

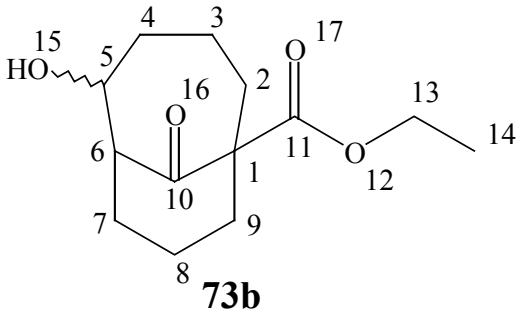
Spectroscopic data of **72b** are consistent with those reported in R 24.

R 78: Conversion of 2-allyl-2-methyl-cyclohexanone (92)

Amounts:	1.0 g	(6.5 mmol)	2-allyl-2-methyl-cyclohexanone (**92**)
	16.7 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	1.44 g	(1.05 % mol)	(*cy*-hex)$_2$BCl (**159**)
	48.0 mg	(1.8 % mol)	XANTPHOS (**160**)
	722.0 mg	(7.1 mmol)	TEA
	20 ml		dry DCM

Procedure: Analogously to R 77; 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 72 h.

Work-up: 1.08 g as a colorless oil mixture of 5-hydroxy-1-methyl-bicyclo[4.3.1]decan-10-one **(164)** ($C_{11}H_{18}O_2$, 182.259 g/mol) and 7a-methyl-2,4,5,6,7,7a-hexahydro-1*H*-indene-3-carbaldehyde (**101**) ($C_{11}H_{16}O$, 164.250 g/mol) in the ratio of 9:1 detected by NMR analysis. The presence of **164** is identified by the most significant peaks:



73b

Spectroscopic data of **164**: **IR** (KBr-film): $\tilde{\nu}$ [cm^{-1}] = 3399 (s), 2935 (vs), 2861 (vs), 1731 (vs). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 1.16 (s, 3H, CH_3-11), 1.51-2.18 (approx. 12H), 2.32 (m, 1H), 2.50 (m, 1H), 3.61 (m, 1H, CH-5). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 16.4 (CH_3, C-11), 19.9, 20.9, 29.9, 32.7, 37.1, 41.4 (CH_2, C-2/3/4/7/8/9), 49.3 (CH, C-6), 62.4 (Cq, C-1), 70.5 (CH, C-5), 203.1 (CO, C-10).

Spectroscopic data of **101** are consistent with those reported in R 56.

R 79: Conversion of ethyl 3-allyl-3-methyl-2-oxo-cyclohexane-carboxylate (93)

Amounts:	1.0 g	(4.4 mmol)	ethyl 3-allyl-3-methyl-2-oxo-cyclohexane-carboxylate (**93**)
	16.0 mg	(1.0 % mol)	[Rh(acac)$(CO)_2$] (**28**)
	0.98 g	(1.05 mmol)	(*cy*-hex)$_2$BCl (**159**)
	46.0 mg	(1.8 % mol)	XANTPHOS (**160**)
	488.0 mg	(4.8 mmol)	TEA
	20 ml		dry DCM

Procedure: Analogously to R 77, 80 bar [p(CO):p(H_2) = 1:1]; T = 90 °C, 72 h.

Work-up: Evaporation in vacuum of the filtrate and bulb-to-bulb distillation of the crude mixture (T = 90 °C, P = 4.0 x 10^{-2} mbar) gives 0.51 g (2.01 mmol, 46 % yield) of ethyl 2-hydroxy-3,5-dimethyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (**97**) ($C_{14}H_{22}O_4$, 254.329 g/mol) as a colorless oil.

Spectroscopic data of **97** are consistent with those reported in R 55.

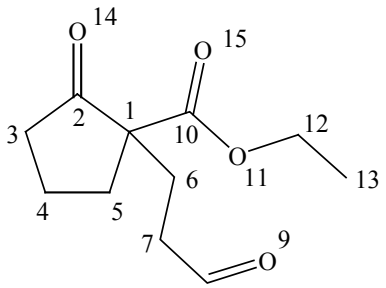
4.7 Stepwise Michael addition and aldol cyclization

a. Preparation of ethyl 2-oxo-1-(3-oxo-propyl)cycloalkane carboxylates

R 80: Synthesis[158] of ethyl 2-oxo-1-(3-oxo-propyl)cyclopentane carboxylate (173a)

To a solution of 5.0 g (32.0 mmol) of ethyl 2-oxo-cyclopentane carboxylate (**65a**) in 50 ml of DMF are added 0.44 ml (0.32 g, 3.2 mmol) of TEA and the mixture is stirred for 1h at room temperature. A solution of acrolein (**172**) (2.16 ml, 1.79 g, 328.0 mmol) in 15 ml of DMF is added and the solution is stirred for 18h at room temperature. Then, the solution is neutralized with a solution of HCl (5%) and the aqueous layer is extracted with Et_2O (3 x 20 ml). The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 6.10 g (28.7 mmol, 90 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cyclopentane carboxylate[182] (**173a**) ($C_{11}H_{16}O_4$, 212.242 g/mol) are isolated, as a colorless liquid, by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar).

Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.20 (t, 3H, ^{3}J = 7.23 Hz, CH_3-13), 1.80-2.00 (m, 4H), 2.09-2.15 (m, 1H), 2.20-2.29 (m, 1H), 2.35-2.49 (m, 3H), 2.62-2.68 (m, 1H), 4.11 (q, 2H, ^{3}J = 7.23 Hz, CH_2-12), 9.7 (br s, 1H, C*H*O-8). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-13), 19.4, 25.3, 33.9, 37.8, 39.4 (CH_2, C-3/4/5/6/7), 60.1 (Cq, C-1), 61.4 (CH_2, C-12), 171.0 (CO, C-10), 201.0 (CO, C-8), 214.5 (CO, C-2).



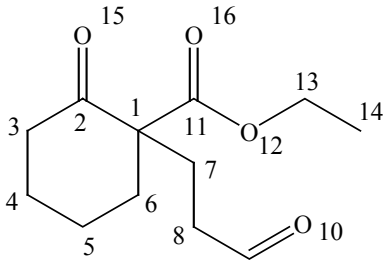
173a

R 81 Synthesis[158] of ethyl 2-oxo-1-(3-oxo-propyl)cyclohexane carboxylate (173b)

Amounts:	10.0 g	(58.0 mmol)	ethyl 2-oxo-cyclohexane carboxylate (**65b**)
	0.80 ml	(5.8 mmol)	triethylamine (TEA)
	3.91 ml	(58.0 mmol)	acrolein (**172**)
	50 ml		DMF

Procedure: Analogously to R 80.

Work-up: The organic extracts are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 6.54 g (28.9 mmol, 50 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cyclohexane carboxylate[158] (**173b**) ($C_{12}H_{18}O_4$, 226.269 g/mol) are isolated as a colorless liquid by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar).



173b

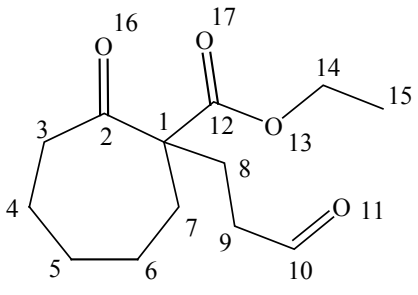
Spectroscopic data: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.18 (t, 3H, ^3J = 7.23 Hz, CH_3-14), 1.35-1.40 (m, 1H), 1.52-1.57 (m, 2H), 1.67-1.69 (m, 1H) 1.76-1.82 (m, 1H), 1.91-1.93 (m, 1H), 2.02-2.08 (m, 1H), 2.26-2.52 (m, 5H), 4.11 (q, 2H, ^3J = 7.23 Hz, CH_2-13), 9.63 (brt, 1H, ^3J = 1.0 Hz, C*H*O-9). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-14), 22.3, 26.6, 27.3, 36.4, 39.1, 40.8 (CH_2, C-3/4/5/6/7/8), 59.6 (Cq, C-1), 61.3 (CH_2, C-13), 171.6 (CO, C-11), 200.9 (CO, C-9), 207.5 (CO, C-2).

R 82: Synthesis[158] of ethyl 2-oxo-1-(3-oxo-propyl)cycloheptane carboxylate (173c)

Amounts:	2.0 g	(10.0 mmol)	ethyl 2-oxo-cycloheptane carboxylate (**65c**)
	0.14 ml	(1.0 mmol)	TEA
	0.73 ml	(10.0 mmol)	acrolein (**172**)
	20 ml		DMF

Procedure: Analogously to R 80.

Work-up: The organic layers are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 1.63 g (6.79 mmol, 68 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cycloheptane carboxylate[182] (**173c**) ($C_{13}H_{20}O_4$, 240.296 g/mol) is isolated as a colorless liquid by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar).



173c

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 240 (M^+, 1), 211 (2), 195 (2), 166 (38), 138 (98), 124 (10), 110 (40), 95 (78), 67 (65), 55 (35). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.18 (m, 3H, CH_3-15), 1.38-2.00 (approx. 11H), 2.03 (m, 1H), 2.40 (m, 1H), 2.54 (m, 1H), 4.10 (m, 2H, CH_2-14), 9.66 (m, 1H, C*H*O-10). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-15), 24.7, 25.3, 27.5, 29.6, 33.7, 39.6, 42.1 (CH_2, C-3/4/5/6/7/8/9), 60.4 (Cq, C-1), 60.9 (CH_2, C-14), 172.1 (CO, C-12), 201.2 (CO, C-10), 209.3 (CO, C-2).

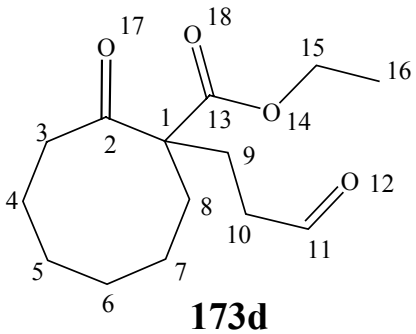
R 83: Synthesis[158] of ethyl 2-oxo-1-(3-oxo-propyl)cyclo-octane carboxylate (173d)

Amounts:	2.0 g	(10.0 mmol)	ethyl 2-oxo-cyclo-octane carboxylate (**65d**)
	0.14 ml	(1.0 mmol)	TEA
	0.67 ml	(10.0 mmol)	acrolein (**172**)
	20 ml		DMF

Procedure: Analogously to R 80.

Work-up: The organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 1.90 g (7.49 mmol, 75 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cyclo-octane carboxylate[183] (**173d**) ($C_{14}H_{22}O_4$, 254.322 g/mol) is isolated as a colorless liquid by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar).

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 254 (M^+, 15), 180 (58), 165 (98), 152 (80), 137 (60), 123 (22), 109 (62), 95 (43), 81 (38), 67 (63), 55 (37). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.20 (t, 3H, ^{3}J = 6.98 Hz, CH_3-16), 1.36-1.80 (approx. 9H), 1.97 (m, 2H), 2.35 (m, 2H), 2.50 (m, 2H), 2.69 (m, 1H), 4.13 (q, 2H, ^{3}J = 6.98 Hz, CH_2-15), 9.71 (t, 1H, ^{3}J = 1.0 Hz, C*H*O-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-16), 23.1, 23.6, 24.1, 25.4, 29.1, 29.6, 38.9, 39.6 (CH_2-3/4/5/6/7/8/9/10), 61.3 (Cq, C-1), 61.4 (CH_2, C-15), 171.6 (CO, C-13), 201.2 (CO, C-11), 212.3 (CO, C-2).



173d

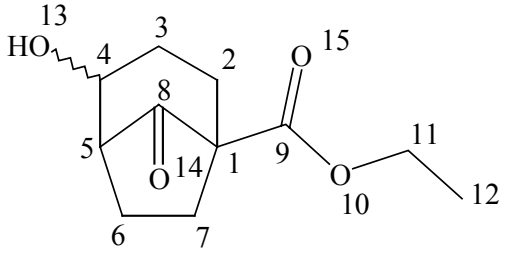
b. Stepwise cyclization under acidic conditions

R 84: Synthesis[63] of ethyl 4-hydroxy-8-oxo-bicyclo[3.2.1]octane carboxylate (174a)

To a solution of ethyl 2-oxo-1-(3-oxo-propyl)cyclopentane carboxylate (**173a**) (1.0 g, 4.7 mmol) in 20 ml of dioxane are added 15.0 ml of HCl (7N) and the mixture is stirred for 18h at room temperature. Then, the solution is neutralized with a solution of $NaHCO_3$ and the aqueous layer is extracted with Et_2O (3 x 20 ml). The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 775.9 mg (3.66 mmol, 78 % yield) of ethyl 4-hydroxy-8-oxo-bicyclo[3.2.1]octane carboxylate[184] (**174a**) ($C_{11}H_{16}O_4$, 212.242 g/mol) are isolated as a colorless liquid by

bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar) as a mixture of two diastereoisomers in a ratio of 1:3.8 detected by NMR analysis.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 213 (M^++1, 100), 212 (5), 195 (16), 184 (10), 166 (55), 110 (30), 55 (98). **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3467 (m), 2960 (s), 2883 (m), 1754 (vs), 1716 (vs), 1455 (m), 1368 (m), 1271 (s), 1074 (s), 1016 (s). Major diastereoisomer **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.24 (t, 3H, ^{3}J = 7.23 Hz, CH_3-12), 1.66 (m, 1H), 1.85-2.07 (m, 6H), 2.47 (m, 1H), 2.56 (m, 1H), 4.06 (m, 1H, CH-4), 4.11 (q, 2H, ^{3}J = 7.23 Hz, CH_2-11). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.1 (CH_3, C-12), 16.3, 26.5, 27.1, 31.1 (CH_2, C-2/3/6/7), 54.2 (CH, C-5), 55.7 (Cq, C-1), 61.2 (CH_2, C-11), 73.6 (CH, C-4), 172.2 (CO, C-9), 210.9 (CO, C-8). The minor diastereoisomer is identified by the most significant peaks **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 19.4, 25.5, 25.8, 33.9 (CH_2, C-2/3/6/7), 54.0 (CH, C-5), 77.6 (CH, C-4).



174a

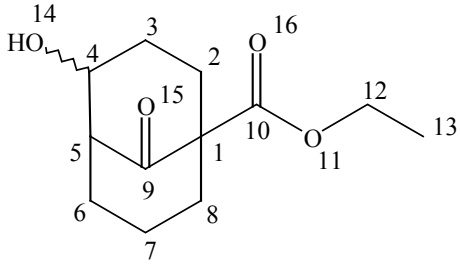
R 85: Synthesis[63] of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]nonane carboxylate (174b)

Amounts:	1.0 g	(4.4 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclohexane carboxylate (**173b**)
	14.0 ml		HCl (7N)
	20 ml		Dioxane

Procedure: Analogously to R 84.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 872.0 mg (3.85 mmol, 87 % yield) of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]octane carboxylate (**174b**) ($C_{12}H_{18}O_4$, 226.269 g/mol) are isolated as a colorless liquid, by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar), as a mixture of two diastereoisomers in a ratio of 1:1.6 detected by NMR.

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 226 (M^+, 10), 208 (12), 180 (100), 135 (30), 107 (32), 79 (55), 55 (8). **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3469 (m), 2934 (s), 2864 (m), 1737 (vs), 1732 (vs), 1454 (m), 1367 (m), 1255 (s), 1075 (s), 1027 (s). Major diastereoisomer **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.17 (t, 6H, ^{3}J = 7.23



174b

Hz, CH_3-13), 1.51 (m, 1H), 1.68 (m, 1H), 1.79-2.03 (m, 5H), 2.17-2.35 (m, 1H), 2.60 (m, 1H), 2.73 (m, 1H), 3.95 (m, 1H, CH-4), 4.07-4.11 (q, 2H, ^3J = 7.23 Hz, CH_2-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 13.9 (CH_3, C-13), 20.2, 28.3, 30.1, 30.7, 36.1 (CH_2, C-2/3/6/7/8), 54.3 (CH, C-5), 57.7 (Cq, C-1), 60.9 (CH_2, C-12), 75.6 (CH, C-4), 172.2 (CO, C-10), 212.8 (CO, C-9). The minor diastereoisomer is identified by the most significant peaks **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 19.1, 26.2, 27.8, 30.0, 35.7 (CH_2, C-2/3/6/7/8), 53.7 (CH, C-5), 57.6 (Cq, C-1), 72.3 (CH, C-4), 212.1 (CO, C-9).

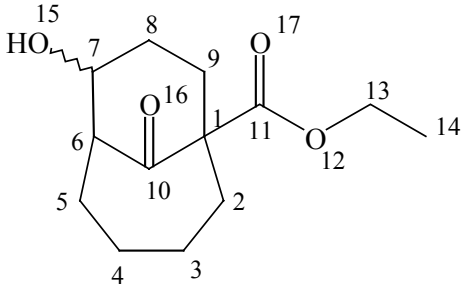
R 86: Synthesis[63] of ethyl 7-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (174c)

Amounts:	2.0 g	(8.3 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cycloheptane carboxylate (**173c**)
	26.5 ml		HCl (7N)
	30 ml		Dioxane

Procedure: Analogously to R 84.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 1.72 g (7.16 mmol, 55 % yield) of ethyl 7-hydroxy-10-oxo-bicyclo[4.3.1]nonecan carboxylate (**174c**) ($C_{13}H_{20}O_4$, 240.296 g/mol) are isolated as a colorless liquid by bulb-to-bulb distillation (T = 85 °C, P = 7.2 x 10^{-2} mbar) as a mixture of 2 diastereoisomers in a ratio of 5.4:1 detected by NMR.

Spectroscopic data: GC-MS (EI, 70 eV): m/z (%) = 240 (M^+, 1), 222 (2), 211 (2), 194 (18), 121 (51), 84 (68), 55 (54). **High Resolution Mass (FAB-m-NBA matrix)**: Calculated: for $C_{13}H_{21}O_4$ $[M+H]^+$: 241.1434; Found: 241.1439. **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3490 (w), 2933 (vw), 2863 (m), 1731 (vw), 1712 (vw), 1698 (vw), 1454 (w), 1367 (m), 1234 (w), 1180 (w), 1027 (w). Major diastereoisomer **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.21 (t, 3H, ^3J = 7.23 Hz, CH_3-14), 1.50-1.80 (approx. 9H), 2.05-



174c

2.44 (m, 3H), 2.60 (m, 1H), 2.73 (m, 1H), 4.05 (m, 1H), 4.14 (q, 2H, ^3J = 7.23 Hz, CH_2-13). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-14), 25.4, 23.4, 27.3, 29.6, 32.8, 42.0 (CH_2-2/3/4/5/8/9), 57.0 (CH, C-6), 61.1 (CH_2, C-13), 73.1 (CH, C-7), 172.1 (CO, C-11), 209.2 (CO, C-10). Minor diastereoisomer **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 24.7, 25.3, 27.2, 30.0, 33.4, 42.0 (CH_2-2/3/4/5/8/9), 55.6 (CH, C-6), 60.5 (Cq, C-1), 61.4 (CH_2, C-13), 70.4 (CH, C-7), 173.6 (CO, C-11), 210.0 (CO, C-10).

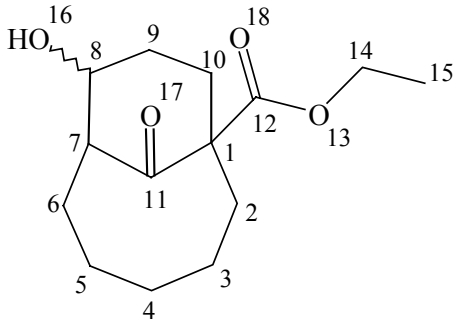
R 87: Synthesis[63] of ethyl 8-hydroxy-11-oxo-bicyclo[5.3.1]undecane carboxylate (174d)

Amounts:	0.5 g (1.9 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclo-octane carboxylate (**173d**)
	9.89 ml	HCl (7N)
	15 ml	Dioxane

Procedure: Analogously to R 84.

Work-up: The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. 299.0 mg (1.17 mmol, 62 %) as a colorless liquid mixture of 2 diastereoisomers in a ratio of 4:1, detected by NMR, of ethyl 8-hydroxy-11-oxo-bicyclo[5.3.1]undecan carboxylate (**174d**) ($C_{14}H_{22}O_4$, 254.322 g/mol) are isolated by bulb-to-bulb distillation (T = 85 °C, P = 7.2 x 10^{-2} mbar).

Spectroscopic data: **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3430 (s), 2927 (vs), 2857 (s), 1731 (s), 1704 (vs), 1698 (vs), 1469 (s), 1446 (s), 1365 (m), 1351 (m), 1267 (s), 1255 (s), 1226 (s), 1218 (s), 1187 (s), 1081 (s), 1064 (s), 1025 (s). Major diastereoisomer **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.22 (t, 3H, ^3J = 7.2 Hz, CH_3-15), 1.63-2.70 (approx. 14H), 2.73-2.78 (m, 1H), 3.95 (m, 1H), 4.08 (m, 1H), 4.13 (q, 2H, ^3J = 7.48 Hz, CH_2-14). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-14), 23.1, 23.6, 24.1, 24.7, 25.6, 30.7, 31.2 (CH_2, C-2/3/4/5/6/9/10), 57.5 (CH, C-7), 61.3 (CH_2, C-14), 72.5 (CH, C-8), 170.9 (CO, C-12), 204.3 (CO, C-11). The minor diastereosomer is detected by the most significant peaks **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 57.5 (CH, C-7), 71.5 (CH, C-8).



174d

4.7.1 One–Pot Michael addition /aldol cyclization under basic conditions

a. Acrolein chain

R 88: Synthesis of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]nonane carboxylate (174b)

To a solution of ethyl 2-oxo-cyclohexane carboxylate (**65b**) (10.0 g, 58.0 mmol) in 50 ml of EtOH is added a solution of DBU (7.66 ml, 8.36 g, 58.0 mmol) in 10 ml of EtOH, and the mixture is stirred for 1h at room temperature. 3.71 ml (3.08 g, 58.0 mmol) of acrolein (**172**) in EtOH (10 ml) is added, then slowly and the solution is stirred for 18h at room temperature. Then, the solvent is first eliminated under reduced pressure, the residue is dissolved in Et_2O, acidified with a solution HCl and the aqueous layers are extracted with diethylether. The combined organic phases are washed with water and dried over anhydrous $MgSO_4$. The solvent is removed under reduced pressure and the crude mixture is purified by column chromatography on alumina N (III), using as eluent cyclohexane-diethylether (1:10). 12.656 g (17.87 mmol, 96 %) of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]nonane carboxylate (**174b**) are obtained as a colorless liquid mixture of 2 diastereoisomers in a ratio of 1:1, detected by NMR analysis. Its spectroscopic data are consistent with those reported in R 85.

R 89: Synthesis of ethyl 7-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (174c)

Amounts:	2.0 g	(10.0 mmol)	ethyl 2-oxo-cycloheptane carboxylate (**65c**)
	0.6 g	(10.0 mmol)	acrolein (**172**)
	1.52 g	(10.0 mmol)	DBU
	50 ml		EtOH

Procedure: Analogously to R 88.

Work-up: The combined organic phases are washed with Et_2O (3 x 20 ml), dried over anhydrous $MgSO_4$. After evaporation of solvent under reduced pressure, the crude mixture is separated by a column chromatography on alumina N (III), using as eluent cyclohexane-Et_2O (1:10). 1.872 g (7.8 mmol, 78 % yield) of ethyl 7-hydroxy-10-oxo-bicyclo[4.3.1]decane carboxylate (**174c**) are obtained as a colorless liquid mixture of 2

diastereoisomers in a ratio of 5:1, detected by NMR analysis. Its spectroscopic data are consistent with those reported in R 86.

R 90: Synthesis of ethyl 8-hydroxy-11-oxo-bicyclo[5.3.1]undecan carboxylate (174d)

Amounts:	4.0 g	(20.0 mmol)	ethyl 2-oxo-cyclo-octane carboxylate (**65d**)
	3.04 g	(20.0 mmol)	DBU
	1.2 g	(20.0 mmol)	acrolein (**172**)
	30 ml		EtOH

Procedure: Analogously to R 88.

Work-up: The aqueous layer is extracted with Et_2O (3 x 20 ml). The combined organic phases are dried over anhydrous $MgSO_4$. Evaporation of solvent under reduced pressure yielded 3.858 g (15.17 mmol, 76 % yield) of ethyl 8-hydroxy-11-oxo-bicyclo[5.3.1]undecan carboxylate (**174d**) as a colorless liquid mixture of 2 diastereoisomers in a ratio of 4:1, detected by NMR analysis. Its spectroscopic data are consistent with those reported in R 87.

b. Crotonic aldehyde chain

R 91: Synthesis of ethyl 4-hydroxy-2-methyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (182b)

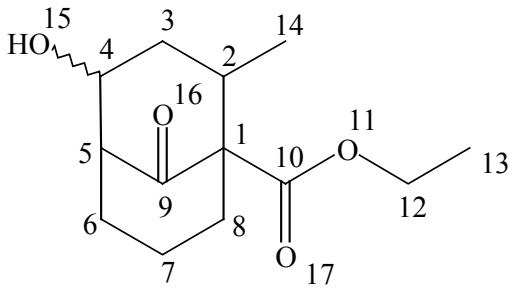
Amounts:	10.0 g	(58 mmol)	ethyl 2-oxo-cyclohexane carboxylate (**65b**)
	8.92 g	(21.0 mmol)	DBU
	4.06 g	(58.0 mmol)	crotonic aldehyde (**181**)
	80 ml		EtOH

Procedure: Analogously to R 88.

Work-up: The solvent is removed under reduced pressure, the residue is dissolved in Et_2O, acidified with a solution of HCl and the aqueous layers are extracted with diethyether (3 x 20 ml). The combined organic phase is dried over anhydrous $MgSO_4$. The solvent is removed under reduced pressure and the crude mixture is purified by column chromatography on alumina N (III), using as eluent cyclohexane-diethylether (1:10). 11.97 g (49.8 mmol, 86 % yield) are obtained as a colorless oil mixture of 4

diastereoisomers in a ratio of 8.3:3.6:1.5:1, detected by NMR, of ethyl 4-hydroxy-2-methyl-9-oxo-bicyclo[3.3.1]nonane carboxylate (**182b**) ($C_{13}H_{20}O_4$, 240.296 g/mol).

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 240 (M^+, 5), 222 (2), 194 (8), 84 (100), 73 (4), 55 (16). **High Resolution Mass**: Calculated: 240.1362; Found: 240.1362. **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3482 (m), 2960 (s), 2937 (s), 2874 (m), 1731 (vs), 1716 (vs), 1646 (m), 1450 (m), 1367 (m), 1247 (s), 1216 (s), 1095 (s), 1049 (s), 993 (m). Major diastereisomer DS-1 **^{1}H-NMR** (400 MHz, $CDCl_3$): δ [ppm] = 0.91 (d, 3H, ^3J = 6.78 Hz, CH_3-14), 1.19 (t, 3H, ^3J = 7.03 Hz, CH_3-13), 1.48-2.31 (approx. 8H), 2.50 (m, 1H), 3.03 (m, 1H), 4.02 (m, 1H, CH-4), 4.14 (q, 2H, ^3J = 7.28 Hz, CH_2-12). Mixture of diastereoisomers DS-1/2/3/4 **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-13), 16.4 (CH_3, C-14), 19.2, 29.6, 30.4, 36.1 (CH_2, C-3/6/7/8), 33.3, 34.2, 34.8, 36.1 (CH, C-2), 53.0, 53.3, 53.6, 56.4 (CH, C-5), 60.9 (CH_2, C-12), 69.9, 70.5, 73.9, 74.3 (CH, C-4), 171.8 (CO, C-10), 213.9 (CO, C-9).



182b

R 92: Synthesis of ethyl 7-hydroxy-9-methyl-10-oxo-bicyclo[4.3.1]decane carboxylate (182c)

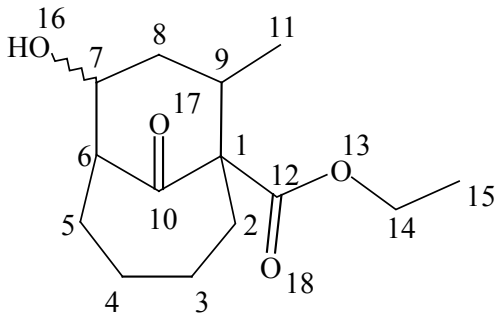
Amounts:	4.0 g	(21.0 mmol)	ethyl 2-oxo-cycloheptane carboxylate (**65c**)
	3.19 g	(21.0 mmol)	DBU
	1.47 g	(21.0 mmol)	crotonic aldehyde (**181**)
	30 ml		EtOH

Procedure: Analogously to R 88.

Work-up: The purification of the crude mixture by column chromatography on alumina N (III), using as eluent cyclohexane-Et_2O (1:10), gave 4.26 g (16.75 mmol, 80 % yield) of ethyl 7-hydroxy-9-methyl-10-oxo-bicyclo[4.3.1]decane carboxylate (**182c**) ($C_{14}H_{22}O_4$, 254.322 g/mol) as a colorless oil mixture of 6 diastereoisomers in a ratio of 9:4.7:2:2:1.7:1, detected by NMR analysis.

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 254 (M^+, 1), 208 (3), 73 (3), 55 (53). 45 (12), 29 (100), 18 (1). **IR** (KBr-Film): $\tilde{\nu}$ [cm^{-1}] = 3428 (m), 2962 (s), 2933 (s), 2869 (m), 1733 (vs), 1698 (vs), 1454 (m), 1365 (m), 1259 (s), 1238 (s), 1209 (s), 1180 (s), 1108 (s), 1062 (s), 1025 (vs). Major diastereoisomer DS-1 **^{1}H-NMR** (400 MHz,

$CDCl_3$): δ [ppm] = 0.85 (d, 3H, ^3J = 7.03 Hz, CH_3-11), 1.20 (t, 3H, ^3J = 7.28 Hz, CH_3-15), 1.53 (m, 2H), 1.67-1.87 (approx. 6H), 2.2 (m, 1H), 2.4 (m, 1H), 2.6 (ddd, 1H, ^3J = 6.78 Hz, ^3J = 1.51 Hz, ^3J = 4.27 Hz, CH-6), 2.94 (m, 1H), 3.99 (m, 1H, CH-7), 4.12 (q, 2H, ^3J = 7.28 Hz, CH_2-14). Mixture of diastereoisomers DS-1/2/3/4/5/6 **^{13}C-NMR** (100 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-15), 16.2 (CH_3, C-11), 24.5, 25.4, 28.8, 31.4, 37.1 (CH_2, C-2/3/4/5/8), 28.3, 29.4, 30.2, 30.7, 31.9, 33.3 (CH_2, C-9, DS-1/2/3/4/5/6), 53.7, 55.3, 55.9, 56.5, 57.2, 57.8 (CH_2, C-6, DS-1/2/3/4/5/6), 60.7 (CH_2, C-14), 66.5, 69.5, 70.5, 72.3, 72.4, 73.3 (CH, C-7, DS-1/2/3/4/5/6), 171.8 (CO, C-12), 212.3 (CO, C-10).



182c

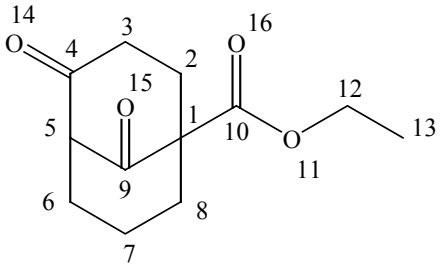
4.7.2 Preparation of tricylic compounds

a. Preparation of starting materials

R 93: Preparation of ethyl 4,9-dioxo-bicyclo[3.3.1]nonane carboxylate (190)

A flask equipped with a Argon inlet, dropping funnel, and mechanical stirrer is charged with ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]nonane carboxylate (**174b**) (5.0 g, 22.0 mmol) in abs. CH_2Cl_2. The flask is immersed in an ice-water bath. 3.13 ml (3.45 g, 44.0 mmol) of DMSO and 5.62 g (39.6 mmol) of phosphorus pentoxide are added sequentially. The reaction mixture is allowed to stir and warm to room temperature until disappearance of starting material controlled by TLC (30 min). The flask is immersed again in the ice-water bath; then, 10.7 ml (7.7 g, 77.0 mmol) of TEA is added dropwise over 10 min. Stirring is continued for 30 min. The reaction is quenched with aqueous HCl (10 %) and extracted with CH_2Cl_2. The organic extracts are washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The crude mixture is purified by bulb-to-bulb distillation (T = 130 °C, P = 3.8 x 10^{-2} mbar) giving 4.329 g (18.04 mmol, 82 % yield) of ethyl 4,9-dioxo-bicyclo[3.3.1]nonane carboxylate[185] **(190)** ($C_{12}H_{16}O_4$, 224.253 g/mol).

Spectroscopic data: **GC-MS** (EI, 70 eV): m/z (%) = 225 (M^++1, 2), 207 (45), 149 (85), 73 (100). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.27 (t, 3H, ^3J = 7.28 Hz, CH_3-13), 2.55-2.70 (approx. 10H), 4.00 (m, 1H), 4.22 (q, 2H, ^3J = 7.28 Hz, CH_2-12). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-13), 18.7, 25.0, 34.7, 38.1, 39.6 (CH_2, C-2/3/6/7/8), 57.6 (Cq, C-1), 61.6 (CH_2, C-12), 62.5 (CH, C-5), 171.5 (CO, C-10), 206.6 (CO, C-9), 208.8 (CO, C-4).



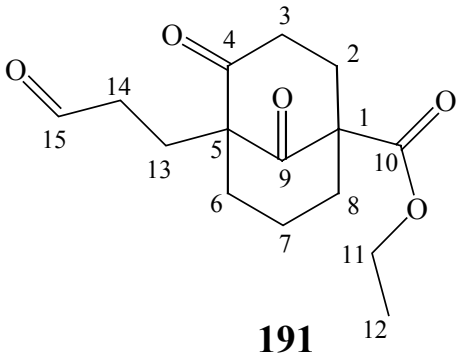
190

R 94: Synthesis of ethyl 4,9-dioxo-5-(3-oxo-propyl)-bicyclo[3.3.1]nonane carboxylate (191)

Amounts:	1.0 g	(4.46 mmol)	ethyl 4,9-dioxo-bicyclo[3.3.1]nonane-1-carboxylate (**190**)
	45.0 mg	(4.46 mmol)	triethylamine (TEA)
	0.68 mg	(4.46 mmol)	acrolein (**172)**
	30 ml		DMF

Procedure: Analogously to R 80.

Work-up: The organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum obtaining 1.259 g (98 % GC-conv.) as a mixture of ethyl 4,9-dioxo-5-(3-oxo-propyl)-bicyclo[3.3.1]nonane carboxylate (**191**) ($C_{15}H_{20}O_5$, 280.316 g/mol) and ethyl 8-hydroxy-11,12-dioxo-tricyclo[5.3.1.1.^{1,5}]dodecanane-5-carboxylate (**192**) ($C_{15}H_{20}O_5$, 280.316 g/mol). The products could not be completely separated. The presence of the compound **191** is observed by the most significant peaks by NMR: **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.31 (t, 3H, ^3J = 7.03 Hz, CH_3-12), 1.50-2.98 (approx. 14H), 4.27 (q, 2H, ^3J = 7.03 Hz, CH_2-12), 10.01 (bs, 1H, C*H*O-15). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-12), 17.1, 22.2, 26.8, 30.8, 33.8, 40.9, 46.6 (CH_2, C-2/3/6/7/8/13/14), 61.9 (CH_2, C-11), 178.0 (CO, C-10), 203.6 (CO, C-15), 214.0 (CO, C-9).



191

Spectroscopic data of ethyl 8-hydroxy-11,12-dioxo-tricyclo[5.3.1.1.^{1,5}]dodecanane-5-carboxylate (**192**) are described in the next reaction R 95.

a. Intramolecular aldol addition

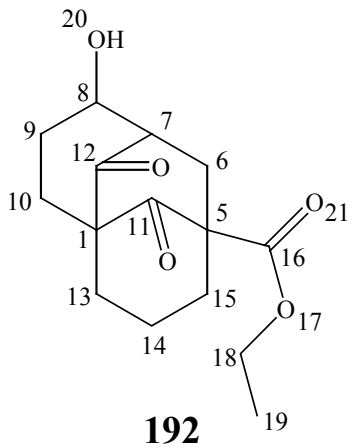
R 95: ethyl 8-hydroxy-11,12-dioxo-tricyclo[5.3.1.1.^{1,5}]dodecanane-5-carboxylate (192)

Amounts:	1.259 g	(4.5 mmol)	mixture of compounds **191** and **192** from R 94
	14.4 ml		HCl (7N)
	40 ml		dioxane

Procedure: Analogously to R 84.

Work-up: The combined organic phase is dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum obtaining 1.112 g (3.9 mmol, 88 % of yield) of ethyl 8-hydroxy-11,12-dioxo-tricyclo[5.3.1.1.^{1,5}]dodecanane-5-carboxylate (**192**) ($C_{15}H_{20}O_5$, 280.316 g/mol) as a mixture of 4 diastereoisomers detected by NMR.

Spectroscopic data of **192**: **GC-MS** (Low Resolution-FAB): m/z (%) = 281.21 (M^++1, 18), 263 (17), 136 (42), 107 (107), 77 (18), 55 (12). **HRMS-FAB (m-NBA-matrix)**: calculated for $C_{15}H_{21}O_5$, $[M+H]^+$: 281.1389; observed: 281.1362. **IR** (KBr-film): [cm^{-1}] = 3419 (s), 2962 (s), 2944 (s), 2865 (s), 1737 (vs), 1716 (vs), 1698 (vs), 1455 (s), 1367 (s), 1259 (vs), 1211 (s), 1079 (vs), 1024 (vs), 873 (s), 800 (s). major diastereoisomer **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 1.23 (t, 3H, ^{3}J = 7.03 Hz, CH_3-19), 1.60-2.80 (approx. 12H), 4.04 (m, 1H, CH-7), 4.25 (q, 2H, ^{3}J = 7.03 Hz, CH_2-18), 4.5 (m, 1H, CH-8). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 14.0 (CH_3, C-19), 17.0, 19.2, 20.3, 24.5, 26.3, 28.4, 30.1, 30.2, 31.0, 33.7, 35.8, 36.2 (CH_2, C-6/9/10/13/14/15, DS-1/2/3/4), 47.7, 48.2, 53.8, 54.4 (CH, C-8, DS-1/2/3/4), 57.3, 57.8 (Cq, C-1/5), 61.0, 61.1, 62.0, 62.1 (CH_2, C-18, DS-1/2/3/4), 72.6, 73.8, 75.9, 76.7 (CH, C-8, DS-1/2/3/4), 172.4, 176.4, 177.8, 178.0 (CO, C-16, DS-1/2/3/4), 211.6, 213.2 (CO, C-11/12).



192

b. Attempted preparation of α,β-unsaturated bicyclic compound

R 96: Attempted preparation of ethyl 4-oxo-bicyclo[3.3.1]non-4-ene carboxylate (193)

To a stirred suspension of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]nonane carboxylate (**174b**) (3.0 g, 13.0 mmol) and 7.25 g (19.5 mmol) of cerium(III) chloride heptahydrate in 70 ml acetonitrile are added 2.92 g (19.5 mmol) of sodium iodide, and the resulting mixture is stirred for 10 h at reflux.. The reaction mixture is diluted with Et_2O and treated with HCl (0.5 N). The organic layer is separated, and the aqueous layer is extracted with diethylether (3 x 25 ml). The combined organic layers are washed twice with an aqueous saturated $NaHCO_3$ solution and a saturated NaCl solution and dried over anhydrous Na_2SO_4. The extracts are then concentrated under reduced pressure and the residue gave only starting material.

R 97: Attempted preparation of α,β-unsaturated bicyclic compound by cerium(III) salt

To a solution of ethyl 2-oxo-1-(3-oxo-propyl)cyclohexane carboxylate (**174b**) (5.0 g, 22.0 mmol) in 15 ml of EtOH is added a solution of DBU (3.08 ml, 3.35 g, 22.0 mmol) in 15 ml of EtOH, and the mixture is stirred for 48h under refluxing conditions. Then, the solvent is first eliminated under reduced pressure, the residue is dissolved in Et_2O, acidified with a solution of HCl (5 %) and the aqueous layer is extracted with Et_2O. The combined organic phases are washed with water and dried over anhydrous $MgSO_4$. Evaporation of solvent under reduced pressure gives an intractable mixture.

R 98: Attempted preparation of α,β-unsaturated bicyclic compound by $BF_3 \cdot OEt_2$

To a solution of ethyl 2-oxo-1-(3-oxo-propyl)-cyclohexane carboxylate (**173b**) (5.0 g, 22.0 mmol) in dry dichloromethane at room temperature is added a solution of boron trifluoride etherate (5.56 ml, 6.28 g, 44.0 mmol) and the solution is stirred at room temperature for 24 h. Then, the solution is neutralized with saturated aqueous sodium bicarbonate solution. The resulting mixture is extracted with chloroform (3 x 20 ml).

The combined extracts are washed with saturated aqueous sodium chloride solution; the organic phases are washed with water and dried over anhydrous $MgSO_4$. The removal of the solvent gives 4.32 g (19 mmol, 87 % yield) of ethyl 4-hydroxy-9-oxo-bicyclo[3.3.1]octane carboxylate (**174b**) ($C_{12}H_{18}O_4$, 226.269 g/mol) are isolated by bulb-to-bulb distillation (T = 75 °C, P = 7.2 x 10^{-2} mbar).

Spectroscopic data are consistent with those reported in R 85.

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