Synthesis of Bridged Bicycles and Macrocycles from Cycloalkanones via Tandem Reactions and Ring Expansion

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“Considerate la vostra semenza:
fatti non foste a viver come bruti,
ma per seguir virtute e canoscenza”

Dante Alighieri
Inferno XXVI, 118-120

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I can’t immagine what the last years would have been like without being able to go through them with my husband Sergio, whose patience and understanding made the work possible.

for Sergio

Index of abbreviations and symbol

abs.	absolut, dry
Ac	acetyl
acac	acetylacetonato
br	broad (FTIR)
br s	broad singulet (NMR)
CAN	cerium(IV)ammonium nitrate
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
DIA	diisopropylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EI	Electron impact (MS)
Et	ethyl
eV	electronvolt (MS)
FAB	Fast-Atom Bombardment
FT	fourier–transformation
GC	gas chromatography
HMPA	hexamethylphosphoroamide
Hz	Hertz
i	iso
IR	infrared spectroscopy
J	NMR coupling costant (Hz)
LDA	lithium diisopropylamide

m	multiplet (NMR), medium intensity (IR)
M^+	molecular peak (MS)
MARDi	Michael additio retro-Dieckmann
Me	methyl
mp	melting point
Ms	mass spectroscopy
MTBE	*t*-butylmethylether
MS	molecular sieves
n-	normal
NMR	Nuclear magnetic resonance spectroscopy
p	total pressure
ppm	part per milion (NMR)
q	quartet (NMR)
R	reaction
RT	room temperature
s	singulet (NMR), strong (IR)
SM	starting material
t	reaction time, triplet (NMR)
t	tertiary
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl (IR)
vs	very strong
w	weak (IR)
ϑ	Reaction temperature
$\tilde{\nu}$	wavelenght [cm^{-1}]

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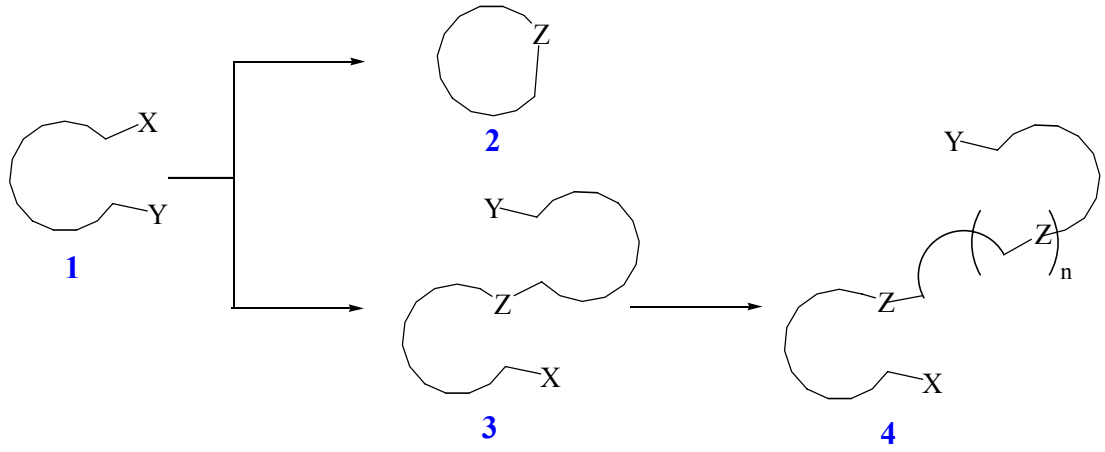
1. Introduction.

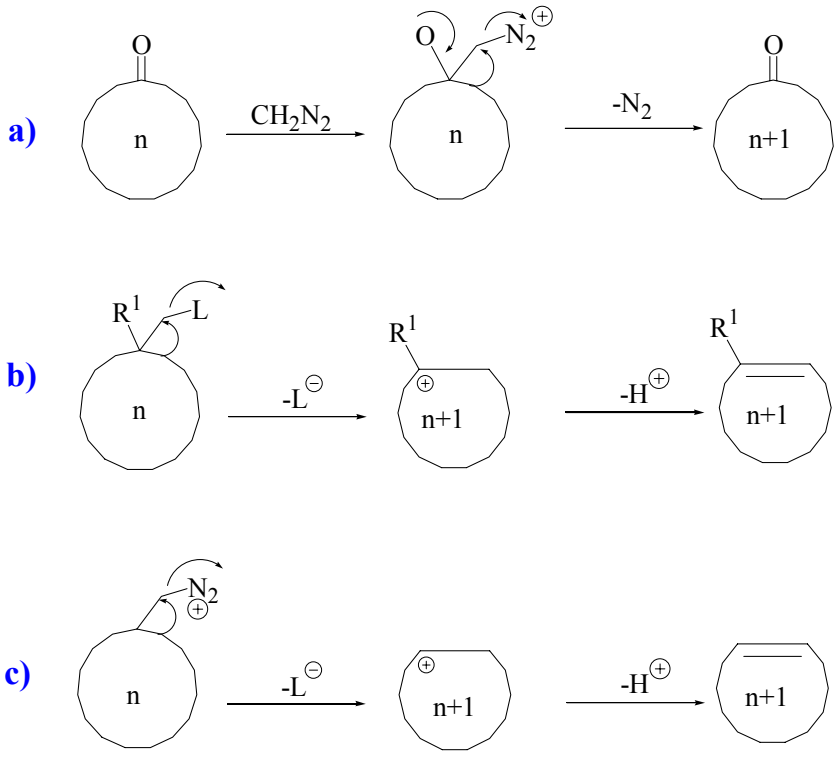
The interest in compounds containing rings in the C_{10} – C_{20} range stems from the discovery of their importance in many natural products or biologically active compounds. Since then, the development of synthetic methods for the formation of macrocyclic compounds has increased enormously and the construction of large rings with appropriately situated functional groups poses a synthetic challenge of substantial utility. Among methods employed directed ring-closing reactions of open chain precursors of bifunctional molecules is described by Illuminati and Mandolini[1]. In the 1920s and 1930s Ruzicka et al.[2] and Ziegler et al.[3] studied macrocyclization reactions. Macrocyclic ring formation requires an intramolecular cyclization reaction of a bifunctional molecule such as **1** (Scheme 1), where cyclisation gives the macrocycle **2**. In this model, X and Y are reactive functional groups that generate a new group Z (which could contain X, Y or both). An important reaction, which competes with cyclization, is the intermolecular reaction where initial coupling generates the dimeric product **3**. Repeated intermolecular reactions give the oligomer or polymer **4** (Scheme 1).



Scheme 1: Intramolecular cyclization reaction of a bifunctional molecule (**1**)

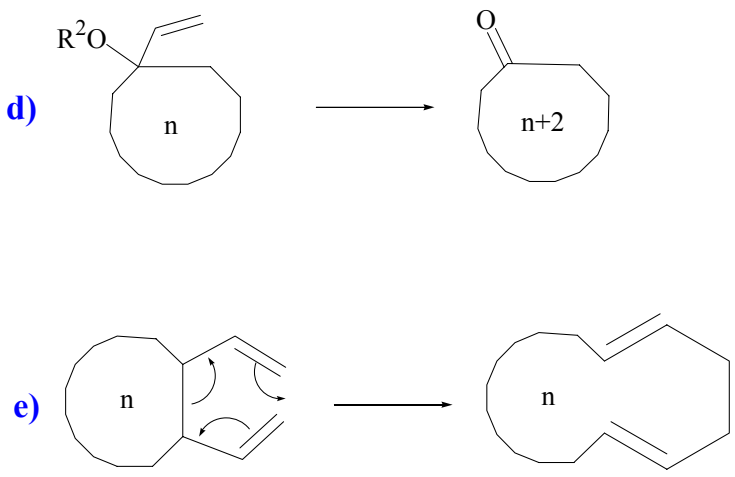
Ruggli discovered that high substrate concentrations favor polymerization while low concentrations favor cyclization[4]. The rate of cyclization is a function of the structure of the open-chain precursor and that of the product-like transition state. The activation energy for ring closure is largely determined by the strain energy of the final ring[5].

Strain energy is due to 1) bond opposition forces due to imperfect staggering (Pitzer strain), 2) deformation of the ring bond angles (Baeyer strain) and 3) transannular strain due to repulsive interactions between atoms across the ring when they are forced close to each other[1,6]. As the chain length increases for a cyclization reaction, the probability of the chain terminals approaching each other decrease (negative $\Delta S^{\ddagger}$ due to less freedom of internal rotation around single bonds of the molecular backbone when the disordered, open chain precursor is converted into the ring shaped transition state). In general, the ring product is a good model of the transition state of cyclization for the shorter chains[7]. In short chains, there is an advantage in terms of entropy but it is offset by enthalpy due to extremely large strain energies. Ziegler first used this principle of a ring-shaped transition state to generate large membered rings by the high dilution method[8]. A strategy to overcome the entropic factors cited above is to make use of cyclic compounds (such as cycloalkanones) converting these via ring expansion or contraction. The synthesis of macrocycles by means of a ring enlargement strategy are performed using different reaction types which could be classified according to the number of atoms being incorporated in the ring enlargement step. For example, carbocyclic compounds augmented by one atom could be achieved by Wolff rearrangement[9] (Scheme 2, example a) and related reactions such as Schmidt[10], Baeyer – Villiger[11] and the Tiffenau[12] reaction representing formal 1,2-migrations. Pinacol[13] and α-ketol[14] type rearrangements proceed by a similar mechanism. The Wagner-Meerwein[15] (example b) and Demjanov[16] (Scheme 2, example c) reactions have also been used for ring enlargement reactions.



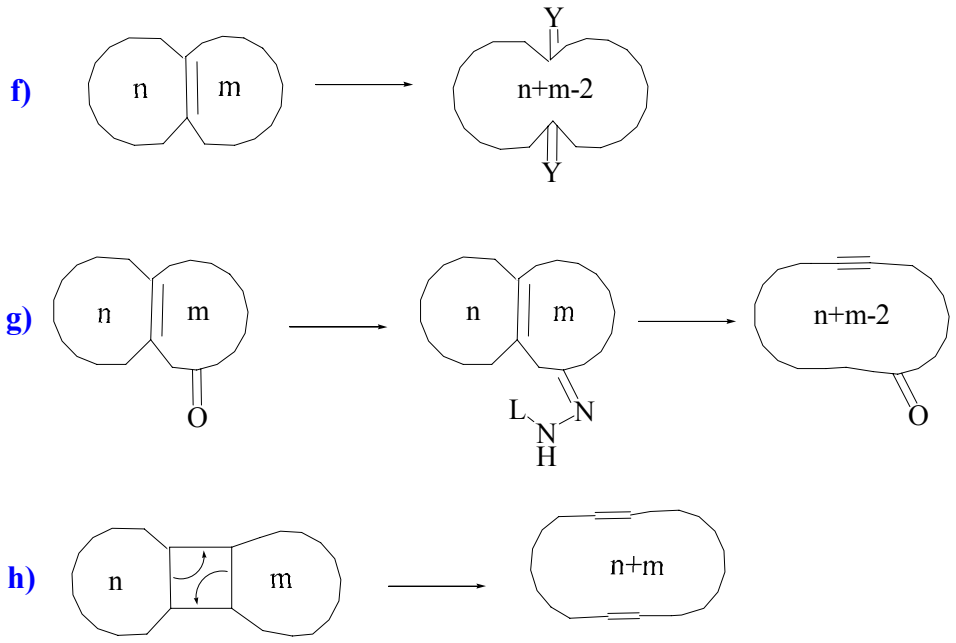
Scheme 2: Synthesis of macrocyclic compounds by ring enlargement

A second reaction could be represented by a formal 1,3-migration of allylic alcohols or ethers[17] which could lead to (n+2)-membered rings (Scheme 3, example d). Expansion of cyclic compounds by four atoms can be achieved by the Cope rearrangement[18] (example e, Scheme 3).



Scheme 3: Expansion of cyclic compounds by two or four carbon-atoms.

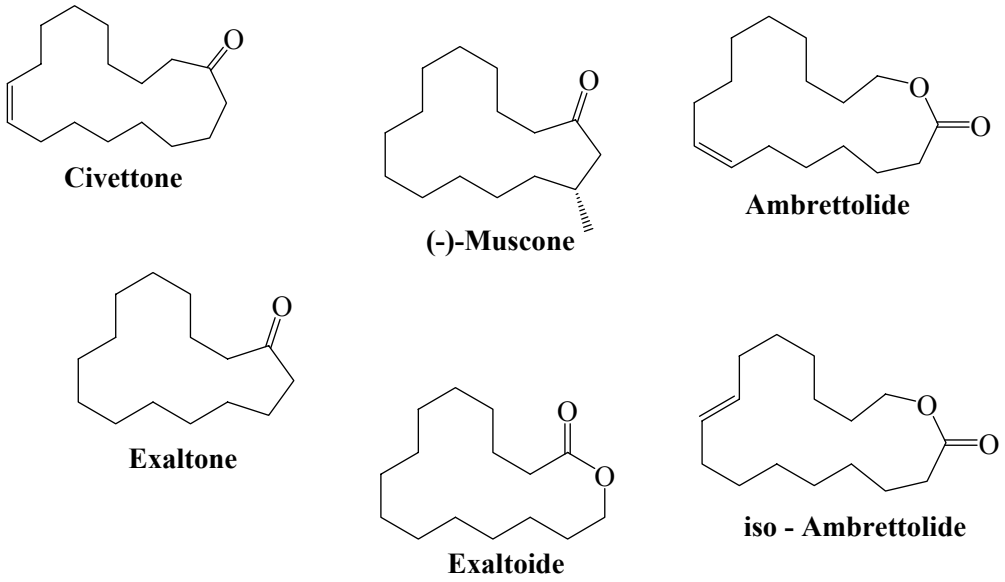
Besides the reactions mentioned so far, in which a specific number of atoms are being incorporated to an existing ring, there are other methods of ring enlargement, allowing expansions by a variable number of atoms. Examples pointing out these strategies are the oxidative cleavage of bridge bonds in bicyclic systems[19] (example f), the α,β-enone-alkynone fragmentation[20] (example g) and the thermal cycloreversion of tricyclic [2+2]-adducts (example h, Scheme 4).



Scheme 4: Expansion of cyclic compounds by a variable number of carbon-atoms

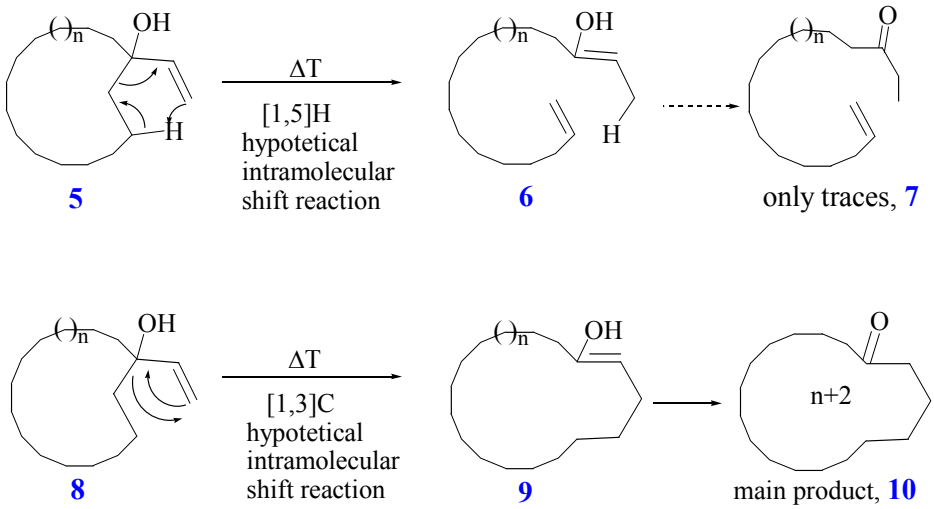
The advent of readily available twelve-membered ring systems provides an attractive starting point for rings expansion or ring contraction to gain access to larger or smaller rings[21]. Ring expansion reactions based on cyclododecanone as starting material are by far the most economical approaches to 15-membered macrocyclic musks.

Musk has been used in perfumes for over 900 years[22] and it is an important odor class. Natural sources of musk possessing macrocyclic structures mainly originate from animals, whose death is sometimes a prerequisite for the extraction of the musk scent.[23] As a result, the price of natural and synthetic musks, depicted in the Scheme 5, has always been high[24].



Scheme 5: Natural and synthetic macrocyclic musks.

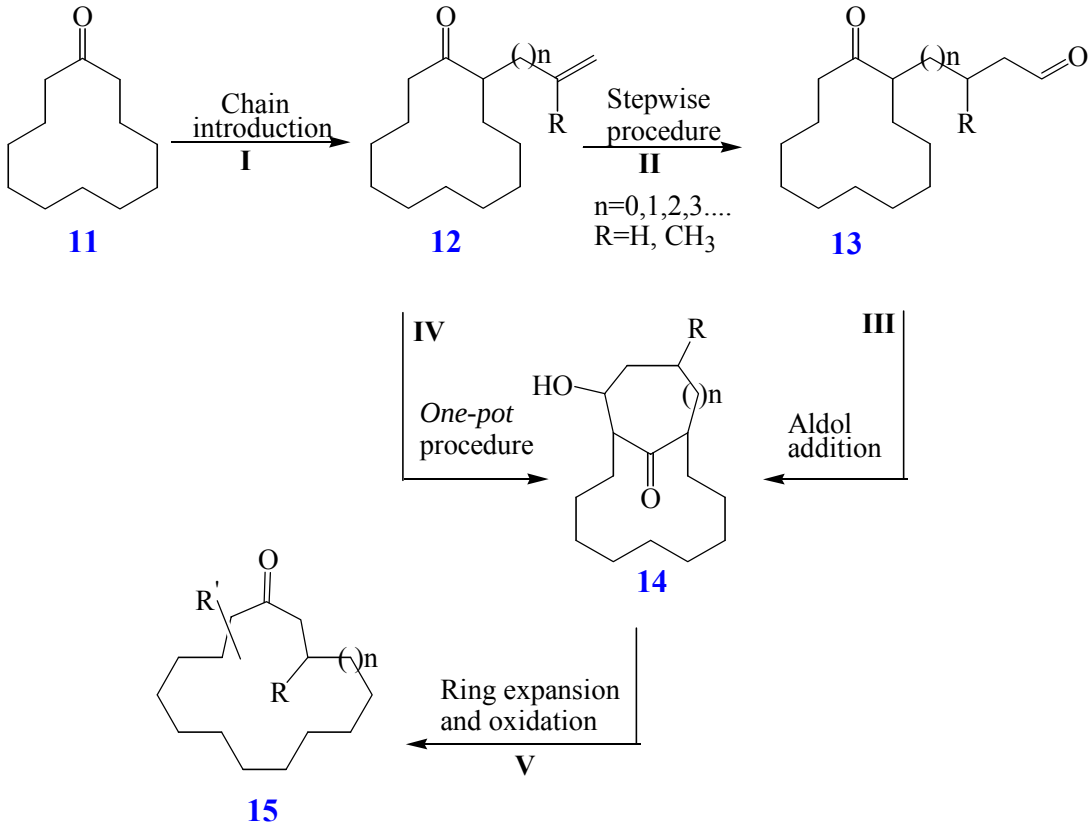
While, Exaltone® was first synthesized by Ruzicka in 1926 yielding the macrocycle in low yields, the first industrial synthesis of compounds Exaltone® and Muscone are elaborated using an intramolecular acyloin condensation[25]. Since then, numerous syntheses of these cyclic ketones have been reported[20a,26].One important approach is the three-carbon ring expansion of easily available cyclododecanone[27]. These attempts utilize mostly bicyclo[10.3.0]pentadec-1(12)-en-13-one as a precursor. Several methods for the synthesis of this ketone and its expansion reactions have been reported[28]. Recently, a two-carbon ring enlargement procedure, in which medium-and large-ring l-vinylcycloalkanols are thermally isomerized at temperatures of 600 °C to about 650 °C, producing the isomeric ring-expanded cycloalkanones.



Scheme 6: Thermo-isomerization of the corresponding ethynylic cycloalkanols

This ring expansion protocol can easily be applied in the preparation of Exaltone® from cycloundecanone in two repetitive cycles[29].

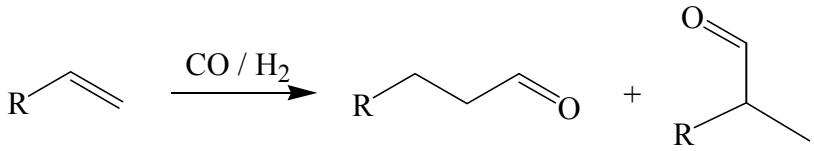
The aim of the project presented here is to investigate a new approach towards the synthesis of macrocyclic musks. 2-alkenyl cyclododecanones (**12**) (Scheme 7), easily prepared from cyclododecanone (**11**), is chosen as starting material, and the strategy is depicted in the Scheme 7. The general idea is to begin from an optimization of one-pot tandem hydroformylation / aldol addition sequence as key step towards the formation of precursor of type **14** (step IV) being available after only three steps followed by a ring-expansion (step V). Moreover, the application of the stepwise approach, directed to prepare the compound **14** , could allow investigating the regio-, chemo-selectivity of the whole process (step II and III).



Scheme 7: A new strategy towards the intermediates **15** in the preparation of the natural macrocycles musk.

In general, reaction sequences combining hydroformylation with various subsequent transformations of the oxo-aldehydes in one pot procedures are gaining growing interest[30,31]. Aldol reactions are often observed as side products under hydroformylation conditions[32]. Then, following earlier investigations in the tandem hydroformylation / aldol addition different conditions are performed allowing the aldol product formation directly under the hydroformylation conditions. Therefore, the aim, at first is to find out how to control the regioselectivity of the hydroformylation reaction and how to direct the aldol cyclisation.

Since its discovery, by O. Roelen[33] in 1938, the hydroformylation is considered as one of the most important homogeneously catalyzed industrial processes.

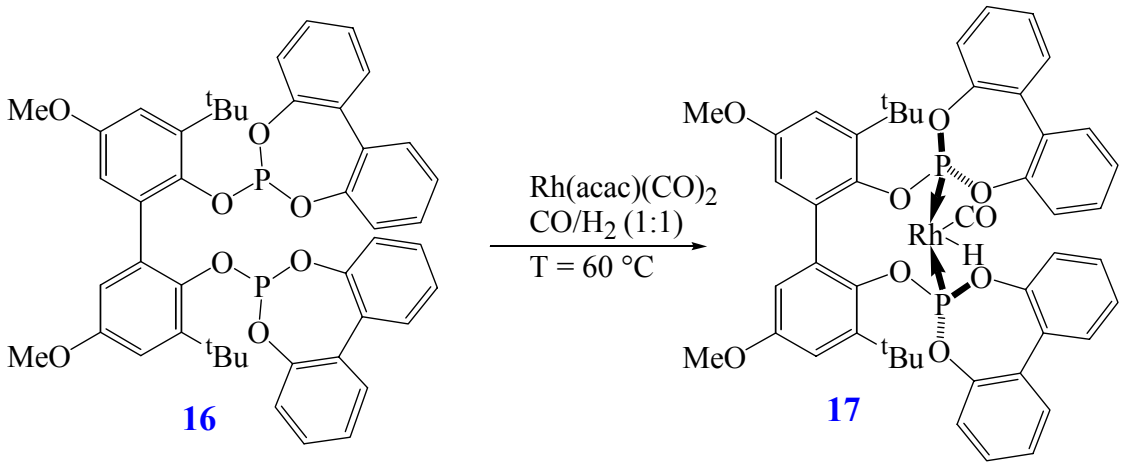


Scheme 8: General scheme of hydroformylation of *n*-alkenes.

Usually in hydroformylation of teminal alkenes are obtained two different regioisomers (Scheme 8). Control of the regiochemistry, the influence of the substrate as well the reaction parameters of the hydroformylation of terminal alkenes in the presence of phosphorus ligands has been extensively investigated[31,34]. The important discovery by Wilkinson[35] that rhodium complexes afford active and selective hydroformylation catalysts under mild conditions in the presence of triphenylphosphine as a ligand triggered intensive research on hydroformylation, especially on ligand effects and mechanistic aspects. Shortly after the discovery of Wilkinson, Pruett and Smith of UCC reported the beneficial effect of phosphite ligands in the rhodium catalyzed hydroformylation of 1-octene and methyl methacrylate[36]. They studied a wide variety of phosphite and phosphine ligands[36] finding out that the general trend is an increasing selectivity for the linear aldehyde when the electron withdrawing properties of the ligand increases. Moreover, the high catalytic activity of rhodium complexes modified by bulky phosphite system was also evident in the hydroformylation of 1-alkenes[37]. The high reactivity induced by bulky phosphite ligands has also led to the application of hydroformylation in functionalization of natural product derivatives that are otherwise hardly reactive. Syntheses of important intermediates to fine chemicals have been reported by hydroformylation of dihydrofuran[38], glucal derivatives[39] and methyl oleate[40].

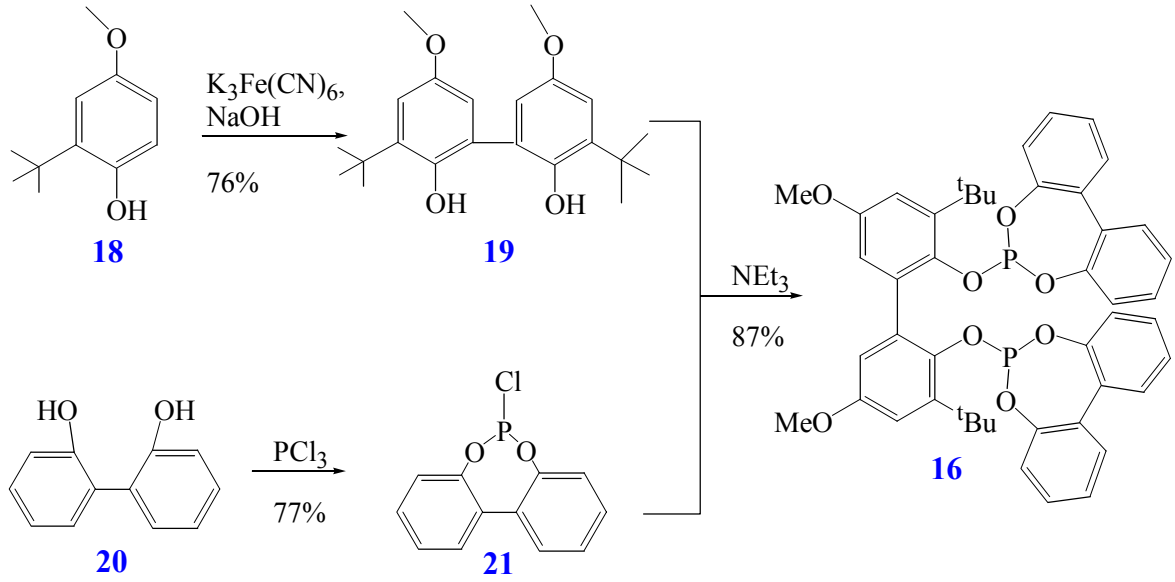
As reported above, phosphite ligands, especially bulky phosphates, are very useful in rhodium-catalyzed hydroformylation because of the higher reaction rates obtained when compared to triphenylphosphine. An important drawback, however, is the loss of selectivity. The change from bulky monophosphite to bulky diphosphite ligands by using bisphenol linkers resulted, in several cases, in a tremendous increase of the selectivity towards the linear aldehyde in rhodium catalyzed hydroformylation of 1 -alkenes[41,42]. The reaction rates are in general much lower than those of the bulky

monophosphite system, but still relatively high if compared with the triphenylphosphine based catalyst. The selectivity is found to be highly dependent on the ligand structure[43]. The bridge length of the diphosphites has a large influence on the selectivity for the linear aldehyde. As it is found for diphosphine ligands[44] the bite angle of the diphosphite ligands is probably an important parameter determining the selectivity of the hydroformylation reaction. The highest selectivities are achieved using bisphenol bridges. Along these lines, in 1988, a catalytic system derived from bis-organophosphite rhodium complex **17**, which gives high *n: iso* ratio and operates under mild conditions[45], has been found to affect the regioselectivity in the hydroformylation of terminal olefins producing a variety of ω–functionalized aldehydes[46]. This catalyst system notably demonstrates increased regioselectivity, and it is tolerant of a variety of potentially reactive functional groups. The active hydroformylation catalyst, presumably **17**, is generated in situ, in the presence of the substrate, by addition of the bis-organophosphite ligand[47,48] BIPHEPHOS (**16**) to dicarbonylacetylacetonato rhodium at 60°C (Scheme 9).



Scheme 9: Active hydroformylation species **17** of BIPHEPHOS (**16**)

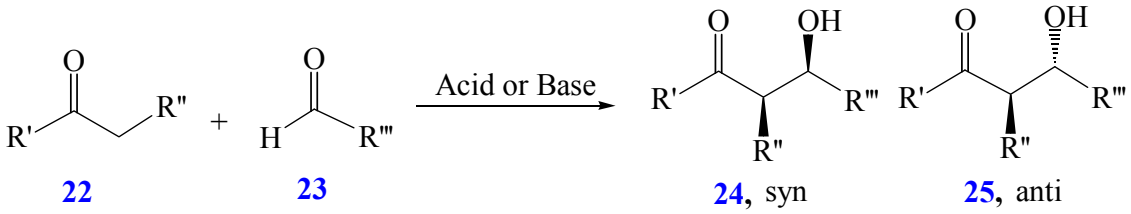
The synthesis of the BIPHEPHOS (**16**) is achieved following the method described by Cuny and Buchwald, starting from 3-t-butyl-4-hydroxyanisol (**18**) and 2, 2'-biphenol (**20**) through a three-step sequence in high yield (87%, Scheme 10).



Scheme 10: Synthesis of BIPHEPHOS (**16**)

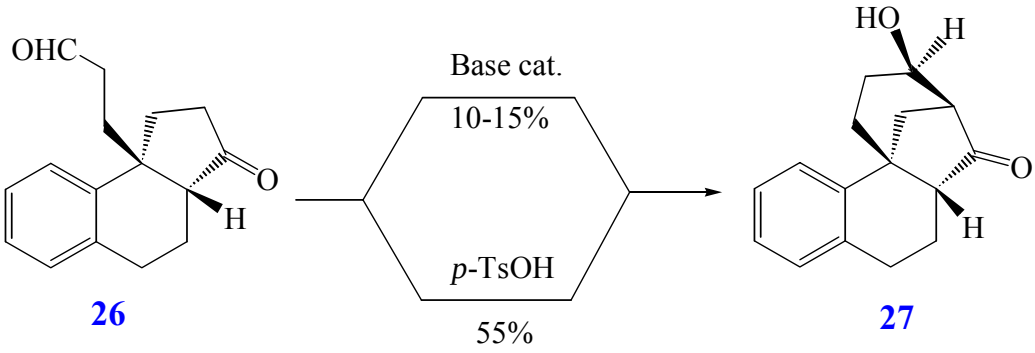
The bis-organophosphite rhodium complex **17**, operating under significantly milder conditions, notably with increasing regioselectivity, and being tolerant of a variety of potentially reactive functional groups could be chosen as ligand in the hydroformylation of 2-alkenyl-cyclododecanones.

As reported in the Scheme 7, following a general trend in organic chemistry[49], hydroformylation can also be integrated into tandem or domino reaction sequences. Thus, reduction, nucleophilic addition, such as aldol condensation or reductive amination can be achieved directly under the reaction conditions of hydroformylation. Traditionally, the aldol reactions are carried out in protic solvents with a base or acid as catalyst, wherein the enol or enolate of the nucleophilic carbonyl component **22** is generated reversibly in the presences of the electrophilic component **23**[50](Scheme 11).



Scheme 11: Aldol addition of ketone **22** with aldehyde **23**.

Then, aldol reactions, under different catalyzed conditions, provide an efficient method for formation of new carbon-carbon bonds and could be used for the preparation of key intermediates in the synthesis of important natural products. As reported by Hegarty and Mann[51] a variety of base-catalyzed aldolizations of tricyclic keto aldehyde **26** gives poor results in the construction of the stemodin skeleton **27**. In contrast, reaction of **26** with a catalytic amount of *p*-TsOH results in complete conversion and production of β-hydroxy ketone **27** in 55% yield after equilibration (Scheme 12).

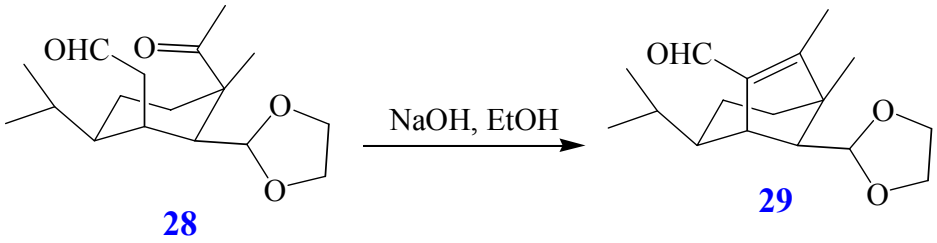


26 **27**

Scheme 12: Construction of stemodin skeleton **27**

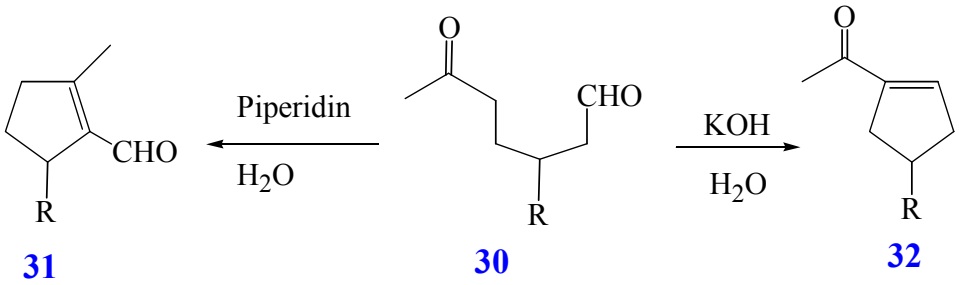
Keto aldehyde **26** involved in an intramolecular mixed aldol reaction, such as reported in the Scheme 12, are intrinsically unsymmetrical, and at least two or three isomeric compounds are usually possible. Conditions are known in which either the ketone or the aldehyde could function as the nucleophilic component.

Corey and Nozoe cyclized a keto-aldehyde in one-step in a total synthesis of helminthosphoral[52]. In this case, the aldehyde enolate of compound **28** adds to the more hindered ketone carbonyl to form a five-membered ring **29** (Scheme 13). The alternative addition of the ketone enolate to the aldehyde would give a seven-membered ring.



Scheme 13: Intramolecular aldol reaction in the synthesis of helminthosphoral[52]

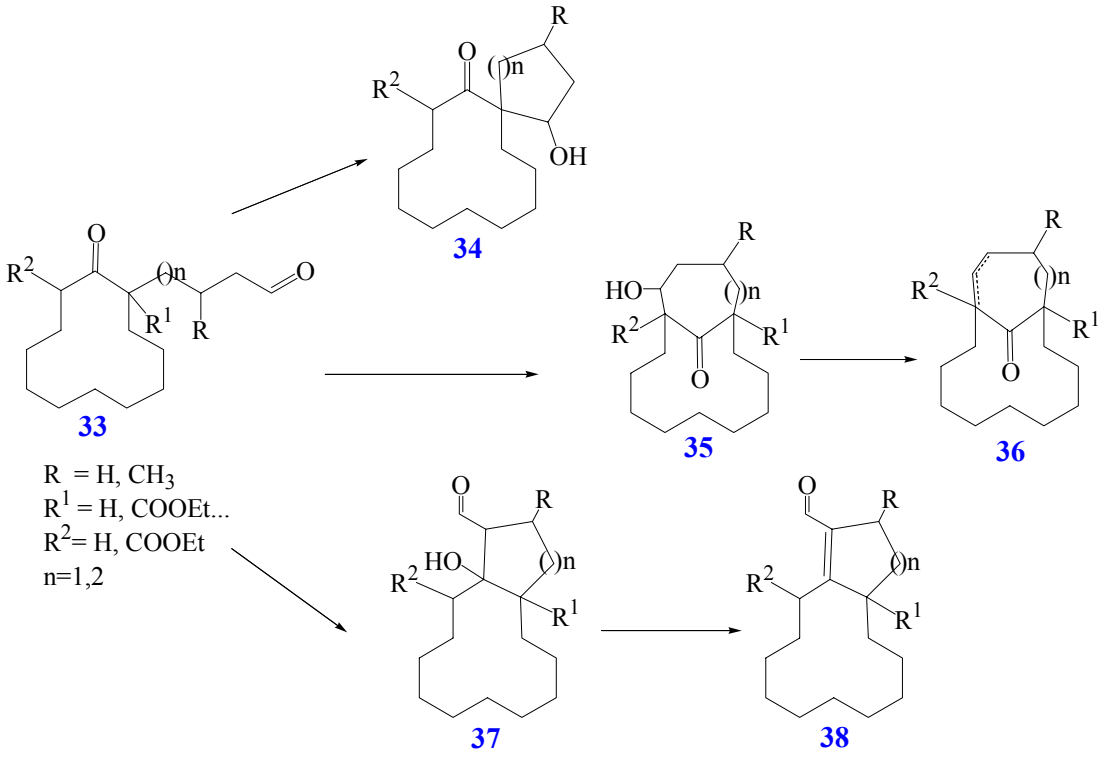
The regiochemistry of cyclisation the keto-aldehyde **30** is studied by Lalande and coworkers[53] and the results are shown in the Scheme 14.



Scheme 14: Chemoselectivity of intramolecular aldol condensation of keto-aldehyde **30**.

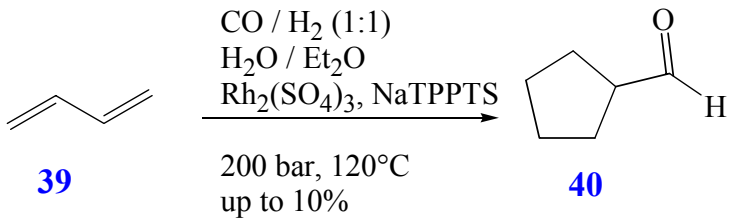
In this system, aqueous KOH gives exclusively the cyclopentenyl methyl ketone **32**, while piperidine acetate leads to cyclopentene carbaldhyde **31** (Scheme 14).

Taking into account these observations, the keto aldehyde **33**, could cyclize in three different ways. Moreover, under certain conditions the secondary alcohol **35** or alcohol **37** generated could undergo dehydration resulting in α,β-unsaturated carbonyl compounds **36** or **38**, respectively (Scheme 15). Then, controlling aldol addition conditions of preformed ketoaldehydes such as **33**, compound of type **34**, **35** or **37** could be obtained.



Scheme 15: Possible pathways in the aldol cyclization of compound **33**

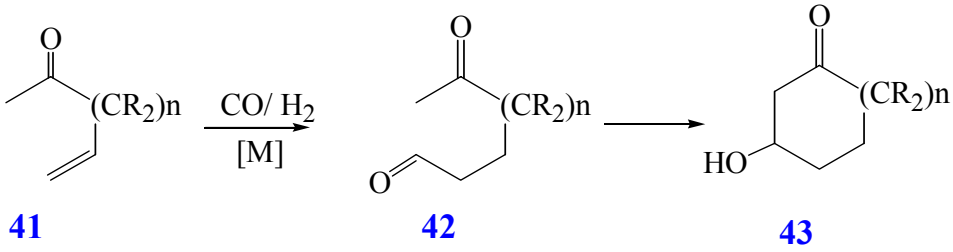
As previously mentioned, aldol reactions are often observed as a side reaction under hydroformylation conditions. An intramolecular aldol reaction is observed in the hydroformylation of 1, 3-butadienes (**39**) forming formyl cyclopentanes (**40**) (Scheme 16), in low yields[54,55,56,57].



Scheme 16: Intramolecular aldol reactions hydroformylation of 1,3-butadienes (**39**).

The synthesis of carbocyclic rings via hydroformylation / aldol addition sequences starting from a variety of acyclic carbonyl compounds bearing remote olefinic

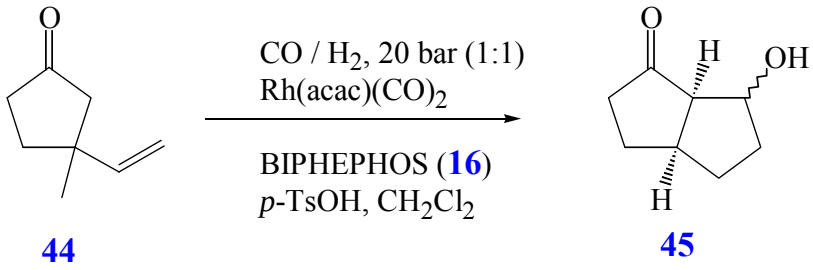
functions, catalyzed by the rhodium (I) complex in the presence of catalytic amounts of acid is also reported[58]. Using the bidentate diphosphite ligand BIPHEPHOS (**16**) the hydroformylation proceeds with high *n*-selectivity generating dicarbonyl compounds that undergo an intramolecular aldol reaction in a one-pot procedure.



41 **42** **43**

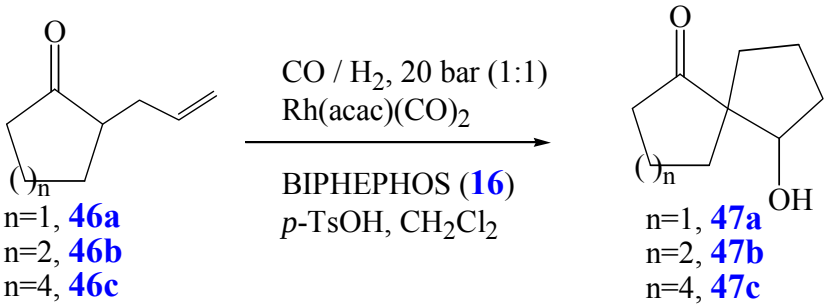
Scheme 17: General scheme of tandem hydroformylation / aldol addition.

Thus, unsatured ketones of type **41** can undergo *n*-selective hydroformylation at the olefinic double bond followed by an intramolecular aldol addition of keto aldehyde **42** to form **43** (Scheme 17). The second step of the sequence, the mixed aldol addition, usually shows high chemo- and regioselectivity in agreement with the literature[59] in which is reported that ketone moieties and especially activated methylene groups of malonic acid or β-keto carboxylate derivatives act as the enol equivalent and add to the stronger electrophile, the oxo aldehyde function. Starting from unsymmetrical β,γ- or γ,δ-unsaturated ketones with C, H acidic α and α'-positions, in most cases the cyclisations take place via the kinetically more stable enol regioisomers generating the thermodynamically favored five or six-membered rings. Thus, the method offers a convenient access to carbocyclic aldols and α,β-unsaturated carbonyl compounds. In addition, this one-pot procedure could be applied in the synthesis of bicyclic products starting from vinyl- and allylsubstituted cycloalkanones[60]. Thus, starting with 3-vinyl substituted cyclic ketone **44**, the tandem hydroformylation reaction offers an approach to ring annulations and bicyclic systems of type **45** (Scheme 18).



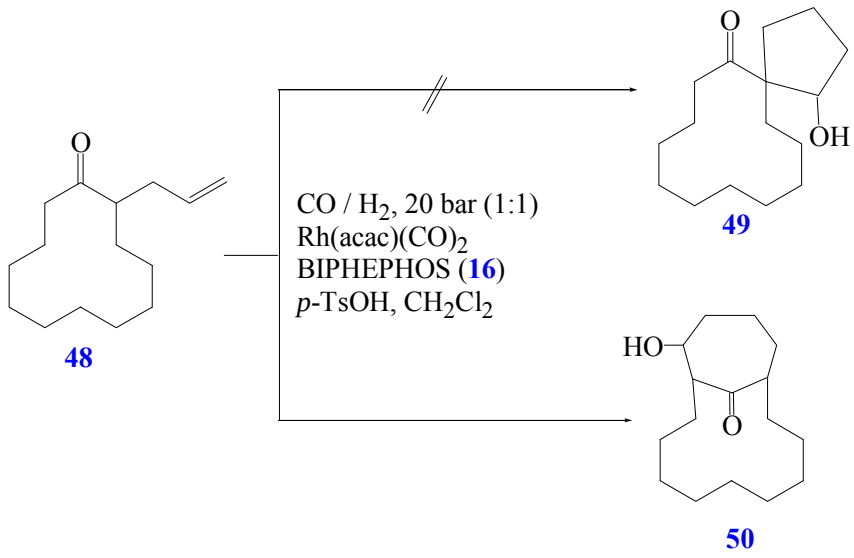
Scheme 18: Tandem hydroformylation / aldol addition of 3-vinyl cyclopentanone (**44**).

Besides the synthesis of annulated carbocycles, the method also offers an access to spirocyclic compounds. There, the conversions of 2-allyl-cyclopentanone (**46a**), -cyclohexanone (**46b**) and -cyclooctanone (**46c**) gives the spirocyclic β-hydroxy-ketones **47a-c** in medium to good yields (Scheme 19). According to the results discussed above the cyclisations proceed regioselectively via the keto enols of the intermediate keto aldehyde that generate the five-membered rings.



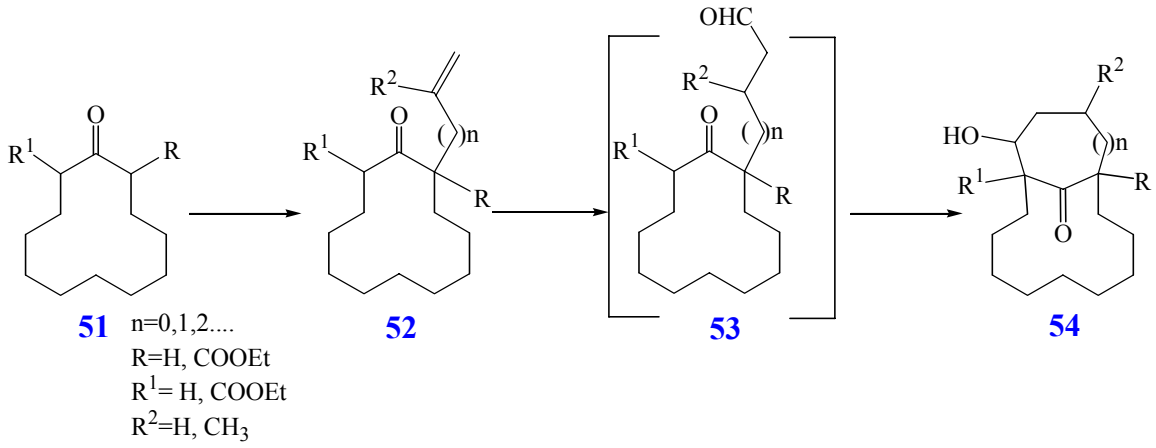
Scheme 19: Syntheses of the hydroxy-spiroalkanones **47a-c**.

Surprisingly, if starting with 2-allyl-cyclododecanone (**48**) the tandem reaction does not lead to the spirocyclic aldol adduct (**49**) but the cyclisation gives the bicyclo[9.4.1]hexadecane **50** (Scheme 20). Presumably, formation of the quaternary center is avoided in this case because of lower ring strain in the large annulated ring of **50**.



Scheme 20: Synthesis of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**)

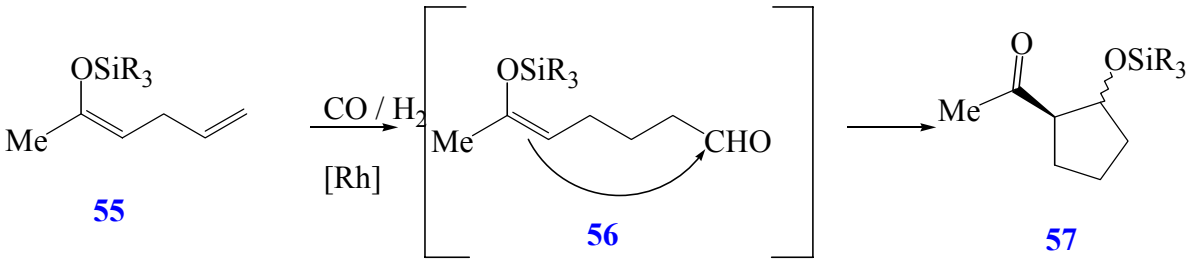
In this project, taking into consideration the results reported above, cyclododecanone derivatives such as compounds **52** would be involved in the tandem hydroformylation / aldol addition (Scheme 21). When a tandem reaction sequence is run with functionalized cyclododecanones highest possible selectivity in each single transformation is required in order to obtain good yields for the overall sequence. Thus, to achieve regioselectivity in the hydroformylation of terminal, monosubstituted olefinic double bonds the rhodium catalyzed hydroformylation under mild conditions have to be run using the ligand BIPHEPHOS (**16**)[46] which is known to be one of the most efficient ligands for highly *n*-selective hydroformylation of many functionalized olefins with excellent yields. As previously discussed, intramolecular aldol additions, involving ketoaldehyde, present problems of chemoselectivity. In order to circumvent these problems many investigations have been accomplished in this area.



51 **52** **53** **54**

Scheme 21: Preparation of substituted bicyclic cycloalkanones (**54**)

Directed aldol additions of activated ketones in the presence of a large number of transition metal complexes have been tested[61]. Among various examples, rhodium (I) catalyzed reactions of enol silanes and aldehyde are investigated by Matsuda[62], Reetz[63] and Heathcock[64]. Previous work[65] has shown that a rhodium-catalyzed hydroformylation / Mukaiyama aldol addition of the corresponding preformed silyl enol ether such as compound **55** bearing remote olefinic functionalities is an effective method to prepare aldol adducts **57** in a one-pot procedure with good yields. Moreover, silyl enol ethers are reported to be stable under hydroformylation conditions[84] and undergo selective *n*-hydroformylation at the olefinic double bond followed by a Mukaiyama type aldol addition[66] (Scheme 22).

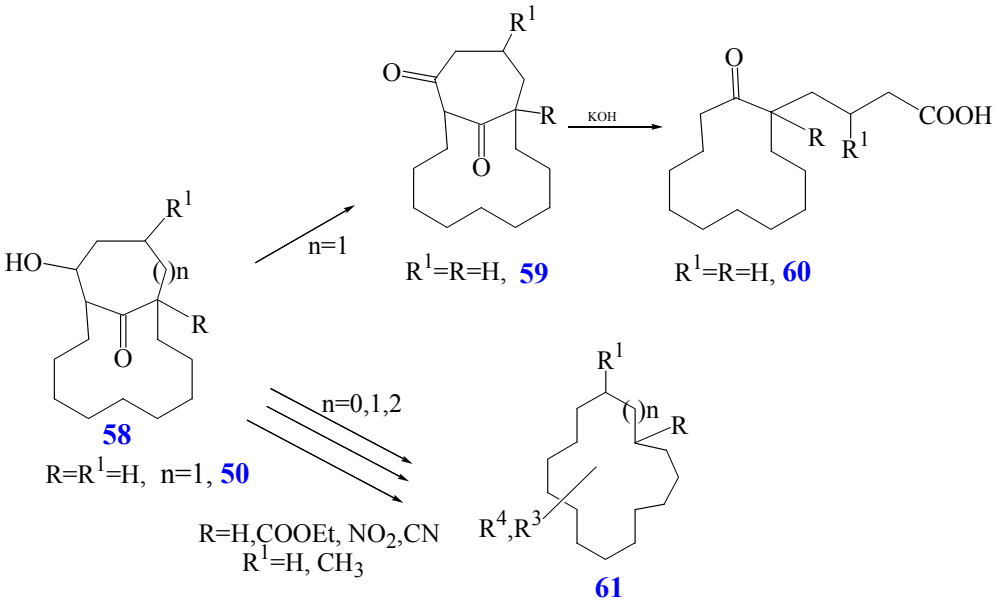


55 **56** **57**

Scheme 22: Tandem hydroformylation /aldol addition under Mukaiyama conditions

The application of the latter conditions on cyclododecanones derivatives of type **52** could offer a new method to obtain the corresponding aldol adducts from ketoaldehydes and subsequently to build up a precursor of natural macrocyclic musk.

Initial attempts to accomplish the preparation of macrocycles have been conducted, making use of 1,3 diketone **59** in the presence of KOH (Scheme 23). Unfortunately, the reaction proceeds with the formation of the retro-aldol product **60** in high yield. When considering the skeleton of products of type **58** and compound **50** (R=R_1=H, n=1), it could be useful to envisage alternative ring-enlargement methods involving the cleavage of the keto-bridge in the presence of other functional groups in appropriate positions.



Scheme 23: Ring-enlargement towards the preparation of compounds of type **61**

Along these lines, the base-promoted Grob fragmentation[67] of tosylates of bicyclo[9.4.1]hexadecane **50**[68] will be investigated as well as a retro-Dieckmann reaction could be tested. Finally, an oxidative approach, such as Baeyer-Villiger oxidation followed by lactone hydrolysis could be performed. Consequently, various unsaturated cyclododecanone derivatives of type **52** (Scheme 21) should be prepared. As mentioned above by introduction or variation of the functional groups, such as –NO_2, -COOEt, -CN, the precursor **58** could undergo subsequent conversions to compounds of type **61** (Scheme 23).

2. Theoretical part

2.1. One-pot hydroformylation / aldol addition of 2-alkenyl cyclododecanones and unsaturated β-ketoesters

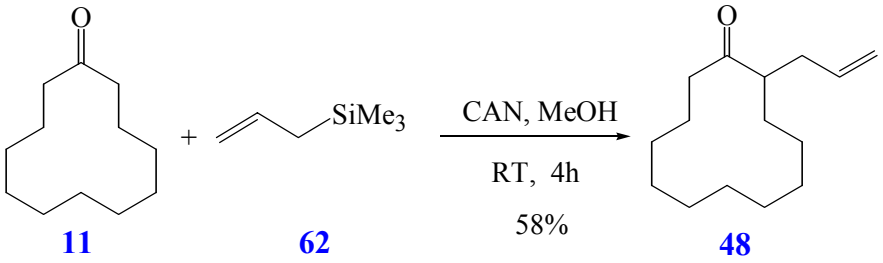
2.1.1. Preparation of starting materials

2-Allyl-cyclododecanone (48)

As stated in the introduction, choosing 2-alkenyl cyclododecanones of type **52** (Scheme 21) as first substrates for the tandem hydroformylation / aldol addition, an efficient preparation of α-substituted cycloalkanones has to be developed.

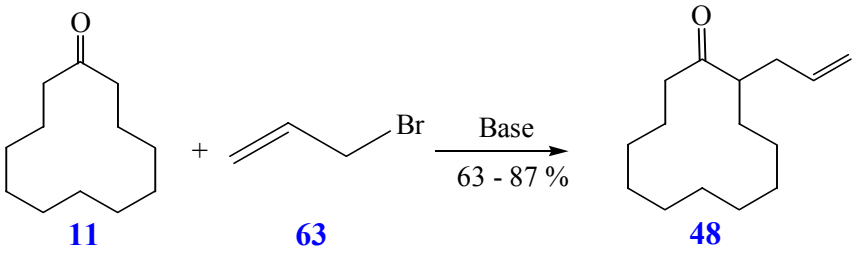
General methods to synthesize 2-alkenyl cycloalkanones are reported. These compounds could be obtained by alkylation of the corresponding cycloalkanones, or, more conveniently, by an adaptation of the Claisen rearrangement performed by heating the ketone with allyl alcohol and 2,2-dimethoxypropane in the presence of an acid catalyst[69]. This results in the *in situ* generation and thermal rearrangement of allyl vinyl ether intermediate. A different approach could be represented as a rearrangement of allyl enol carbonates, prepared from ketones or aldehydes by trapping their enolates, with allyl chloroformate catalyzed by Pd – phosphine under mild conditions[70].

Alternatively, oxidative additions applied to C-allylation of 1, 3-dioxo compounds by using allylsilanes are reported[71]. Oxidative additions of 1,3-dioxo compounds to alkenes can be initiated by use of one-electron oxidizing agents,[72] such as ceric ammonium nitrate[73] (CAN). Application of this reaction to 1, 3-dioxo compounds by using a combination of allyltrimethylsilane and CAN afforded the monoallylated products in good to excellent yields. Although combination of allyltrimethylsilane and CAN in methanol efficiently monoallylated most 1, 3-dioxo compounds, this method is not applied widely to monoketones with the only exception for conversion of cyclododecanone. Then, following the procedure reported by Hwu and al., the preparation of 2-allyl-cyclododecanone (**48**) is performed in the presence 1.6 eq. of allyltrimethylsilane (**62**) and 3 eq. of ceric ammonium nitrate (CAN) (Scheme 24) give **48** in 58 % yield (R 1).



Scheme 24: Preparation of 2-allyl-cyclododecanone (**48**) in the presence of CAN.

In order to improve the yield of **48**, the alkylation reaction is performed by generating the enolate of cyclododecanone (**11**) and use of allylbromide as alkylating agent (**63**) (Scheme 25). Treatment of **11** with a strong base such as LDA[74] (generated in situ from *n*-BuLi and DIA) allows a slightly higher yield compared to this obtained when *n*-BuLi[75] is used (Table 1, R 2, R 3). If the alkylation of **11** is run in the presence of a weaker base such as K_2CO_3[76] no product is detected in the reaction mixture and only starting material is recovered (Table 1, R 4).



Scheme 25: Preparation of 2-allyl-cyclododecanone (**48**)

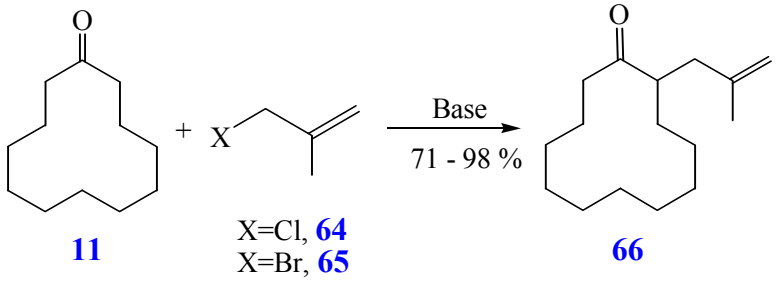
In addition to the last results, an efficient and convenient method is employed if a solution of **11** in toluene is treated with allylbromide (**63**) in the presence of KOH and a phase transfer catalyst (dibenzo-[18]-crown-6)[77]. The alkylation proceeds with good yield (76% yield, Table 1, R 5) and 2-allyl-cyclododecanone (**48**) could be obtained in shorter reaction time.

Table 1: Preparation of 2-allyl-cyclododecanone (**48**).

R	t, [h]	ϑ, [°C]	Reaction conditions	Yield 48, [%]
R 2	18	20	LDA, THF	87
R 3	20	20	*n*-BuLi, THF	63
R 4	16	80	K_2CO_3, MeOH	starting material
R 5	6	125	KOH, toluene, dibenzo-[18]-crown-6	79

2-(2-Methylprop-2-enyl)cyclododecanone (66).

If using the tandem hydroformylation / aldol addition to prepare bicyclic compounds, bearing a methyl group in 1, 3 relationships to the ketone moiety, a methallyl chain has to be introduced. Using the same methods as reported above, the methallylation of **11** to synthesize 2-(2-methylprop-2-enyl)-cyclododecanone (**66**) is performed with 3-halo-2-methylpropene starting from different enolate anions of cyclododecanone (**11**) (Scheme 26, Table 2).



Scheme 26: Synthesis of 2-(2-methylprop-2-enyl)-cyclododecanone (66).

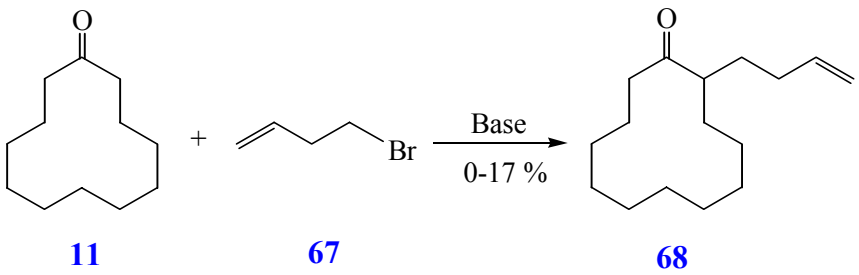
Table 2: Methallylation of cyclododecanone (**11**)

R	t, [h]	ϑ, [°C]	Reaction conditions	Yield 66, [%]
R 6	18	80	**64** (X=Cl); NaH, HMPA, THF	98
R 7	18	20	**64** (X=Cl), LDA, THF	SM
R 8	18	20	**65** (X=Br), LDA, THF	85
R 9	6	125	**64** (X=Cl), KOH, toluene, dibenzo-[18]-crown-6	71

According to the results compiled in Table 2, the methallylation of **11** is best carried out using HMPA and NaH[78] (98%yield, R 6) but cost and safety considerations discourage its use for larger scale synthesis. In contrast to these results no conversion is observed when 3-chloro-2-methyl-1-propene (**64**) and LDA are used (Table 2, R 7). If using 3-bromo-2-methyl-1-propene (**65**) and LDA changes the outcome of the reaction (Table 2, R 8) and compound **66** is obtained in good yield. However, alkylating reagent **65** is more expensive and this procedure is not convenient to scale up the reaction. Finally, similar results as compared to use of unsubstitued olefinic chains are obtained if compound **66** is prepared by allylation in the presence of potassium hydroxide with catalytic amounts of dibenzo-[18]-crown-6. This method presents an alternative route towards **66** with low cost and good yield[77] (Table 2, R 9).

2-(But-3-enyl)cyclododecanone (68).

In contrast with to the good yields previously obtained (Table 2, R 8 - R 9), attempts to synthesize the 2-(but-3-enyl)cyclododecanone (**68**) using 4-bromobut-1-ene (**67**) in the presence of different bases, failed and only small amounts of **68** were obtained (Scheme 27). As summerized in Table 3, in the presence of KOH and catalytic amounts of dibenzo-[18]-crown-6, the alkylation of **11** does not occur and only starting material is recovered (Table 3, R 10). In addition, the reaction performed in the presence of *t*-BuOK and KI[79] (R 11) does not offer an access to compound **68** (Table 3, R 12). Although in small yields the compound **68** is obtained if using LDA as base but the conversion is still too low (Table 3, R 12).

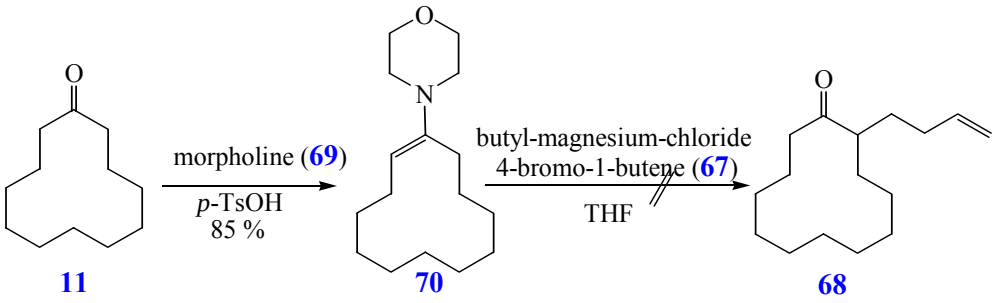


Scheme 27: Synthesis 2-(but-3-enyl)cyclododecanone (**68**)

Table 3: Preparation of 2-but-3-enylcyclododecanone (**68**).

R	t, [h]	ϑ, [°C]	Reaction conditions	Yield 68, [%]
R 10	24	80	*t*-BuOK, KI, *t*-BuOH	--
R 11	6	125	KOH, toluene, dibenzo-[18]-crown-6	--
R 12	16	20	LDA, THF	15

In regard to these low yields obtained in R 10-R 12, the synthesis of 2-but-3-enylcyclododecanone (**68**) alternatively could be run by making use of enamines as enolate equivalents. The 4-cyclododec-1-en-1-yl-morpholine (**70**) of **11** could be conveniently prepared by the usual azeotropic method[80]. Treatment of ketone **11** which reacts sluggishly with morpholine (**69**) in the presence of catalytic amounts of *p*-TsOH·H_2O under reflux, after 72 hours furnishes compound **70** in 85% yield (Scheme 28, R 13).

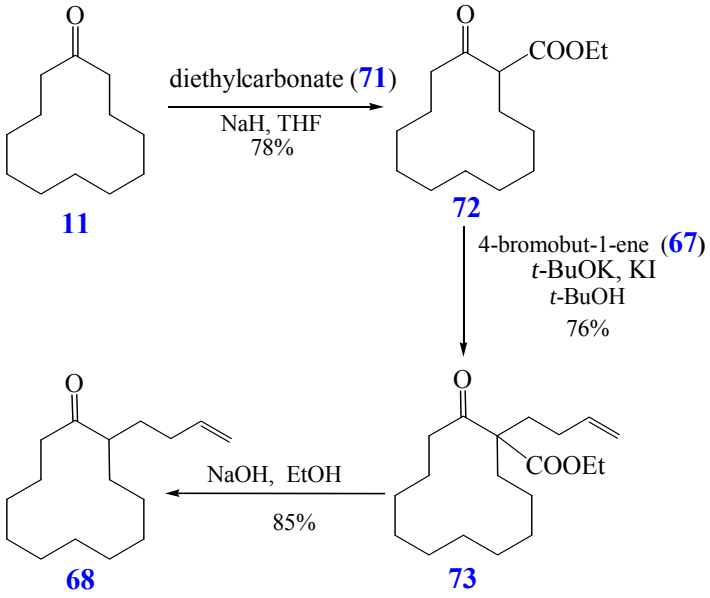


Scheme 28: Enamines as intermediates in the synthesis of 2-but-3-enylcyclododecanone (**68**).

Attempt for the alkylation of **70** is performed according to a general procedure, previously described by Borowitz et al. using 4-bromo-but-1-ene (**33**) in the presence of butylmagnesiumchloride (Scheme 28). However, after hydrolysis with a solution of HCl, only cyclododecanone (**11**) is recovered (R 14).

As an alternative method, the synthesis of 2-(but-3-enyl)cyclododecanone (**68**) could be achieved by use of ethyl 2-oxocyclododecane carboxylate(**72**) (Scheme 29). Following the Deslongchamps variant[81], cyclododecanone (**11**) is, first treated with NaH and

diethylcarbonate (**71**), at reflux. Finally, by quenching with acetic acid, compound **72**, after distillation of the crude mixture is obtained in 78% (R 15).



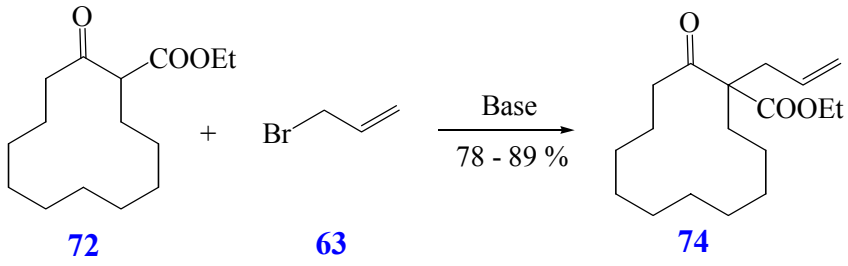
Scheme 29: Preparation of 2-but-3-enyl-2-oxo-cyclododecane (**68**)

Alkylation[82] of β-keto esters **72**, using 4-bromobut-1-ene (**67**) as the alkylating agent and t-BuOK as base, gives ethyl 1-but-3-enyl-2-oxo-cyclododecane carboxylate (**73**) in 76 % yield (R 16) Finally, decarboxylation[83] in the presence of NaOH in refluxing EtOH furnishes 2-(but-3-enyl)cyclododecanone (**68**) 85% yield (Scheme 29, R 17).

Ethyl 1-allyl- 2-oxo-cyclododecane carboxylate (74).

Among the suitable and compatible functional groups under hydroformylation conditions[84], the ester function could be chosen and the preparation of β-ketoester could be performed.

A general method to produce the compound **74** (Scheme 30) is the allylation of β-keto-ester **72** with NaH and allylbromide[85] (**63**). The product **74** is obtained in 78% yield, as a colorless crystalline solid, after recrystallization from *n*-hexane (R 18).



72 **63** **74**

Scheme 30: Preparation of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)

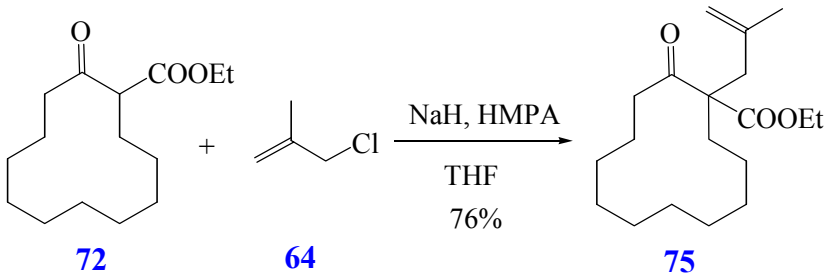
Alternatively, the β-keto-ester **72** is treated with *t*-BuOK in *t*-BuOH[86] in the presence of allylbromide **63**. A moderate improvement in yield (89% yield, Table 4) is observed and the product can be isolated without any further purification (R 19).

Table 4: Preparation of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)

R	**Base**	**Solvent**	**ϑ, [°C]**	**Yield 74, [%]**
R 18	NaH	THF	80	78
R 19	*t*-BuOK	*t*-BuOH	90	89

Ethyl 1-(2-methyl-allyl)-2-oxo-cyclododecane carboxylate (75).

To preapare compound **75**, the starting material **72** is alkylated with 3-chloro-2-methylprop-1-ene (**64**) in the presence of the HMPA-NaH system[87] (Scheme 31). The product **75** is isolated in 76% yield after distillation of a crude mixture (R 20).



72 **64** **75**

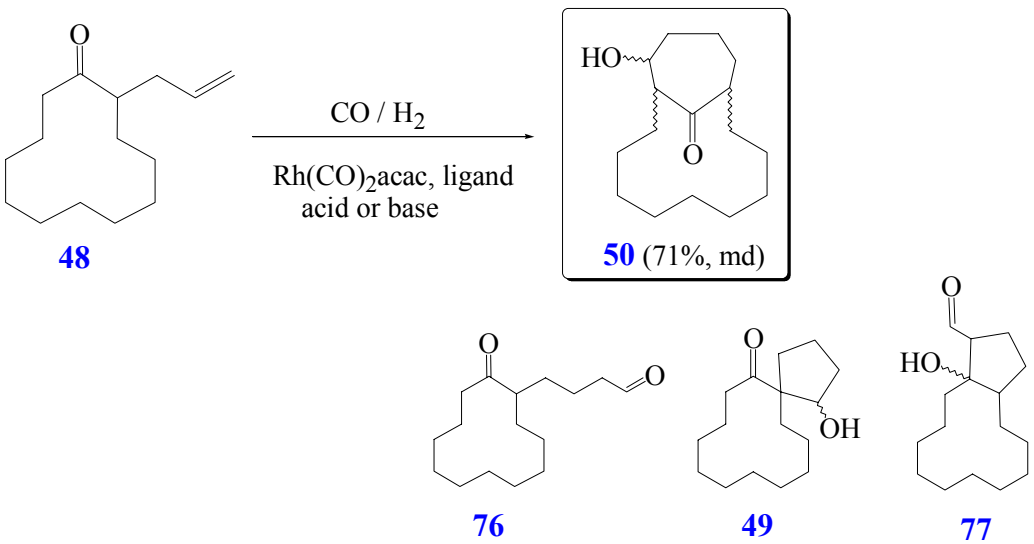
Scheme 31: Preparation of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**)

2.1.2. One-pot tandem hydroformylation aldol addition of 2-alkenyl cyclododecanones

Tandem hydroformylation / aldol addition has been reported as an efficient and convenient method to transform cycloalkanones bearing remote olefinic side chains, into the corresponding aldol adducts. In these previous investigations, it has been found that *p*-toluenesulfonic acid (*p*-TsOH) is the most useful catalyst for performing these transformations. Using the BIPHEPHOS (**16**) (Scheme 9) ligand the hydroformylation proceeds with high *n*-selectivity generating keto aldehydes that undergo an intramolecular aldol reaction in a one-pot procedure.

Conversion of 2-allyl-cyclododecanone (48).

According to the reaction conditions optimized by C.Hollmann, the tandem hydroformylation / aldol addition of 2-allyl-cyclododecanone (**48**) is carried out with the $Rh(CO)_2(acac)$ catalyst in the presence of 5 mol % of *p*-TsOH and 4 mol % of BIPHEPHOS (**16**), under mild conditions of 20 bar of CO/H_2, 100°C for 3 d (Scheme 32). The reaction is observed to proceed with complete chemoselectivity giving exclusively aldol adduct **50** in 71% yield as a mixture of two diastereoisomers (11:1 ratio) that could not completely be separated and assigned (Table 5, R 21).



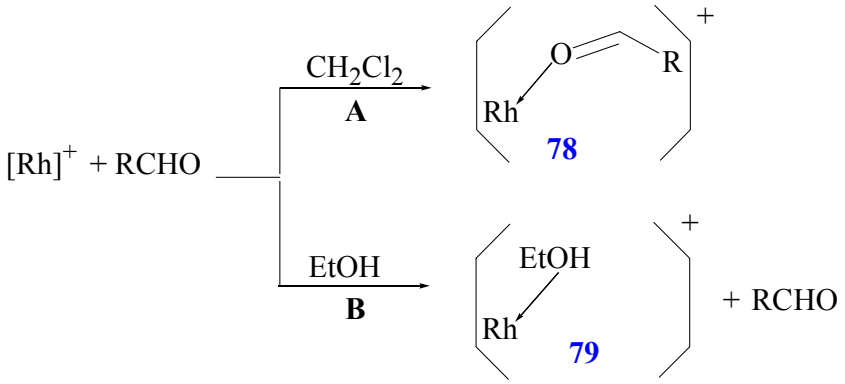
Scheme 32: Tandem hydroformylation / aldol cyclisation of 2-allyl-cyclododecanone (**48**)

The tandem reaction conditions applied to compound **48** does not lead to the spirocyclic aldol adduct **49** nor to the five-fused compound **77** arising from the reversal of chemoselectivity. The formation of the quaternary center is avoided, probably, due to lower tension in the large annulated ring of **50** compared to those derived from its formation in the spirocyclic compound **49**.

Table 5: Tandem hydroformylation / aldol cyclisation of 2-allyl-cyclododecanone (**48**)

R	acid / base	solvent	dr	Yield 50 [%],
R 21	*p*-TsOH	CH_2Cl_2	11:1	71
R 22	DBU	dioxane / EtOH	--	--

Alternatively, the hydroformylation of **48** is performed under basic conditions in the presence of catalytic amounts of DBU (4 mol %) using a mixture of EtOH / dioxane (9:1) as solvent (Table 5, R 22). The presence of the linear aldehyde **76** (Scheme 32) as the only product of the reaction shows that the aldol cyclisation in the presence of transition metals such as Rh does not proceed in strongly coordinating solvents such as EtOH, THF or acetonitrile.



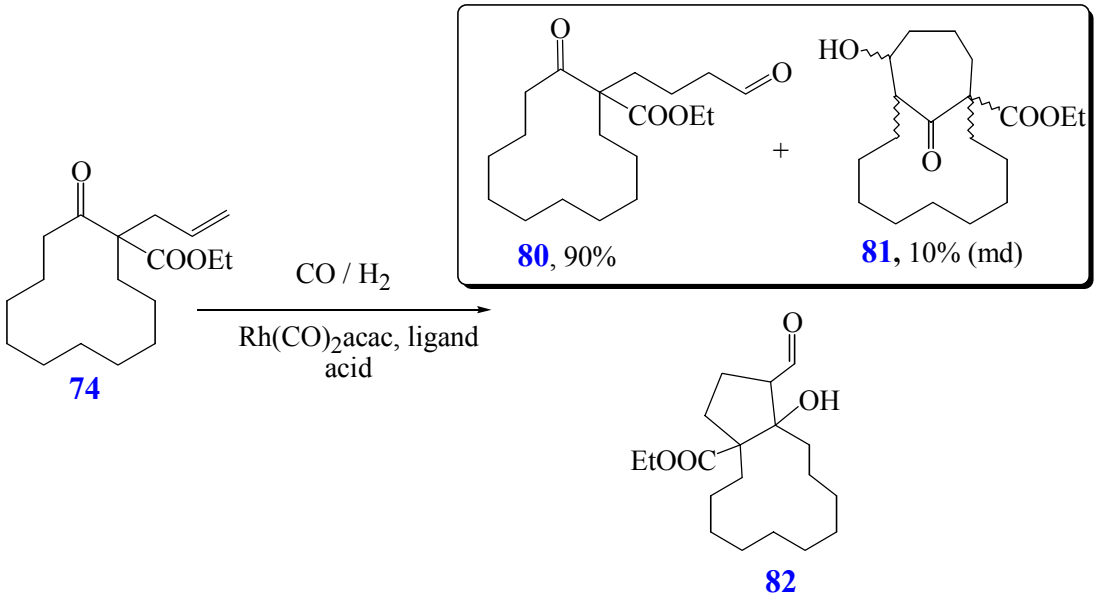
Scheme 33: Different coordination of [Rh] in the presence of CH_2Cl_2 or EtOH

This may be an indication that the mechanism of aldol addition in apolar solvents such as CH_2Cl_2, involves coordination of one or more aldehyde molecules at rhodium resulting in the formation of **78** (Scheme 33, pathway **A**) leading to an activation of the

carbonyl function[88] whereas EtOH is known to be involved in Lewis acid / Lewis base adducts with the Rh-catalyst forming the complex **79**[89] (Scheme 33, pathway **B**).

Conversion of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)

The tandem hydroformylation / aldol addition of γ,δ-unsatured cycloalkanones bearing an ester function in α–position, such as β-ketoester **74**, is performed w ith $Rh(CO)_2(acac)$ catalyst and BIPHEPHOS (**16**) (4% mol) in the presence of 5 mol % *p*-TsOH under 20 bar CO/H_2 (1:1) at 60°C (Scheme 34). Under these mild conditions, compound **74** is expected to react like allylated cyclododecanone **48** and indeed the reaction proceeds, although in low yields, with formation of compound **81** as a mixture of diastereoisomers in a ratio of 1.4: 3.2 detected by NMR analysis, whereas the *n*-aldehyde **80** is generated in 90% isolated yield (R 23).

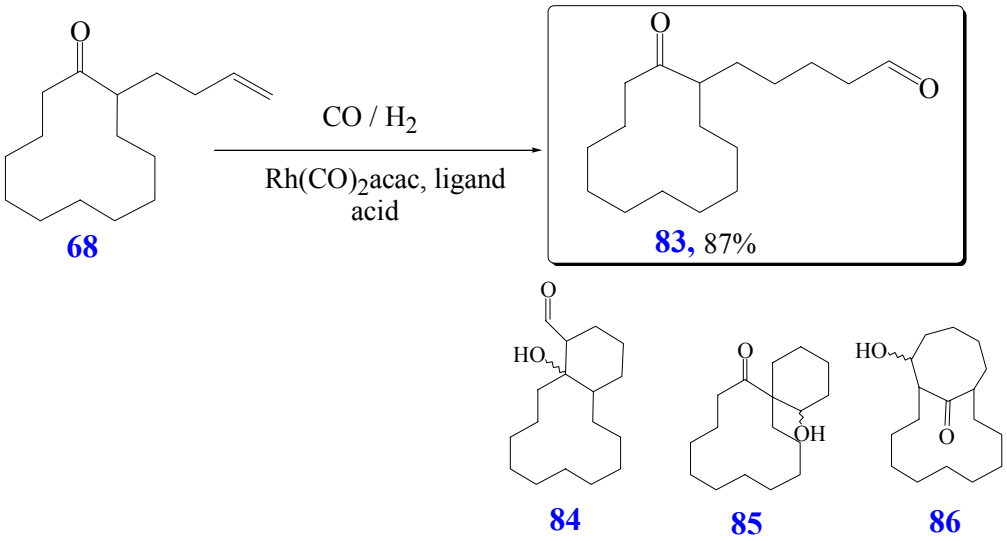


Scheme 34: Tandem hydroformylation / aldol addition of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**).

The low reactivity of 1,6-ketoaldehyde **80** towards the aldol addition could be attributed to the presence of the α-substituent present in the starting material. Again compounds such as **82** resulting from attack of the aldehyde enolate, generated during the hydroformylation, on the ketone, are not formed.

Conversion of 2-(but-3-enyl)cyclododecanone (68).

As it has been previously observed that the 2-allyl-cyclododecanone (**48**) affords the aldol adduct **50** when hydroformylated under mild conditions, the corresponding compound **85** is not observed and none of two other competitive intramolecular aldol additions occur (Scheme 32). Proceeding with the investigations of tandem hydroformylation / aldol addition of cycloalkanones bearing remote olefinic side chain, 2-(but-3-enyl)cyclododecanone (**68**) is investigated. Hydroformylation is performed in the presence of 5 mol % of *p*-TsOH and BIPHEPHOS (**16**) under mild conditions (20 bar of $CO:H_2$, 60°C) (Scheme 35, R 24).

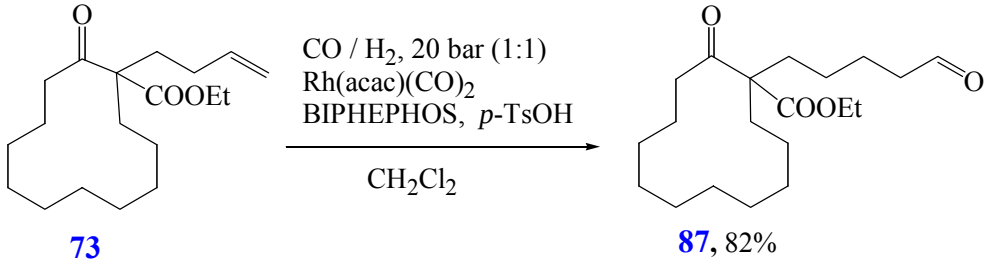


Scheme 35: Hydroformylation aldol condensation of 2-(but-3-enyl)cyclododecanone (**68**)

Only the *n*-product of hydroformylation 5-(2-oxo-cyclododecyl)pentanal (**83**) is observed in 87% yield (R 24). According to the Baldwins' rule the 6-enol-endo-exo-trig compounds **84** and **85** should be favored. Besides Baldwins' rule to the ketone enolate[90], the formation of 8-membered ring of compound **86** could not occur because of low flexibility in the chain to attain the required approach angle (Bürgi-Dunitz trajectory[91]). However, the outcome of the reaction could mean that the required orientations of p-orbitals of the enolate do not have the correct angle of approach.

Conversion of ethyl 1-(but-3-enyl)-2-oxo-cyclododecane carboxylate (73).

Similar to 2-but-3-enylcyclododecanone (**68**), compound **73** reacts, under the same mild conditions, to give the 1,7-ketoaldehyde **87** in 82 % yield (R 25). Once again, none of the aldol adducts is formed (Scheme 36) under these conditions.

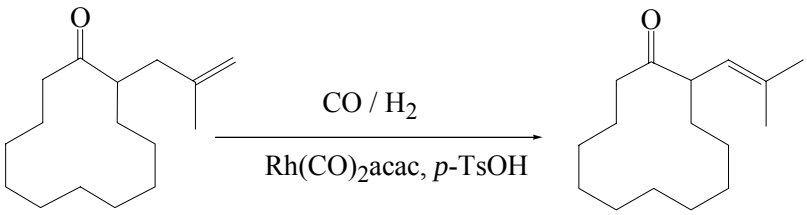


73 **87,** 82%

Scheme 36: Hydroformylation of ethyl 1-(but-3-enyl)-2-oxo-cyclododecane carboxylate (**73**).

Conversion of 2-(2-methylprop-2-enyl)cyclododecanone (66).

When compound **66** is converted with $Rh(CO)_2(acac)$ catalyst in the presence of 5 mol % *p*-TsOH using the relatively harsh hydroformylation conditions of 80 bar CO/H_2, 100 °C for 3d, is expected to react like the unsaturated cycloalkanone **48**, which affords the desired aldol adduct **50** (Scheme 32). On the contrary the isomeric compound 2-(2-methylprop-1-enyl)cyclododecanone (**88**) (R 26, Scheme 37) is generated in 93% yield, arising from a double-bond migration. This type of isomerization is known to be catalyzed by transition metal complexes[92].



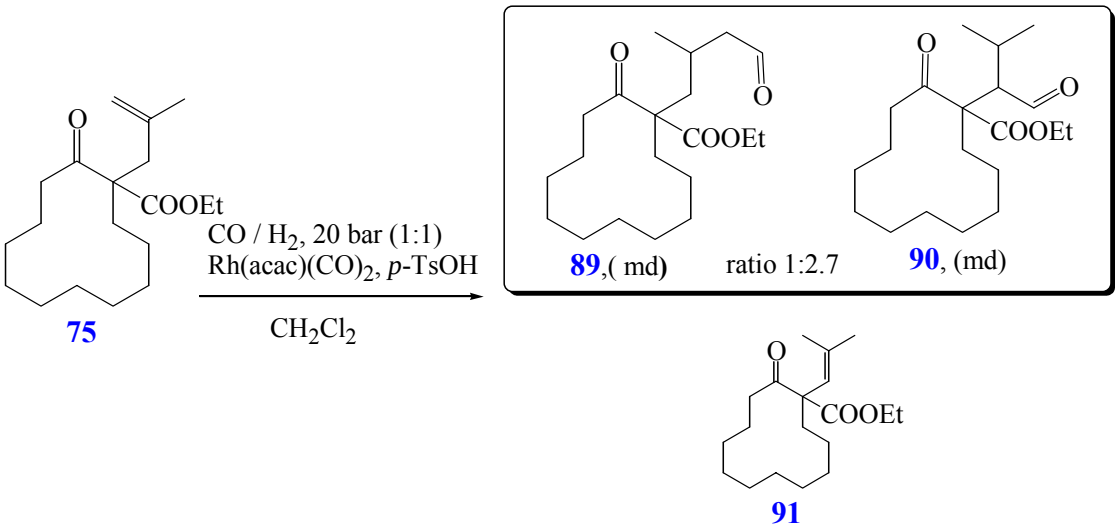
66 **88**, 93%

Scheme 37: Isomerization of double bond of 2-(2-methyl-1-propen)cyclododecanone (**66**).

Compound **88** thus generated contain a triply substituted double bond, which if hydroformylated, should require the generation of quaternary centre unfavorable for steric and / or thermodynamic reasons[93]. Even the hydroformylation of the less substituted but hindered carbon of the double bond does not occur. According to the literature, this type of olefins is hydroformylated only under harsh conditions[94] (high temperature[95,96] and pressure[97]) and in the presence of bulky ligands[94a]. The lack of reactivity towards a sequential tandem hydroformylation / aldol addition shows that cyclization to construct the bicyclic compound cannot be accomplished using this methodology.

Conversion of ethyl 1-(2-methyl-allyl)-2-oxo-cyclododecane carboxylate (75).

In analogy to the previous results concerning the tandem procedure applied on cycloalkanones bearing substituted olefinic chain ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**) undergoes isomerization of the double bond. Although the isomerization process is tried to be controlled by modifications of the reaction conditions (60 °C, 20 bar instead of 90°C and 80 bar) and its isomerized compound **91** is formed, but not isolated (Scheme 38, R 27).



75

91

Scheme 38: Hydroformylation of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**).

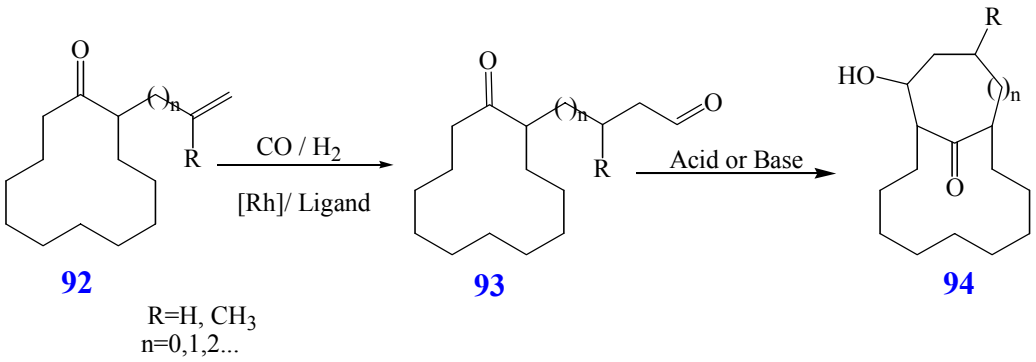
Here, in contrast to the latter results both the keto ester **75** and isomerized ketoester **91** undergo hydroformylation. Thus, a mixture of the branched aldehyde **90** and the *n*-aldehyde **89** in a ratio of 1:2.7 (detected by NMR analysis) is obtained.

It can be concluded from these results that although several substrates, as established in previous investigations in the sequential tandem hydroformylation / aldol addition, are able to form the aldol adducts, this procedure with starting materials such as compounds homoallylated cyclododecanone **68** and β-ketoester **73** and **66** could not satisfactorily be employed. Thus, in order to prepare bicyclic compounds other methods are needed.

2.2. Stepwise hydroformylation / aldol addition

2.2.1. Introduction

Alternatively, to the tandem procedures an aldol addition of preformed aldehydes is investigated. Regioselective hydroformylation of terminal olefins of type **92** (R=H), should lead to aldehydes of type **93** (R=H). While methallyl chains (R=CH_3), under milder conditions preferably could form the linear aldehydes, hydroformylation of monosubstituted olefins leads to a mixture of linear and branched regioisomers and therefore requires additional regiocontrolling P ligands (Scheme 39).



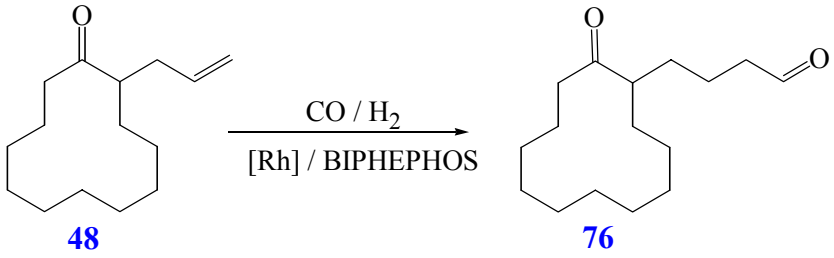
Scheme 39: Preparation of bicycle[9.n.1]cycloalkanone (**94**)

Then, keto-aldehydes of type **93** are then used as the substrates in intramolecular aldol addition catalyzed by base or acid to give the aldol adduct of type **94**.

2.2.2. Hydroformylation of 2-alkenyl-cyclododecanones and unsaturated β-ketoesters

Conversion of 2-allyl-cyclododecanone (48).

For initial investigations towards the stepwise transformation, the hydroformylation of **48** with catalytic amounts of $Rh(CO)_2(acac)$ (1 mol %) in CH_2Cl_2 under 20 bar of CO/H_2 at 60°C is performed (Scheme 40). The regioselectivity of the reaction is achieved by use of 4 mol % of BIPHEPHOS (**16**) giving exclusively the *n*-aldehyde, 4-(2-oxo-cyclododecyl)butanal (**76**) (Scheme 40). The results for different reaction times are shown in Table 6



Scheme 40: Hydroformylation of 2-allyl-cyclododecanone (**48**)

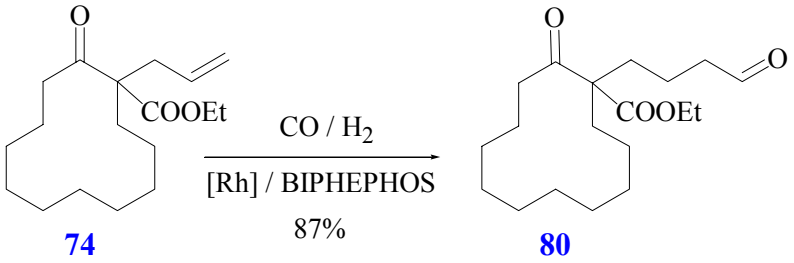
Table 6: Variation of the reaction time in the hydroformylation of compound (**48**)

R	t, [h]	Yield 76, [%]
R 28	24	67
R 29	48	79
R 30	72	91

As indicated in Table 6 after increased reaction times (up to three days) a positive effect on the yield of compound **76** has been observed ranging from 67% in 24 hours to 91% in 72 hours (R 28, R 29, R 30).

Conversion of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (66)

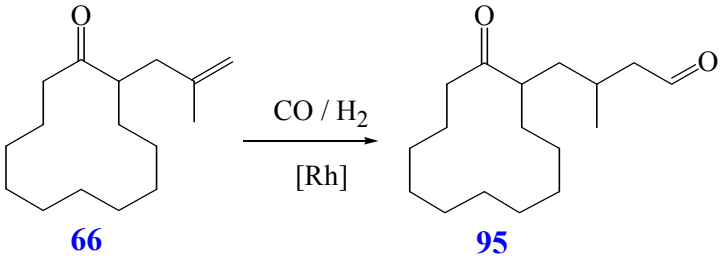
Under the same reaction conditions, the hydroformylation of **74** proceeds in good yield to the give the corresponding *n*-aldehyde **80** is obtained in 87% yield (Scheme 41, R 31).



Scheme 41: Hydroformylation of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**).

Conversion of 2-(2-methylprop-2-enyl)cyclododecanone (75)

In contrast to the results obtained in hydroformylation of 2-allyl cyclododecanone (**48**), compound **66** (Scheme 42), with a methyl group at the double bond, when hydroformylated under similar reaction conditions, reacts with slightly lower conversion.



Scheme 42: Hydroformylation of 2-(2-methylprop-2-enyl)cyclododecanone (**66**).

The lower conversion of the reactions could be attributed to the lower reactivity of the substituted double bond of **66**[98].

Table 7: Hydroformylation of 2-(2-methylprop-2-enyl)cyclododecanone (**66**)

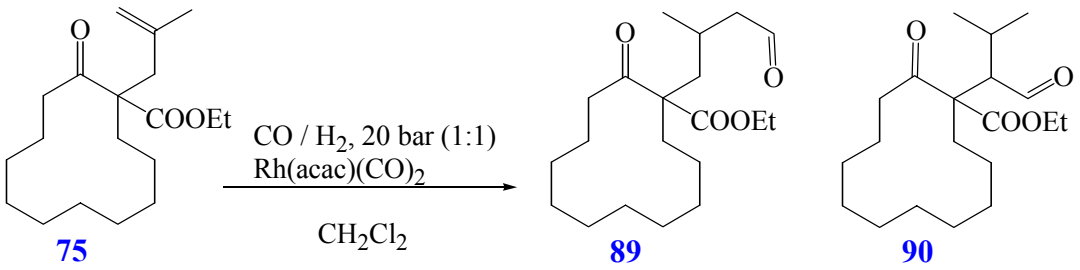
R	ϑ, [°C]	t, [h]	[a]dr	Yield 95, [%]
R 32	60	72	1:1.33	48
R 33	100	24	1:1.33	47
R 34	100	48	1:1.19	52
R 35	100	72	1:1.1	62

a)ratio calculated with respect to the CH_3

As summarized in Table 7, all yields are around 50% and 3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**) is obtained as a mixture of two diastereoisomers in 1:1.33 ratio by NMR analysis (R 32). Thus, upon increasing the temperature, from 60°C (R 32) to 100°C (R 35, R 33, R 34) the conversions of **66** remain unaffected. Moreover, at this temperature, no double bond migration is observed.

Conversion of 1-(2-methyl-allyl)-ethyl 2-oxo-cyclododecane carboxylate (75)

In contrast the hydroformyalation of substituted alkene **75** performed in the presence of Rh(I) (Scheme 43) leads to a mixture of compound **89** and **90** in the ratio of 1: 2.17 detected by NMR analysis (R 36).



75 **89** **90**

Scheme 43: Hydroformylation of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**)

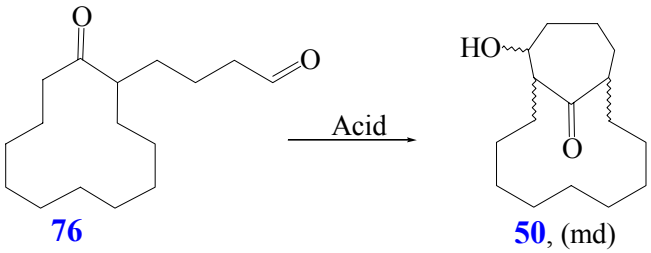
Once again, the isomerization of the double bond followed by the hydroformylation of the internal double is observed.

2.2.3. Intramolecular base and acid catalyzed aldol addition

Conversion of 4-(2-oxo-cyclododecyl)butanal (76)

As discussed in the introduction 1,6-ketoaldehydes of type **33** (Scheme 15) are intrinsically unsymmetrical and they could cyclize, depending on the reaction conditions, in three different ways. Moreover, under certain conditions the secondary alcohol **35** or tertiary alcohol **37** formed, could undergo dehydration resulting in α,β–unsaturated carbonyl compounds. Therefore, intramolecular aldolization of **76** is run under acidic and basic conditions. Again, as observed in the one-pot procedure (see Scheme 32), under acidic conditions the cyclization of the ketone enolate function with the aldehyde (Scheme 44) is favored and the bridged 7-membered ring of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) is formed. Treatment of ketoaldehyde **76** with strong mineral acid leads to the formation of the bicyclic aldol **50** in very low yield when HCl[99] is used (R 37, 20% yield) whereas the use of H_2SO_4[100] in the aldolization is

not of interest because of the formation of an intractable mixture due to decomposition (R 38).

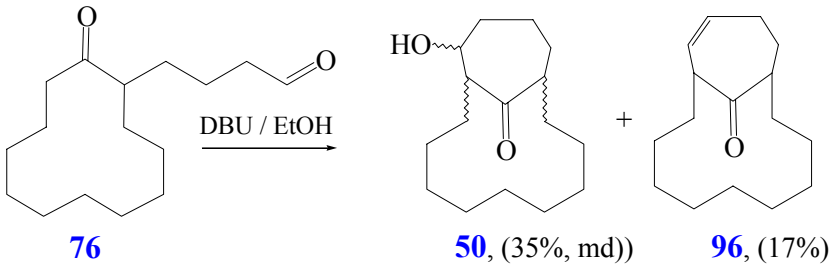


Scheme 44: Aldol cyclization of 4-(2-oxo-cyclododecyl)butanal (76).

Table 8: Aldol addition of 4-(2-oxo-cyclododecyl)butanal (**76**).

R	acid	dr	Yield [%], 50
R 37	HCl	1:2.9	20
R 38	H_2SO_4	--	4

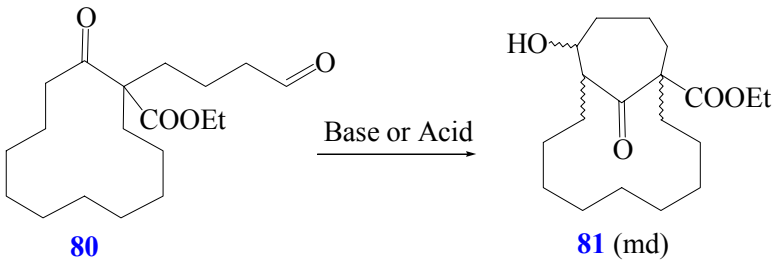
In contrast to the results above, compound **76** undergo base-catalyzed aldol cyclisation, DBU[101] in EtOH (Scheme 45), proceeds with good yield and the compound **50** is formed as a mixture of four diastereoisomers (R 39).



Scheme 45: Aldol condensation of 4-(2-oxo-cyclododecyl)butanal (**76**) in the presence of DBU.

Conversion of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (80).

The intramolecular aldol condensation of the 1,6 dicarbonyl compound **80** has been carried out under basic or acidic conditions for 20 hours and room temperature (Scheme 46).



80 **81** (md)

Scheme 46: Preparation of ethyl 12-hydroxy-16-oxo-bicyclo [9.4.1]hexadecan carboxylate (**81**).

Table 9: Intramolecular aldol addition of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**).

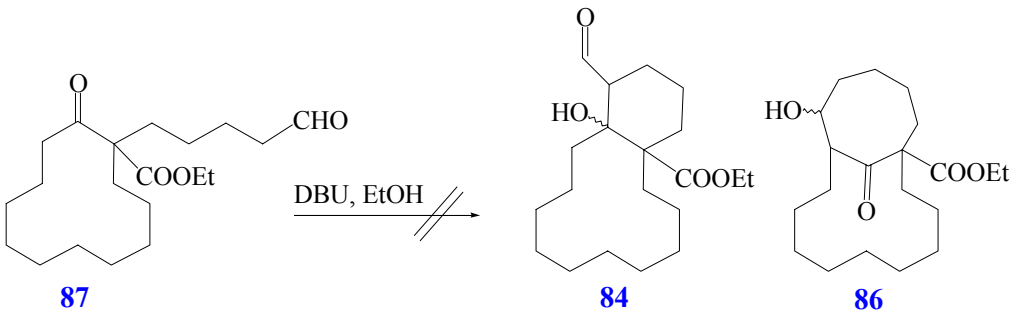
R	Acid / base	Solvent	dr	Yield, 81 [%]
R 40	HCl(7N)	Dioxane	1:6	35
R 41	H_2SO_4	EtOH	--	--
R 42	LDA	THF	1:1.8	34
[a]R 43	DBU	EtOH	1:1:6	90

a) 72 hours

As listed in Table 9 the compound **80** reacts in the presence of HCl (7N) to afford product **81** in yield 35% as a mixture of two diastereoisomers in a ratio of 1:6 detected by NMR (R 40), whereas upon use of H_2SO_4[102] an intractable mixture is formed resulting from decomposition (R 41). By replacing the mineral acids with bases such as LDA and DBU, the yields are significantly different. According to the results reported above best results are achieved (R 43) in the intramolecular aldol condensation if

DBU[103] in EtOH at room temperature is used whereas use of LDA furnish the compound **81** in only low yield (34% yield, R 42)

Applying the best conditions reported above, the ethyl 2-oxo-1-(5-oxo-pentyl)-cyclododecane carboxylate (**87**) bearing a longer side chain treated with DBU for 20 hours at room temperature (Scheme 47) does not give any aldol addition product (R 44).

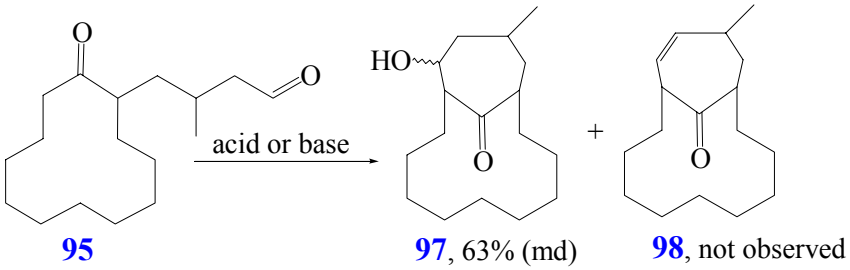


87 **84** **86**

Scheme 47: Attempted cyclization of ethyl 2-oxo-1-(5-oxo-pentyl)-cyclododecane carboxylate (**87**) with DBU

Conversion of 3-methyl-4-(2-oxo-cyclododecyl)butanal (95)

Confirming the results obtained as with 1,6 ketoaldehyde **76** (Scheme 44) containing nonbranched chain, upon acid catalysis with a solution of HCl (7N) the aldol reaction of the 2-substituted aldehyde **95** proceeds with poor yield exclusively towards the formation of compound **97** as a mixture of diastereoisomers (Table 10, R 46). If H_2SO_4 is used, the reaction does not occur and decomposition is again observed (Table 10, R 47, Scheme 48).



Scheme 48: Aldol addition under basic or acidic conditions of 3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**).

Then, in order to test basic conditions for the preparation of 12-hydroxy-14-methylbicyclo[9.4.1]hexadecan-16-one (**97**), conversion of ketoaldehyde **95** under identical conditions (DBU in ethanol), proceeds with good yield (Table 10, R 45) whereas, as observed from NMR analysis of the crude mixture, no signal is present in the olefinic region indicating the absence of the β,γ–unsaturated carbonyl compound **98**.

Table 10: Aldol addition of 3-methyl-4-(2-oxo-cyclododecyl)butanal (95).

R	Acid / Base	solvent	[a]dr	Yield 97, [%]
R 45	DBU	EtOH	1:2.3:1.5:1.5	63
R 46	HCl	dioxane	1:2.8	15
R 47	H_2SO_4	dioxane	--	--

a) ratio calculated with respect to the CH_3

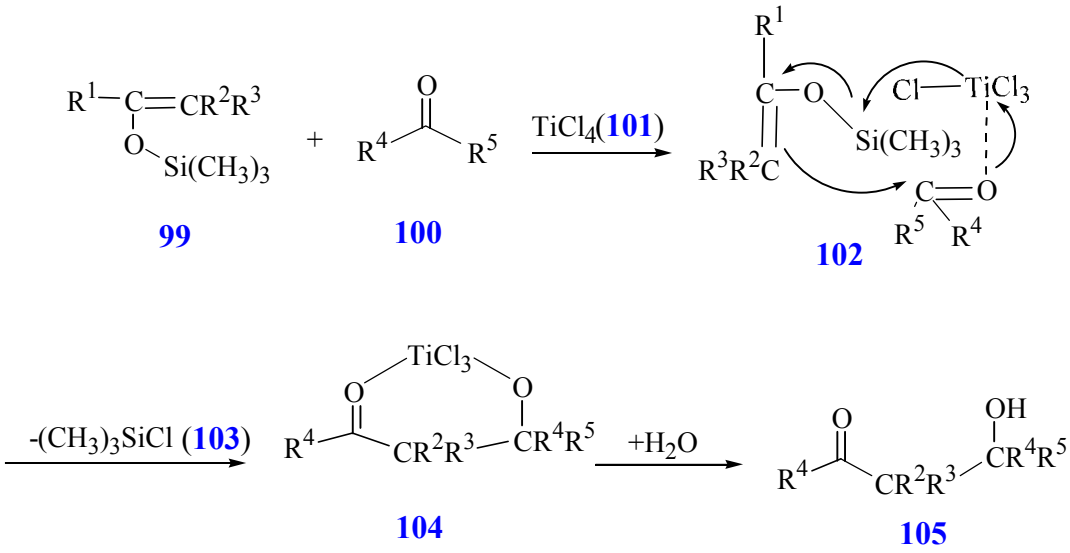
In conclusion, aldol addition base-catalyzed can be employed to achieve the formation of bridged system where the one-pot procedurefailed, whereas stepwise acid-catalysized aldol reaction proceeds with lower yield or with decomposition. Unfortunately, as observed in the reaction performed in the presence of DBU (Scheme 32), these basic conditions, are often incompatible in combination with transition-metal catalyzed hydroformylation. Once again, other methods of activation are necessary to be employed such as one-pot sequential hydroformylation / Mukaiyama aldol addition of preformed silyl enol ethers.

2.3. Sequential hydroformylation / aldol addition of enol ethers

2.3.1. The rhodium-catalyzed Mukaiyama aldol addition

2.3.1.1. Introduction

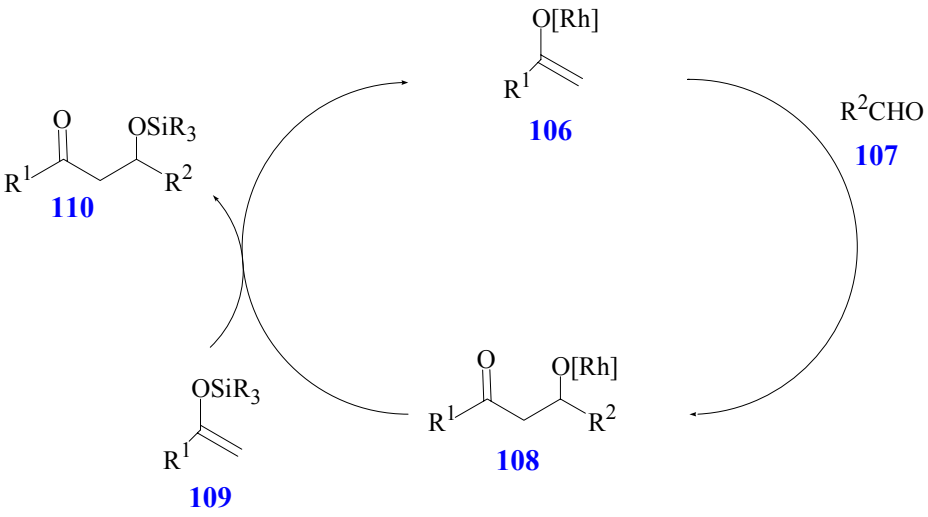
In order to circumvent the chemoselectivity problems in cross-aldol reaction, synthetic procedures have been developed by Wittig and Heme[104] using lithium derivatives of imines. In addition, House and coworkers[105] reported the use of lithium enolates and metal salts in the aldol condensation reaction. Prior to House, Mukaiyama[106,107] and shortly thereafter House[108], published a general method to accomplish the cross-aldol addition products starting silyl enol ethers of various carbonyl compounds which react with aldehydes and ketones in the presence of titanium tetrachloride under mild conditions (Scheme 49). Titanium tetrachloride is found to be a powerfully activator of the carbonyl carbon for nucleophilic reactions



Scheme 49 : The Mukaiyama aldol addition reaction of enolsilanes with aldehydes or ketones.

Silyl enol ether **99** readily attacks a carbonyl compound **100** activated by titanium tetrachloride (**101**) in a nucleophilic fashion to form trimethylsilyl chloride (**103**) and an intermediate chelate **104** (Scheme 49). Hydrolysis of this intermediate should then afford aldol **105**. In order to follow the interest in tandem reactions which combine the

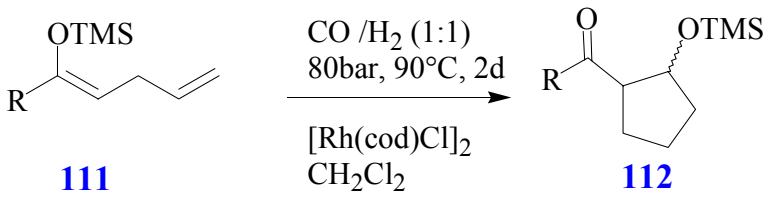
two reaction steps described above in an efficient one-pot procedure, the application of a Rh-catalyzed Mukaiyama aldol reaction of preformed enol silyl ethers was investigated. The first example of aldol reactions between trimethylsilyl enol ethers and aldehydes by the aid of rhodium complex has been reported in 1986 by Matsuda[58]. Following these first results, Reetz el al.[59] observed that intermediate rhodium enolates may be formed which in turn undergo aldol additions. Extensive investigations concerning the mechanism of the rhodium(I) catalysed Mukaiyama aldol reaction have been made by Heathcock[60] and co-workers who proposed rhodium enolate and aldolate intermediates with a final intermolecular transfer of the silyl fragment to generate the O-siIylated aldols (Scheme 50). Four important features must be incorporated into this catalytic process: (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 toward the organic enol derivatives, and (4) the enol source and the aldehyde must not condense without the catalyst[109].



Scheme 50: Generalization of a rhodium-catalyzed aldol reaction

According to the mechanism proposed, the formation of the rhodium enolate **106** occurs via transmetalation of the enolsilane, which adds to the aldehyde **107**. This addition resulting in the formation of rhodium enolate **108** can stereoselectively be incorporated

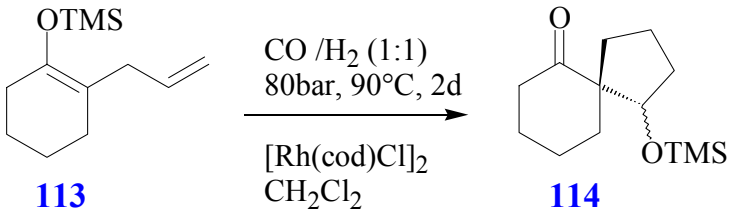
into the reaction by using enolsilane of a fixed geometry. Finally, a transfer of the silyl moiety from another enolsilane **109** follows, resulting in the formation of the final adduct **110** with regeneration of the reactive rhodium enolate. In previous investigations using $[Rh(cod)Cl]_2$ as catalyst[110], starting from unsaturated silyl enol ethers of type **111** five membered rings of type **112** are generated, as depicted in the Scheme 51. The reaction proceeds with high selectivity by converting only one of two different double bonds to form the intermediate aldehyde.



111 **112**

Scheme 51: Silyl enol ether in intramolecular aldol addition

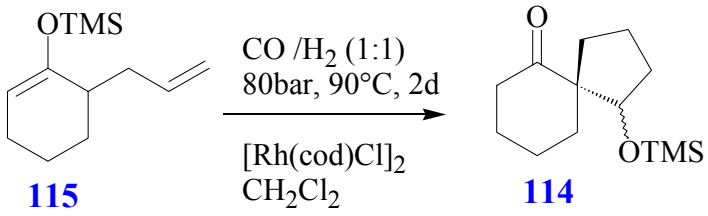
Using this protocol, silylated spiro compound of type **114** are obtainable if the enol silyl ethers **113**, obtained under thermodynamical control, is used as starting materials. The intramolecular aldol addition proceeds with satisfying selectivities (Scheme 52).



113 **114**

Scheme 52: Intramolecular aldol addition of trimethyl silyl ether **113** of 2-allyl-cyclohexanone

If starting from the silyl enol ether **115**, formed under kinetic control, again, the spirocyclic aldol product **114** was obtained. Here obviously a rhodium catalyzed isomerisation of the silyl enol ether double bond to form the thermodynamically favored species is involved (Scheme 53).



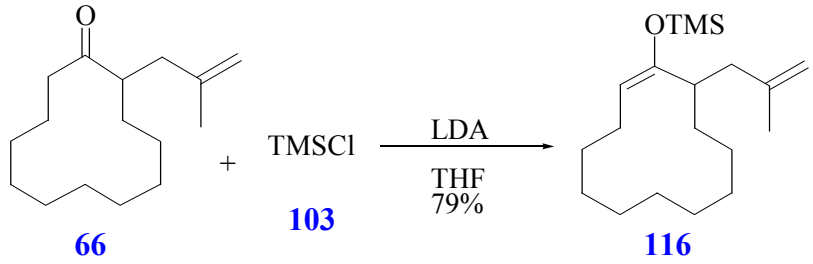
Scheme 53: Intramolecular aldol addition of trimethyl silyl ether **115**

At first, to investigate this procedure on the starting materials described above, a number of enolsilane have been prepared. Finally, the hydroformylation of these enol silyl ethers have been performed.

2.3.1.2. Preparation of trimethylsilyl enol ethers of cyclododecanones and β-ketoesters

A general preparative method for the synthesis of silyl enol ethers involves 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, such as 2-alkenyl-cyclododecanones (**52**) (Scheme 21) could be achieved by control of the reaction conditions. House and co-workers[111] reported that silyl enol ethers, under kinetic control, are very selectively formed from ketones by using first lithium diisopropylamide to generate the lithium enolate at low temperarure and then O-silylating with chlorotrimethylsilane. Paterson and al. [112] find that the method can be improved by generating the lithium enolate at —78° and by avoiding the aqueous work-up to give in high yields and regioselectivities.House et al. found that silyl enol ethers, under thermodynamic control, are best prepared by equilibrating the mixture of silyl enol ethers 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.

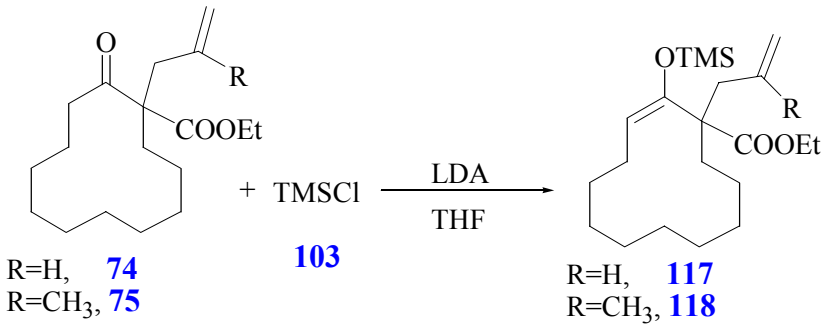
Following these observations and taking into account the investigations proposed here, the silyl enol ethers, under kinetic control, has to be prepared. If starting from 2-(2-methylprop-2-enyl)-cyclododecanone (**66**), the required compounds **116** is synthesized by using TMSCl (**103**) and LDA, at -78°C for 4 hours (Scheme 54, R48).



66 **103** **116**

Scheme 54: Preparation of silyl enol ethers **116** of 2-(2-methylprop-2-enyl)-cyclododecanone (**66**).

Upon the same reaction conditions the β-ketoester **74** and **75** with TMSCl (**103**) are converted in the silyl enol ether **116** in 79 % yield, after filtration through a short pad of neutral alumina.



R=H, **74**
R=CH_3, **75**

103

R=H, **117**
R=CH_3, **118**

Scheme 55: Preparation silyl enol ethers **117** and **118** of β-ketoester.

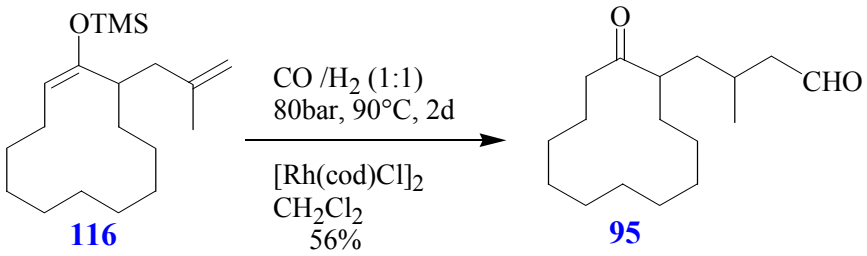
Table 11: Synthesis of silyl enol ethers **117** and **118**

Entry	R	Compounds	Yield [%]
R 49	H	**117**	78
R 50	CH_3	**118**	74

Both reactions proceed with high yield and the compounds **117** and **118** are isolated after filtration of LiCl through a short pad of neutral alumina (Table 11, R 49, R 50).

2.3.1.3. Hydroformylation of trimethylsilyl enol ethers

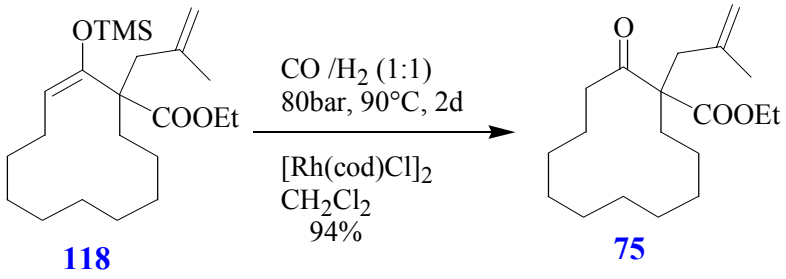
As described above, stereoselectivity can be achieved by using enolsilanes of fixed geometry. If starting from cyclic ketones, only E(O)-enolates are formed due to the geometrical requirements of the ring systems, which would cause higher strain in the Z (O) enolates[113]. In order to evaluate the behavior of these enol silyl ethers towards the Mukaiyama aldol addition, compound **116** is subjected to the standard conditions, previously optimezed. In contrast to the open chain substrates upon these conditions, the aldol addition of **116** does not take place and the keto aldehyde **95** is isolated after distillation of crude mixture (R 51, Scheme 56).



Scheme 56: Hydroformylation of trimethyl-[12-(2-methyl-allyl)-1-cyclododece-1-enyloxyl]-silane (**116**).

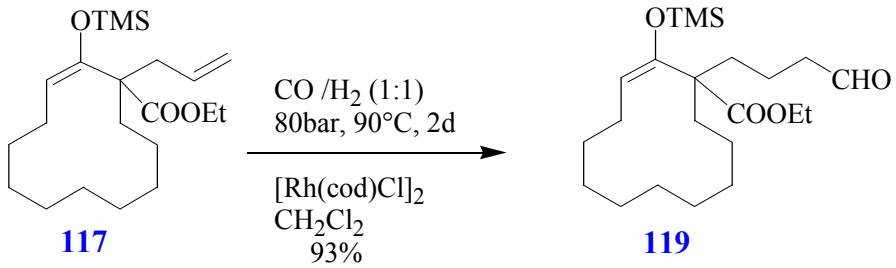
Obviously, the trimethylsilyl enol ether is too labile under these conditions and decomposes under the hydroformylation conditions, thus not permitting the formation of rhodium enolate.

Similar results are obtained if using 1-(2-methyl-allyl)-2-trimethylsilanoxy-cyclododec-2-enecarboxylic acid ethyl ester (**119**). As can be seen in Scheme 57, under standard conditions for Rh-catalyzed Mukaiyama aldol addition again a desilylation process occurs (R 52) and the ketoester **75** is isolated as a sole product.



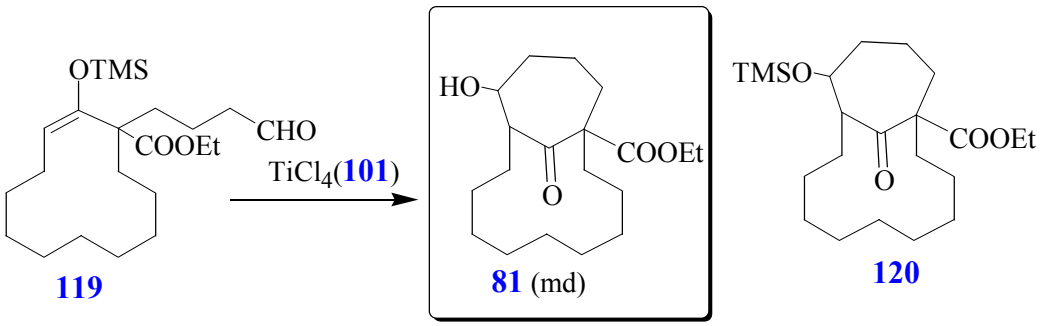
Scheme 57: Attempted hydroformylation of 1-(2-methyl-allyl)-2-trimethylsilanoxy-cyclododec-2-enecarboxylic acid ethyl ester (**118**)

In contrast to the substates with substituted olefinic chain **116** and **118** the O-silylated compound **117** (R 53) under similar conditions leads to the *n*-aldehyde **119** is isolated without hydrolyzing the silyl enolate (Scheme 58).



Scheme 58: Hydroformylation of silyl enol ethers **117**.

However, by appling Mukaiyama's aldol conditions, ethyl 1-(4-oxo-butyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**119**) if treated with an equimolecular amount of $TiCl_4$ in CH_2Cl_2 at room temperature (R 54, Scheme 59) gives a diastereomeric mixture of compound **81** is formed whereas compound **120** is not observed.

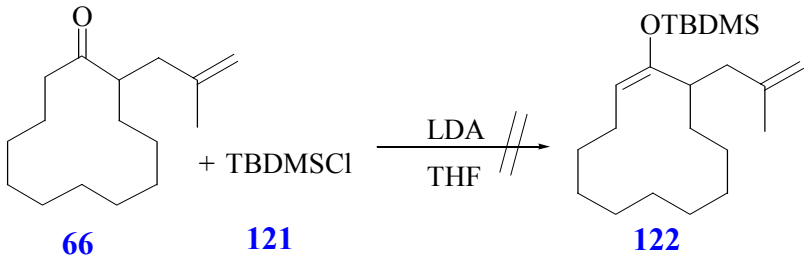


Scheme 59: Aldol addition of compound **119** under Mukaiyama conditions.

Further investigations in one-pot Rh-catalyzed hydroformylation /alol addition have been conduct performing the reactions in the presence of more stable TBDMS-enolsilane.

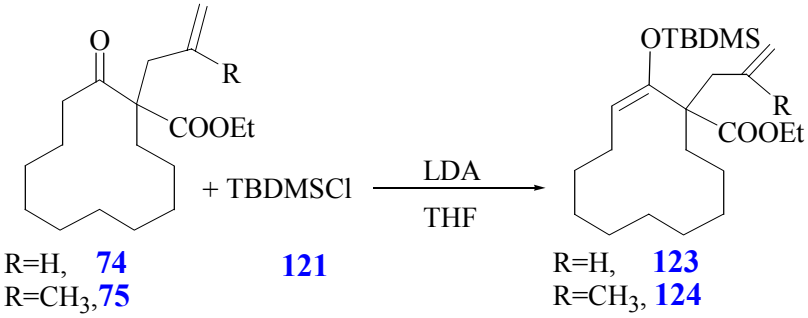
2.3.1.4. Preparation of TBDM-silyl enol ethers

Under the conditions applied for the preparation of TMS-enol silyl ether, allylated cyclododecanone **66** is treated with LDA and TBDMSCl (**121**). Unfortunately, the formation of O-silylated compound **122** is not observed (Scheme 60, R 55).



Scheme 60: Attempted preparation of silyl enol ethers **122** of 2-(2-methylprop-2-enyl)-cyclododecanone (**66**).

In contrast, as indicated in Table 12 the reaction of compound **74** with TBDMSCl (**121**) proceeds with good yield to give the silyl compounds **123**, whereas the compound **75** leads to the silyl enol ether **124** (34% conversion detected by GC-analysis) (Scheme 61).



Scheme 61: Preparation of silyl enol ethers **123** and **124**

Table 12: Synthesis of silyl enol ethers **123** and **124**

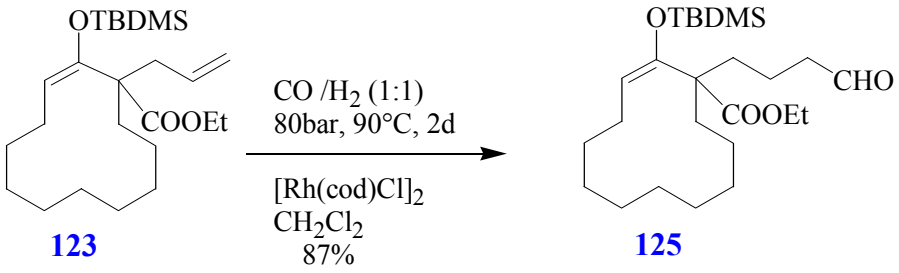
Entry	R	Compounds	Yield, %
R 56	H	**123**	78
R 57	CH_3	**124**	34[a]

a) Conversion detected by GC analysis.

The problems met into the separation of the crude mixture do not allow the employment of starting compound **124** in the following investigations.

2.3.1.5. Hydroformylation of TBDM-silyl enol ethers

Results similar to TMS-enol ether reaction (Scheme 58) are observed if compound **123** is treated with 1 mol % of $[Rh(cod)Cl]_2$ under 80 bar of CO/H_2 at 90 °C for 2d, leading to *n*-aldehyde **125**. Again, no Mukaiyama aldol adducts are obtained, indicating that the trans-metallation of the enolsilane by the active Rh-catalyst does not occur (R 58, Scheme 62).



123 **125**

Scheme 62: Hydroformylation of silyl enol ethers **123**.

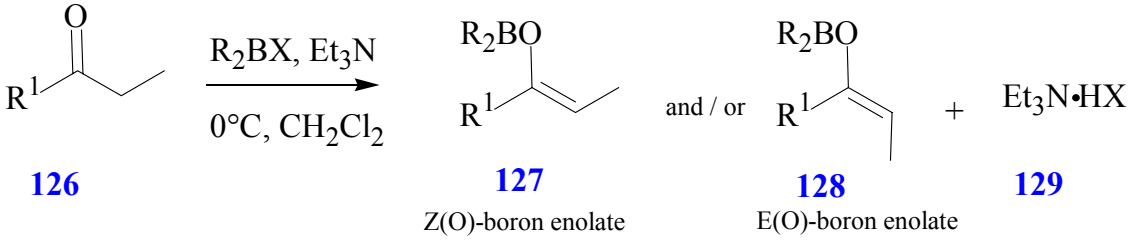
It can be concluded that the one-pot intramolecular aldol addition under Mukaiyama conditions proceeds with satisfying results with various types of enolsilanes, whereas cyclododecane derivatives appear to be unable to generate bicyclic compounds. Therefore, if considering the difficulties met using these procedures, an alternative method of enolization of ketones, followed by sequential hydroformylation / aldol addition has to be investigated.

Boron enolates are highly reactive, are used as important intermediates in organic synthesis[114] and are useful reagents for directed stereo controlled aldol reactions[115].

2.3.2. Enolboration / hydrofomylation / aldol addition

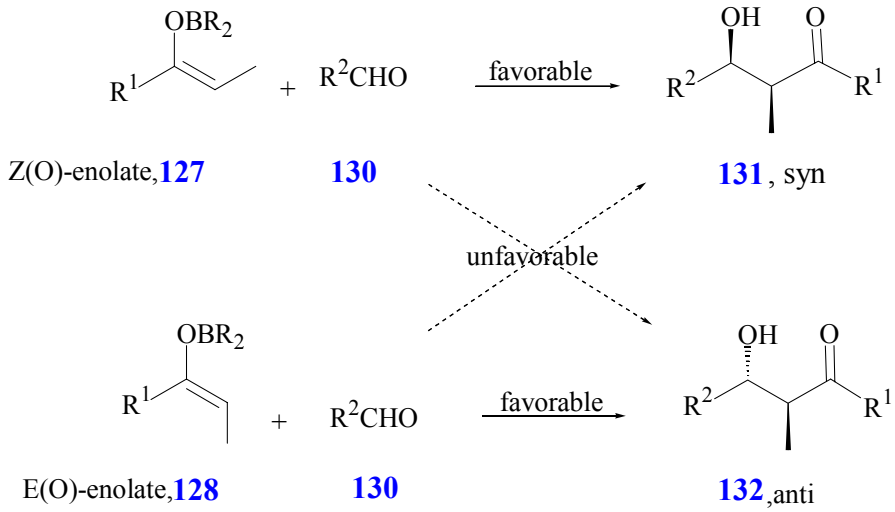
2.3.2.1. Introduction

One of the methodologies towards the preparation of boron enolates involves the reaction of ketone with a suitable organoboron derivative, R_2BX, having a good leaving group, in the presence of a suitable tertiary amine. Dialkylboron chlorides in the presence of tertiary amines rapidly and quantitatively convert ketones into the corresponding enol borinates[116]. In fact, the poor Lewis acidity of **(***cy*-hex)$_2$BCl, combined with the relatively large steric requirements of the cyclohexyl groups, may contributet to prevent the non-complexation of the amines used as base. As the result, **(***cy*-hex)$_2$BCl becomes a versatile reagent which can effect the enolization in the presence of a wide variety of tertiary amines of variable steric requirements. In the case of smaller amines, such as Me_2EtN, instead of abstracting the α-proton of the ketone leading to enolization, the amine preferentially reacts with the organoboron reagent forming a strong complex, resulting in a low yield. On the other hand, in the case of strongly sterically hindered amines, such as *i*-Pr_2NH, the large steric requirements of the amine must play a major role in the observed poor yield. Only moderately hindered tertiary amines are efficient for quantitative enolboration. Moreover, the R_2BCl reagents greatly influence the stereochemistry of the enol borinate formed, making it possible to produce preferentially either Z(O)-or E(O)-boron enolates[117] (Scheme 63). Indeed dicyclohexylchloroborane **(***cy*-hex)$_2$BCl, produces E enol borinates either exclusively or predominantly from various ketones[118].



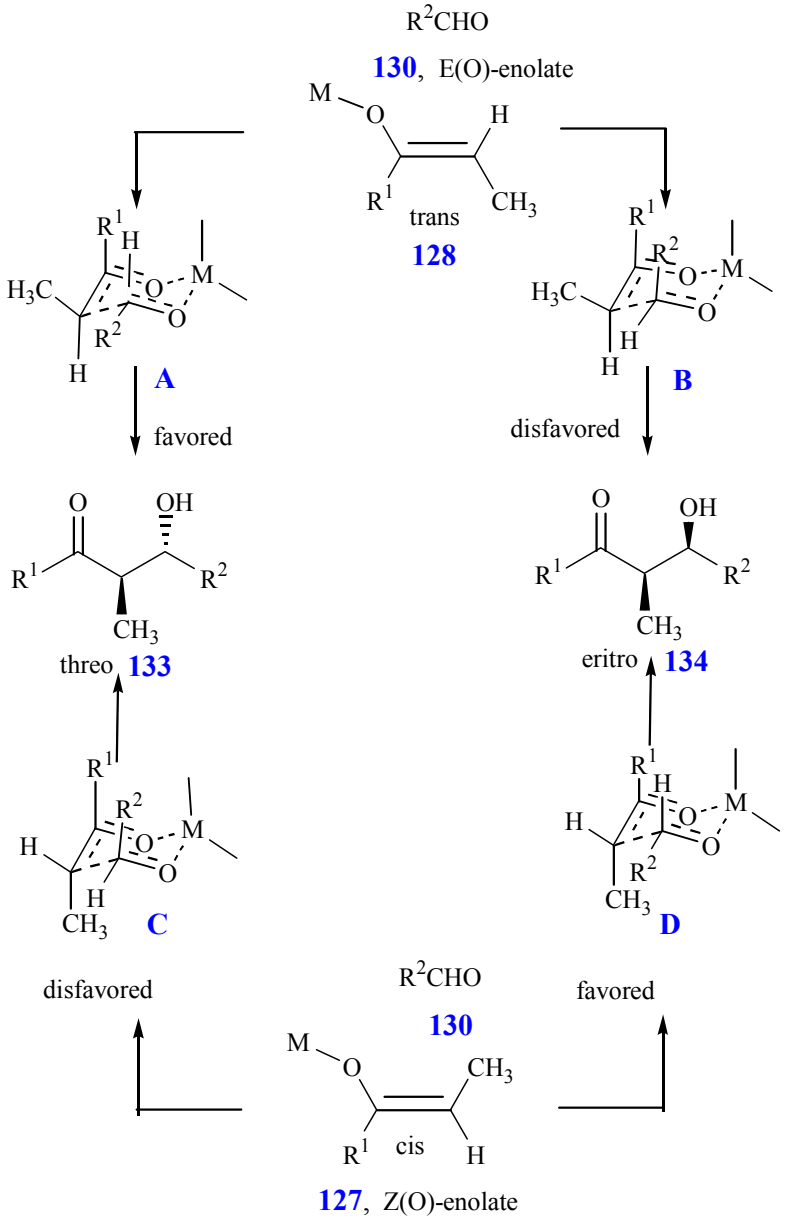
Scheme 63: General preparation of Z(O)-or E(O)-boron enolates **127** and **128**

It was also observed the steric requirements of the amine influence the stereoselectivity. Brown[119] in a systematic study to achieve an understanding of the various effects influencing the stereochemistry of the enolboration process, observed smaller amines favor formation of kinetic enolates (E(O)-boron enolate), while bulkier amines favor formation of thermodynamic enolates (Z(O)-boron enolate), regardless of the ketone as well as the organoboron reagent used. Then, the boron enolates derived from these acyclic ketones undergo aldol condensation. Fenzl and Koster[120] demonstrated that boron enolate additions are highly stereoselective with the Z (O)-or E (O)-boron enolates giving syn (**131**) and anti (**132**) aldols, respectively (Scheme 64).



Scheme 64: Boron enolates in aldol addition reaction.

In 1957**,** in conjunction with a stereochemical study of the Ivanov and Reformatsky reactions, Zimmerman and Traxler accounted for the observed aldol diastereoselection by advancing the hypothesis that the reaction proceeded via a preferred chair-like transition state involving cooperative metal ion ligation of both the enolate and carbonyl substrates[121].

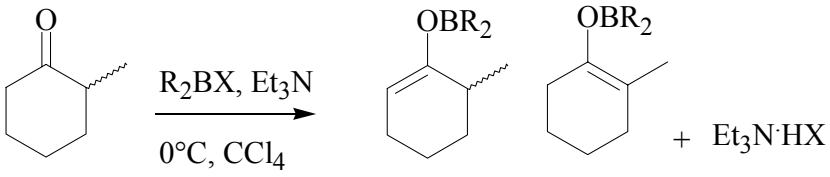


Scheme 65: Different transition states for (Z) - and (E)-enolates

As shown in Scheme 65 four possible transition state **A**, **B**, **C**, **D**, reflecting the different orientations of the enolates with respect to the aldehyde **130** as well as the (E/Z) geometry of the enolates **127** and **128**

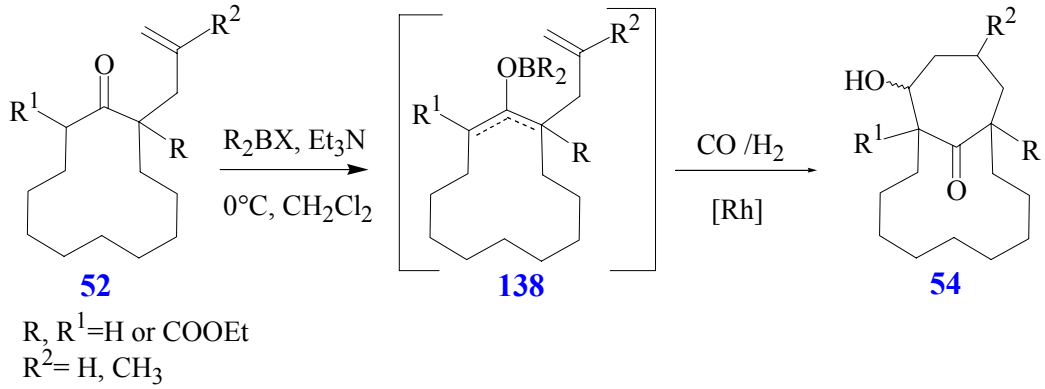
For trans enolates transition state **B** is destabilized relative to **A** owing to $R_1 \leftrightarrow R_2$ interactions whereas for cis-enolate the transition state **D** is stabilized relative to **C**. Then, the syn aldol adduct (erythro) **134** is formed for the cis-enolate and anti product **133** is observed for the trans enolate.

Moreover, the conversion of a number of cyclic ketones into pure (E)-enol borinates, required by their cyclic structures, provided aldols which analyzed predominantly or exclusively for the anti aldol products. Brown et al observed excellent stereoselection with cyclic ketones Exclusively E enol borinates have been obtained from cyclopentanone (100%), cyclohexanone (98%), cycloheptanone (97%), and cyclooctanone (100%), confirmed by the essentially exclusive formation of anti aldols in the reaction of benzaldehyde at -78 °C. Excellent regioselectivities have been achieved with substituted cyclohexanones. In the case of 2-methylcyclohexanone, the kinetic enolate **136** has been obtained exclusively (Scheme 66).



Scheme 66: Boron enolates of cyclohexanone (**135**).

In a preliminary investigation[122] concerning the suitability of rhodium catalyzed hydroformylation combined with aldol addition of enolborinates, it has been observed that a sequential enolboration / hydroformylation / aldol addition could offers an efficient method for preparations of aldol adducts similar to bridged system of type **54** .

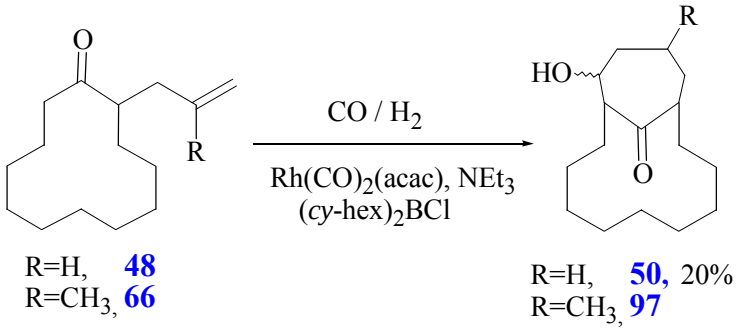


Scheme 67: Enol borinates of cyclododecanone derivatives **52** in one-pot hydroformylation / aldol addition

Therefore, several cyclic ketones such as compounds **52** (Scheme 67) have been chosen as starting materials in order to test whether they are able to undergo this one-pot procedure.

2.3.2.2. Enolboration / hydroformylation / aldol addition of 2-alkenyl cyclododecanones

Starting from 2-alkenyl-cyclododecanone, the boron enolate is smoothly generated in situ by treating of cyclic ketones with NEt_3, as the base, and $(cy\text{-hex})_2BCl$ at 0°C, under argon atmosphere. After approximately 40 minutes the 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 (Scheme 68).



Scheme 68: Enolboration hydroformylation / aldol addition of 2-alkenyl-cyclododecanone **48** and **66**.

After oxidative workup of the crude reaction mixture, containing the boron chelate and ammonium salts 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 reaction. The results are summarized in Table 13.

Table 13 Enolboration hydroformylation / aldol addition of 2-alkenyl-cyclododecanone **48** and **66**

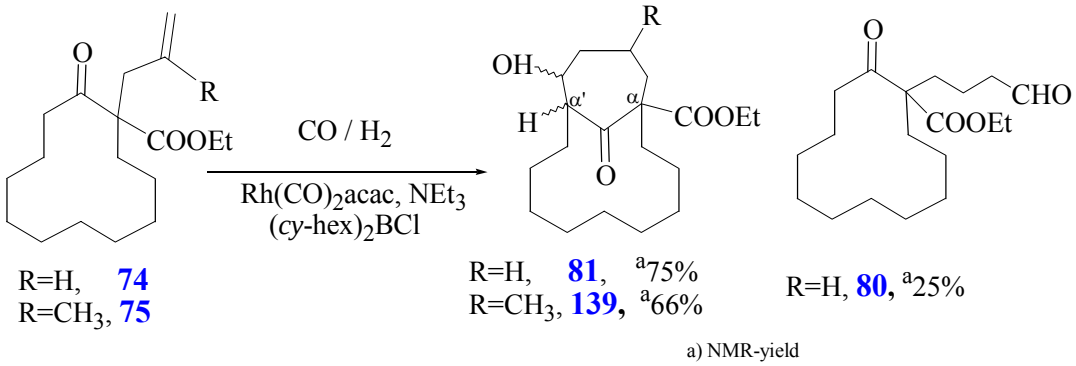
Entry	R	Compounds	Yield, %
R 59	H	**50**	20
R 60	CH_3	**97**	--[a]

a) ratio of 2.48:1 of compound **97**: **66** (calculated by NMR analysis).

Under these conditions, aldol additions of enolates are obtained from both cyclic ketones under kinetic control. The reactions proceed with high chemoselectivity but low yields. In contrast to the one-pot procedure under acidic conditions, the reaction of 2-allyl-cyclododecanone (**48**) proceeds with drastic decrease of yield (71% to 20%). On the other side, the compound **66** leads to the bicycle **97** whereas the one-pot acid-catalyzed method failed. The crude mixture analyzed by ^{1}H-NMR analysis contains the bicyclic compound **97** and compound **66** in 2.48: 1 ratio (NMR calculated). Both reactions proceed with high degree of diastereoselectivity furnishing only one diastereoisomer.

2.3.2.3. Enolboration / hydroformylation / aldol addition of unsaturated β-ketoesters

If applying the optimized reaction conditions of enolboration /hydroformylation to β-ketoester possessing a C-3 olefinic chain in α-position, again, the bicyclic compounds are obtained (Scheme 69). As listed in Table 14, ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**) reacts to form a mixture of compound **81,** as a single diastereoisomer, and linear aldehyde **80** in 75 % and 25% yield respectively (NMR calculated) (R 62, Table 14). As expected the aldol addition is observed to occur in the α'-position.



Scheme 69: Sequential enolboration /hydroformylation / aldol addition of β-ketoester **74** and **75**

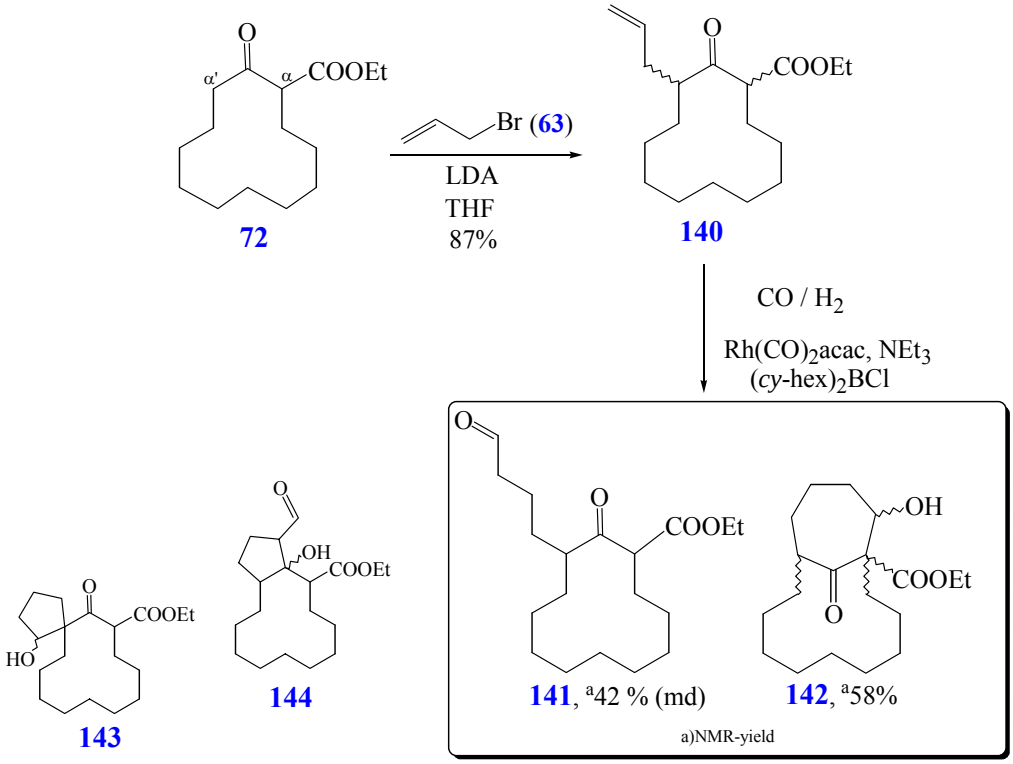
Table 14: Enolboration /hydroformylation / aldol addition of β-ketoester **74** and **75**

Entry	R	Compounds	Yield, [%]
R 61	H	**81**	[a]75
R 62	CH_3	**139**	--[b]

a) NMR yield, b) ratio of 2:1 of compound **139**: **75** (calculated by NMR analysis).

With compound **75** (R 62, Table 14), although, the reaction is successful, its conversion proceeds to afford the corresponding aldol adduct **139** in slighly lower yield, presumably due to lower reactivity of the substituted double bond. Both reactions once again lead to the formation of only one diastereoisomers and the syn-aldol would be predicted.

The suitability of this cascade reaction to form differently functionalized bicycles is tested starting from β-keto-ester **72**. The allylation reaction in the α´-position of the **72** is performed in the presence of 2 eq. of LDA and allylbromide (**63**)[123] (Scheme 70, R 63). The ethyl 3-allyl-2-oxo-cyclododecane carboxylate (**140**) is obtained in 87 % yield after purification by distillation of the crude mixture as colorless crystals.



Scheme 70: Sequential enolboration /hydroformylation / aldol addition of allylated β-ketoester **140**

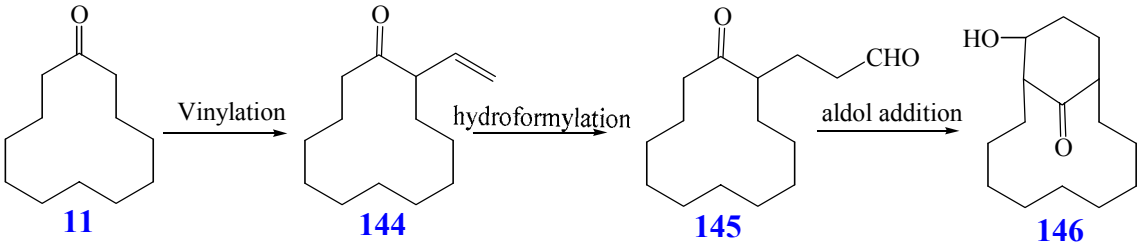
The conversion of compound **140** under the reaction conditions of enolboration / hydroformylation leads, once again, to the formation of the bicyclic cyclic ketone **142** (R 64) 58% yield (calculated by NMR-analysis). The reaction proceeds with high degree of chemo- and regio-selectivity and only one diastereoisomer is detected confirming again the high diastereoselectivity of the whole process.

In conclusion, bicyclic compounds with control of chemo- and diastereoselectivity are easily accessible from cyclododecanone derivatives via enolboration / hydroformylation / aldol addition. This convenient and efficient one-pot method allows variations of the substitutents leading to cyclisation products with the same substitution patterns.

2.4. Michael addition / aldol reaction

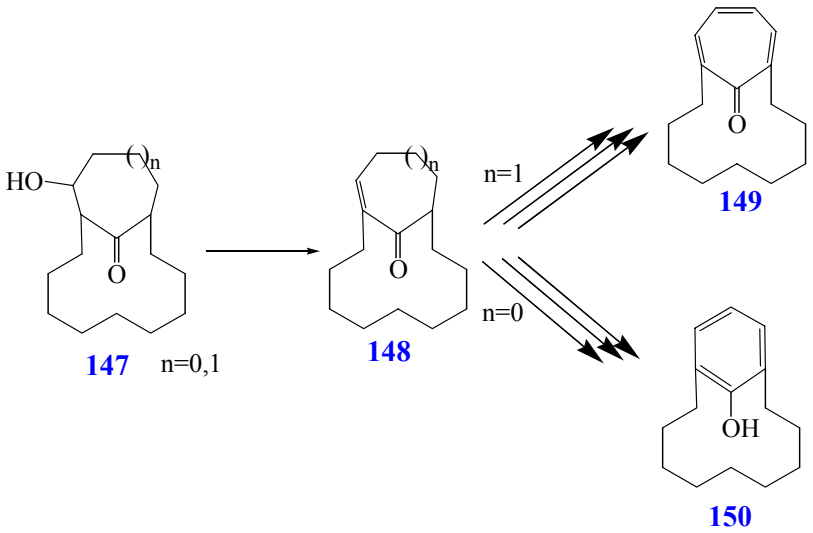
2.4.1. Introduction

Following interest in tandem reactions, which combines multiple transformations in an efficient one-pot procedure, the sequential hydroformylation / aldol addition of α-vinyl cycloalkanones could be investigated. As depicted in Scheme 71, cyclododecanone (**11**) is chosen as starting material and the vinyl group could be introduced by a number of methods as discussed later. The preparation of β-hydroxy ketones of type **146** should be accomplished by application of 2-vinyl cyclododecanone **144** in tandem hydroformylation / aldol addition.



Scheme 71: Preparation of β-hydroxybicyclo[9.3.1]pentadecane-15-one of type **146**

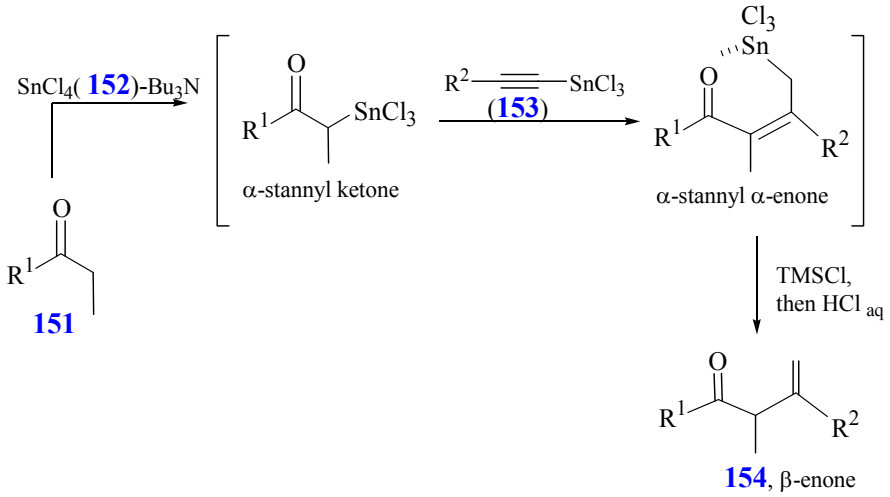
Moreover by analyzing the skeleton of compound **147** depicted in the Scheme 72, such compound (n=0) appear to be a key intermediates towards the preparation of 15-hydroxy[9]metacyclophane **150** as well as the bicyclo[9.4.l]hexadecan-16-one (n=1) could be considered as an effective intermediate in the preparation of 2,7-nonamethylene bridged tropone **149**[124](Scheme 72). These compounds belonging to the class of cyclophanes[125] or bridged aromatics tropones[126] are fascinating compounds due to their unique physical and chemical properties. The territory of "phanes"[127] includes heterocyclophanes and bridged nonbenzenoid aromatics[128].



Scheme 72: Nonamethylene-bridged phenols (**150**) and tropones (**149**)

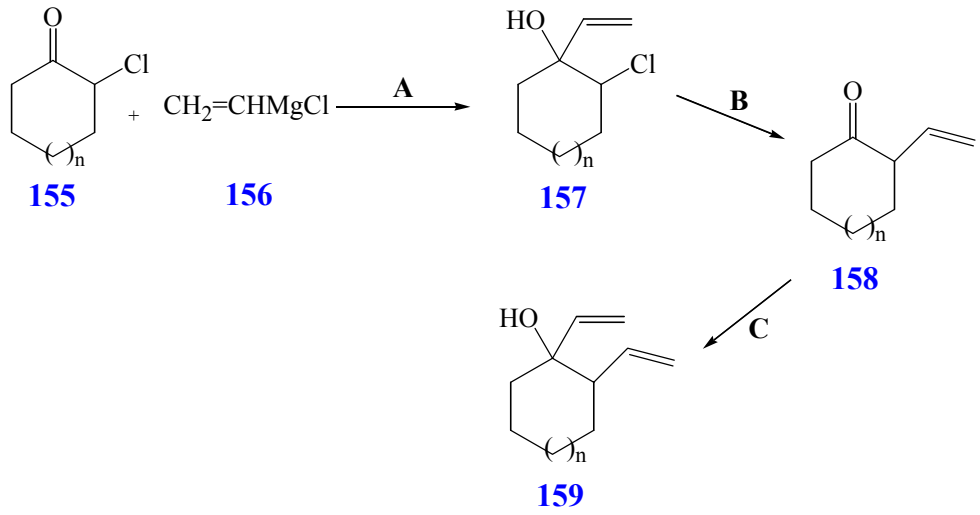
Recent syntheses of systems **147** or **148** are elaborated in numerous steps, while an approach to such compounds involving the one-pot procedure described above, consequently could afford the compounds **149** and **150** more easily.

Beginning with the preparation of 2-vinyl-cyclododecanone (**144**), starting material **11** could be allylated by a number of methods reported in literature. In contrast to the easily accessible 2-allylcyclododecanone (**48**), α-vinylation reactions of cycloalkanones are not well developed in organic synthesis. Among the most general is the α-alkenylation of ketones with 1-alkynes of type **153**, such as phenylacetylene (R^2=Ph) in the presence of $SnCl_4$ (**152**), Bu_3N and TMSCl (**103**), which provides a certain range of β-enones with acidic α-protons[129] (Scheme 73).



Scheme 73: α-alkenylation of ketones (**151**) with 1-alkynes (**152**).

The preparation of 2-vinyl-cycloalkanones of type of **144** could be accomplished in the preparation of 1,2 divinyl cycloalkanols[130] (**159**) (Scheme 74).

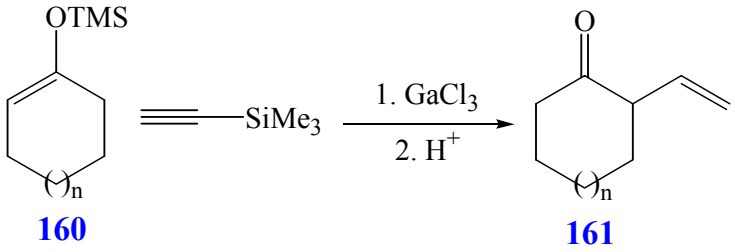


Scheme 74: α-alkenylation of Cl-ketones (**155**) via 1,2 divinyl cycloalkanols **159**

In fact, α-chloro-cycloalkanones (**155**) could react with vinylmagnesium chloride (**156**) [131,132] to afford the chlorohydrin (**157**) which smoothly undergoes 1,2-migration of the

vinyl group to afford the 2-vinylcycloalkanone (**158**) when its magnesium salts of heated[131,132,133,134,135]

Recently, M. Yamaguchi et al.[136] developed an ethenylation reaction of cyclic ketones and β-dicarbonyl compounds with trimethylsilylethyne in the presence of $GaCl_3$[137]. The reaction converts silyl enol ethers of type **160** into a α-ethenylated products **161** 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 trimethylsilylethyne in high yields.

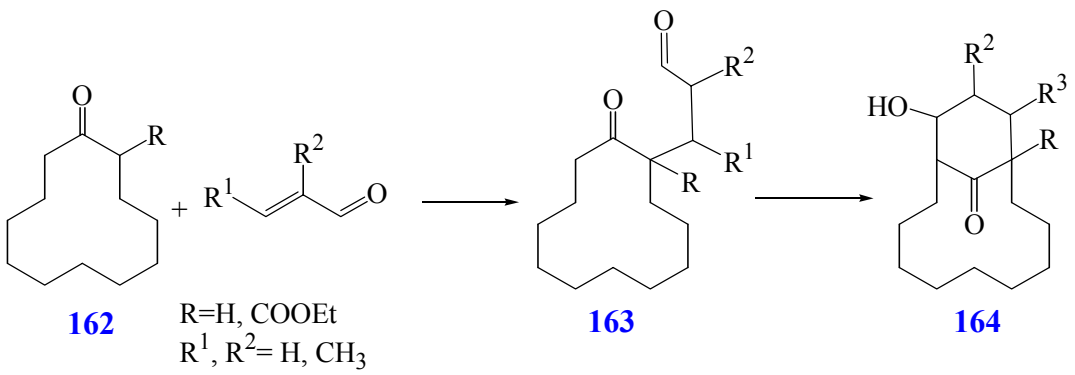


160 **161**

Scheme 75: α-alkenylation of silyl enol ethers with trimethylsilylethyne

A limitation of the method, however, is that cyclic ketones with relatively small ring number such as cyclohexanone and cycloheptanone gives considerable amounts of the conjugated α-enones. In the presence of $GaCl_3$, silyl enol ethers derived from α-substituted-β-ketoesters or malonates are ethenylated at the α-carbon atom with

Problems in the preparation of α-vinyl cycloalkanones are caused by the high cost of the reagents such as $GaCl_3$ and the multi-step approach. Besides these considerations, analysis of the aldehyde **163** revealed that these products could also be obtained in a more straightforward route. In fact, the 1,5-dicarbonyl compound of type **163** should be obtained if starting from cyclododecanone or its derivatives of type **162** by a Michael addition employing α,β-unsaturated aldehydes such as acrolein (Scheme 76).



Scheme 76: Stepwise Michael reaction and aldol addition

An aldol addition of preformed keto-aldehyde of type **163** could be performed as well as ae one-pot Michael addition / aldol reaction

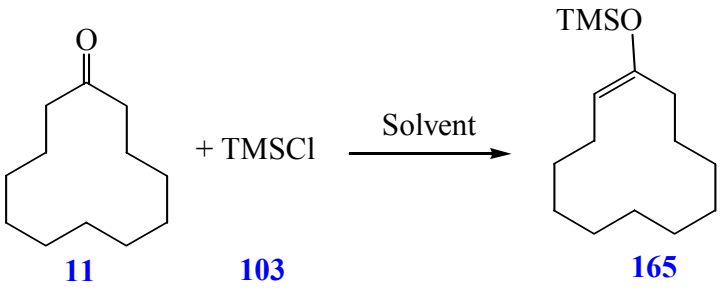
2.5. Stepwise Michael addition / aldol cyclysation of cyclododecanone

2.5.1. Preparation of 12-hydroxy-bicyclo[9.3.1]pentadecan-15-one

Michael addition has attracted enormous attention as one of the most important carbon-carbon bond forming reactions in organic synthesis[138]. In general, Michael additions are conjugate additions of enolates to α, β-unsaturated carbonyl compounds affording 1,5-dioxo compounds and are generally carried out under strongly basic conditions[139]. However, such base-catalyzed methods are sometimes detrimental[140] to base sensitive functionalities and often lead to side reactions like autooxidation or retro-Michael type condensation.

In order to circumvent this problem considerable attention has been directed towards the search for more convenient methods[141]. Preformed enamines or silyl enol ethers, for example, constitute an important class of Michael donors that have been utilized[142] under milder conditions. However, a literature survey revealed that in comparison to enolates, the use of enamines as Michael donors is significantly less common. The major disadvantage associated with enamines is their susceptibility to hydrolysis[143], causing restrictions to their general use in Michael addition reactions. Consequently, further developments in the use of enamines for an efficient Michael addition offers advantages and remain a challenging problem to organic chemistry.

Then, to begin this route towards the preparation of bicyclo[9.3.1]pentadecane derivatives of type **164**, the preparation of silyl enol ether from cyclododecanone with TMSCl (**103**) has to be conducted (Scheme 77), whereas the synthesis of 4-cyclododec-1-en-1-ylmorpholine (**70**) is accomplished starting from **11** in the presence of morpholine (**69**) and catalytic amount of *p*-TsOH·H_2O (see R 13). The silyl enolization via electron-transfer mechanism[144] by treatment of cyclododecanone (**11**) with Mg-turnings, trimethychlorosilane, (**103**), in N,N-dimethylformammide at RT[145] does not give any conversion (Table 15, R 65).

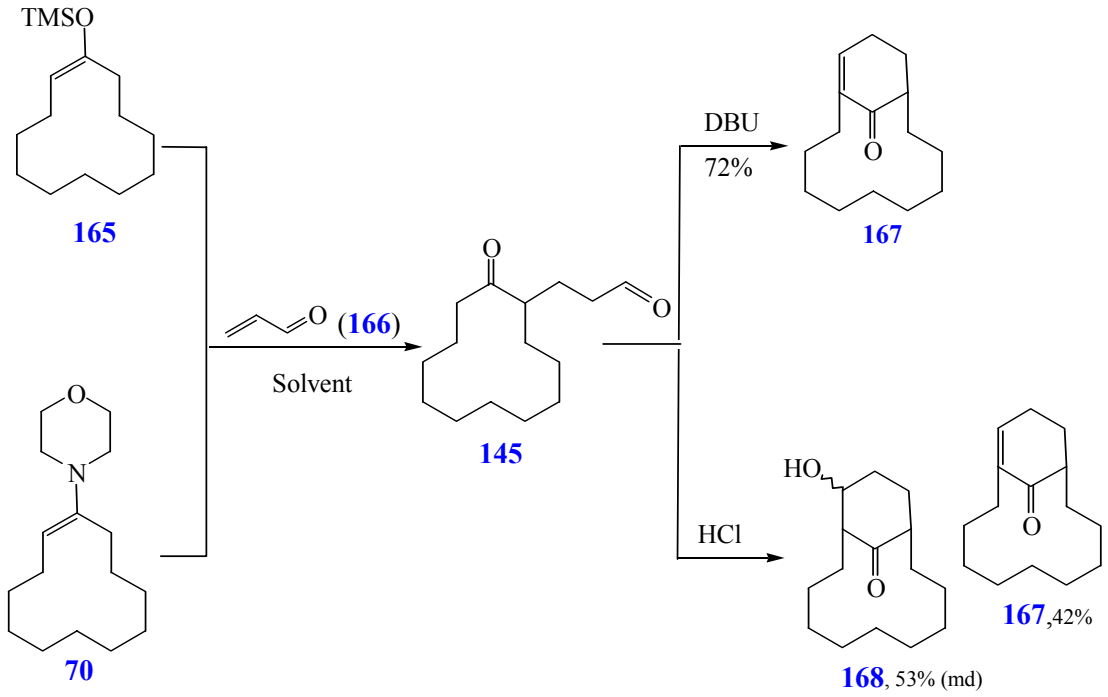


Scheme 77: Preparation of cyclododec-1-enyloxy-trimethyl-silane (**165**).

Table 15: Preparation of cyclododec-1-enyloxy-trimethyl-silane (**165**).

R	Reaction conditions	ϑ, [°C]	t,[h]	Yield 165, [%]
R 65	Mg, DMF	5-7	18	--
R 66	NaI, NEt_3, CH_3CN	20	12	38
R 67	LDA, THF	-78	6	78

Following the procedure reported by Dunogues et al.[146] the reaction of cyclododecanone (**11**) in the presence of Me_3SiCl-NaI-Et_3N as the reagent proceeds at room temperature and the corresponding silyl enol ether **165** is obtained in 38% yield (Table 15, R 66). Finally, best results are achieved if the reaction is performed with the LDA as base. As compiled in Table 15 (R 67) compound **165**, after distillation, is obtained in 78% yield. To obtain the compound **145** (Scheme 78), the Michael addition reaction of silyl enol ethers is carried out with acrolein (**166**) proceeding smoothly to afford the corresponding adducts in 78% yield (Table 16, R 68). On the other hand, if the reaction is performed starting from 4-cyclododec-1-en-1-ylmorpholine (**70**), treated with acrolein (**166**) (Scheme 78), the results depend on the reaction conditions applied as presented in Table 16.



Scheme 78: Preparation 3-(2-oxo-cyclododecyl)propanal (**145**) as intermediate in aldol addition

In the presence of dioxane[147], Michael addition reaction at 90°C does not occur and after hydrolysis with a solution of HCl, only cyclododecanone is recovered (**11**) (R 69).

Table 16: Preparation 3-(2-oxo-cyclododecyl)propanal (**145**)

R	Starting material	Solvent	ϑ, [°C]	t, [h]	Yield 145, [%]
R 68	**165**	CH_2Cl_2	-78	9	78
R 69	**70**	dioxane	90	66	--
R 70	**70**	MeOH	20	25	--
R 71	**70**	MeOH	80	25	--
R 72	**70**	Et_2O	0	25	96

Same results are observed if the reactions are carried out with in MeOH[148] either at room temperature (R 70), or at reflux temperature MeOH (R 71). In contrast, by replacing MeOH with Et_2O and decreasing temperature to 0°C the Michael adduct **145** is isolated after distillation in 96% yield (R 72).

Intramolecular aldol cyclisation of the ketoaldehyde **145** (Scheme 78) is performed under both acidic and basic conditions. Via a basic approach, using DBU in EtOH[149] (R 73), the reaction affords the desired α,β-unsaturated ketone **167** in 72% yield. Under acidic conditions, in the presence of HCl (7N) [98] (R 74), a mixture of aldol adduct **168** (53% yield, mixture of diastereoisomers in a ratio 1:2.38, detected by ^{1}HNMR with respect to the CHOH) and the corresponding dehydrated compound **167** (42% yield) is obtained.

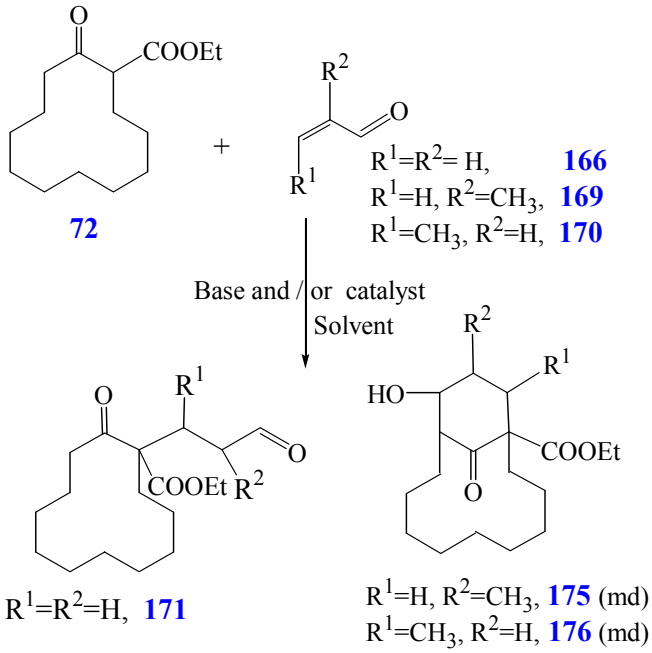
In conclusion, Michael addition, starting from activated cyclododecanone (**70**) to give compound **145** proceeds with acrolein (**166**) in high yields if low temperatures and Et_2O are employed. An aldol condensation occurs under both acidic and basic aldol addition furnishing the aldol adduct **168** and the enone **167** (Scheme 78).

Since β-keto esters are important classes of compounds for the construction of substituted bicyclic skeletons Michael additions can also be extended to these substates.

2.5.2. Stepwise Michael addition / aldol cyclisation of β-keto esters

2.5.2.1. Preparation of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate

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[150], including rearrangements, secondary condensations, isomerizations, polymerizations, bis additions, and transesterifications. Recently, phase-transfer catalysis has been utilized to circumvent some of these problems with *α,β*–unsaturated aldehydes[151] or mild conditions using alumina[152] as catalyst without any solvent are reported. Following the previous observations, several attempts of introducing the aldehyde chain, including the more classical, have been performed. The results from these investigations are presented in Table 17 (Scheme 79). In the absence of a solvent, ethyl 2-oxo-cyclododecane carboxylate (**72**) does not react with acrolein (**166**) in the presence of Al_2O_3[153] (activated at 100°C for 2 hours prior to use) (R 75). Furthermore, the failures of the reaction by using of Na_2CO_3[154] in toluene (R 76) or piperidine[155] (R 77) indicate that both are not sufficiently strong bases for the Michael additions.



Scheme 79: Michael addition / aldol reaction of ethyl 2-oxo-cyclododecane carboxylate (**72**).

In attempts to convert the compound **72** into the Michael-addition adduct molecular sieves[156] turned out to be poor catalyst in terms of yield for the reaction (R 78). Indeed, after filtration on a short pad of Celite the crude mixture analyzed by GS-analysis shows only 10% conversion; this result is not in accordance with the general observations from literature of the crucial action of molecular sieves as an initiator for the Michael addition.

Table 17: Michael addition of β-dicarbonyl compounds **72**

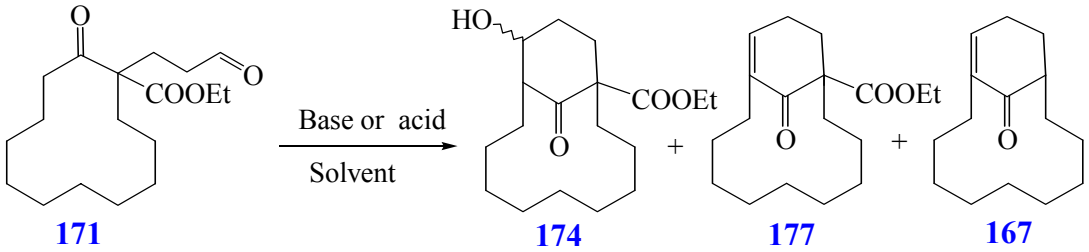
R	Base and /or catalyst	Solvent[a]	Acceptors	t,[h]	Michael adducts [%][b]
R 75	Al_2O_3	--	**166**	20	--
R 76	Na_2CO_3	toluene	**166**	24	--
R 77	Piperidine	THF	**166**	72	--
R 78	Molecular sieves	toluene[c]	**166**	12	**171**[10][d]
R 79	NEt_3	DMF	**166**	20	**171**[83]
R 80	NEt_3	DMF	**169**	16	**175** [61] (1:1:1)[e]
R 81	NEt_3	DMF	**170**	16	**176** [54] (1:1.4:1.1)[e]

a)Unless otherwise noted, all reactions are performed at room temperature; b) isolated yield; c) refluxing toluene; d) detected by GC analisys; e) mixture of diastereoisomers in ratio calculated with respect to the methyl group

However, NEt_3 in DMF proved to be a superior base in the Michael addition. Indeed, in the presence of catalytic amounts of base at room temperature[157] the reaction afforded the expected ethyl 2-oxo-1-(3-oxo-propyl)cyclododecan carboxylate (**171**) in 83% yield, isolated by distillation (R 79). In contrast, under the same reaction conditions the reaction of **72** performed with compound **169** and **170** proceeds with good selectivity in favor of the corresponding substituted hydroxy substituted bicyclic adducts **175** and **176**, respectively (R 80, R 81) as a mixture of diastereoisomers.

2.5.2.2. Intramolecular aldol addition of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate.

Based on the results observed in intramolecular acid or base – catalyzed aldol addition of 1,6 keto-aldehyde **76** (Scheme 38) attempts to utilize this methodology to convert the Michael adducts into β-hydroxy bicyclic compounds of type **164** (Scheme 76) have been investigated. All results obtained are listed in Table 18. These results reveal that the formation of aldol adduct **174** in 82% is exclusively observed when HCl is used (R 82, whereas an aldol condensation occurs under all other conditions used.



171 **174** **177** **167**

Scheme 80: Aldol addition and / or condensation of compound **171**

By replacing the strong mineral acid with a Lewis acid such as $BF_3 \cdot OEt_2$ the reaction proceeds at room temperature with high yield resulting in compound **177** in 81 % yield (R 83).

Table 18: Aldol cyclisation and condensation of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecan carboxylate (**171**).

R	Base /or acid	Solvent	ϑ, [°C]	t [h]	Products [%]
R 82	HCl	Dioxane	20	16	**174** [82] (1:1.6)[a]
R 83	$BF_3 \cdot OEt_2$	CH_2Cl_2	20	20	**177** [81]
R 84	NaOH	EtOH	80	24	**177** [86]
R 85	NaOH	EtOH	80	72	**167** [97]

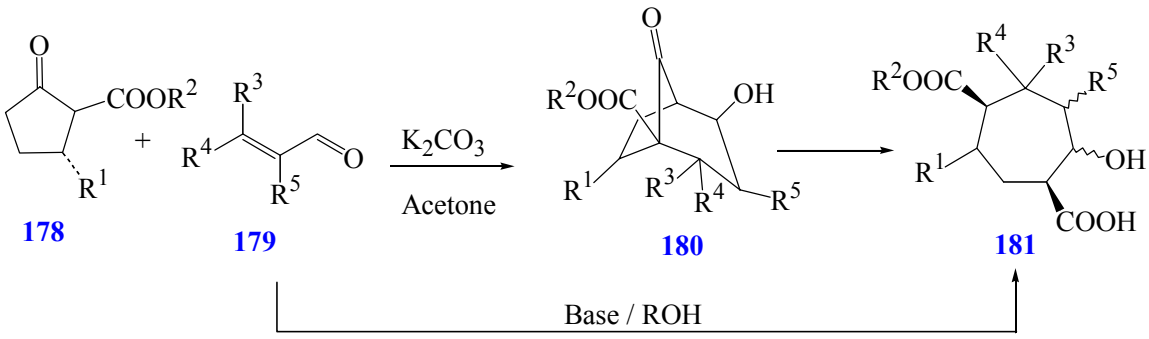
a) Mixture of diastereoisomers in ratio calculated by ^{1}HNMR analysis with respect to the ester groups

As shown in Table 18, the aldol condensation performed in the presence of NaOH as base is dependent on reaction time. When the conversion of compound **171** is carried out at 80°C for 72 h (R 85) a convenient one-pot aldol condensation-decarboxylation reaction occur furnishing α,β-unsaturated ketone **167** whereas compound **177** has been obtained with high yield under the same conditions with shorter reaction times (R 84).

2.5.3. One-pot Michael addition / aldol reaction 1,3-dicarbonyl compounds

2.5.3.1. Introduction

In the course of the study on the stereoselective synthesis of the naturally occurring Prelog-Djerassi lactone, Rodriguez et al.[158] found a very useful base-catalyzed diastereoselective three centre Michael addition of chiral β-ketoester (**178**) to α, β-unsaturated carbonyl compounds **179**. 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 **180** by a slight modification of their initial conditions for the Michael addition[159]. These bicyclic derivatives are involved as intermediates in the ring expansion of cyclopentanones to seven-membered ring[160] such as compound **181**. The one-pot condensation-cyclisation takes place under very mild conditions with α, β-unsaturated aldehydes of type **179** in acetone at room temperature in the presence of 1.5 eq. of K_2CO_3 (Scheme 81). Moreover, if compound **180** is treated with K_2CO_3 in the presence of MeOH or EtOH, they smoothly undergo a reverse-Dieckmann reaction[161] to the corresponding substituted cycloheptane derivatives **181**[162].



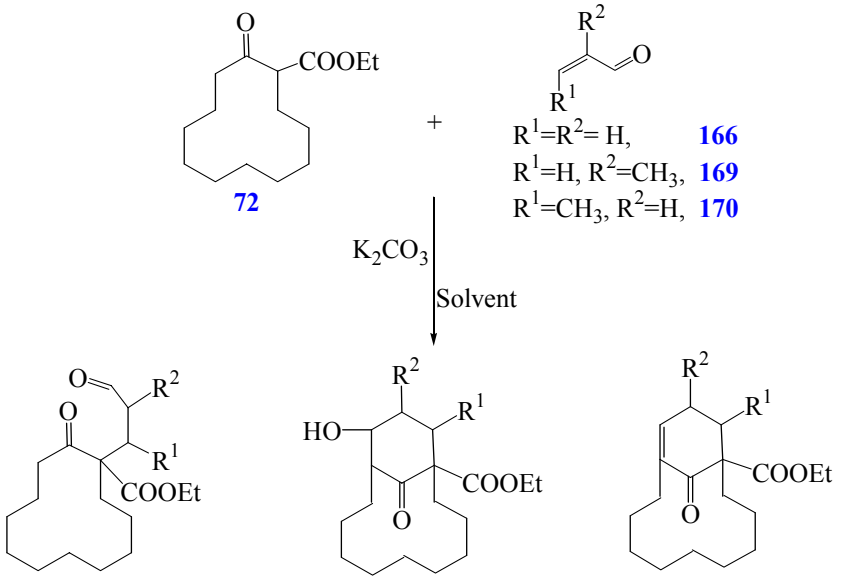
Scheme 81: Base-catalyzed two carbon ring expansion of cyclopentanones **178**

In 1997, Filippini et al[163] reported an base-induced anionic sequence involving five different reactions starting from **178** by replacing acetone with MeOH or EtOH. 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 result is the facile one-pot disatereoselective

formation of highly functionalized and synthetically valuable cycloheptanes **171** bearing two stereogenic centres and two chemically differentiated carboxylic groups (Scheme 81). The applicability of this procedure on β-ketoester **72** will be investigated by the use of different bases and solvents in the presence of α,β-unsaturated enals.

2.5.3.2. Michael addition / aldol reaction of 1,3-dicarbonyl compounds.

The initial studies of the MARDi cascade of β-ketoester begin with the screening of the reactions in the presence of K_2CO_3 as base in acetone or MeOH with variation of reaction time and temperature. The results from these investigations are presented in Table 19. In contrast to the results observed by Filippini et al. with cyclopentanone derivatives, starting material **72** does not lead to the substituted pentadecane. The expected one-pot expansion does neither take place in EtOH in the presence of catalytic amount of K_2CO_3 at room temperature nor in refluxing solvent (Scheme 82).



Scheme 82: Base-promoted one-pot Michael addition aldol cyclisation of ethyl 2-oxo-cyclododecane carboxylate (**72**).

If the reaction is performed in the presence of acrolein (**166**), via an aldol addition the compound **174** is obtained in good yield (R 86, R 87, R 88) whereas an aldol condensation occurs if the reaction is carried out for prolonged reaction time (72 hours) at refluxing EtOH (R 89) furnishing compound **177** in 67% yield.

Table 19: One-pot Michael addition / aldol cyclisation of β-ketoester **72** in the presence of K_2CO_3

R	Solvent	t,[h]	ϑ, [°C]	Acceptors	Products [%][a]
R 86	EtOH	18	20	**166**	**174** [61]
R 87	EtOH	72	20	**166**	**174** [58], (1:1)[c]
R 88	EtOH	18	80	**166**	**174**[56] (1:1.09)[c]
R 89	EtOH	72	80	**166**	**177** [67]
R 90	Acetone	18	20	**166**	**171** [78]
R 91	Acetone	72	20	**166**	**174** [67]
R 92	EtOH	18	20	**169**	**175** [58]
R 93	EtOH	72	20	**169**	**175** (30), **182** (35), (**175** 1:1.33)[f]
R 94	EtOH	18	80	**169**	**175** [43], (1:1.68:1.37)[f]
R 95	EtOH	72	80	**169**	**175** (37.5)[d], **182** (62)[d], (**175** 1:1)[f]
R 96	Acetone	18	20	**169**	**172** [85] (1:1.6)[e]
R 97	Acetone	72	20	**169**	**175**(61), **172** (33) (**175** 1:2:1)[f]
R 98	EtOH	18	20	**170**	**176** [53] (1:1.15)[f]
R 99	EtOH	72	80	**170**	**183** [76]
R 100	Acetone	18	20	**170**	**173** [84] (1:2.8)[e]
R 101	Acetone	72	20	**170**	**176** [57]

a) isolated yield; b) yield analyzed by ^{1}HNMR calculated with respect to CHO/CH-OH; c) diastereoisomeric ratio calculated by ^{1}HNMR with respect to CHOH; d) ratio analyzed by ^{1}HNMR calculated with respect to C=CH/CH-OH, e) ratio analyzed by ^{1}HNMR calculated with respect to aldehydic group, f) ratio analyzed by ^{1}HNMR calculated with respect to methyl group

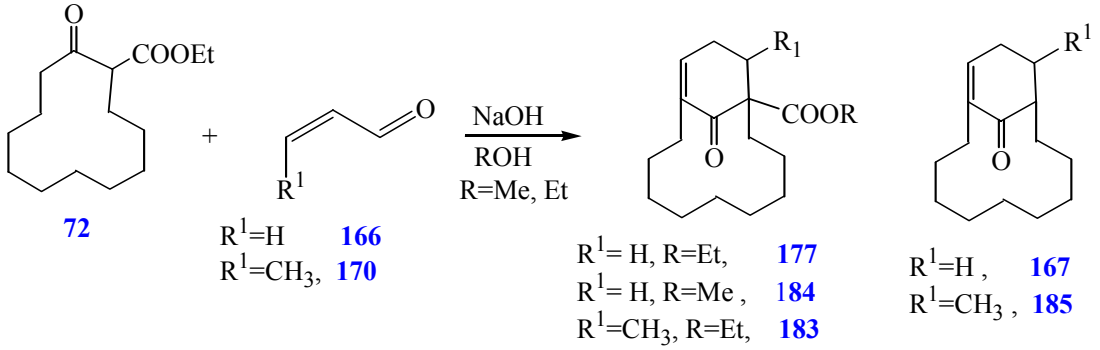
Moreover, in contrast to the the results observed by Rodriguez in the preparation of bicyclic β-hydroxy compounds, Michael adduct **171** is exclusively isolated in 78% yield

(R 90) after 18 hours if the reaction of **72** with **166** is carried out in the presence of 1.5 eq. of K_2CO_3 in acetone, while aldol adduct **174** is observed in 67% after a period of 72 h (R 91).

Based on the above results Michael addition / aldol reaction is also observed if starting from β-ketoester **72** and methacrolein (**169**). In contrast to the unsubtituted aldehyde **166**, if the reaction is carried out with methacrolein (**169**) in EtOH for a period of 72 h an aldol condensation takes place and a mixture of aldol adduct **175** and α,β-unsaturated ketoester **182** is obtained at room temperature (R 93) as well as in refluxing solvent (R 95). Using shorter reaction time (R 92, R 94), however, the aldol adduct **175** is exclusively formed. The reactions of β-ketoester **72** and methacrolein (**169**) in the presence of K_2CO_3 in acetone show similar trends as observed for acrolein (R 96). Nevertheless, the reaction carried out for 72 hours, proceeds with formation of a mixture of aldol products **175** and unsaturated β-ketoester **172** (R 97).

The Michael addition / aldol addition of crotonic aldehyde (**170**) to the ketoester **72** is also dependent of the conditions. Again, for longer reaction times (72 hours), under refluxing conditions and employing EtOH as solvent, an aldol condensation takes place and the enone **183** is isolated (R 99). Shorter reaction time (20 hours) at room temperature furnishes the aldol adduct **176** as the only product (R 98). As previously observed, treatment of β-ketoester **72** with crotonic aldehyde (**170**) in the presence of K_2CO_3 in acetone furnishes the corresponding β-hydroxy ketone **176** only if the reaction is run for a period of 72 hours (R 101) whereas shorter reaction time leads to the Michael adduct **173** as a misture of diastereoisomers (R 100). In conclusion, the reactions using K_2CO_3, regardless of the solvent and the α,β-unsaturated aldehydes employed proceed with formation of the aldol adducts. Furthermore an aldol condensation occurs if the reaction is conducted for longer reaction times at high temperatures.

Proceeding in searching for an efficient base/solvent system for performing the MARDi cascade NaOH / ROH (R=Me or Et) is investigated (Scheme 83). All results are listed in Table 20.



Scheme 83: Aldol condensation of β-ketoester (**72**) in the presence of NaOH / EtOH.

First, the conversions are performed with of acrolein (**166**). In contrast to the results observed in the presence of sodium carbonate with NaOH, all reactions proceed with an aldol condensation resulting in the formation of α,β-unsaturated ketoester **177** or **184** dependent of solvent used (R 102, R 103). Moreover, higher temperature favors the decarboxylation process furnishing compound **167** as main product (R 104). On the other hand, prolonged reaction time results in lower yield owing to degradation and the compound **167** is obtained in only 7 %.(R 105).

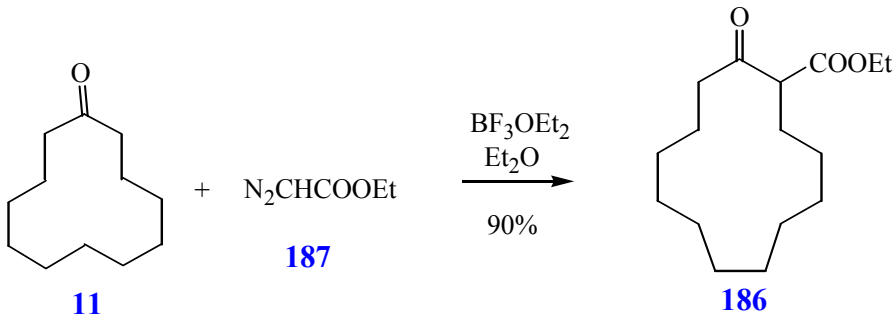
Table 20: Effects of the temperature and reaction time in the aldol reactions of β-ketoester **72** in the presence of NaOH.

R	t, [h]	ϑ, [°C]	Acceptors	Solvent	Aldol adducts [%]
R 102	18	20	**166**	EtOH	**177** (63)
R 103	72	20	**166**	MeOH	**184** (72)
R 104	18	80	**166**	EtOH	**177** (18), **167**(63)
R 105	72	80	**166**	EtOH	**167** (7)
R 106	18	20	**170**	EtOH	**183** (23)
R 107	72	20	**170**	EtOH	**183** (71)
R 108	18	80	**170**	EtOH	**185** (51)
R 109	72	80	**170**	EtOH	**185** (21)

According to the previous results, the reactions performed in the presence of crotonic aldehyde (**170**) show similar trends. At higher temperature aldol condensation followed by decarboxylation is observed either for a period of 24 h or longer leading to the β-enone **185** in 51% (R 108) and 21% yield (R 109). At room temperature, if the reaction is run for 72 hours the compound **183** is exclusively formed in 71% yield (R 107) whereas lower yield is observed for a reaction carried out in a period of 24 hours (R 106).

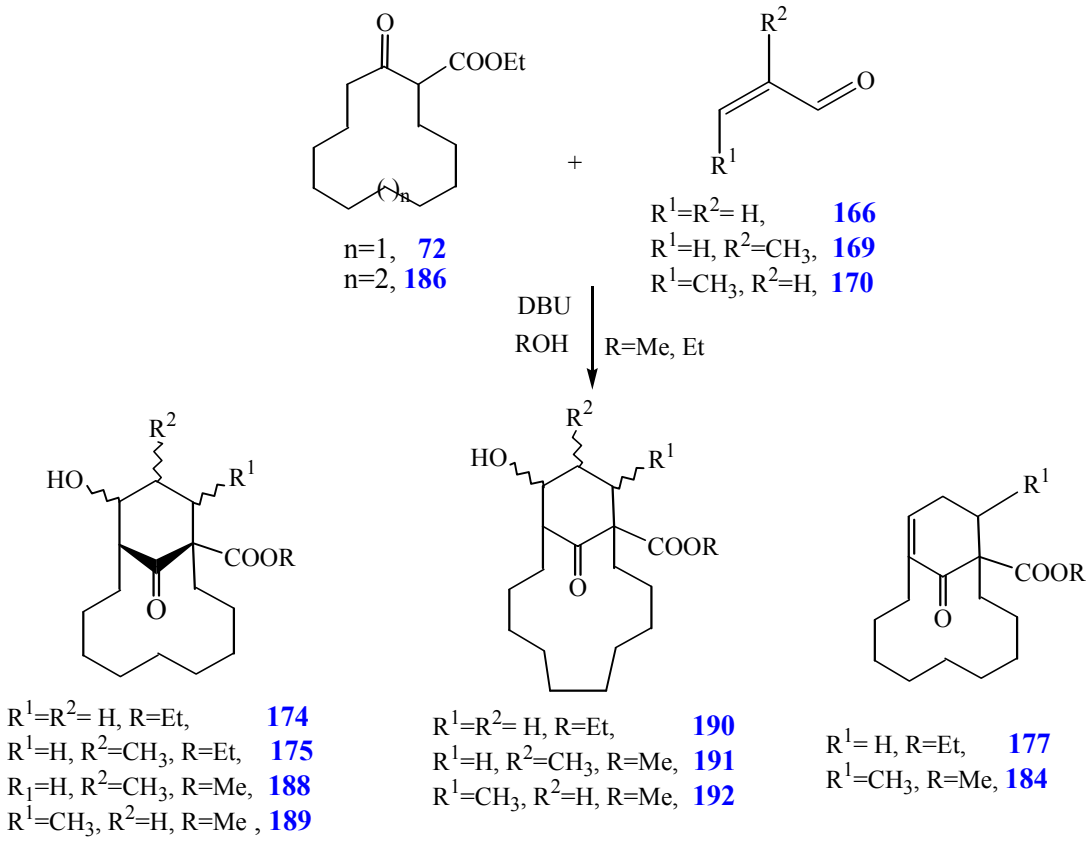
These results suggest that the selectivity of condensations could be controlled by the modification of temperature and the base. Indeed, while in all case an aldol condensation occurs, further decarboxylation is observed only with NaOH at high temperature regardless the reaction time.

In continuation of the investigation concerning the applicability of MARDi cascade, an amidine such as 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) is employed. Moreover, in order to test the overall process on larger cycloalkanoness the preparation of ethyl 2-oxo-cyclotridecane carboxylate (**186**) is performed in the presence of boron trifluoride etherate with ethyl diazoacetate (**187**) in diethylether (R 110, Scheme 84).



Scheme 84: Preparation of ethyl 2-oxo-cyclotridecane carboxylate (**186**).

The sequential Michael addition-intramolecular aldolization between 1 equiv of β-ketoester **72** and **186** with 1 equiv of enals **166**, **169** and **170** are carried out in the presence of DBU as base in ROH (R=Me or Et) with variation of temperature (Scheme 85). The results are summarized in Table 21.



Scheme 85: Aldol condensation of β-ketoester **72** and **186** in the presence of DBU / EtOH.

The reaction of β-ketoester **72** with acrolein (**166**) proceeded very smoothly giving the corresponding bicyclic compound **174** in 72% yield as a mixture of two diastereoisomers. Only one diastereoisomers is isolated in 32% yield after recrystallization from Et_2O (R 111) and in addition as an oil a mixture of two epimers due to the different orientation of 12-hydroxy group is obtained. According to the results observed with NaOH condensation reaction between **72** and **166** occurs under refluxing conditions furnishing compound **177**. Furthermore, prolonged reaction time does not favour decarboxylation. Regardless of the solvent employed, only higher yield in the α,β-unsaturated ketoester is obtained after prolonged reaction times (R 112, R 113).

Table 21: Effects of the temperature and reaction time in the aldol reactions of β-ketoester **72** and **186** in the presence of DBU.

R	n	Acceptors	t, [h]	ϑ, [°C]	Solvent	Aldol adducts, [%]	dr
R 111	1	**166**	18	20	EtOH	**174** (72)	1:1.8
R 112		**166**	18	80	EtOH	**177** (41)	--
R 113		**166**	72	80	EtOH	**177** (73)	--
R 114		**169**	18	20	MeOH	**175**(10), **188**(71%),	1:1.5[a,b]
R 115		**170**	18	20	MeOH	**189** (62)	1:1.33[a]
R 116	2	**166**	18	20	EtOH	**190** (78)	1:1.25[c]
R 117		**169**	18	20	MeOH	**191** (68)	1:3:8:2[a]
R 118		**170**	18	20	MeOH	**192** (62)	1:1.37[a]

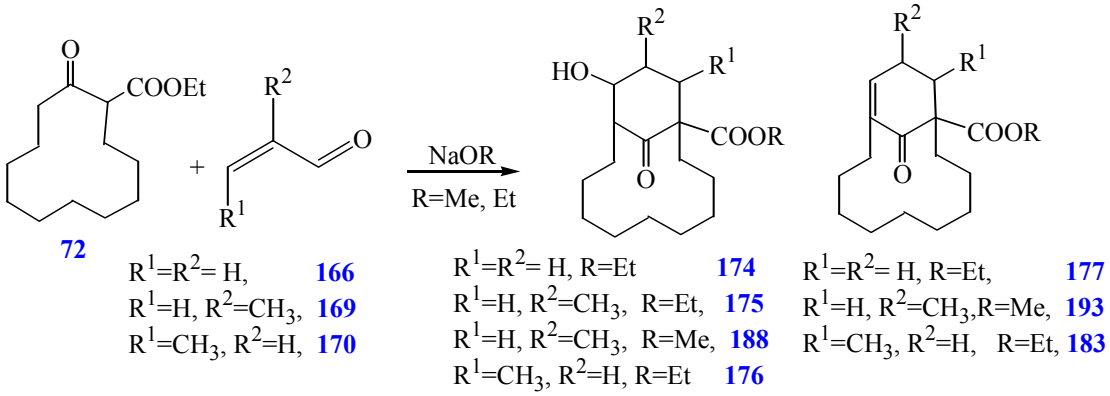
a) ratio of diastereoisomers calculated with respect to CH_3, b) ratio for the compound **188**, c) ratio of diastereoisomers calculated with respect to CH_2CH_3.

The reaction of methacrolein (**169**) with compound **72** in MeOH proceeds with the formation of aldol adducts **175**, **188** (R 114). The presence of compound **188** is attributed to the use of MeOH as solvent; indeed a transesterification takes place under these reaction conditions. Both aldol adducts **175**, **188** are present as a mixture of two diasteroisomers which are not separable.

The use of crotonic aldehyde (**170**) in MeOH in Michael addition / aldol reaction of **72** gives the aldol adduct **189** in slightly lower yield (62%, R 115) as a mixture of two diastereoisomers. As observed above one diastereoisomer is isolated in 49% yield after recrystallization from Et_2O and again, in addition a mixture of both epimers due to different orientations of 12-hydroxy and / or methyl group is obtained.

As expected on the base of these results, in all reactions of ethyl 2-oxo-cyclotridecane carboxylate (**186**) with α,β-unsaturated aldehydes in the presence of DBU, a Michael addition / aldol reaction takes place. Indeed, regardless the solvent used, the DBU-mediated reaction proceeds smoothly giving the corresponding alcohols **190**-**192** in good yield (R 116, R 117, R 118). Finally, attempts for performing the MARDi cascade are investigated by the reaction carried out in the presence of NaOR. Reactions have

been conducted at room temperature for 20 hours and the results are compiled in Table 22.



72

R^1=R^2= H, **166**
R^1=H, R^2=CH_3, **169**
R^1=CH_3, R^2=H, **170**

R^1=R^2= H, R=Et **174**
R^1=H, R^2=CH_3, R=Et, **175**
R^1=H, R^2=CH_3, R=Me, **188**
R^1=CH_3, R^2=H, R=Et **176**

R^1=R^2= H, R=Et, **177**
R^1=H, R^2=CH_3,R=Me, **193**
R^1=CH_3, R^2=H, R=Et, **183**

Scheme 86: Aldol reaction of β-ketoester (**72**) in the presence of NaOR.

In contrast to the results above observed, Michael addition / aldol condensation occurs even at room temperature(R 119, R 121).

Table 22: Effects of the temperature and reaction time in the aldol reactions of β-ketoester **72** in the presence of NaOR

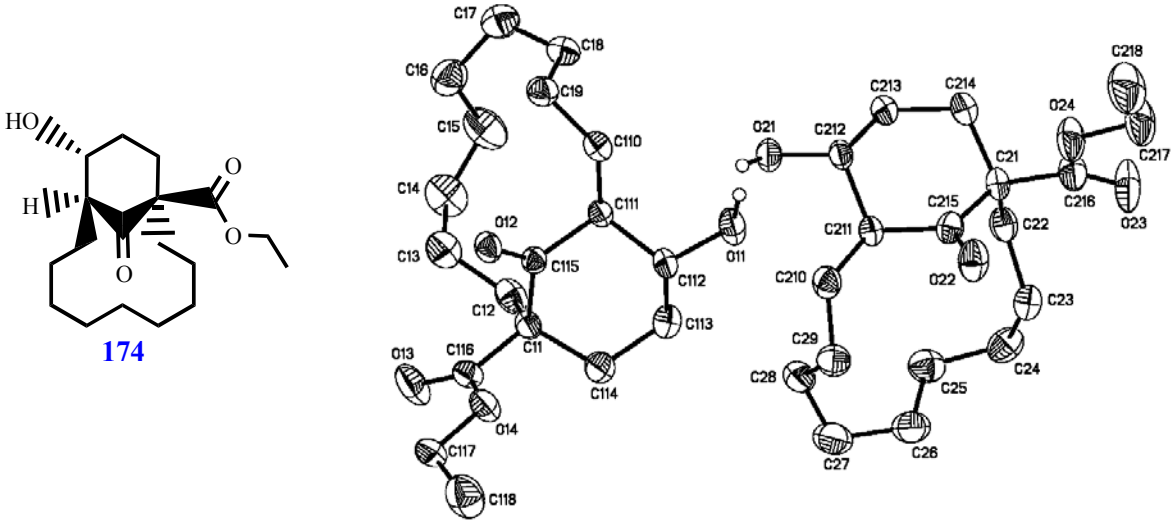
R	t, [h]	ϑ, [°C]	Acceptor	Solvent	Aldol adducts[%][a]
R 119	18	20	**166**	EtOH	**174** (56%), **177** (30%)
R 120	18	20	**169**	MeOH	**188** (46)[b], **193** (54)[b]
R 121	18	20	**170**	EtOH	**183** (68)

a) Isolated yield, b)NMR-yieldcalculated with respect CH=C /CHOH

Furthermore, if the reaction is performed with acrolein (**166**) a mixture of aldol product **174** and corresponding α,β-unsaturated ketoester **177** is formed in 56% and 30 % yield, respectively (R 119). Same result is observed if the reaction is carried out with methacrolein (**169**) leading, again, to a mixture of aldol product **188** and corresponding α,β-unsaturated ketoester **193** (R120)

From all these results, stereochemical differences could be assumed responsible for isolation of bicycles β-hydroxy cycloalkanones whereas the analogous product from

cyclopentanone is not isolated since further conversion via retro-Dieckman condensation readily occurred (cfr Scheme 81). Then, in order to attribute a stereochemistry two crystals probes of compound **174** and **176** an analysis by X-ray is required. As could be observed from the crystal structure, an asymmetric unit of ethyl rac-(1R, 11S, 12R)-12-hydroxy-15-oxo-bicyclo[9.4.1]pentadecan carboxylate[164](**174**) contains conformers molecules, which are described as a *trans*-fused bicyclic system. The carbonyl group lies on the same as the carbetoxy function, while the OH is in the opposite site. The six-membered rings have a chair conformation and the conformations of the twelve-membered rings are similar in the two molecules. Four molecules linked via H-bond and a centrosymmetric center sixteen-membered heterocycle with four O-H···O hydrogen bond plus six atoms from two six-membered rings is formed. These four molecules are separated by Van der Waals interactions from their surroundings (Scheme 87).

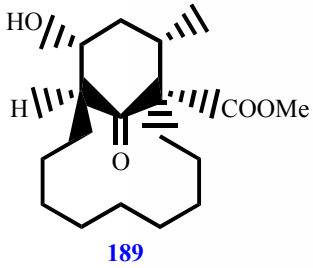


174

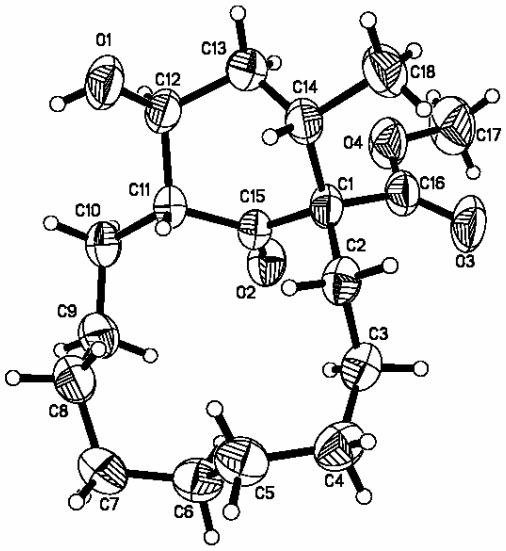
Scheme 87: Crystal structure of ethyl rac-(1R, 11S, 12R) 12-hydroxy-15-oxo-bicyclo[9.4.1]pentadecan carboxylate (**174**).

As it is shown in the crystal structure, methyl rac-(1R, 11S, 12R) - 12-hydroxy-14-metyl-15-oxo-bicyclo[9.4.1]pentadecan carboxylate[165] (**189**) is also described as a

trans-fused bicyclic system. The carbonyl group lies on the same side as the methoxycarbonyl group, while the OH group is on the opposite side. In contrast to the previous structure, the six-membered ring has a twist formed conformation, presumably due to the presence of the methyl group next to a bulky methoxycarbonyl group (Scheme 88).



189



Scheme 88: Crystal structure of methyl rac-(1R, 11S, 12R)-12-hydroxy-14-metyl-15-oxo-bicyclo[9.4.1]pentadecan carboxylate (**189**).

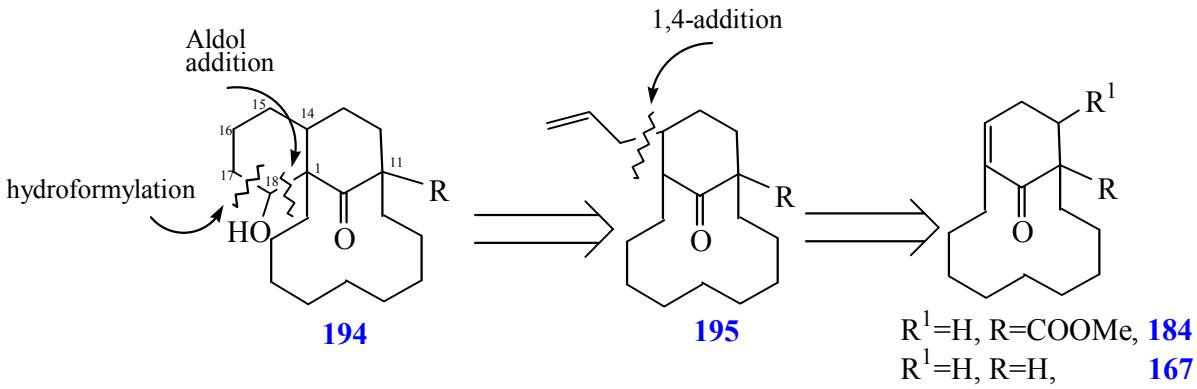
In conclusion, the failure of the MARDi cascade could be explained if considering the observed *tran*-fused stereochemistry of the products, whereas the analogous products formed from cyclopentanone is the *cis*-fused compound.

The lack of reactivity of such compounds towards the formation of macrocycles requires to investigate alternative procedures. As stated in the introduction of the project presented here ring-enlargement methods involving the cleavage of the keto-bridge in the presence of other functional groups in appropriate positions could be applied.

2.6. Preparation of tricyclic compounds

2.6.1. Introduction

Although the results reported above concerning attempts to perform the MARDi cascade show the impossibility to accomplish the synthesis of pentadecane derivatives, compounds such as β-ketoester **184** or enone **167** appear to be interesting intermediates in the preparation of tricyclic compound. Indeed, as shown in Scheme 89, compounds of type **194** involve the disconnection C14-C15, which can be built up by means of a 1, 4 conjugate addition to α,β-unsaturated cyclic ketoester **184** or **167**, followed by sequential hydroformylation / aldol condensation.

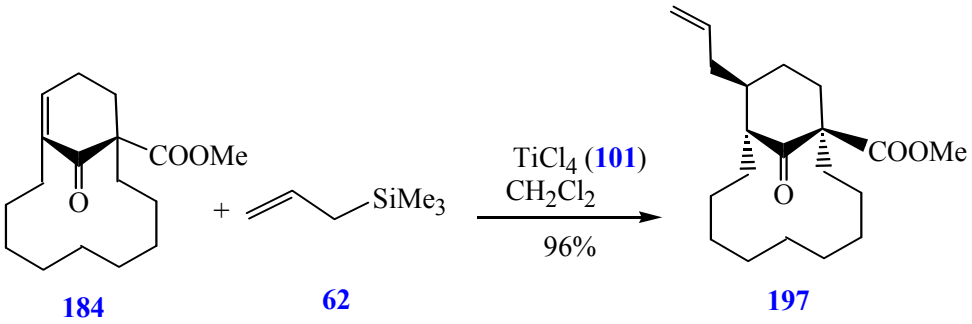


Scheme 89: Preparation of tricyclic compounds of type **194**

Therefore, in order to test methods of formation of such compounds under hydroformylation conditions, an allyl or vinyl chain is needed to be introduced.

2.6.2. Preparation of 12-alkenyl-bicyclo[9.3.1]pentadecan-15-one

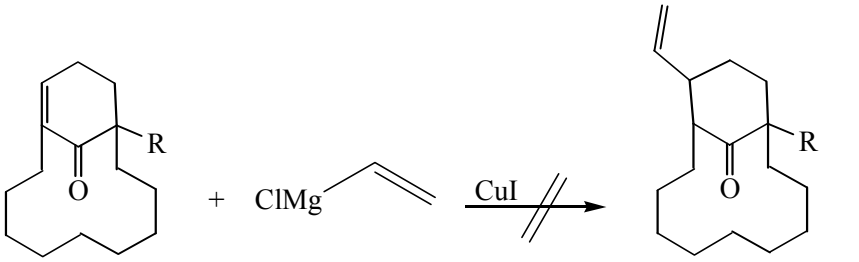
The allyl chain could be inserted in the compounds **184** or **167**, readily available, via a Sakurai reaction[166] in which Lewis acids promote 1,4-addition of allylsilanes with enones. Keith et al.[167] reported a method involving α,β-unsaturated cycloalkanones with allyltrimethylsilane in the presence of $TiCl_4$ (Scheme 90). Compound **197** in 96% yield isolated without any purification (R 122).



184 **62** **197**

Scheme 90: Preparation of methyl 12-allyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**197**).

Alternatively, by replacing the allyl chain with vinylic chain an 1,4-conjugate addition using organocopper reagents could be performed. Proceeding from β-enone **167** and β -ketoester **184** the results of the reactions are shown in Scheme 91. Both reactions proceeding with decomposition of starting materials upon the conditions applied, affording an intractable mixture (R 123, R 124).



R=COOMe, **184**
R=H, **167**

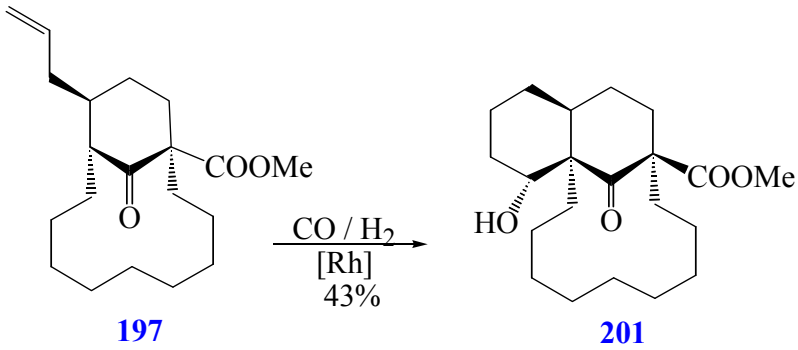
198

R=COOMe, **200**
R=H, **199**

Scheme 91: Attempted for vinyl-chain introduction.

2.6.3. Hydroformylation of methyl 12-alkenyl-bicyclo[9.3.1]pentadecan-15-one carboxylate

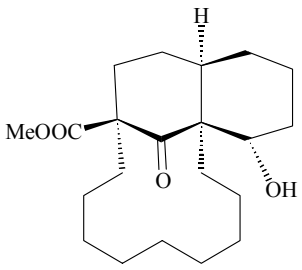
For the initial investigation into tandem hydroformylation / aldol addition the compound **197** is hydroformylated under acidic conditions with a catalytic amount of *p*-TsOH (5 mol %) Rh (I) (1 mol %) of $Rh(acac)(CO)_2$ and 4 mol % of BIPHEPHOS (**16**) in CH_2Cl_2 under 20 bar CO / H_2 (1:1) at 60° for 3d. Only cyclized product **201** is observed and after recrystallization from diethylether one diastereoisomer is isolated in 43% yield (R 125) (Scheme 92).



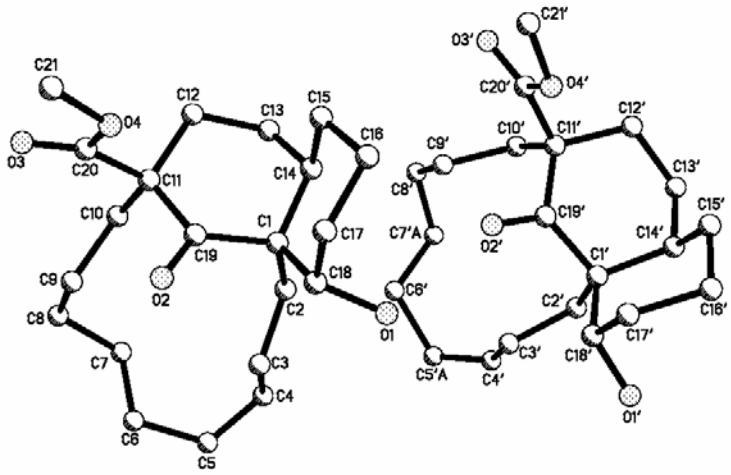
197 **201**

Scheme 92: Preparation of methyl rac-(1R, 11R, 14S, 18R)18-hxdroxy-19-oxo-tricyclo[9.7.1.$0^{1.14}$]nonadecane-11-carboxylate (**201**).

Owing to the complex tricyclic structure of methyl rac-(1R, 11R, 14S, 18R)18-hxdroxy-19-oxo-tricyclo[9.7.1.$0^{1.14}$]nonadecane-11-carboxylate (**201**) bearing four stereogenic centres, an X-ray analysis has been performed.



201



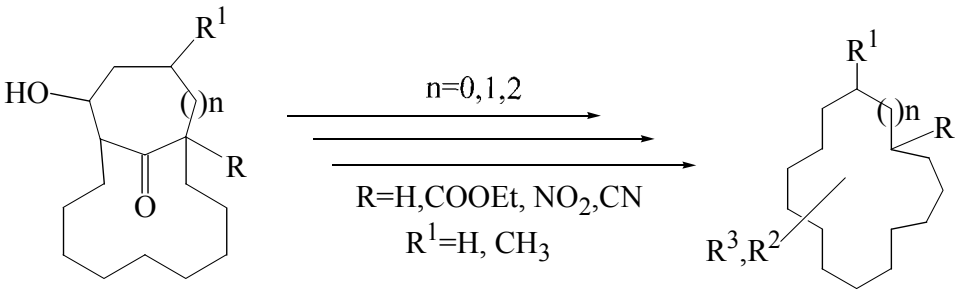
Scheme 93: Crystal structure methyl 18-hxdroxy-19-oxo-tricyclo[9.7.1.0$^{1.14}$]nonadecan-11-carboxylate (**201**)

The structure shows a *cis*-fused decaline system attached to the cyclododecanone in the position α,α' to its carbonyl[168] group. Thus, the Michael reaction and the subsequent hydroformylation /aldol addition occur from the side of the carbonyl group of the bicyclic starting compound, whereas the OH group is at the opposite side. Both six-membered rings have a chair conformation. Four molecules linked via two O-H···O hydrogen bonds and a centrosymmetric sixteen-membered heterocycle containing four hydrogen bonds is formed.

2.7. Fragmentation reactions and ring expansion methods

2.7.1. Introduction

As stated in the introduction, the ultimate aim of this work is to perform a general way to synthesize macrocycles via ring expansion. As illustrated in Scheme 94 it could be useful to envisage ring-enlargement methods involving the cleavage of the keto-bridge in the presence of other functional groups in appropriate positions.



58
R=R^1=H **50**

61

Scheme 94: Macrocycles accomplished via ring expansion

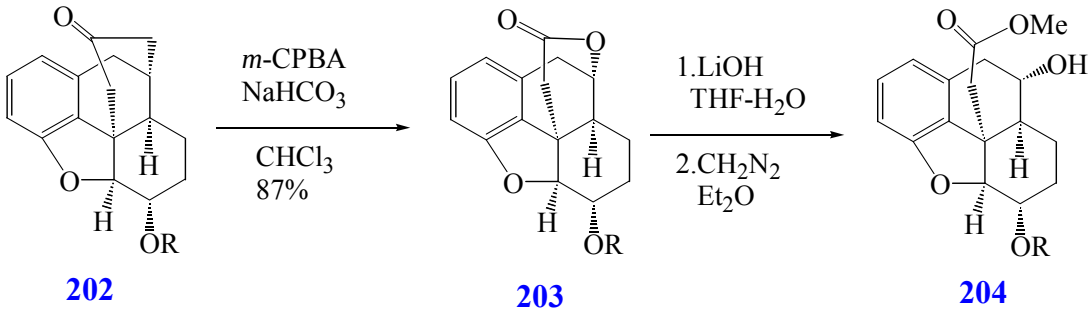
Along this line, an oxidative approach, such as Baeyer-Villiger (BV) oxidation followed by lactone hydrolysis could be valid approach. Alternatively, the base-promoted Grob fragmentation[169] of tosylates of bicyclo[9.4.1]hexadecane **50**[170] will be investigated whereas the retro-Dieckmann failed.

2.7.2. Baeyer-Villiger oxidation

2.7.2.1. Introduction

The Baeyer-Villiger oxidation of ketones with organic peroxy acid, hydrogen peroxide or alkyl hydroxyperoxide to give esters / lactones is of considerable synthetic use as a component of methods for converting carbocycles to hetero-cycles and opening cyclic array to prepare functionalized chains and/or rings.

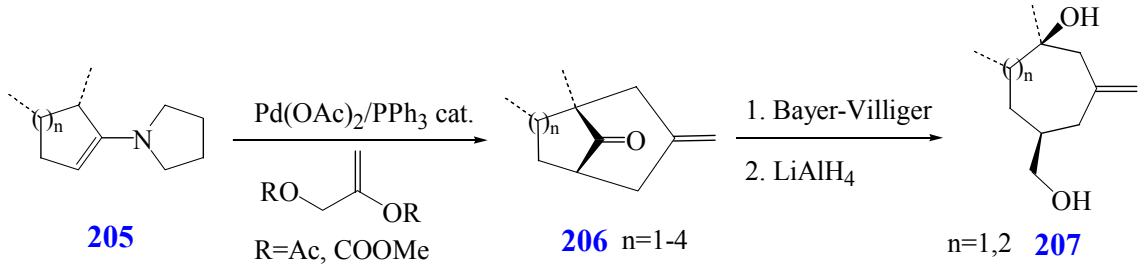
In a recent asymmetric synthesis of morphine reported from White et al.[171] ring expansion and ring fragmentation products were synthesized from pentacyclic ketone **202** via Baeyer-Villiger oxidation followed by opening of the lactone ring of **203**. Indeed, exposure of **202** to *m*-chloroperbenzoic acid led smoothly to δ-lactone **203** resulting from migration of the more highly substituted carbon[172] (Scheme 95). Next, basic hydrolysis of lactone followed by acidification and then treatment of the resultant hydroxy acid with diazomethane, produced methyl ester **204**.



202 **203** **204**

Scheme 95: Ring expansion and ring fragmentation via Baeyer-Villiger oxidation of ketone **201**

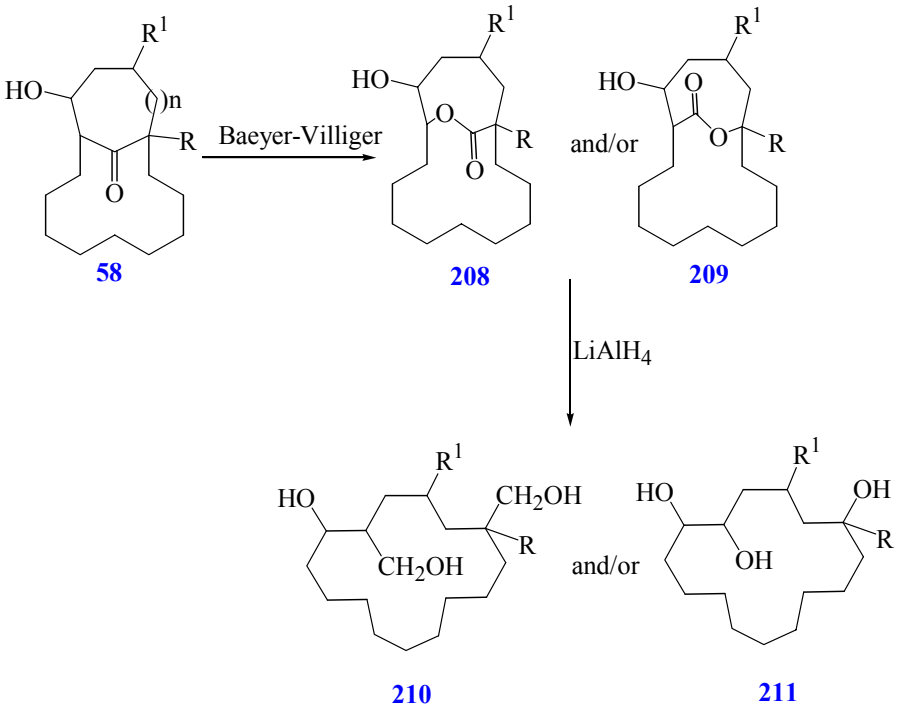
In 2000, Buono et al.[173] in connection with studies on transition - metal - catalyzed cyclizations towards natural product targets reported a straightforward route to functionalized cycloheptanols from cyclopentanones. The key reaction involves a Pd-catalyzed bicyclic annulation and a two-carbon-atom ring expansion sequence based on Baeyer-Villiger oxidation followed by reductive lactone opening (Scheme 96).



Scheme 96: Preparation of stereodefined functionalized cycloheptanols and cyclooctanols **207**

Baeyer-Villiger oxidation[174] of bicyclic ketones with peracetic acid in the presence of Na_2CO_3 occurred smoothly yielding the corresponding lactones in excellent yields. Reductive lactone ring opening was performed at room temperature using $LiAlH_4$ (two equiv.) in ether, affording 3-methylene-*cis*-5-hydroxymethylcycloheptanols **207** in good yields as single diastereoisomer.

Following these results bicycles of type **58** (Scheme 97), synthesized as previously described could be employed as starting material in Baeyer-Villiger oxidation giving lactones of type **208** and / or **209**.

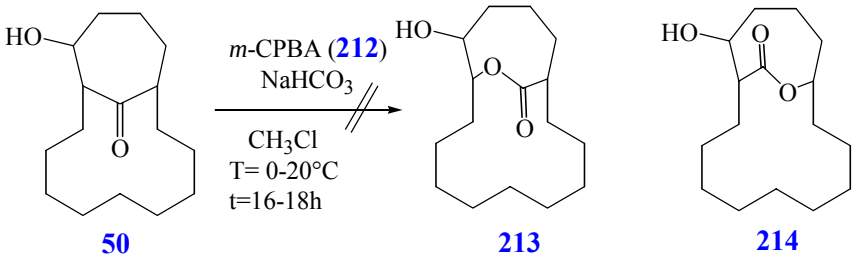


Scheme 97: Ring expansion and fragmentation of compound **58** via Baeyer-Villiger oxidation

The ring expansion could be performed using this mixture of compounds and the corresponding triols **210** and / or **211** could be prepared if $LiAlH_4$ is used as reductive agent.

2.7.2.2. Baeyer-Villiger oxidation of bicyclo[9.4.1]hexadecan-16-one derivatives.

For initial investigation into applicability of Baeyer-Villiger oxidation, the simplest starting material **50** is subjected to the standard reaction conditions (Scheme 98).



50 **213** **214**

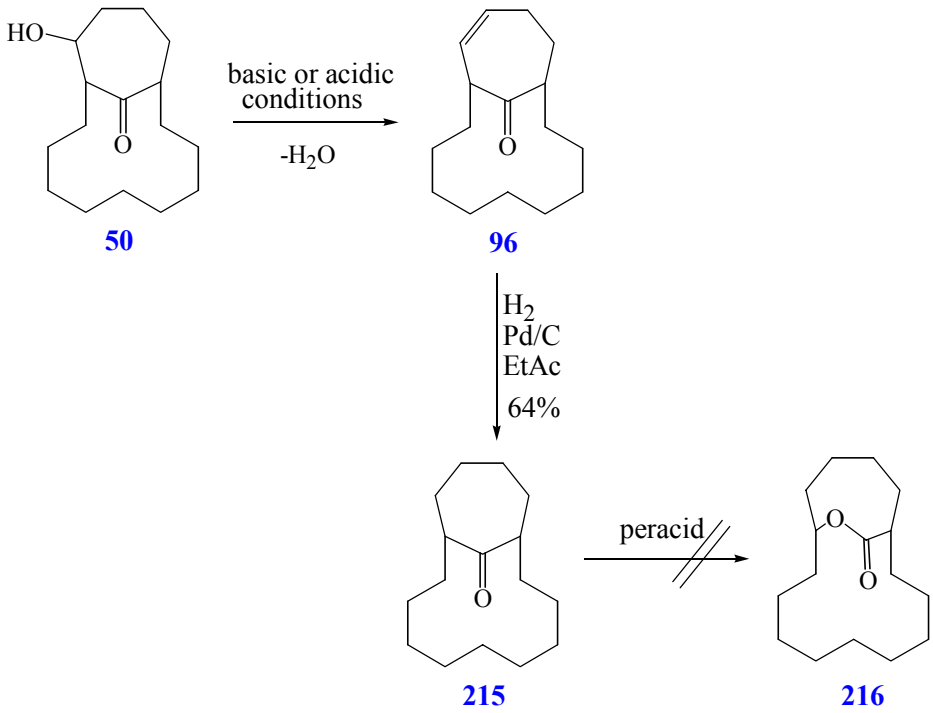
Scheme 98: Attempted Baeyer-Villiger oxidation of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**).

In the case of β-hydroxy ketone **50**, the oxidation reactions to produce lactones **213** and /or **214** were unsuccessful regardless of the reaction conditions and the starting material is recovered upon workup. The reaction, performed in the presence of *m*-CPBA (**212**) CH_2C1_2 at 0°C for 16 hours[175], proceeds without any conversion of compound **50** (R 126). The addition of $NaHCO_3$[176] was not effective for accelerating the rate of the reaction of **50** with *m*-CPBA (**212**) in CH_2C1_2 (R 127). This inertess of **50** could be explained in terms of the steric hindrance to the carbonyl face. Bulky undecane ring and hydroxylic groups covered both faces of the carbonyl group, thus preventing nucleophilic attack of *m*-CPBA. In fact it has been reported that the oxidation reaction of the ketone having a bulky group adjacent to the carbonyl requires a longer reaction times[177,178]. The rate of the Baeyer-Villiger reaction depends on the size of substituents adjacent to the carbonyl group.

Based on these results Baeyer-Villiger oxidation of β-hydroxy ketone **50** is not suitable for obtaining the intermediate lactones on which to test the ring opening for the preparation of substituted cyclopentadecane **210** and **211** (Scheme 97). In further the use of symmetric ketones in the Baeyer-Villiger oxidations was examined. Moreover,

using such starting materials seemed very useful when regioselectivity problems are considered.

To begin the route for the preparation of saturated ketone **215** has to be accomplished (Scheme 99). The most obvious method is to carry out the hydrogenation reaction of the compound **96**, which could be prepared by means of dehydration reaction under acidic or basic conditions. The results are listed in Table 23.



Scheme 99: Attempted Baeyer-Villiger oxidation of bicyclo[9.4.1]hexadecan-16-one (**215**)

When a mixture of secondary alcohol **50** in the presence of $CuSO_4/SiO_2$ in toluene[179] is heated at 120°C, no conversion into unsaturated ketone **96** is observed. Indeed, upon inspection of the crude mixture after filtration through a short pad of alumina only starting material is recovered (R 131). However, attempts to prepare the compound **96** are carried out under acidic conditions by use of H_2SO_4 in toluene to give the desired compound in only 15% yield (R 128) due to a decomposition of the starting material. Again, low yields are obtained when the reactions are performed in the presence of *p*-TsOH (35%, R 129) in toluene and $SOCl_2$ (25%, R 130) in pyridine[180]. Finally, high yields are obtained when the reaction is performed in the presence of P_2O_5[12] in toluene

(73%, R 132). Alternative reaction conditions need to be employed if considering difficulties to isolate the compound **96** from the crude mixture. Thus, DBU-EtOH[181] turns out to be an efficient system towards the preparation of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) in high yield (85%) after acidic workup (R 133).

Table 23: Preparation of bicyclo[9.4.1]hexadec-12-en-16-one (**96**).

R	Acid / Base	Solvent	t, [h]	ϑ, [°C]	96, [%]
R 128	H_2SO_4	toluene	20	20	15
R 129	*p*-TsOH	toluene	20	20	35
R 130	$SOCl_2$	pyridine	12	20	25[a]
R 131	$CuSO_4/SiO_2$	toluene	20	120	--
R 132	P_2O_5	toluene	18	120	73
R 133	DBU	EtOH	16	80	85

a) conversion detected by GC analysis.

Hydrogenation of compound **96** was carried out in the presence of Pd/C in AcEt[182] (R 134) to furnish compound **215** in 64% as a single diastereoisomer (Scheme 99).
Saturated ketone **215** was then treated with oxidative agent such as peracetic acid (PAA) (**217**) and *m*-CPBA (**212**) under different conditions as listed in Table 24.

Table 24: Baeyer-Villiger on bicyclo[9.4.1]hexadecan-16-one (**215**)

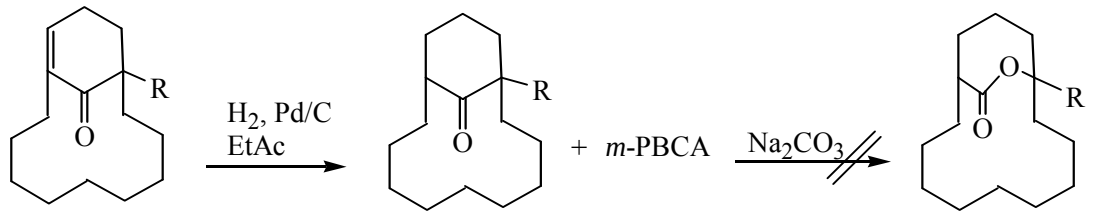
R	Oxidant	Catalyst	Solvent	t, [h]	ϑ, [°C]	216, [%]
R 135	PAA	$NaHCO_3$	CH_2C1_2	10	0	--
R 136	*m*-CPBA	$NaHCO_3$	$CHC1_3$	20	20	--
R 137	*m*-CPBA	$NaHCO_3$	$CHC1_3$	48	80	--
R 138	PAA	$BF_3{\cdot}OEt_2$	CH_3CC1_3	120	50	--

The reaction conducted with PAA in the presence of $NaHCO_3$ as buffering agent at 0°C (R 135) does not lead to the lacton **216**. The outcome of the reaction does not change by

replacing PAA (**217**) with *m*-CPBA (**212**) (R 136) or in refluxing chloroform (R 137) and again starting material is recovered. Moreover, reaction of compound **96** with an excess of PAA (**217**) in CH_3CCl_3 and catalytic amount of $BF_3 \cdot OEt_2$ at high temperature (50°C) failed (R 138).

Proceeding with investigations of Baeyer-Villiger oxidation the bicyclo[9.3.1]pentadecan-15-one (**218**) and β-ketoester **219** are chosen as starting materials (Scheme 100). Such compounds are synthesized in high yield via analogous hydrogenation of compound preparated above, by treating in the presence of Pd/C in AcEt at room temperature. Both compounds **218** and **219** are isolated as white solids after recristallization from cyclohexane (R 139, R 141).

Toda et al[183] have observed a remarkable acceleration in the rate of the Baeyer-Villiger reaction for sterically congested ketones by the addition of powdered sodium bicarbonate under solvent-free conditions[184]. According to the procedure reported by Yakura et al.[185] the reaction is carried out dissolving the solid reactants **218** and **219** in $CHC1_3$ and after immediate evaporation of the solvent, starting the reaction. After workup, the lactones **220** and **221** are not detected and only starting material are recovered (R 140, R 142).



R=COOEt, **177**
R=H, **167**

R=COOEt, **219** (74%)
R=H, **218** (96%)

212

R=COOEt, **221**
R=H, **220**

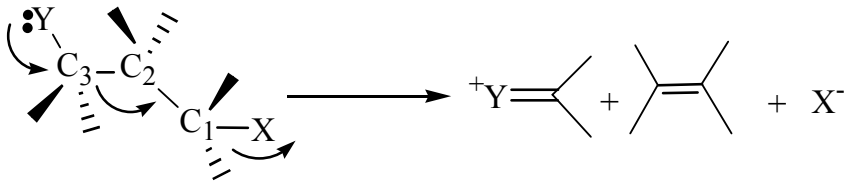
Scheme 100: Attempted Baeyer-Villiger oxidation of bicyclo[9.3.1]pentadecan-15-one (**218**)

From all these results, it could be concluded that the preparation of macrocycles could not accomplished by means of the Baeyer-Villiger oxidation and an alternative procedure has to be investigated.

2.7.3. Fragmentation reactions of bridged compounds

2.7.3.1. Introduction

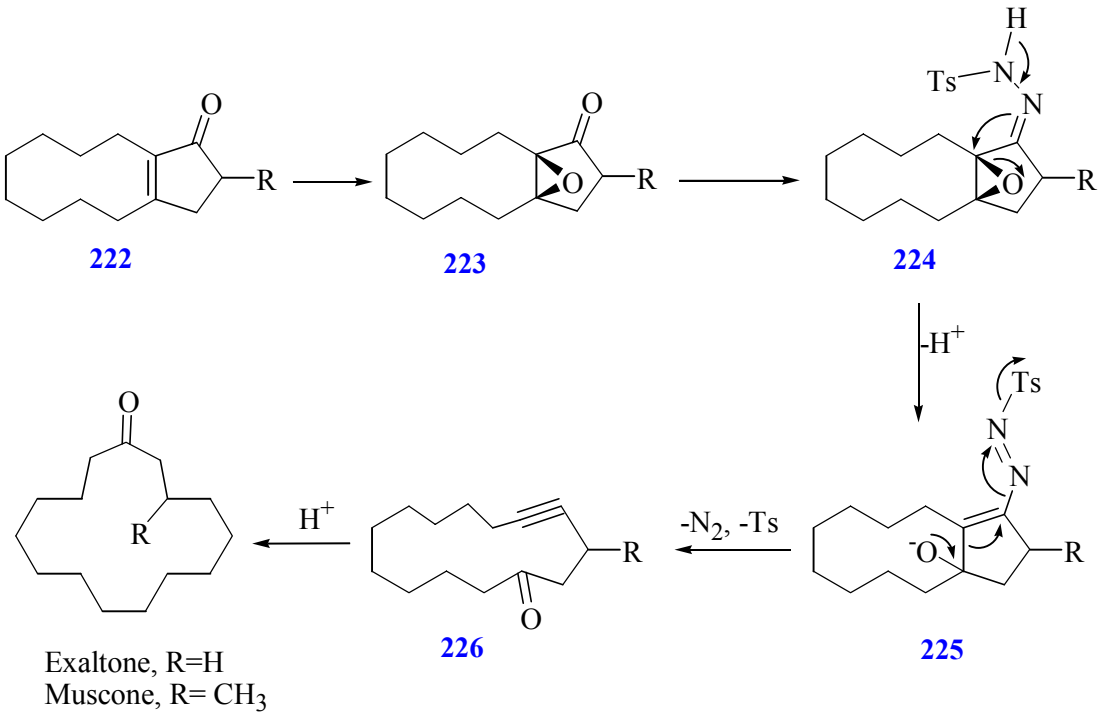
System containing a function with a negative charge or an unshared electron pair and a leaving group in 1,4-relationship are known to undergo heterolytic fragmentation process. In extension 1,3-diol derivatives may undergo concerted base-promoted fragmentations to give a carbonyl compound (Y=oxygen), an alkene and an anion as shown in Scheme 101.



Scheme 101: Basic mechanismus of fragmentation

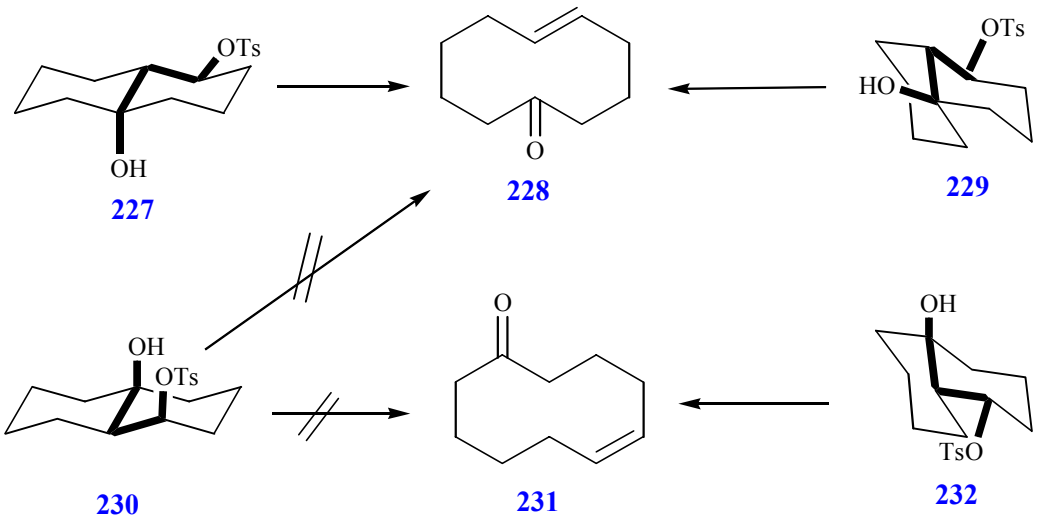
The one-step synchronous fragmentation is allowed only when the compound can adopt a conformation where the leaving group X as well as the electron pair of the electrofuge Y is antiperiplanar to the C_2-C_3 bond.

Effective examples to demonstrate the synthetic power of these methods are shown by the preparation of Exaltone and Muscone via Eschenmoser-type fragmentation[186]. Starting from the α,β-unsaturated ketones (**222**) and proceeding via the epoxy ketones (**223**) the tosylhydrazone **224** is cleaved to give the cycloalkanones such as Exaltone and Muscone after hydrogenation of compound **226** (Scheme 102).



Scheme 102: Preparation of Exaltone and Muscone via Eschenmoser-type fragmentation

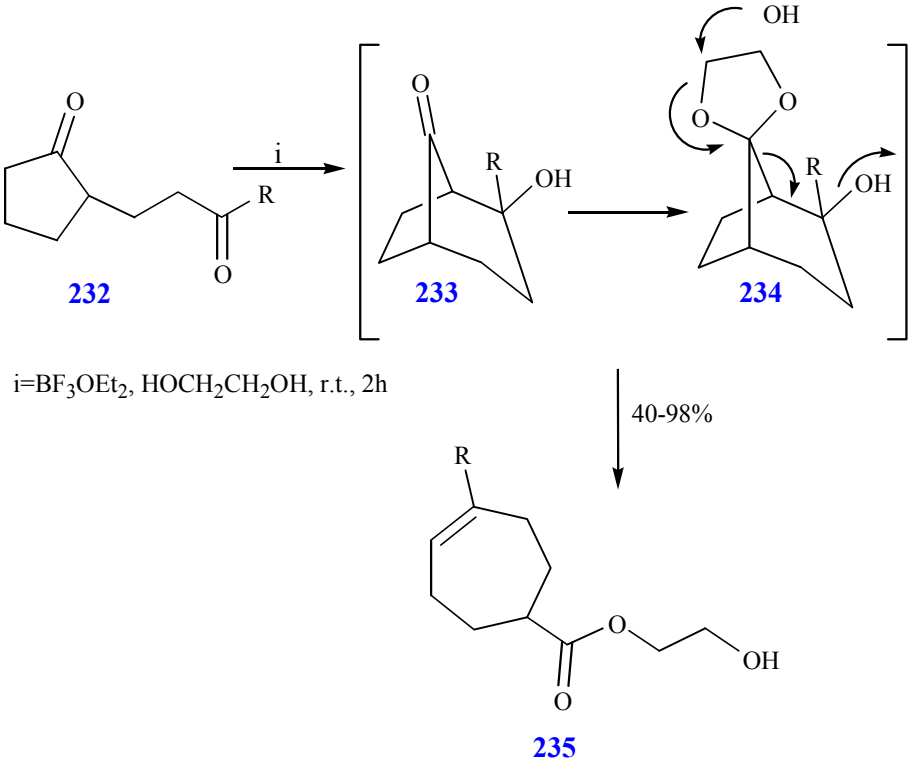
The versatile utility of fragmentation, especially those of 1,3-diol monosulfonate, for the construction of functionalized medium-sized cycloalkenes was demonstrated by Wharton[187,188] by applying Grob's observations[189]. Stereochemical arrangement has been investigated by Wharton for the four stereoisomeric tosylates (Scheme 103).



Scheme 103: Stereochemical arrangement in the fragmentation reaction

Compounds such as **227**, **229** and **232** show the crucial bond to be *anti*, and in these cases fragmentation to the cyclododecenone **228** and **231** occurs in 90% yield. The stereochemistry of C-C bond forming the double bond is strictly retained (**227**, **229** gives **228**; **232** gives **231**). The isomer **230**, having the bonds which may undergo cleavage in a *gauche* orientation remains largely unchanged. On the other hand, it has been found that the synperiplanar relationship between breaking bonds is required for facile fragmentation in a bridged bicyclic system[190].

An alternative procedure under acetalization condition has been reported by Sakai et al. [191]. Here cyclopentanone and cyclohexanone of type **232** with carbonyl functions in an appropriate position in a side chain undergo facile ring cleavage to construct a new ring. Particularly useful is the reaction sequence starting from a cyclopentanone with carbonyl function at the C-3 position of the α-position side chain (Scheme 104).



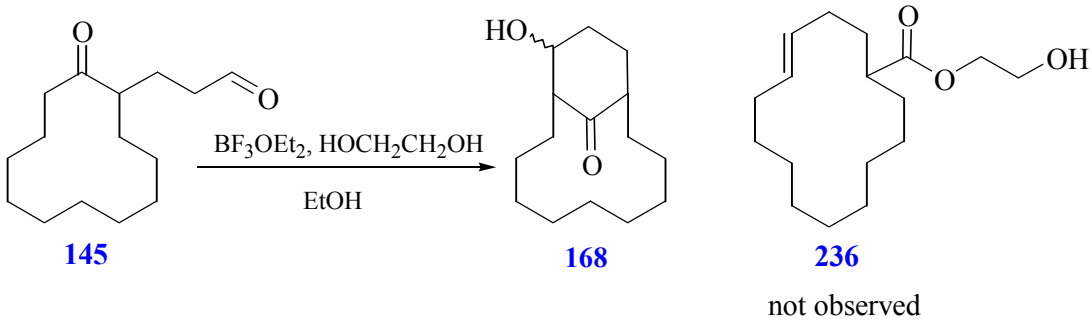
Scheme 104: Unusual Grob fragmentation via acetalization conditions (Sakai's investigations).

After aldol addition and acetalization a fragmentation takes place, which may be considered as one of the unusual cases of the Grob fragmentation. This ring expansion has been applied to the synthesis of bulnesol. Similarly, bicyclo[m.n.0]alkanes are converted to spirocyclic skeletons.

2.7.3.2. Attempted fragmentation under acetalization conditions

As above reported, by treatment with $BF_3 \cdot OEt_2$/ethyleneglycol, cyclopentanones with carbonyl function at the exposition of α-side chain undergo the ring cleavage to build up the seven membered rings. The expected ring enlargement to fourteen membered ring would involved the following three steps; a) aldol condensation, b) acetalization, c) ring enlargement due to the cleavage of the five membered ring as shown in Scheme 104.

Following the procedure reported by Tanaka at al., treatment of the ketoaldehyde **145** under the acetalization conditions at room temperature, for 16 hours, furnishes the β-hydroxy ketone **168** in 63% yield (Scheme 105) whereas the desired half ethyleneglycol ester **123** is not observed (R 143).



145 **168** **236**

not observed

Scheme 105: Preparation of 12-hydroxy bicyclo[9.3.1]pentadecan-16-one (**145**)

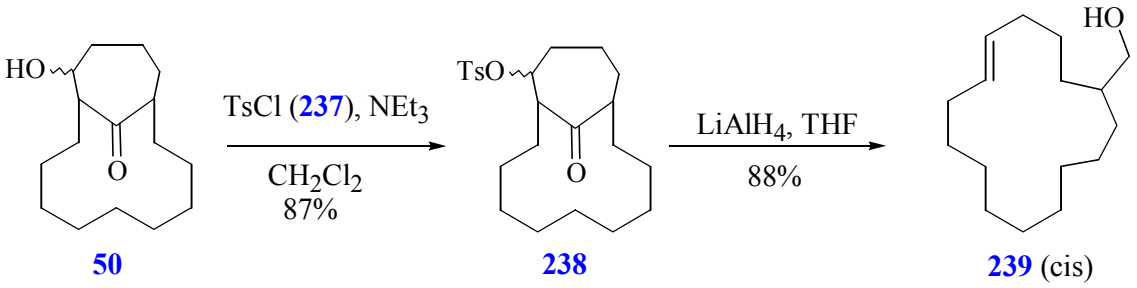
Thus, it is likely that the aldehyde is too reactive and an aldol addition occurs before the acetalization could take place and then this reaction could be not applied for the ring transformation.

2.7.3.3. Grob fragmentation of bicyclo[9.4.1]hexadecan-16-one derivatives

An alternative method for preparation of 14-, 15-membered ring via fragmentation reaction of bridged rings could be accomplished by means of macrocyclic compound of type **239**.

Synthesis of a fragmentable bicyclic precursor (Scheme 106) from β-hydroxy ketone **50** requires stereoselective conversion into of keto tosylate **238**, which has to bear the equatorial leaving group in order to satisfy the rigorous *anti*-periplanar geometry required of the breaking bonds in the transition state[192] (Scheme 106).

Treatment of the crude mixture of **50**, with 1 equiv. of tosyl chloride (**237**), in pyridine[193] for 72 hours at room temperature, furnishes the keto tosylate **238** in 87% yield as a white solid (R 144).

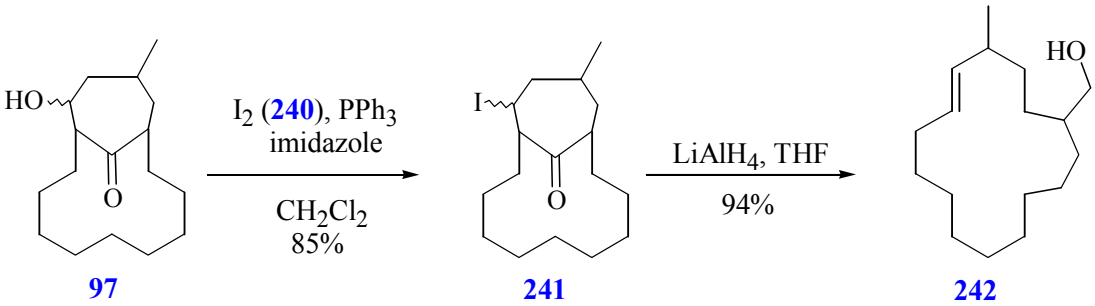


50 **238** **239** (cis)

Scheme 106: Preparation of 1-cyclopentadec-5-enyl-methanol (**239**)

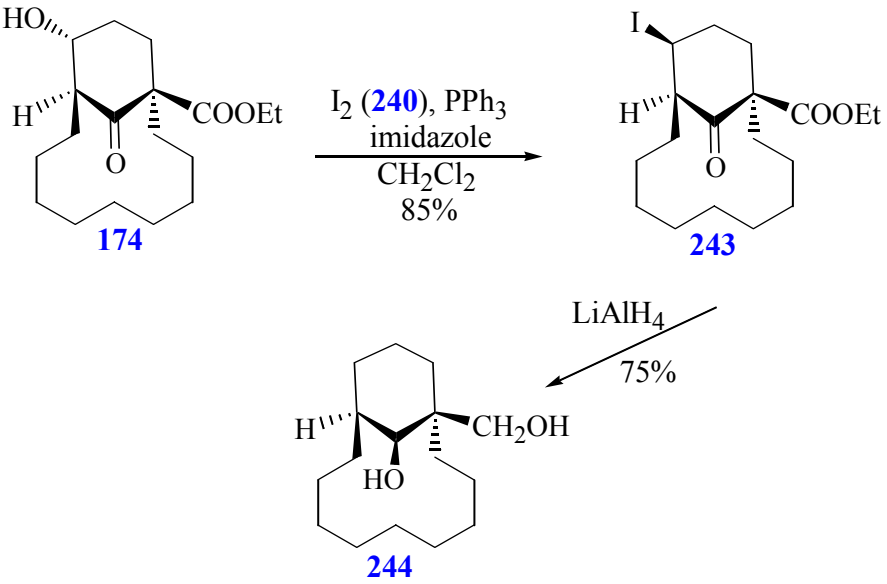
The fragmentation of tosylate **238** employed lithium aluminum hydride as a combined basic initiator and reducing agent furnishes, as expected, 1-cyclopentadec-5-enyl-methanol (**239**) in 88% yield (R 145).

Although, the most widely used leaving group in heterolytic fragmentation process is the tosylate or mesylate group, no study has been performed to provide data on how the rate of fragmentation vary as a function of the leaving group. Alternatively, iodine could be employed if comparing the reaction time of both reaction for the formation of intermediates **238** and **241** (R 144 and R 146). A rapid and convenient procedure for the preparation of iodide ketone **241** is the application of Appel reaction[194], described by Gottardo et al.[195] employing the PPh_3/I_2/imidazole combination in dichlorometane solvent (R 146).



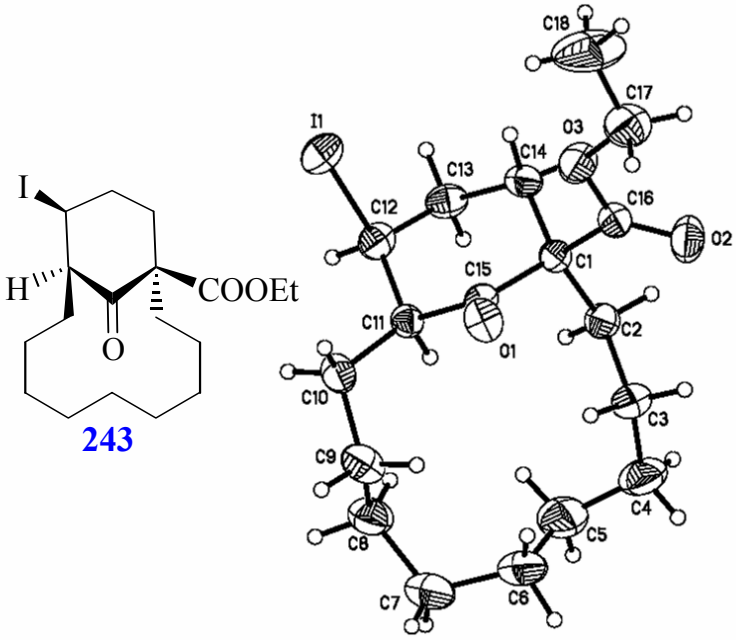
Scheme 107: Preparation of 1-cyclopentadec-5-enyl-methanol (**247**)

The reaction is carried out at room temperature for a period of 16 hours and after filtration on a pad of silica gel furnishes the compound **241** in 85% yield (R 146).
According to the previous results, the fragmentation step is performed in the presence of $LiAlH_4$ under refluxing conditions and, as expected, the reaction proceeds with the formation of 1-cyclopentadec-5-enyl-methanol (**242**) (R 147). In an approach to the substituted fourteen-membered ring ethyl rac-(1R*, 11S*, 12R*)-12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) is chosen as starting material. According to the previous procedure, compound **243** is prepared via the Appel reaction from the corresponding alcohol **174** (R148).



Scheme 108: Attempted fragmentation reaction of ethyl 15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (**243**).

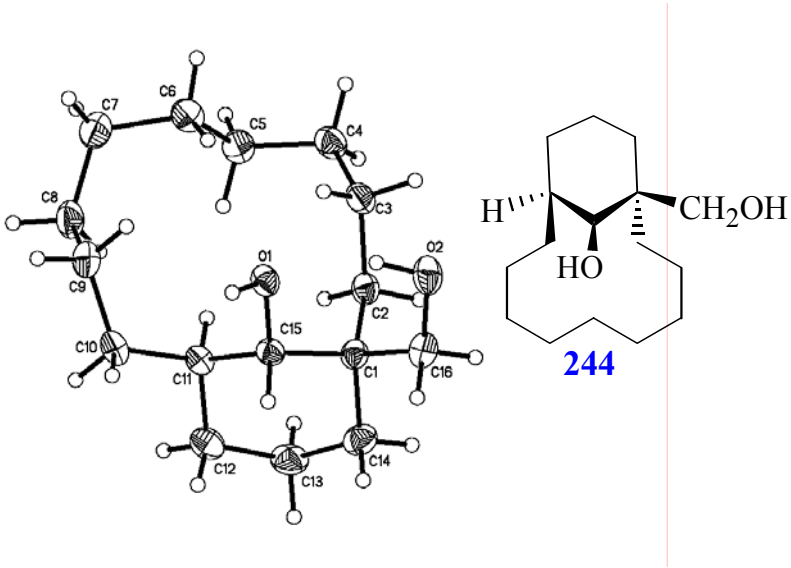
Conversion of **174** with iodine and PPh_3 occurs via a nucleophilyc substitution and according to reaction mechanism the result proceeds with an inversion of the configuration at C-12 (Scheme 108). In order to confirm the stereochemistry of the compound **243** an X-Ray analysis is required.



Scheme 109: Crystal structure of ethyl rac-(1R*, 11S*, 12S*)-15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (**243**)

Ethyl rac-(1R*, 11S*, 12S*)-15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (**243**) is described as a trans-fused bicyclic system[196] (Scheme 109). The carbonyl group lies on the same side as the carbethoxy function and iodine. The six membered rings have a chair conformation. The axial iodide bicyclic β-ketoester **243** does not undergo fragmentation process. The outcome of the reaction is in contrast with the previously results (Scheme 14). The compound **243** reacts differently toward $LiAlH_4$. Indeed, the reaction carried out in the presence of $LiAlH_4$ (R 149) proceeds with high yield into formation of 1-hydroxymethyl-bicyclo[9.3.1]pentadecane-15-ol (**244**) and the difference could be attributed to stereoeletronic effects. The presence of bridgehead ester group is crucial to the fragmentation of axial iodide. In fact, in the system without the ester

group, the keto tosylates **239** or iodide **241** is found to fragment whereas the axial iodide **243** undergoes reduction and elimination. An X-ray analysis is investigated for the compound **244**.



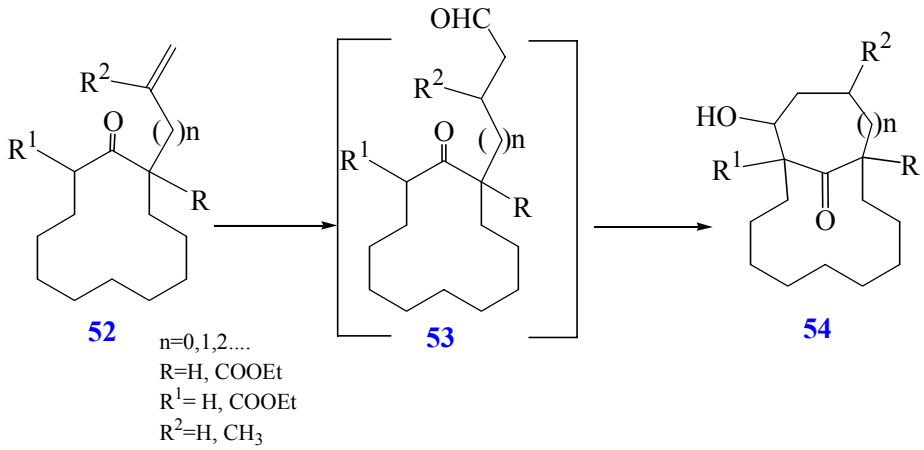
Scheme 110: Crystal structure of 1-hydroxymethyl-bicyclo[9.3.1]pentadecane-15-ol (**244**)[197]

The investigated crystal is described as a bicyclic *trans* - system. Both hydroxy groups lie on the same side, whereas the six-membered rings has a distorted-chair lies in the opposite side.

From all these results, although the last investigation is not the desired fourteen-membered ring, the method could be considered an important method because it represent a net chemoselective fragmentation of equatorial 1,3-diol derivatives.

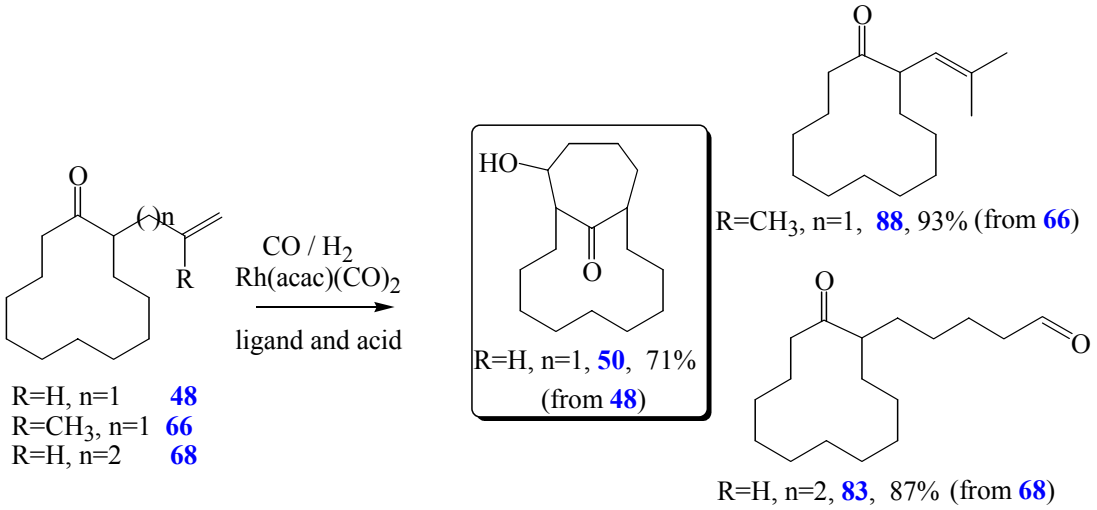
3. Conclusion and outlook

In this work an investigation on the ring expansion methods involved in the preparation of fourteen-, fifteen-membered rings towards the construction of Exaltone and Muscone via bridged compounds was conducted. Following preliminary results observed by Hollmann concerning the sequential hydroformylation / aldol addition, a variety of unsaturated ketones or ketoester have been chosen as starting materials as depicted in Scheme 111.



Scheme 111: Sequential hydroformylation / aldol addition of unsaturated substrates.

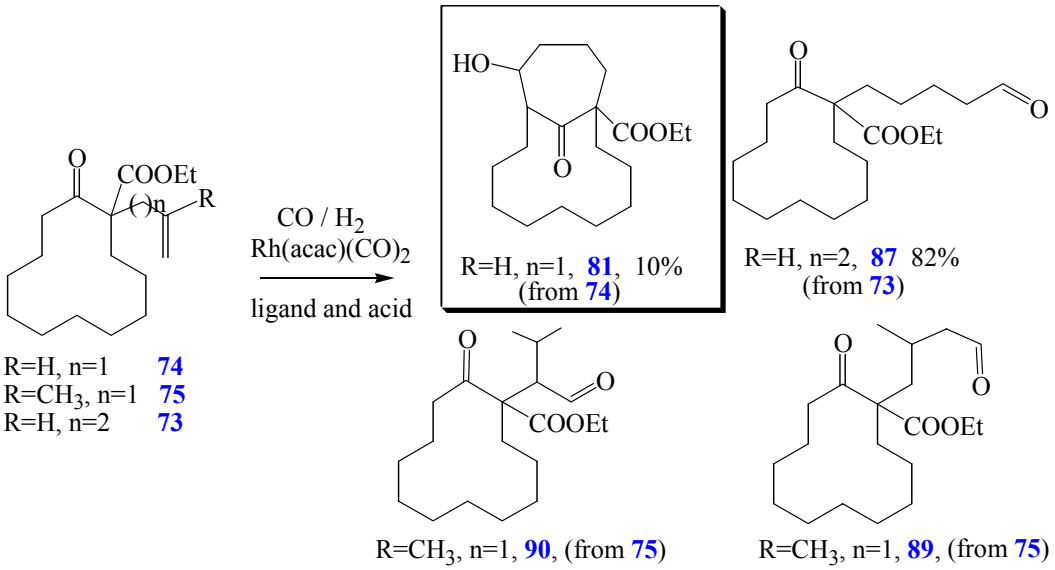
First the sequential hydroformylation / aldol addition was tested for 2-alkenyl-cyclododecanone **48**, **66** and **68** are employed (Scheme 112). Preliminary studies have shown that the one-pot sequence proceeds with the formation of a bicyclic compound if 2-allylcyclododecanone (R=H, n=1, **48**) is employed giving the compound **50** in high yield (71%). Under the same conditions, the substituted allyl chain (R=CH_3, n=1, **66**) and homologated allyl chain (R=H, n=2, **68**) do not allow the formation of bridged system.



Scheme 112: Reactivity of 2-alkenyl-cyclododecanone (**48**, **66** and **68**) under tandem hydroformylation / aldol cyclisation

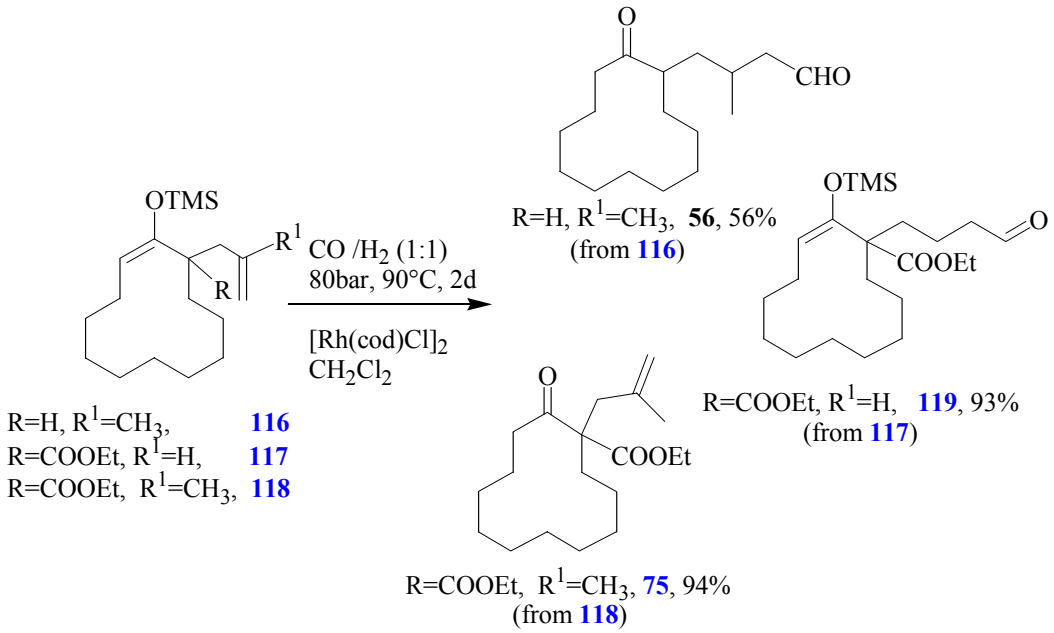
For the compound **68** only the *n*-product resulting from simple hydroformylation **50** is obtained in 87% yield, whereas compound **66** with substituted chain undergoes isomerizzation of the double bond (**88**).

Proceeding with these investigations the sequential tandem hydroformylation / aldol addition were tested with the keto ester **74**, **75** and **73**, as depicted in Scheme 113.



Scheme 113: Reactivity of ethyl 2-alkenyl-cyclododecanone carboxylate (74, 75 and 73) under tandem hydroformylation / aldol cyclisation.

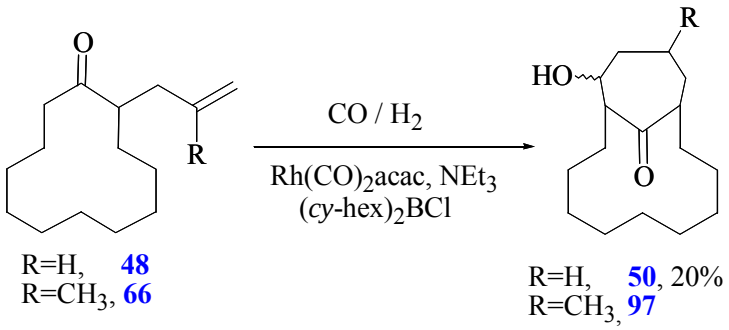
Although the aldol addition is observed in low yield when compound **74** is used, upon hydroformylation in the presence of mild acid catalysis the α-substitued ketoester designed for the preparation of macrocycle derivatives gave no aldol products. As an alternative various Z(O)-silyl enol ethers of the unsaturated ketones **117** and ketoesters **118** and **119** were similarly converted.



Scheme 114: Attempted synthesis of bridged compounds *via* hydroformylation /Mukaiyama aldol additions

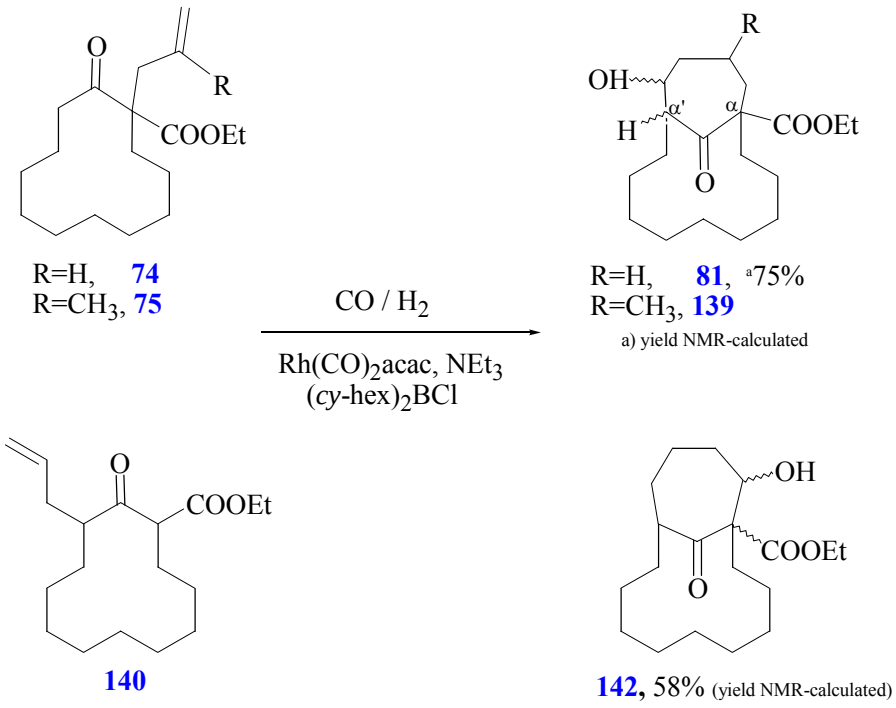
This method allowed access to the aldehyde **119** if starting from enolsilane **116** in 93% yield. For the others enolsilanes **116** and **118** under the same hydroformylation conditions only the desilylation process was observed. Once again, the directed preparation of the bicyclic compounds could not be accomplished via this methodology. Finally, a cascade reaction via enolboration / hydroformylation / aldol addition was investigated accomplishing the formation of bridged system in all cases.

The reactions proceed with good yields, unless when 2-allyl-cyclododecanone (**48**) gave compound **50** is isolated in 20% yield.



Scheme 115: Preparation of bridged compounds *via* enoboration /hydroformylation / aldol additions of 2-alkenyl-cyclododecanone

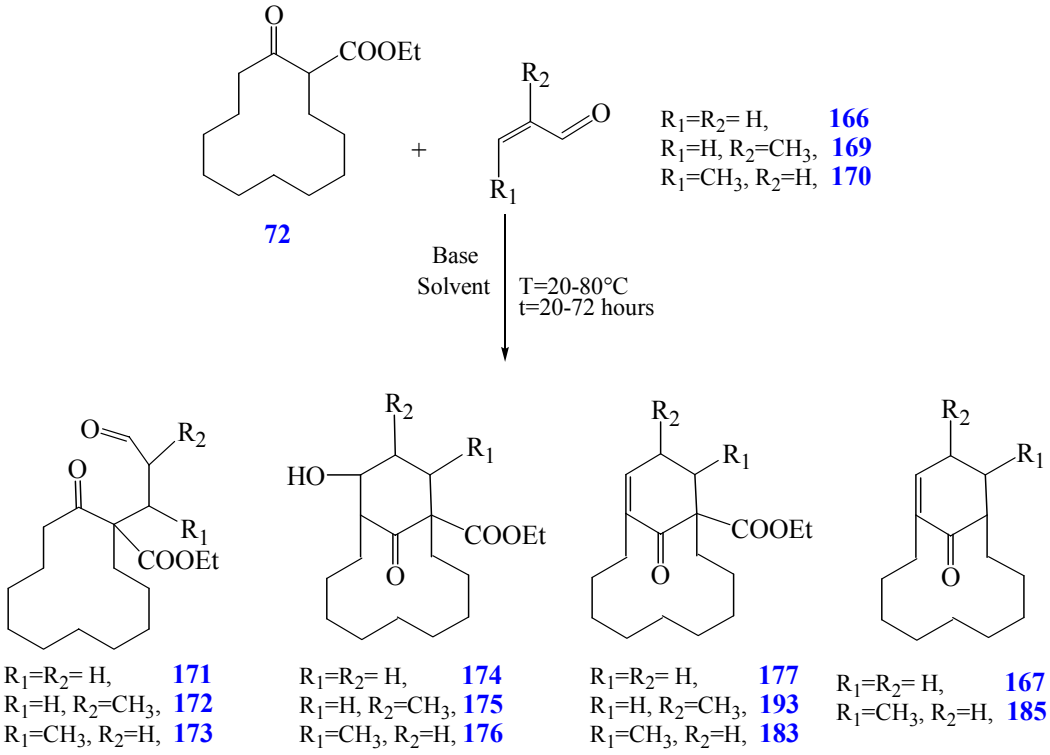
On the other hand, for trisubstituted olefin in subtrates as compound **66** and **75** the reactions proceed with good yield into the formation of bicycles **97** and **139**, respectively. No isomerization process of the double bond is observed.



Scheme 116: Synthesis of bridged compounds *via* enoboration/hydroformylation / aldol additions of β-keto ester.

Moreover, a control of stereoselectivity could be achieved. The reaction cascade of the substrate **140** that bears more than one enolizable site, proceeds with formation of the more sterically hindered aldol adduct **142**.

Proceeding in the studies towards the preparation of bridged systems, the conversion of the β-ketoester **72** into β-hydroxy[9.3.1]pentadecan-15-one could be performed starting from cyclododecanone or its derivatives by a Michael reaction employing the α,β-unsaturated aldehydes (**166**, **169**, **179**). All investigations suggest that the selectivity of condensation could be controlled by the modification of temperature, time and base (Scheme 117). While, an aldol addition occurs to give compounds of type **174**-**176** regardless the base used (K_2CO_3, NaOH, DBU and Na/EtOH), only Michael addition is observed if K_2CO_3 in acetone is used at room temperature for 24 hours furnishing compound **171**-**173**.

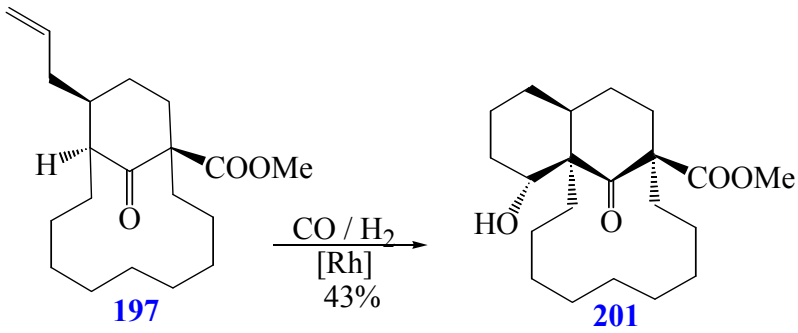


Scheme 117: Study of reactivity of β-ketoester **72** with variation of reaction conditions

An aldol condensation furnishing unsaturated β-ketoester **177**, **183** and **193** takes place if K_2CO_3 or DBU in EtOH is used and the reactions are carried out under refluxing

solvent and long reaction time. Furthermore, NaOH in EtOH or NaOR are able to undergo the aldol condensation even at room temperature in a period of 24 hours. Moreover, although in low yield a sequential Michael addition / aldol condensation / decarboxylation is observed in the presence of NaOH / EtOH under refluxing conditions for a period of 72 hours and the β-enones **167**, **185** are isolated in 7 % and 21 % yield, respectively.

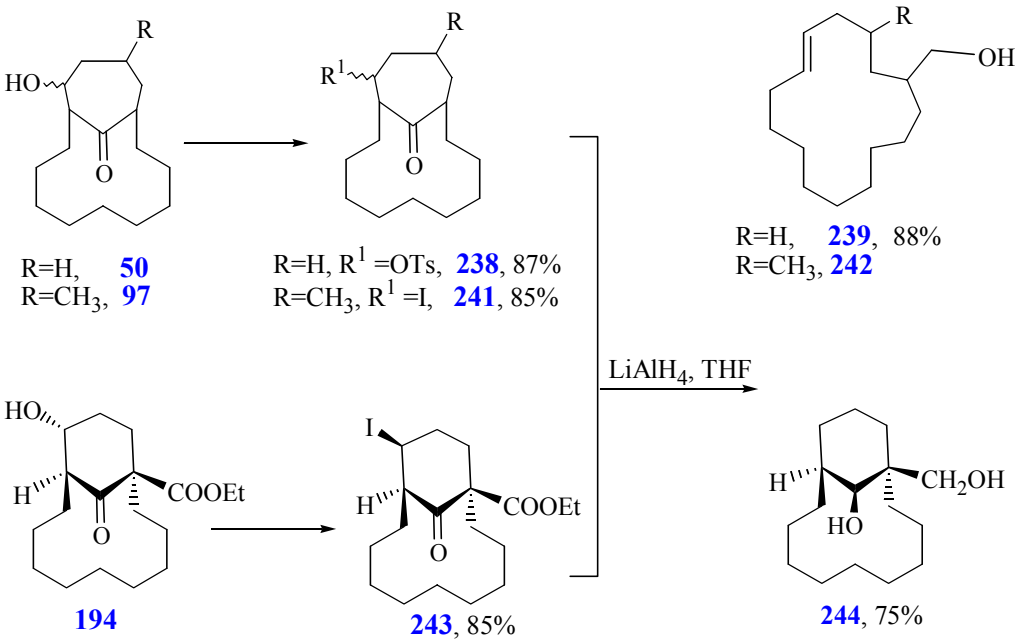
A preliminary investigation towards the preparation of tricyclic system (Scheme 118) was attempted via sequential hydroformylation / aldol addition starting from compounds compound **197**. Using this method, the cyclized product **201** is obtained in 43% yield.



197 **201**

Scheme 118: Preparation of methyl 18-hxdroxy-19-oxo-tricyclo[9.7.10.1.14]nonadecan-11-carboxylate (**201**).

In completion of this work, the synthesis of macrocycles involved in the preparation of musk compounds was attempted. While the bridged system **238** and **241** could smoothly undergo Grob fragmentation furnishing the fifteen-membered rings **239** and **242** in excellent yield (Scheme 119), a failure of the method is observed if the reaction is carried out with compound **174**. Instead, only the compound **244** resulting from a reduction is isolated in 75 % yield (Scheme 119).



Scheme 119: Bridged system involved in fragmentation reaction.

At present, until further optimizations are successful, the fragmentation procedure is a fast and high-yielding approach for the preparation of fifteen-membered rings, as potential intermediates of odour musk or its derivatives.

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[198], 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 $CHCl_3$ (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, respectively **Elemental analysis** were recorded with a Leco CHNS-932. **Melting points** (mp) were determined using Büchi melting point apparatus B-540 and are not corrected.

Chromatoghraphic / 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 aluminium-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 hydroformylation / aldol addition of 2-alkenyl cyclododecanones and unsaturated β-ketoesters

4.2.1. Preparation of starting materials

Preparation of 2-allyl-cyclododecanone (48).

R 1: To 50.0 ml of abs. methanol containing 5.0 g (27.0 mmol) of cyclododecanone (**11**) and 6.9 ml (5.0 g, 44.0 mmol) of allytrimethylsilane (**62**), 4.5 g (82.0 mmol) of CAN are added. The orange mixture is stirred at room temperature until the color disappeared. After 16h, the solvent is removed under reduced pressure. The residue is dissolved in 30 ml of diethylether and washed with water (3 x 30 ml). The combined organic layers are dried over anhydrous $MgSO_4$ and the solvent is removed in vacuum. The residue is purified by column chromatography on silica gel using a mixture of cyclohexane-MTBE (20:1) as eluent to give 3.5 g (15.6 mmol, 58 % yield) of 2-allyl-cyclododecanone (**48**) ($C_{15}H_{26}O$, 222.37 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in ref. 71.

R 2: A solution of 22.0 ml (3.54 g, 55.0 mmol) of a solution of *n*-butyllithium (2.5 M in *n*-hexane) is added dropwise over a period of 30 min. to a cold (0°C) solution of 7.6 ml (5.54 g, 55 mmol) of freshly distilled of diisopropylamine in THF. After 20 min 10.0 g (55.0 mmol) of cyclododecanone (**11**) is added and the mixture is stirred for 30 min. 5.9 ml (7.9 g, 66.0 mmol) of 3-bromo-1-propene (**63**) in THF is added dropwise. The reaction mixture is maintained at 0°C for 45 min. and gradually warmed to room temperature and is maintained at room temperature for 16 hours. Then, 30 ml of a solution of HCl (5 %) is added, and the aqueous layer is extracted three times with diethylether (3 x 40 ml). The organic layer is washed once with 30 ml of a solution of HCl (5 %) and once with brine and dried over anhydrous $MgSO_4$. The solvent is removed in vacuum giving a crude product. Distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 90°C gives 5.2 g of 2-allyl-cyclododecanone (**48**) (23.5 mmol, 87 % yield) ($C_{15}H_{26}O$, 222.37 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in ref. 71.

R 3: To a solution containing 2.0 g (10.9 mmol) of cyclododecanone (**11**) in 45 ml of THF, under argon, is added at 0°C a solution of 4.5 ml (0.6 g, 10.9 mmol) of *n*-butyllithium (solution in *n*-hexane 2.5 M). The mixture is stirred for 1h, then, 1.1 ml (1.56 g, 13.0 mmol) of 3-bromo-1-propene (**63**) is added at 0°C. The temperature is increased to 20°C and the solution is stirred for 16h. Then, 30 ml of water is added and the aqueous layer is extracted with diethylether (3 x 30 ml). The combined organic layers are dried with $MgSO_4$ and the solvent is removed in vacuum. Distillation under reduced pressure (2 x 10^{-2} mbar) at 90°C gives 1.5 g (6.8 mmol, 63 % yield) of 2-allyl-cyclododecanone (**48**) ($C_{15}H_{26}O$, 222.37 g / mol). Its spectroscopic data are consistent with those reported in ref. 71.

R 4: A mixture of 50.0 ml of abs. methanol containing 2.0 g (10.9 mmol) of cyclododecanone (**11**) and 1.52 g (10.9 mmol) of K_2CO_3 is stirred for 1h, then, 1.6 ml (1.56 g, 13.0 mmol) of 3-bromo-1-propene (**63**) is added and the solution is stirred at 80°C for 16h. After cooling, the solvent is removed under reduced pressure. The residue is dissolved in 40 ml of diethylether and washed with water (3 x 30 ml). The combined organic layers are dried over anhydrous $MgSO_4$ and the solvent is removed in vacuum. Starting material is recovered.

R 5: A mixture of 10.0 g (55.0 mmol) of cyclododecanone (**11**), 6.5 ml (7.9 g, 66 mmol) of 3-bromo-1-propene (**63**) in 80 ml of abs. toluene is heated with 6.0 g (105 mmol) of finely ground potassium hydroxide in the presence of 40.0 mg (1 mol %) of the catalyst phase transfer dibenzo-[18]-crown-6 for 4 hours. The reaction mixture is poured into 50 ml of water, and the organic layer is separated, washed with water (3 x 20 ml), and dried over anhydrous $MgSO_4$. After removing of solvent the crude product is distilled under vacuum 90°C (4.5 x 10^{-2} mbar) to give 9.6 g (43.4 mmol, 79 % yield) of 2-allyl-cyclododecanone (**48**) ($C_{15}H_{26}O$, 222.37 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in ref. 71.

Preparation of 2-(2-methylprop-2-enyl)-cyclododecanone (66)

R 6: A solution of 30.0 g (164.0 mmol) of cyclododecanone (**11**) in 80 ml of abs. THF is added dropwise over 30 min. to a suspension of 8.8 g of NaH (382 mmol, 60 % suspension in mineral oil) in 120 ml of abs. THF containing 66.3 ml (16.6 g, 382 mmol) of HMPA at RT under Argon. The reaction mixture is heated to reflux for 30 min, then, 16.6 ml (14.8 g, 164 mmol) of 3-chloro-2-methylprop-1-ene (**64**) in abs. THF is added dropwise. The reaction mixture is heated to reflux for 16 hours and poured into 150 ml of diethylether. The organic layer is washed with a solution of sodium thiosulfate solution (5 %, 200 ml) and once with water (100 ml). The aqueous layer is extracted three times with diethylether, dried over $MgSO_4$ and filtrated. After removing of solvent the crude product is distilled under vacuum 90°C (4.5 x 10^{-2} mbar) to give 38.0 g (161 mmol, 98 % yield) of 2-(2-methylprop-2-enyl)-cyclododecanone (**66**) ($C_{16}H_{28}O$, 236.40 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in ref. 78.

R 7 Amounts:

30.0 g	(164 mmol)	cyclododecanone (**11**)
14.8 g	(164 mmol)	3-chloro-2-methylprop-1-ene (**64**)
11.5 g	(180 mmol)	*n*-BuLi
18.8 g	(180 mmol)	diisopropylamine
150 ml		abs. THF

Procedure: Analogously to R 2

Starting material is recovered as a crude product.

R 8 Amounts:

30.0 g	(164.0 mol)	cyclododecanone (**11**)
22.14 g	(164.0 mol.)	3-bromo-2-methylprop-1-ene (**65**)
11.52 g	(180.0 mmol)	*n*-BuLi
18.8 g	(180.0 mmol)	diisopropylamine
150 ml		abs. THF

Procedure: Analogously to R 2, 18h, 20°C.

After removing of solvent the crude product is distilled under vacuum 90°C (4.5×10^{-2} mbar) to give 33.0 g (139 mmol, 85 % yield) of 2-(2-methylprop-2-enyl)-cyclododecanone (**66**) ($C_{16}H_{28}O$, 236.40 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in lit. 78.

R 9 Amounts:

10.0 g	(55.0 mmol)	cyclododecanone (**11**)
6.0 g	(66.0 mmol)	3-chloro-2-methylprop-1-ene (**64**)
14.7 g	(105 mmol)	potassium hydroxide
36.0 mg	(1 mol %)	dibenzo-[18]-crown-6
150 ml		abs. toluene

Procedure: Analogously to R 5, 64 h, refluxing toluene.

After removing of solvent the crude product is distilled under vacuum 80-90°C (4.5×10^{-2} mbar) to give 9.3 g (39 mmol, 71 % yield) of 2-(2-methylprop-2-enyl)-cyclododecanone (**66**) ($C_{16}H_{28}O$, 236.40 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in lit 78**.**

Preparation of 2-(but-3-enyl)-cyclododecanone (68)

R 10: A solution of 2.0 ml (4.0 g, 30 mmol) of 4-bromobut-1-ene (**67**) in 15 ml of *t*-butanol is added dropwise to a stirred solution of 5.0 g (55 mmol) of cyclododecanone (**11**), 3.4 g (30.1 mmol) of potassium *t*-butoxide in 50 ml of *t*-butanol. 262.0 mg of KI are added under stirring at room temperature. The mixture is stirred at room temperature for 2h. Then, the reaction mixture is stirred at 80°C on oil bath for 22 hours. The cooled reaction mixture is diluted with 40 ml of water, extracted with diethylether (3 x 40 ml), and after removing of solvent under reduced pressure starting material is recovered.

R 11 Amounts:

10.0 g	(55.0 mmol)	cyclododecanone (**11**)
8.9 g	(66.0 mmol)	4-bromobut-1-ene (**67**)
14.7 g	(105.0 mmol)	potassiumhydroxide
36.0 mg	(1 mol %)	dibenzo-[18]-crown-6
150 ml		abs. toluene

Procedure: Analogously to R 5.

Starting material is recovered.

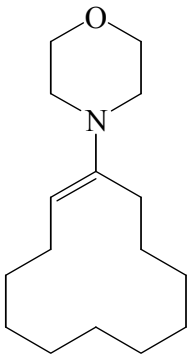
R 12 Amounts:

5.0 g (27.0 mmol)	cyclododecanone (**11**)
3.7 g (27.0 mmol)	4-bromobut-1-ene (**67**)
1.9 g (29.7 mmol)	*n*-BuLi
2.9 g (29.7 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2, 18h, 20°C.

After removing of solvent the crude product is distilled under vacuum 95°C (5.2 x 10^{-2} mbar) to give 0.9 g (4.0 mmol, 15 % yield) of 2-but-3-enylcyclododecanone (**68**) ($C_{16}H_{28}O$, 236.40 g / mol) as a colorless oil.

R 13: To a solution of 10.0 g (109.0 mmol) of cyclododecanone (**11**) in 60 ml of toluene are added 22.0 ml (21.0 g, 250 mmol) of morpholine (**69**) and 1.5 g (7.45 mmol) of *p*-TsOH (5 mol %). The mixture is stirred at reflux temperature for 48 hours. Then, the solution is allowed to cool at room temperature and the solvent removed under reduced pressure. The crude product is purified by bulb to bulb distillation at 85°C (4 x 10^{-2} mbar) giving 23.2 g (92.6 mmol, 85 % yield) of 4-cyclododec-1-en-1-yl-morpholine (**70**) ($C_{16}H_{29}NO$, 251.41 g / mol) as a colorless liquid. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.32 (t, 1H, ^3J = 7.7 Hz, CH), 3.67 (m, 4H, CH_2), 2.71 (m, 4H, CH_2),



70

2.17 (t, 2H, ^{3}J = 7.0 Hz, CH_2), 2.06 (m, 2H, CH_2), 1.47-1.24 (m, 16H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 148.23 (CH=*C*), 106.17 (*C*H=C), 67.17 (2 x CH_2), 49.28 (2 x CH_2), 28.60 (CH_2), 25.22 (CH_2), 25.14 (CH_2), 24.74 (CH_2), 24.54 (CH_2), 23.64 (CH_2), 23.07 (CH_2), 22.67 (CH_2), 22.48 (CH_2), 22.17 (CH_2).

R 14: A solution of 5.0 g (2.0 mmol) of 4-cyclododec-1-en-1-yl-morpholine (**70**) in 50 ml of abs. THF is added to 2.4 ml (2.3 g, 20 mmol) of butylmagnesiumchloride in abs. THF and the mixture is heated to reflux for 2 hours and cooled. 2.0 ml (2.7 g, 20 mmol) of 4-bromobut-1-ene (**67**) in 15 ml of abs. THF is added slowly and the resulting mixture is heated at reflux for 15 hours and cooled. After hydrolysis with 30 ml of a solution of HCl (10 %) at reflux for 20 h, the mixture is extracted with diethylether (3 x 40 ml). The organic layer is washed with 30 ml of a solution of $NaHCO_3$, dried and the solvent removed. Starting material is recovered.

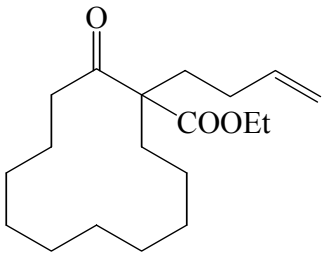
R 15: In a three-necked flask, equipped with a reflux condenser and dropping funnel, are placed 24.0 g (0.5 mmol, 60 % suspension in mineral oil) of NaH in 80.0 ml of abs. THF. 35.7 ml (47.5 g, 0.4 mmol) of diethylcarbonate (**71**) in 80 ml of abs. THF are added dropwise with stirring. A solution 38.5 g (0.2 mmol) of cyclododecanone (**11**) in 120.0 ml of THF is added dropwise over a period of one hour. After the addition is completed, the reaction is stirred at 120°C for 24 hours. Then the mixture is cooled to 0°C and a solution of acetic acid and water (3:1) is added carefully. The organic phase is separated, and the aqueous layer is extracted with Et_2O (3 x 30 ml). The combined organic layers are washed with 30 ml of a solution of $NaHCO_3$; the organic layer is separated and dried over $MgSO_4$. After removing of the solvent, distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 90°C gives 39.6 g (156 mmol, 78 % yield) of ethyl 2-oxo-cyclododecane carboxylate (**72**) ($C_{15}H_{26}O_3$, 254.37 g / mol) as a colorless oil. Its spectroscopic data are consistent with those in ref.82

R 16 Amounts:

10.0 g	(38.7 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
5.8 g	(60.4 mmol)	4-bromobut-1-ene (**67**)
4.8 g	(38.7 mmol)	*t*-BuOK
0.3 g	(3 mol %)	KI
150.0 ml		*t*-BuOH

Procedure: Analogously to R 10

After removing of solvent the crude product is distilled under vacuum 90°C (4.5×10^{-2} mbar) to furnish 9.0 g (29.4 mmol, 76 % yield) of ethyl 1-but-3-enyl-2-oxo-cyclododecane carboxylate (**73**) ($C_{19}H_{32}O_3$, 308.46 g / mol) as a colorless oil.



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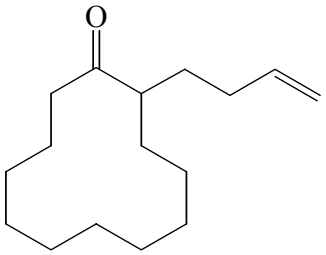
Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.74 (tdd, 1H, ^{3}J = 16.9 Hz, ^{3}J = 10.2 Hz, ^{3}J = 6.23 Hz, C*H*=CH_2), 4.99 (dd, 1H, ^{3}J = 16.9 Hz, J_{gem} = 1.7 Hz, CH=CH*H*), 4.90 (dd, 1H, ^{3}J = 10.2 Hz, J_{gem} = 1.7 Hz, CH=C*H*H), 4.14 (q, 2H, ^{3}J = 7.2 Hz, *C*H_2CH_3), 2.90-2.87 (dd, 0.5H, ^{3}J = 17.9 Hz, ^{3}J = 2.4 Hz, CH_2), 2.86-2.80 (dd, 0.5H, ^{3}J = 17.9 Hz, ^{3}J = 2.2 Hz, CH_2), 2.17–1.95 (m, 8H, CH_2), 1.90–1.70 (m, 4H, CH_2), 1.23 (t, 3H, ^{3}J = 7.2 Hz, CH_2*C*H_3), 1.31-1.17 (m, 8H, CH_2), 0.83 (m, 2H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]**= 206.95 (CO), 172.78 (CO), 137.79 (CH=CH_2), 114.70 (CH=CH_2), 63.10 (C_q), 61.02 (CH_2CH_3), 33.93 (CH_2), 29.33 (CH_2), 28.49 (CH_2), 28.16 (CH_2), 26.49 (CH_2), 26.31 (CH_2), 23.44 (CH_2), 22.62 (CH_2), 21.92 (CH_2), 21.79 (CH_2), 21.46 (CH_2), 18.86 (CH_2), 13.99 (CH_2CH_3). **IR (KBr/film), ṽ [cm^{-1}]** = 3076 (w), 2923 (s), 2864 (s), 2852 (s), 1746 (s), 1712 (s), 1635 (m), 1464 (m), 1376 (m). **LR-MS (EI, 70 eV): m/z (%)** 308 (M^+, 19.89), 267 (46.76), 254 (26.04), 109 (39.67), 95 (66.19), 81 (69.20), 67 (50.64), 55 (100), 41 (76.77). **HR-MS (EI, 70 eV)**: Calcd 308.2352, Found 308.2377.

R 17: A solution of 3.0 g (9.7 mmol) of ethyl 1-but-3-enyl-2-oxo-cyclododecane carboxylate (**73**) is decarboxylated by refluxing under argon for 12 hours in 80 ml of an aqueous ethanolic solution (2:1) and 1.6 g (29 mmol) of KOH. After cooling, the solvent is removed under reduced pressure. The aqueous layers is extracted with

diethylether (3 x 30 ml), the solution is dried over $MgSO_4$ and evaporated. 1.9 g (8.2 mmol, 85 % yield) of 2-but-3-enylcyclododecanone (**68**) is isolated by distillation (4 x 10^{-2} mbar, 110°C), ($C_{16}H_{28}O$, 236.40 g / mol) as colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 5.73 (ddd, 1H, ^3J = 16.7 Hz, ^3J = 10.2 Hz, ^3J = 6.4 Hz, CH=C*H*H), 4.99 (dd, 1H, ^3J = 16.7 Hz, J_{gem} = 1.50 Hz, CH=CH*H*), 4.90 (dd, 1H, ^3J = 10.2 Hz, J_{gem} = 1.5 Hz, CH=CH_2), 2.60–2.53 (m, 2H, CH_2), 2.45–2.35 (m, 1H, CH_2), 2.04-1.94 (m, 2H, CH_2), 1.76–1.61 (m, 5H, CH_2), 1.59–1.52 (m, 1H, CH_2), 1.43–1.36 (m, 1H, CH_2), 1.26–1.15 (m, 7H, CH_2), 0.84 (m, 6H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 214.55 (CO), 138.04 (CH=CH_2), 114.93 (CH=CH_2), 51.19 (CH), 37.21 (CH_2), 31.65 (CH_2), 30.19 (CH_2), 29.46 (CH_2), 26.07 (CH_2), 25.70 (CH_2), 24.02 (CH_2), 23.70 (CH_2), 23.41 (CH_2), 22.51 (CH_2), 22.17 (CH_2), 21.85 (CH_2). **IR (KBr/Film): ṽ [cm^{-1}]** = 3075 (m), 2928 (s), 2864 (m), 2852 (s), 2721 (w), 1709 (s), 1641 (m), 1468 (m), 1414 (w), 1241 (w), 910 (w). **LR-MS (EI, 70 eV): m/z (%)** = 236 (M^+, 18.55), 221 (7.39), 182 (61.69), 125 (16.63), 109 (30.90), 98 (33.38), 81 (63.29), 67 (51.17), 55 (100), 41 (72.96), 29 (23.10). **HR-MS (EI, 70 eV)**: Calcd: 236.2140, Found: 237.5127.



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Preparation of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)

R 18: A solution of 37.0 ml (5.16 g, 43.0 mmol) of 3-bromo-1-propene (**63**) in 20 ml of abs. THF is added dropwise to a stirred solution of 10.0 g (39.0 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) in 45 ml of abs. THF and 1.8 g (78.0 mmol, 60 % suspension in mineral oil) of NaH in 15 ml of abs. THF at reflux temperature over a period of 30 min. Then, the mixture is stirred at 80°C on oil bath for 22 h. Then, the mixture is cooled to 0°C and a solution of acetic acid and water (3:1) is added carefully. The organic phase is separated, and the aqueous layer is extracted with Et_2O (3 x 30 ml). The combined organic layers are washed with a solution of $NaHCO_3$; the organic layer is separated and dried with magnesium sulfate. After removing the solvent, distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 125 °C gives 8.5 g (29 mmol, 78 % yield) of ethyl 1-allyl-2-oxo-cyclododecane carboxylate

(**74**) ($C_{18}H_{30}O_3$, 294.43 g / mol) as colorless crystals. **Melting point**: 56-58°C. Its spectroscopic data are consistent with those reported in ref 87.

R 19 Amounts:

10.0 g	(67 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
5.3 g	(44.0 mmol)	3-bromo-1-butene (**63**)
5.0 g	(44.0 mmol)	*t*-BuOK
150 ml		*t*-BuOH

Procedure: Analogously to R 10, 90°C.

After removing the solvent, distillation of the resulting crude mixture under reduced pressure (3 x 10^{-2} mbar) at 125 °C gives 17.5 g (59 mmol, 89 % yield) of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**) ($C_{18}H_{30}O_3$, 294.43 g / mol) as white crystals. **Melting point**: 56-58°C. Its spectroscopic data are consistent with those reported in ref 87.

Preparation of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (75)

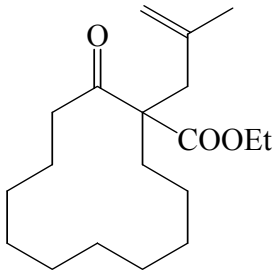
R 20 Amounts:

10.0 g	(67 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
6.9 g	(77.4 mmol)	3-chloro-2-methylprop-1-ene (**64**)
1.0 g	(38.7 mmol)	NaH
6.9 g	(38.7 mmol)	HMPA
150 ml		abs. THF

Procedure: Analogously to R 6

After removing the solvent, the crude product is distilled under vacuum 85°C (4 x 10^{-2} mbar) to afford 15.7 g (51 mmol, 76 % yield) of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**) ($C_{19}H_{32}O_3$, 308.46 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 4.78 (d, 1H, J_{gem} = 1.0 Hz, C*H*H=C), 4.67 (s, 1H, CH*H*=C), 4.14 (q, 2H, ^{3}J = 6.9 Hz, *C*H_2CH$_3$), 2.92-2.86 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.16-2.02 (m, 6H), 1.84-1.78 (m, 2H, CH_2), 1.23 (t, 3H, ^{3}J

= 6.9 Hz, CH_2CH_3), 1.51-1.10 (m, 9H, CH_2), 0.84-0.81 (m, 3H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 206.42 (CO), 173.14 (CO), 141.47 ($CH=CH_2$), 114.51 ($CH=CH_2$), 62.97 (C_q), 61.10 (CH_2CH_3), 38.06 (CH_2), 33.79 (CH_2), 32.09 (CH_2), 29.18 (CH_2), 26.63 (CH_2), 26.34 (CH_2), 23.44 (CH_2), 23.21 (CH_3), 22.63 (CH_2), 22.14 (CH_2), 21.98 (CH_2), 21.46 (CH_2), 13.87 (CH_2CH_3). **IR (KBr/film), $\tilde{\nu}$ [cm^{-1}]** = 3436 (w), 2977 (s), 2930 (s), 2861 (s), 1741 (s), 1711 (vs), 1643 (w), 1469 (m), 1445 (m), 1366 (m), 1241 (m), 1182 (m), 1128 (m), 1030 (m), 724 (m), 917 (m). **LR-MS (EI, 70 eV): m/z (%)** = 308 (M^+, 32.72), 262 (28.10), 221 (66.47), 142 (56.61), 101 (100), 77 (59.33), 55 (15.14), 41 (19.48), 29 (12.70). **HR-MS (EI, 70 eV)**: Calcd: 308.2351, Found: 308.2328.



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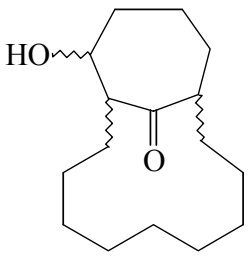
4.2.2. One-pot tandem hydroformylation / aldol addition

Preparation of 12-hydroxy-bicyclo[9.4.1]hexadecane-16-one (50)

R 21: A solution of 3.0 g (13.5 mmol) of 2-allyl-cyclododecanone (**48**), 35 mg (1 mol %) of $Rh(CO)_2(acac)$, 0.5 g (4 mol %) of BIPHEPHOS (**16**) and 129.0 mg (5 mol %) *p*-TsOH in 100 ml anhydrous CH_2Cl_2 is placed in an autoclave. After flushing with argon, the reactor is pressurized with 20 bar CO/H_2 (1:1) magnetically stirred and heated to 60 °C for 24 hours. Then the autoclave is allowed to cool to room temperature. After removing the syn gas, 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. The crude mixture is filtered through a pad of alumina N (III), using cyclohexane / Et_2O (3:1). 12-hydroxybicyclo[9.4.1]hexadecane-16-one (**50**) (2.4 g, 9.7 mmol, 71 % yield) ($C_{16}H_{28}O_2$, 252.39 g / mol) is isolated as a mixture of two diastereoisomers in a ratio of 11:1 (calculated by NMR analysis from OH) as a white solid. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.75, 3.73 (s, 1H, OH), 3.68 (m, 1H, CH), 3.31-3.24 (m, 2H, CH), 2.79 (td, 1H, ^3J = 11.2 Hz, ^3J =



50

2.49 Hz, CH), 2.37-2.31 (m, 2H, CH_2), 2.24-2.19 (m, 1H, CH_2), 2.13-2.07 (m, 3H, CH_2), 2.02-1.91 (m, 5H, CH_2), 1.84-1.01 (m, approx. 12H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = Mixture of diastereoisomers: 218.51, 218.46, 218.29 (CO), 74.95, 74.45, 72.15, 71.55 (CH), 55.68, 64.68, 58.93, 55.92 (CH), 52.81, 51.75, 48.79, 45.89 (CH), 37.13, 37.38, 38.57, 40.03 (CH_2), 31.50, 31.70, 31.73, 31.79 (CH_2), 29.55 (CH_2), 27.27, 27.30, 27.41, 27.53 (2 x CH_2), 26.78, 26.75, 26.81, 26.86 (CH_2), 23.75, 23.84, 24.04, 23.99 (CH_2), 23.12, 23.55, 23.58, 23.33, (CH_2), 22.88 (CH_2), 21.72, 21.75 (CH_2), 21.47, 21.53, 21.56, 21.61 (CH_2), 19.66 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3466 (bs), 3413 (bs), 2928 (s), 2862 (s), 2849 (s), 1692 (s), 1471 (m), 1461 (m), 1448 (m), 1236 (m), 1136 (m), 1088 (m), 914 (m). Spectroscopic characteristics are consistent with those previously reported by C. Hollmann.

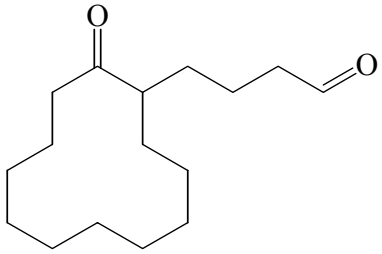
Hydroformylation of 2-allyl-cyclododecanone (48)

R 22 Amounts:

3.0 g	(13.5 mmol)	2-allyl-cyclododecanone (**48**)
35.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
400 mg	(4 mol %)	BIPHEPHOS (**16**)
29.0 mg	(5 mol %)	DBU
100 ml		abs. EtOH / dioxane (9:1)

Procedure: Analogously to R 21.

The products are then separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) furnishing 2.1 g (8.2 mmol, 61 %) of 4-(2-oxo-cyclododecyl)butanal (**76**) ($C_{16}H_{28}O_2$, 252.39 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 9.71 (t, 1H, ^{3}J = 1.2 Hz, C*H*O), 2.61-2.49 (ddd, 2H, ^{3}J = 17.0 Hz, ^{3}J = 8.7 Hz, ^{3}J = 3.5 Hz, CH_2), 2.40 (td, 2H, ^{3}J = 1.2 Hz, ^{3}J = 7.0 Hz, CH_2), 1.73-1.46 (m, approx. 12H, CH_2), 1.39-1.04 (m, approx. 11H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 214.28 (CO), 202.11 (CHO), 51.93 (CH), 43.74 (CH_2), 36.93 (CH_2), 30.22 (CH_2), 29.41 (CH_2), 26.05 (CH_2), 25.73 (CH_2), 23.91 (CH_2), 23.47 (CH_2), 23.11 (CH_2), 22.22 (CH_2), 22.07 (CH_2), 21.73



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(CH_2), 20.04 (CH_2). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 2932 (s), 2864 (s), 2849 (s), 2712 (m), 1705 (s), 1704 (s), 1469 (m), 1119 (m). **LR-MS (EI, 70 eV): m/z (%)** = 251 (M-H, 2.89), 222 (8.54), 182 (40.48), 98 (44.46), 81 (100), 67 (25.71), 55 (66.60), 41 (67.61), 29 (55.39).

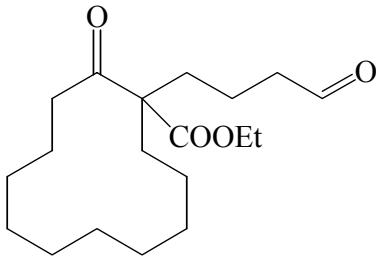
Tandem hydroformylation / aldol addition of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)

R 23 Amounts:

1.0 g	(3.4 mmol)	ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)
12 mg	(1 mol %)	$Rh(CO)_2(acac)$
70 mg	(4 mol %)	BIPHEPHOS (**16**)
45.0 mg	(5 mol %)	*p*-TsOH
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

The products are separated by column chromatography on alumina N (III) with cyclohexane / Et_2O (2:1) to give 110 mg (0.34 mmol, 10 % yield) of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.45 g / mol) as a colorless solid and 990 mg (3.0 mmol, 90 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as a colorless oil. The compound **81** is obtained as a mixture of diastereoisomers in a ratio of 1.4: 3.2 (detected by NMR analysis from CH_2CH_3). **Spectroscopic data** of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**): **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 9.71 (t, 1H, ^3J = 1.2 Hz, C*H*O), 4.10 (q, 2H, ^3J = 6.9 Hz, CH_2CH$_3$), 2.82 (ddd, 2H, ^3J = 9.9 Hz, ^3J = 3.4 Hz, J_{gem} = 1.99 Hz, CH_2), 2.32 (t, 2H, ^3J = 7.2 Hz, CH_2), 1.90 (m, 4H, CH_2), 1.70 (m, 3H, CH_2), 1.40 (m, 1H, CH_2), 1.23 (t, 3H, ^3J = 6.9 Hz, CH$_2$CH_3), 1.31-1.29 (m, 14H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 206.95 (CO), 203.03 (CHO), 169.53 (CO), 64.75 (C_q), 62.63 (*C*H$_2$CH$_3$), 45.29 (CH_2), 35.38 (CH_2), 31.09 (CH_2), 29.96 (CH_2), 27.92 (CH_2), 27.75 (CH_2), 24.88 (CH_2), 24.04 (CH_2), 23.37 (CH_2), 23.22 (CH_2), 22.90 (CH_2), 20.29 (CH_2), 18.03 (CH_2), 15.43 (CH_2CH_3). **IR (KBr/film):**



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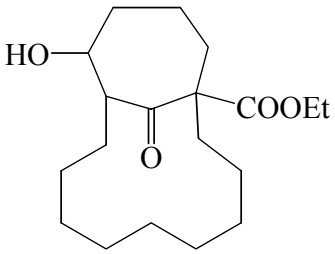
$\tilde{\nu}$ [cm^{-1}] = 3431 (w), 2930 (s), 2865 (s), 2720 (w), 1739 (s), 1724 (s), 1708 (s), 1468 (m), 1445 (m), 1365 (w), 1258 (m), 1236 (m), 1127 (m), 1080 (w), 1055 (w), 1031 (w), 801 (m). **GC-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 3), 321 (48), 293 (3), 229 (5), 254 (16), 236 (4), 109 (14), 96 (14), 84 (100), 71 (32), 55 (28).

Spectroscopic data of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**): **^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 4.15 (q, 4H, ^{3}J = 7.2 Hz, CH_2CH_3), 3.84 (m, 1H, CH), 3.26 (dd, 1H, ^{3}J = 11.9 Hz, ^{3}J = 3.2 Hz, CH), 3.14 (dd, 2H, ^{3}J = 8.4 Hz, ^{3}J = 3.2 Hz, CH), 2.16–2.10 (m, 3H, CH_2), 2.09–2.01 (m, 5H, CH_2), 2.00–1.93 (m, 5H, CH_2), 1.87-1.34 (m, 8H, CH_2), 1.19 (t, 6H, ^{3}J = 7.2 Hz, CH_2CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 210.86 (CO), 172.23 (CO), 73.83, 72.56 (CH), 65.81, 63.78 (Cq), 60.74, 60.64 (CH_2CH_3), 52.70, 50.84 (CH), 38.19 (CH_2), 37.58 (CH_2), 37.32 (CH_2), 36.58 (CH_2), 35.62 (CH_2), 27.84 (CH_2), 27.10, 27.07 (CH_2), 27.00, 26.97 (CH_2), 23.73, 23.70 (CH_2), 23.64, 23.38 (CH_2), 22.36, 22.25 (CH_2), 21.81 (CH_2), 14.09, 14.05 (CH_2CH_3).



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IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3507 (s), 2928 (s), 2864 (s), 1731 (s), 1712 (s), 1469 (m), 1454 (m), 1445 (s), 1252 (m), 1227 (m), 1189 (w), 1122 (m), 735 (m). **LR-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 21.72), 306 (10), 278 (35.66), 109 (29.01), 95 (53.15), 81 (71.71), 55 (100), 29 (76.09). **HR-MS (EI, 70 eV):** Calcd: 324.2301, Found: 324.2276.

Preparation of 5-(2-oxo-cyclododecyl)-pentanal (83)

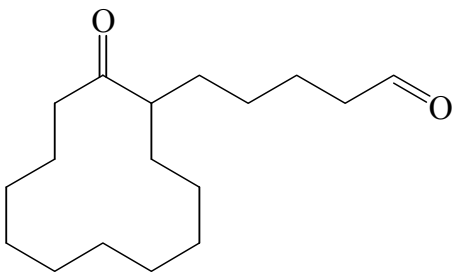
R 24 Amounts:

2.0 g	(8.0 mmol)	2-but-3-enylcyclododecanone (**68**)
20.16 mg	(1 mol %)	$Rh(CO)_2(acac)$
16.3 mg	(4 mol %)	BIPHEPHOS (**16**)
24.7 mg	(5 mol %)	*p*-TsOH
50 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

The crude mixture is filtered on alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.8 g (7 mmol, 87 % yield) are isolated of 5-(2-oxo-cyclododecyl)-pentanal (**83**) ($C_{17}H_{30}O_2$, 266.42 g / mol) as a colorless oil.

Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.69 (t, 1H, ^{3}J = 1.7 Hz, C*H*O), 2.58 (dd, 2H, ^{3}J = 8.5 Hz, ^{3}J = 3.5 Hz, CH_2), 2.40 (td, 2H, ^{3}J = 1.7 Hz, ^{3}J = 7.0 Hz, CH_2), 1.66–1.46 (m, approx. 12H, CH_2), 1.27–1.04 (m, approx. 13H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 215.18 (CO), 202.04 (CHO), 50.38 (CH), 42.35 (CH_2), 35.66 (CH_2), 29.32 (CH_2), 28.11 (CH_2), 27.75 (CH_2), 24.64 (CH_2), 24.03 (CH_2), 22.62 (CH_2), 22.18 (CH_2), 22.01 (CH_2), 21.13 (CH_2), 20.983 (CH_2), 20.63 (CH_2), 18.95 (CH_2). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 3432 (w), 2929 (s), 2862 (s), 2849 (s), 2715 (m), 1707 (s), 1703 (s).



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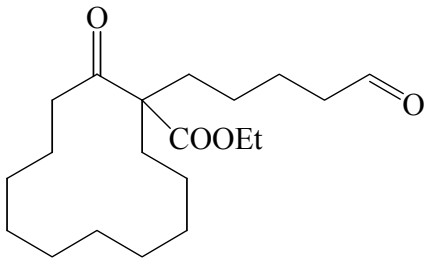
Hydroformylation of ethyl 1-(but-3-enyl)-2-oxo-cyclododecane carboxylate (73)

R 25 Amounts:

2.0 g	(6.5 mmol)	ethyl 1-(but-3-enyl)-2-oxo-cyclododecane carboxylate (**73**)
24.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
70.0 mg	(4 mol %)	BIPHEPHOS (**16**)
90.0 mg	(5 mol %)	*p*-TsOH
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

The crude mixture is filtered by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1). 1.8 g (5.3 mmol, 82 % yield) of ethyl 2-oxo-1-(5-oxo-penthyl)-cyclododecane carboxylate (**87**) ($C_{20}H_{34}O_4$, 338.49 g / mol) are obtained as a colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 9.67 (t, 1H, ^{3}J = 1.7 Hz, C*H*O), 4.10 (q, 2H, ^{3}J = 6.9 Hz, CH_2CH_3), 2.80 (dd, 2H, ^{3}J = 10.2 Hz, ^{3}J = 2.4 Hz, CH_2), 2.36 (t, 2H, ^{3}J = 7.2 Hz, ^{3}J = 1.7 Hz, CH_2), 2.12-1.95 (m, 4H, CH_2), 1.82-1.73 (m, 4H, CH_2), 1.53-1.45 (m, 1H, CH_2), 1.27-1.04 (m, approx. 14H, CH_2), 1.23 (t, 3H, ^{3}J = 6.9 Hz, CH_2CH_3), 0.79 (m, 1H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 206.85



87

(CO), 201.56 (CHO), 172.523 (CO), 63.25 (C_q), 61.13 (CH_2CH_3), 43.79 (CH_2), 33.88 (CH_2), 29.58 (CH_2), 28.46 (CH_2), 26.22 (CH_2), 26.75 (CH_2), 23.37 (CH_2), 22.54 (CH_2), 21.85 (CH_2), 21.70 (CH_2), 21.38 (CH_2), 20.29 (CH_2), 18.79 (CH_2), 16.51 (CH_2), 13.93 (CH_2CH_3). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 3501 (w), 2931 (s), 2864 (s), 2705 (w), 1738 (s), 1708 (s), 1468 (m), 1454 (m), 1366 (w), 1233 (m), 1176 (m), 1129 (m), 1029 (m), 1024 (m), 1031 (w), 916 (m), 713 (s). **LR-MS (EI, 70 eV): m/z (%)** = 339 (M^++1, 12), 292 (58.04), 264 (31.64), 236 (12.74), 208 (17), 98 (100), 84 (82.14), 55 (97.87), 41 (88.29), 29 (60.09).

Isomerization of 2-(2-methylprop-2-enyl)-cyclododecanone (66)

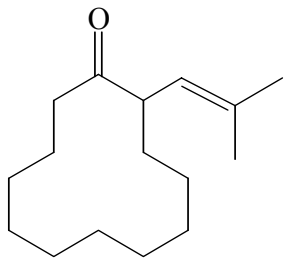
R 26 Amounts:

3.0 g	(12.7 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
32 mg	(1 mol %)	$Rh(CO)_2(acac)$
129 mg	(5 mol %)	*p*-TsOH
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

The crude mixture is filtered on a pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent giving 2.8 g (11.8 mmol, 93% yield) of 2-(2-methyl-propenyl)-cyclododecanone (**88**) ($C_{16}H_{28}O_2$, 236.40 g / mol) as a colorless oil.

Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.04 (dd, 0.5H, ^{3}J = 9.2 Hz, ^{4}J = 1.2 Hz, CH), 5.00 (dd, 0.5H, ^{3}J = 9.2 Hz, ^{4}J = 1.2 Hz, CH), 3.48, (m, 1H), 2.39 (m, 2H, CH_2), 1.68 (d, 3H, ^{4}J = 1.00 Hz, CH_3), 1.65 (d, 3H, ^{4}J = 1.0 Hz, CH_3), 1.96 (m, 3H, CH_2), 1.55-1.13 (m, approx. 14H, CH_2), 0.86 (m, 1H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 212.93 (CO), 134.43 (CH=*C*), 123.18 (*C*H=C), 50.85 (CH), 37.88 (CH_2), 30.88 (CH_2), 26.86 (CH_2), 25.77 (2 x CH_3), 25.47 (CH_2), 24.90 (CH_2), 24.51 (CH_2), 24.30 (CH_2), 24.19 (CH_2), 23.29 (CH_2), 22.21 (CH_2).



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IR (KBr/film): $\tilde{\nu}$ [cm^{-1}] = 3076 (m), 2941 (s), 2869 (m), 2721 (w), 1708 (s), 1640 (m), 1469, 1443 (m), 913 (m). **LR-MS (EI, 70 eV): m/z (%)** = 236 (M^+, 24.85), 95 (31.17), 81 (30.70), 67 (57.13), 55 (57.06), 41 (100), 29 (32.74). **HR-MS (EI, 70 eV)**: Calcd: 236.2140, Found: 236.2105.

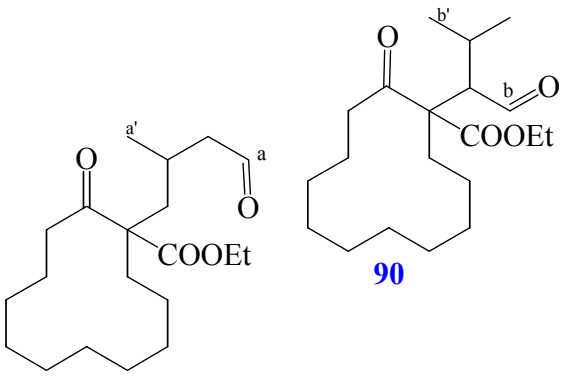
Hydroformylation of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (75)

R 27 Amounts:

1.0 g	(3.2 mmol)	ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**)
10 mg	(1 mol %)	$Rh(CO)_2(acac)$
40 mg	(5 mol %)	*p*-TsOH
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

A mixture of 439 mg (1.3 mmol, 40%) ethyl 1-(1-oxo-isopropyl)-2-oxo-cyclododecane carboxylate (**90**) and ethyl 1-(4-oxo-2-methyl-butyl)-2-oxo-cyclododecane carboxylate (**89**) ($C_{20}H_{34}O_4$, 338.49 g / mol) is obtained in the ratio 1:1.27 from ^{1}H-NMR (from CH_aO). Both aldehydes are present as a mixture of diastereoisomers: the compound **89** is present in a ratio of 1:4 from ^{1}H-NMR (from CH_aO); the compound **90** is present as a mixture of two diastereoisomers in a ratio of 1:1.1 from ^{1}H-NMR (from CH_bO).



Spectroscopic data of mixture of compound 89 and 90: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 9.70 (t, 1H, ^{3}J = 1.7 Hz, CH_aO), 9.68 (t, 1H, ^{3}J = 1.7 Hz, CH_aO), 9.64 (d, 1H, ^{3}J = 1.5 Hz, CH_bO), 9.63 (d, 1H, ^{3}J = 1.2 Hz, CH_bO), 4.10 (m, 6H, CH_2CH_3), 2.87 (dd, 2H, ^{3}J = 18.2 Hz, ^{3}J = 3.49 Hz, CH), 2.84 (dd, 2H, ^{3}J = 18.2 Hz, ^{3}J = 2.74 Hz, CH), 2.38 (dd, 1H, ^{3}J = 1.5 Hz, ^{3}J = 5.7 Hz, CH), 2.35 (dd, 1H, ^{3}J = 1.5 Hz, ^{3}J = 5.9 Hz, CH), 2.31 (m, 2H), 2.16-1.95 (m, 4H, CH_2), 1.91-1.74 (m, 6H, CH_2), 1.23 (m, CH_2CH_3), 1.31-1.29 (m, CH_2), 0.93 (d, 6H, ^{3}J = 6.7 Hz, $CH_{3\ a'/b'}$), 0.79 (d, 6H, ^{3}J = 6.4 Hz, $CH_{3\ b'/a'}$). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 206.69 (CO), 206.26 (CO), 202.19 (CO), 201.89 (CO), 173.66 (CO), 173.26 (CO), 62.74, 62.26 (C_q), 61.29, 61.19 (CH_2CH_3), 61.05, 60.99 (CH_2CH_3), 52.49 (CH_2), 50.69 (CH_2), 45.25, 45.22 (CH), 36.81 (CH_2), 36.38 (CH_2), 33.88 (CH_2), 33.40 (CH_2), 29.87, 29.35 (CH_2), 28.67, 28.65 (CH_2), 26.52 (CH_2), 26.26 (CH_2), 24.42, 24.08 (CH), 23.41, 23.36 (CH_2), 22.60, 22.56 (CH_2), 21.96 (CH_2), 21.91 (CH_3), 21.81, 21.76 (CH_2), 21.47, 21.41 (CH_2),

19.47 (CH_3), 19.14, 19.08 (CH_3), 13.84, 13.79 (CH_2CH_3). **LR-MS (EI, 70 eV): m/z (%)** = 338 (M^+, 0.86), 309 (25.76), 292 (100), 266 (2.92), 18 (0.94).

4.3. Stepwise hydroformylation aldol reactions

4.3.1. Hydroformylation reactions

Preparation of 4-(2-oxo-cyclododecyl)butanal (76)

R 28 Amounts:

3.0 g	(13.5 mmol)	2-allyl-cyclododecanone (**48**)
35.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
0.5 g	(4 mol %)	BIPHEPHOS (**16**)
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, 20 bar CO/H_2 (1:1), 24 hours, 60°C

The crude mixture is filtered on a pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent furnishing 2.3 g (9.0 mmol, 67 % yield) of 4-(2-oxo-cyclododecyl)butanal (**76**) ($C_{16}H_{28}O_2$, 252.40 g / mol) as a colorless oil. Its spectroscopic characteristics are consistent with those reported in R 22.

R 29 Amounts:

3.0 g	13.5 mmol)	2-allyl-cyclododecanone (**48**)
35.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
0.5 g	(4 mol %)	BIPHEPHOS (**16**)
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, 20 bar CO/H_2 (1:1), 48 hours, 60°C

The products are then separated by column chromatography on alumina N (III) using a mixture of cyclohexane / Et_2O (2:1) obtaining 2.7 g (10.7 mmol, 79 % yield) of 4-(2-oxo-cyclododecyl)butanal (**76**) ($C_{16}H_{28}O_2$, 252.40 g / mol). Its spectroscopic characteristics are consistent with those reported in R 22**.**

R 30 Amounts:

3.0 g	(13.5 mmol)	2-allyl-cyclododecanone (**48**)
35.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
0.5 g	(4 mol %)	BIPHEPHOS (**16**)
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, bar CO/H_2 (1:1), 72 hours, 60°C

The products are then separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) giving 3.1 g (12.3 mmol, 91 %) of 4-(2-oxo-cyclododecyl)butanal (**76**) ($C_{16}H_{28}O_2$, 252.40 g / mol). Its spectroscopic characteristics are consistent with those reported in R 22.

Hydroformylation of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)

R 31 Amounts:

2.0 g	(6.8 mmol)	ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)
24.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
140.0 mg	(4 mol %)	BIPHEPHOS (**16**)
40 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21

The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) furnishing 1.9 g (5.9 mmol, 87 % yield) of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**) ($C_{19}H_{32}O_4$, 324.43 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in R 23.

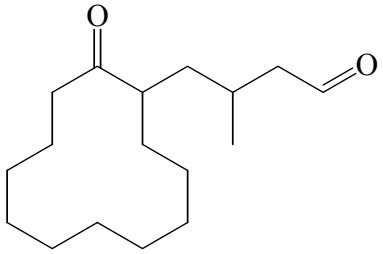
Preparation of 3-methyl-4-(2-oxo-cyclododecyl)-butunal (95)

R 32 Amounts:

3.0 g	(12.7 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
32.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, 20 bar CO/H_2 (1:1), 72 hours, 60°C

The products are separated by column chromatography on alumina N (III), cyclohexane / AcEt (10:1). 1.62 g (6.0 mmol, 48 % yield) of 3-methyl-4-(2oxo-cyclododecyl)-butanal (**95**) ($C_{17}H_{30}O_2$, 266.42 g / mol) are isolated as colorless oil as a mixture of two diastereoisomers in a ratio of 1:1.33 identified by NMR analysis (ratio calculated with respect to the CH_3). **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 9.69 (t, 1H, ^3J = 1.7 Hz, C*H*O), 2.61-2.51 (m, 3H, CH_2), 2.46-2.33 (m, 2H, CH_2), 2.30 (dd, 2H, ^3J = 6.2 Hz, ^3J = 1.7 Hz, CH_2), 2.24-2.20 (m, 3H, CH), 2.04-1.88 (m, 2H, CH), 1.77-1.46 (m, 8H, CH_2), 1.35-1.06 (m, 6H, CH_2), 0.91 (d, 3H, ^3J = 6.5 Hz, CH_3). Diasteroisomers 1 / 2: **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 214.16, 214.12 (CO), 202.27, 202.24 (CHO), 51.25, 50.93 (CH_2), 50.05, 49.37 (CH), 37.95 (CH_2), 37.34 (CH_2), 36.76, 36.66 (CH_2), 36.24 (CH_2), 30.25 (CH_2), 28.98 (CH_2), 26.20 (CH_2), 26.07, 25.85 (CH), 26.03 (CH_2), 25.91, 25.70 (CH_2), 23.85 (CH_2), 23.44 (CH_2), 23.19 (CH_2), 23.05 (CH_2), 22.76 (CH_2), 22.08, 22.02 (CH_2), 22.30 (CH_2), 21.73 (CH_2), 21.6 (CH_2), 19.88, 19.76 (CH_3). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 3432 (w), 2929 (s), 2862 (s), 2849 (s), 2715 (m), 1707 (s), 1703 (s). **LR-MS (EI, 70 eV): m/z (%)** = 266 (M^+, 1.85), 249 (2.14), 222 (1.97), 195 (2.33), 182 (7.35), 135 (2.33), 109 (7.29), 95 (16.30), 81 (33.88), 67 (30.94), 55 (80.61), 41 (100), 29 (31.16). **HR-MS (EI, 70 eV)**: Calcd. 266.2246, Found: 266.2264.



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R 33 Amounts:

3.0 g	(12.7 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
32.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
20 ml		abs.CH_2Cl_2

Procedure: Analogously to R 21, 80 bar CO/H_2 (1:1), 24 hours, 100°C.

The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) furnishing 1.6 g (6.1 mmol, 47 % yield) of 3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**) ($C_{17}H_{30}O_2$, 266.42 g / mol) as a colorless oil as a mixture of two diastereoisomers in ratio of 1:1.33 identified by NMR analysis (ratio calculated

with respect to the CH_3). Its spectroscopic characteristics are consistent with those reported in R 32.

R 34 Amounts:

3.0 g	(12.7 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
32.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, 80 bar CO/H_2 (1:1), 48 hours, 100°C

The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) giving 1.7 g (6.6 mmol, 52 % yield) of 3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**) ($C_{17}H_{30}O_2$, 266.42 g / mol) as a colorless oil as a mixture of two diastereoisomers in a ratio of 1:1.19 as identified by ^{1}H-NMR (ratio calculated with respect to the CH_3). Its spectroscopic characteristics are consistent with those reported in R 32.

R 35 Amounts:

1.5 g	(6.4 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
16.0 mg	(1 mol %)	$Rh(CO)_2(acac)$
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21, 80 bar CO/H_2 (1:1), 72 hours, 100°C.

The products are then separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1). 1.1 g (3.9 mmol, 62 % yield) of 3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**) ($C_{17}H_{30}O_2$, 266.42 g / mol) is obtained as a mixture of two diastereoisomers as a ratio of 1:1.1 identified by ^{1}H-NMR (ratio calculated with respect to the CH_3). Its spectroscopic characteristics are consistent with those reported in R 32.

Hydroformylation of 1-(2-methyl-allyl)-ethyl 2-oxo-cyclododecane carboxylate (75)

R 36 Amounts:

2.0 g (6.5 mmol)	ethyl 1-(2-methyl-allyl)-2-oxocyclododecane carboxylate (**75**)
16 mg (1 mol %)	$Rh(CO)_2(acac)$
40 ml	abs. CH_2Cl_2

Procedure: Analogously to R 21

A mixture of ethyl 1-(1-oxo-isopropyl)-2-oxo-cyclododecane carboxylate (**90**) and ethyl 1-(4-oxo-2-methyl-butyl)-2-oxo-cyclododecane carboxylate (**89**) ($C_{20}H_{34}O_4$, 338.49 g / mol) is obtained in a ratio of 1:2.7 detected by ^{1}H-NMR analysis (from CH_2CH_3). The compound **90** is present as a mixture of two diastereoisomers in a ratio of 1: 0.7 as detected by ^{1}H-NMR (from CH_2CH_3). Spectroscopic data are consistent with those reported in R 27**.**

4.3.2. Intramolecular aldol addition

Preparation of 12-hydroxybicyclo[9.4.1]hexadecane-16-one (50)

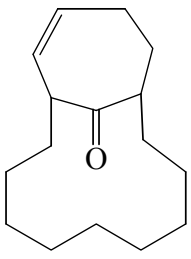
R 37: To a solution of 1.5 g (6.6 mmol) of 4-(2-oxo-cyclododecyl)butanal (**76**) in 10 ml of dioxane is added dropwise 70 ml (7N) HCl and the mixture is stirred for 18 hours at room temperature. Then, the solution is cautiously neutralized with a solution of $NaHCO_3$ (5 %) and the aqueous layer is extracted with diethylether. The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The product is separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1). 330 mg (1.3 mmol, 20 % yield) of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) as a mixture of two diastereoisomers in a ratio of 1: 2.9 as detected by NMR analysis are isolated. Its spectroscopic characteristics are consistent with those previously reported in R 21.

R 38: To a solution of 1.5 g (6.6 mmol) of 4-(2-oxo-cyclododecyl)butanal (**76**) in 10 ml of dioxane are added dropwise 30.0 ml H_2SO_4 (conc.) and the mixture is stirred for

18 hours at room temperature. Then, the solution is cautiously neutralized with a solution of $NaHCO_3$ (5 %) and the aqueous layer is extracted with diehylether. The combined organic phases are dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) to give 66 mg (0.26 mmol, 4 % yield) of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) ($C_{16}H_{30}O_2$, 252.21 g / mol) as a white solid. Its spectroscopic characteristics are consistent with those previously reported in R 21.

Aldol condensation of 4-(2-oxo-cyclododecyl)butanal (76)

R 39: To a solution of 6.0 g (23.8 mmol) of 4-(2-oxo-cyclododecyl)butanal (**76**) in 40 ml of EtOH are added 3.6 ml (23.8 mmol) DBU in 20 ml of EtOH, and the mixture is stirred for 20 at room temperature. 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 (3 x 30 ml). The combined organic phases are filtered, dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gives the crude compound. The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) to give 2.4 g (8.3 mmol, 35 % yield) of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) as mixture of four diastereoisomers in a ratio of 3:1:1:1 (detected by NMR) and 900 mg (4.0 mmol, 17 % yield) of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.38 g / mol) as a white solid compound. **Spectroscopic data** of compound **96**: **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 5.55 (ddd, 1H, ^3J = 11.4 Hz, ^3J = 3.26 Hz, ^3J = 2.76 Hz, CH), 5.14 (m, 1H, CH), 2.30 (m, 4H, CH_2), 2.1-1.96 (m, 5H, CH_2), 1.79-1.55 (m, 6H, CH_2), 1.35-0.98 (m, 9H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 211.23 (CO), 130.42 (CH_2), 129.51 (CH_2), 56.00 (CH), 42.09 (CH), 31.03 (CH_2), 29.84 (CH_2), 28.46 (CH_2), 27.50 (CH_2), 26.87 (CH_2), 26.42 (CH_2), 23.62 (CH_2), 22.85 (2 x CH_2), 22.60 (CH_2), 21.51 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3054 (w), 3022 (w), 2927 (s), 2858 (s), 1708 (s), 1632 (w), 1604 (w), 1467 (m), 1445 (m), 1138 (w), 729 (m). **GC-MS (70 eV): m/z (%)** = 234 (M^+, 78), 207 (38), 191 (17), 149 (25), 121 (44), 107



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(38), 95 (52), 81 (58), 67 (99), 55 (100). **Spectroscopic characteristics** of compound **50** are consistent with those previously reported in R 21.

Aldol addition of ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (80)

R 40 Amounts:

1.3 g (6.6 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**)
70.0 ml	HCl (7N)
80.0 ml	dioxane

Procedure: Analogously to R 37

The products are separated by column chromatography on alumina N(III), cyclohexane / Et_2O (3:1) giving 784 mg (2.3 mmol, 35 % yield) of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.21 g / mol) as a mixture of two diastereoisomers in a ratio of 1:6 detected by NMR analysis as a white solid. Its spectroscopic data are consistent with those reported in R 23.

R 41 Amounts:

1.3 g (6.6 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**)
40 ml	H_2SO_4 (conc.)
80 ml	EtOH

Procedure: Analogously to R 38

Decomposition of starting material is observed.

R 42: A solution of 2.2 ml *n*-butyllithium (2.5 M in *n*-hexane solution, 341.0 mg, 5.32 mmol) is added dropwise over a period of 30 min. to a cold (0°C) solution of 0.8ml of diisopropylamine (freshly distilled, 538.0 mg, 5.32 mmol) in 30 ml of abs. THF. After 20 min. a solution of 0.7 g of ethyl 2-oxo-1-(4-oxo-butyl)cyclododecane carboxylate (**80**) (1.78 mmol) in 25 ml of abs. THF is added and the mixture was stirred for 30' min.

The reaction mixture is maintained at 0°C for 45 min. and gradually warmed to room temperature, 40 ml of a solution of HCl (5 %) is added, and the aqueous layer is extracted (3 x 40 ml) with diethylether. The organic layer is washed once with 20 ml of HCl (5 %) and once with 30 ml of brine, separated and dried over magnesium sulfate. The solvent is removed in vacuum giving a crude mixture. The product is purified by column chromatography on alumina N (III), cyclohexane / EtAc (3:1). 200 mg (0.6 mmol, 34 % yield) is obtained of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.21 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1.8 as a white solid. Its spectroscopic data are consistent with those reported in R 23.

R 43 Amounts:

1.3 g (6.6 mmol)	ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**)
0.6 g (6.6 mmol)	DBU
80 ml	EtOH

Procedure: Analogously to R 39

The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) affording 1.9 g (5.9 mmol, 90 % yield) of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.21 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1:6 detected by NMR analysis. Its spectroscopic data are consistent with those reported in R 23**.**

Aldol addition of ethyl 2-oxo-1-(5-oxo-penthyl)-cyclododecane carboxylate (87)

R 44 Amounts:

1.0 g (6.6 mmol)	ethyl 2-oxo-1-(5-oxo-pentyl)-cyclododecane carboxylate (**87**)
456 mg (6.6 mmol)	DBU
80 ml	EtOH

Procedure: Analogously to R 39

Starting material is recovered.

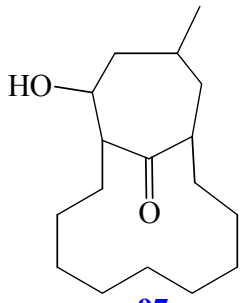
Preparation of 12-hydroxy-14-methylbicyclo[9.4.1]hexadecan-16-one (97)

R 45 Amounts:

1.0 g (3.8 mmol)	3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**)
0.6 g (3.8l mmol)	DBU
80 ml	EtOH

Procedure: Analogously to R 39

The products are purified by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) to give 636 mg (2.4 mmol, 63 % yield) of 12-hydroxy-14-methylbicyclo[9.4.1]hexadecane-16-one (**97**) ($C_{17}H_{30}O_2$, 266.42 g / mol) as a mixture of diastereoisomers in a ratio of 1:2.3:1.5:1.5 detected by ^{1}HNMR analysis (ratio calculated with respect to the CH_3). **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.75 (m, 1H, CH), 3.37-3.05 (m, 3H, CH), 3.02-2.97 (m, 1H, CH), 3.24-3.18 (m, 2H, CH_2), 2.98-2.82 (m, 2H, CH), 2.46-2.20 (m, 3H, CH), 2.03-1.91 (m, 6H, CH_2), 1.44–1.07 (m, 8H, CH_2), 0.89 (d, 3H, ^{3}J = 6.78 Hz, CH_3). Mixture of diastereoisomers **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 218.51 (CO), 75.97, 75.63, 76.03, 773.23 (CH), 56.51, 65.68, 66.47, 62.70 (CH), 50.46, 46.32, 42.32, 35.12 (CH), 37.13, 37.38, 38.57, 40.03 (CH_2), 31.50, 31.70, 31.73, 31.79 (CH_2), 29.63, 28.64,27.63, 26.66 (CH), 27.31, 27.30, 27.43, 27.29 (CH_2), 26.76, 26.71, 26.83, 26.85 (CH_2), 23.77, 23.82, 24.00, 23.89 (CH_2), 23.11, 23.48, 23.56, 23.29 (CH_2), 22.01 (CH_2), 21.69, 21.71 (CH_2), 21.87, 21.85, 21.01, 20.58 (CH_3), 21.44, 21.49, 21.51, 21.55 (CH_2), 19.71 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3466 (bs), 2928 (s), 2862 (s), 2849 (s), 1703 (s), 1650.5 (m), 1469 (m), 1445 (m), 1365 (m), 1253 (m), 1122 (m), 1082 (m), 873 (m). **LR-MS (EI, 70 eV): m/z (%)** = 266 (M^+, 66.0), 248 (52.86), 113 (45.67), 95 (66.16), 81 (73.85), 67 (60.50), 55 (100), 41 (79.78), 29 (29.28), 18 (17.13). **HR-MS (EI, 70 eV)**: Calcd. 266.2246, Found: 266.2234. **Melting point:** 107°C



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R 46 Amounts:

1.5 g	(5.6 mmol)	3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**)
70 ml		HCl (7N)
80 ml		dioxane

Procedure: Analogously to R 37

The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1). 224 mg (0.8 mmol, 15 % yield) of 12-hydroxy-14-methylbicyclo[9.4.1]hexadecan-16-one (**97**) ($C_{17}H_{30}O_2$, 266.42 g / mol) are isolated as a mixture of diastereoisomers in a ratio of 1:2.8 as detected by NMR. Its spectroscopic characteristics are consistent with those reported in R 45**.**

R 47 Amounts:

1.0 g	(3.8 mmol)	3-methyl-4-(2-oxo-cyclododecyl)butanal (**95**)
30 ml		H_2SO_4 (conc.)
80 ml		dioxane

Procedure: Analogously to R 38

After filtration, an intractable mixture of decomposition products is obtained.

4.4. Sequential hydroformyaltion /aldol addition of enol ethers

4.4.1. Preparation of trimethyl silyl enol ethers

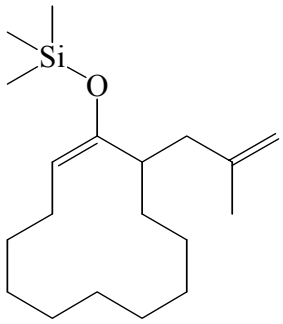
Preparation of trimethyl-[12-(2-methylprop-2-enyl)-cyclododec-1-enyloxyl]-silane (116)

R 48 Amounts:

3.0 g (12.7 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
2.75 g (12.5 mmol)	TMSCl (**103**)
1.6 g (12.5 mmol)	*n*-BuLi
2.55 g (12.15 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2

Distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 120°C gives 3.1 g (10.0 mmol, 79 % yield), of trimethyl-12-(2-methylprop-2-enyl)-cyclododec-1-enyloxyl]-silane (**116**) ($C_{19}H_{36}OSi$, 308.58 g / mol) as a colorless oil.



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Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.78 (s, 1H, CH_2=C), 4.67 (s, 1H, CH_2=C), 4.50 (dd, 2H, ^{3}J = 6.4 Hz, ^{3}J = 1.7 Hz, CH_2), 2.92-2.86 (m, 2H, CH_2), 2.62 (s, 3H), 2.16-2.02 (m, 3H, CH_2), 1.91-1.79 (m, 2H, CH_2), 1.51-1.10 (m, 12H), 0.19 (s, 9H, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 152.00 (C_q), 142.75 (CH=CH_2), 111.25 (CH=CH_2), 108.64 (CH), 43.15 (CH), 41.65 (CH_2), 39.39 (CH_2), 36.72 (CH_2), 29.36 (CH_2), 26.31 (CH_2), 25.50 (CH_2), 24.86 (CH_2), 24.65 (CH_2), 24.46 (CH_2), 24.20 (CH_2), 22.01 (CH_3), 0.78 (3 x CH_3).

Synthesis of ethyl 1-allyl-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (117)

R 49 Amounts:

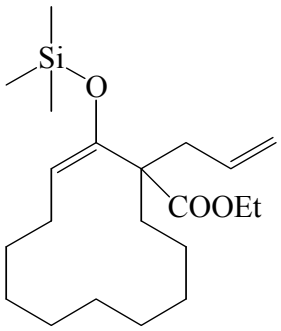
8.0 g (27.2 mmol)	ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)
5.04 g (46.2 mmol)	TMSCl (**103**)
5.04 g (27.2 mmol)	*n*-BuLi

2.75 g (27.2 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2

Distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 120°C gives 7.4 g (21.2 mmol, 78 % yield) ethyl 1-allyl-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**117**) ($C_{21}H_{38}O_3Si$, 366.61 g / mol) as a colorless oil

Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.60 (ddd, 1H, ^{3}J = 17.2 Hz, ^{3}J = 9.97 Hz, ^{3}J = 7.2 Hz, C*H*=CH_2), 5.03 (d, 1H, ^{3}J = 17.2 Hz, CH=C*H*H), 5.00 (d, 1H, ^{3}J = 10.2 Hz, CH=CH*H*), 4.55 (dd, 1H, ^{3}J = 9.47 Hz, ^{3}J = 5.73 Hz, CH), 4.16 (q, 2H, ^{3}J = 7.0 Hz, CH_2CH_3), 2.45 (dd, 1H, ^{3}J = 13.46 Hz, ^{3}J = 6.98 Hz, CH_2), 2.33 (dd, 1H, ^{3}J = 13.46 Hz, ^{3}J = 7.7 Hz, CH_2), 2.00 (m, 2H, CH_2), 1.76 (dd, 1H, ^{3}J = 13.96 Hz, ^{3}J = 6.7 Hz, CH_2), 1.70 (m, 1H, CH_2), 1.51 (m, 1H, CH_2), 1.30 (m, approx. 13H, CH_2), 1.06 (t, 3H, ^{3}J = 7.0 Hz, CH_2CH_3), 0.15 (s, 9H, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 174.84 (CO), 150.59 (*C*=CH), 133.76 (CH=*C*H_2), 117.76 (*C*H=CH_2), 108.26 (C=*C*H), 60.30 (*C*H_2CH_3), 56.26 (C_q), 37.18 (CH_2), 29.93 (CH_2), 26.73 (CH_2), 26.44 (CH_2), 24.94 (CH_2), 24.71 (CH_2), 243.61 (CH_2), 24.45 (CH_2), 24.79 (CH_2), 20.99 (CH_2), 14.14 (CH_2CH_3), 0.80 (3 x CH_3).



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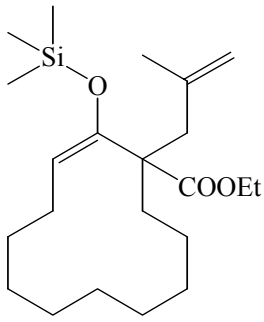
Synthesis of ethyl 1-(2-methylprop-2-enyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (118)

R 50 Amounts:

10 g (32.4 mmol)	ethyl 1-(2-methyl-allyl)-2-oxo-cyclododecane carboxylate (**75**)
6.0 g (55 mmol)	TMSCl (**103**)
2.0 g (32 mmol)	*n*-BuLi
3.3 g (32.4 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2.

Distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 110°C gives 9.2 g of ethyl 1-(2-methylprop-2-enyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**118**) (24.0 mmol, 74 % yield) ($C_{22}H_{40}O_3Si$, 380.63 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 4.8 (s, 1H, C=CH*H*), 4.68 (s, 1H, C=C*H*H), 4.57 (m, 1H, C=C*H*), 4.12 (q, 2H, ^{3}J = 7.2 Hz,, *C*H_2CH$_3$), 2.48 (d, 1H, ^{3}J = 13.4 Hz, CH_2), 2.40 (d, 1H, ^{3}J = 13.4 Hz, CH_2), 2.02 (m, 2H, CH_2), 1.79 (m, 3H, CH_2), 1.66 (s, 3H, CH_3), 1.36 (m, 7H, CH_2), 1.19 (t, 3H, ^{3}J = 7.0 Hz, CH_2CH_3), 0.86 (m, 1H, CH_2), 0.17 (s, 9H, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 175.88 (CO), 151.12 (*C*=CH), 142.42 (CH=*C*H_2), 114.70 (*C*H=CH_2), 108.06 (C=*C*H), 60.42 (*C*H_2CH$_3$), 55.88 (C_q), 40.32 (CH_2), 30.40 (CH_2), 21.59 (CH_2), 26.56 (CH_2), 25.04 (CH_2), 24.82 (CH_2), 24.65 (CH_2), 24.43 (CH_2), 24.19 (CH_2), 23.52 (CH), 21.53 (CH_2), 13.95 (CH_2*C*H$_3$), 0.88 (3 x CH_3)



118

4.4.2. Hydroformylation of trimethyl silyl enol ethers

Hydroformylation of trimethyl-[12-(2-methylprop-2-enyl)-cyclododec-1-enyloxyl]-silane (116)

R 51 Amounts:

1.0 g (3.2 mmol)	trimethyl-[12-(2-methylprop-2-enyl)-cyclododec-1-enyloxyl]-silane (**116**)
8.0 mg (1 mol %)	$[Rh(cod)Cl]_2$
20 ml	abs. CH_2Cl_2

Procedure: Analogously to R 21

The crude mixture is then separated by column chromatography on alumina N (III), cyclohexane / MTBE (2:1). 476 mg (1.8 mmol, 56 % yield) of 3-methyl-(4-oxo-cyclododecyl)butanal (**95**) ($C_{17}H_{30}O_2$, 266.42 g / mol) is isolated as a colorless oil. Its spectroscopic characteristics are consistent with those reported in R 32.

Hydroformylation of ethyl 1-(2-methylprop-2-enyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (118)

R 52 Amounts:

1.5 g (3.65 mmol)	ethyl 1-(2-methyl-2-propen)-2-trimethylsilanoxy-1-cyclododecane carboxylate (**118**)
10 mg (1 mol %)	$[Rh(cod)Cl]_2$
20 ml	abs. CH_2Cl_2

Procedure: Analogously to R 21.

After removing of solvent, distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 125 °C gives 1.0 g (3.4 mmol, 94 % yield) of ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**) ($C_{19}H_{32}O_3$, 308.46 g / mol) as a colorless oil. Its spectroscopic data are consistent with those reported in R 20.

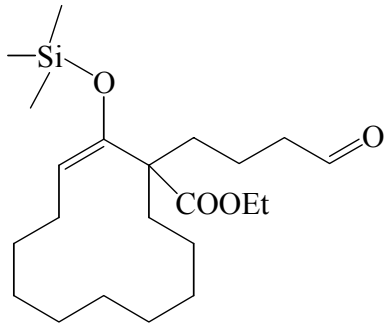
Hydroformylation of ethyl 1-allyl-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (117)

R 53 Amounts:

4.0 g (11.0 mmol)	ethyl 1-allyl-2-trimethylsilanoxy-cyclododec-2-ene carboxylate **(117)**
15.0 mg (1 mol %)	$[Rh(cod)Cl]_2$
20 ml	abs. CH_2Cl_2

Procedure: Analogously to R 21.

The products are then separated by column chromatography on alumina N (III), cyclohexane/ Et_2O (2:1) giving 4.0 g of ethyl 1-(4-oxo-butyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**119**) (10.2 mmol, 93 % yield) ($C_{22}H_{40}O_4Si$, 396.63 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 9.71 (t, 1H, ^3J = 1.2 Hz, CHO), 4.45 (dd, 1H, ^3J = 9.2 Hz, ^3J = 6.0 Hz, CH), 4.12 (q, 2H, ^3J = 7.0 Hz, CH_2CH_3), 2.38 (dd, 1H, ^3J = 6.53 Hz, ^3J = 1.2 Hz, CH_2), 2.05-1.91 (m, 1H, CH_2), 2.02 (m, 3H, CH_2), 1.85-1.47 (m, 5H, CH_2), 1.33 -1.16



119

(m, approx. 8H, CH_2), 1.19 (t, 3H, ^3J = 7.0 Hz, CH_2CH_3), 0.86 (m, 3H, CH_2), 0.14 (s, 9H, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 202.00 (CHO), 174.89 (CO), 150.83 (*C*=CH), 108.15 (C=*C*H), 60.46 (*C*H_2CH_3), 56.26 (C_q), 44.08 (CH_2), 31.94 (CH_2), 29.72 (CH_2), 26.78 (CH_2), 26.43 (CH_2), 24.80 (CH_2), 24.56 (CH_2), 24.48 (CH_2), 20.91 (CH_2), 17.32 (CH_2), 15.23 (CH_2), 14.12 (CH_2CH_3), 0.83 (3 x CH_3).

Preparation of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (81)

R 54: 4.0 g (10.0 mmol) of ethyl 1-(4-oxo-butyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**119**) in 30 ml of abs. CH_2Cl_2 is added to 1.5 ml (2.2 g, 12 mmol) of $TiCl_4$ in 40 ml of CH_2Cl_2 at room temperature under Argon atmosphere. This mixture is stirred for 2 hours. After hydrolysis, the resulting organic layer is extracted with diethylether (3 x 30 ml) and washed with a solution of $NaHCO_3$. The combined extracts are dried on $MgSO_4$ and concentrated under vacuum. The products are separated by column chromatography through a pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 2.1 g (6.48 mmol, 54% yield) as a mixture of four diastereoisomers in a ratio of 1:2:2:1.5 of ethyl 12-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.21 g / mol) as a white solid is isolated. Its spectroscopic data are consistent with those reported in R 23.

4.4.3. Preparation of TBDM-silyl enol ether

Attempted preparation of 1-(2-methylprop-2-enyl)-2-(tert-butyl-dimethyl-silanoxy)-cyclododec-2-ene (122)

R 55 Amounts:

4.0 g (13.6 mmol)	2-(2-methyl-1-propen)cyclododecanone (**66**)
2.52 g (23.1 mmol)	TBDMSCl (**121**)
0.74 g (13.6 mmol)	*n*-BuLi
1.37 g (13.6 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2

Starting material is recovered.

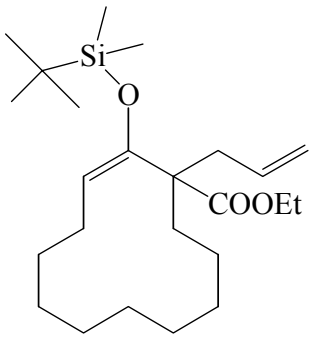
Preparation of ethyl 1-allyl-2-(tert-butyl-dimethyl-silanoxy)-cyclododec-2-ene carboxylate (123)

R 56 Amounts:

8.0 g (27.2 mmol)	ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)
5.04 g (46.2 mmol)	TBDMSCl (121)
1.74 g (27.2 mmol)	*n*-BuLi
2.74 g (27.2 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2.

7.8 g ethyl 1-allyl-2-(tert-butyl-dimethyl-silanoxy-cyclododec-2-ene carboxylate (123) (21.4 mmol, 78 % yield) ($C_{24}H_{44}O_3Si$, 408.69 g / mol) as a colorless oil is obtained. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 5.60 (ddd, 1H, ^3J = 17.2 Hz, ^3J = 9.7 Hz, ^3J = 7.23 Hz, C*H*=CH_2), 4.85 (m, 2H, CH=C*HH*), 4.55 (dd, 1H, ^3J = 9.7 Hz, ^3J = 4.9 Hz, C*H*=C), 4.02 (q, 2H, ^3J = 7.2 Hz, CH_2CH_3), 2.45 (dd, 1H, ^3J = 13.4 Hz, ^3J = 6.9 Hz, CH_2), 2.40 (dd, 1H, ^3J = 13.4 Hz, ^3J = 7.4 Hz, CH_2), 2.22 (dddd, 1H, ^3J = 10.4 Hz, ^3J = 10.2 Hz, ^3J = 9.72 Hz, ^3J = 3.4 Hz, CH_2), 1.86-1.79 (m, 1H, CH_2), 1.76-1.71 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 1.35-1.19 (m, 11H, CH_2), 1.21 (t, 3H, ^3J = 7.2 Hz, CH_2CH_3), 0.9 (m, 9H, CH_3), 0.16 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 174.64 (CO), 149.85 (*C*=CH), 133.76 (*C*H=CH_2), 117.78 (CH=*C*H_2), 108.81 (C=*C*H), 60.38 (*C*H_2CH_3), 56.20 (C_q), 37.76 (CH_2), 34.86 (C_q), 34.05 (CH_2), 29.58 (CH_2), 26.65 (CH_2), 26.34 (CH_2), 26.20 (CH_2), 25.95 (CH_3), 25.27 (CH_2), 24.94 (CH_2), 23.69 (CH_2), 23.66 (CH_2), 21.72 (CH_2), 14.12 (CH_2*C*H_3), -3.34 (3 x CH_3). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 3467 (w), 3073 (s), 2929 (s), 2857 (s), 1736 (s), 1710 (s), 1656 (m), 1463 (m), 1256 (m), 1200 (m), 1097 (w).



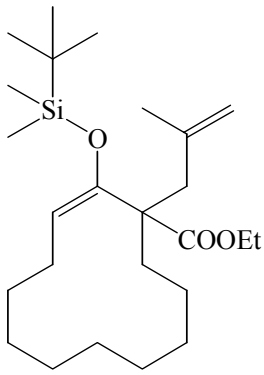
123

R 57 Amounts:

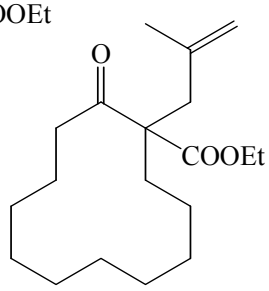
10 g (32.4 mmol)	ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**)
6.0 g (55 mmol)	TBDMSCl (**121**)
2.0 g (32 mmol)	*n*-BuLi
3.3 g (32.4 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2

9.2 g of a mixture of ethyl 1-(2-methyl-allyl)-2-trimethylsilanoxy-cyclododec-2-ene carboxylate (**124**) (34% conversion detected by GC-analysis) and starting material (**75**) is obtained. **Spectroscopic data** of the mixture of **124** and starting material **75**: **^{1}H-NMR (500 MHz, $CDCl_3$) δ [ppm]** = 4.8 (s, 1H, C=C*H*H), 4.79 (s, 1H, C=CH*H*), 4.78 (s, 1H, CH*H*=CH), 4.69 (s, 1H, C=C*H*H), 4.67 (m, 1H, C=CH), 4.14 (q, 2H, ^{3}J = 6.7 Hz, C*H*$_2$CH$_3$), 4.12 (m, 2H, C*H*$_2$CH$_3$), 2.92-2.86 (m, 2H, CH$_2$), 2.60 (s, 2H, CH$_3$), 2.48 (d, 1H, ^{3}J = 13.4 Hz, CH$_2$), 2.40 (m, 1H, CH$_2$), 2.16-2.02 (m, 3H), 2.02 (m, 3H, CH$_2$), 1.91-1.79 (m, 2H, CH$_2$), 1.79 (m, 5H, CH$_2$), 1.66 (s, 6H, CH$_3$), 1.51-1.10 (m, 15H, CH$_2$), 1.36 (m, 6H, CH$_2$), 1.23 (t, 3H, ^{3}J = 6.7 Hz, CH$_2$C*H*$_3$), 1.19 (t, 3H, ^{3}J = 7.0 Hz, CH$_2$C*H*$_3$), 0.86 (m, 7H, CH$_2$), 0.0 (s, 9H, CH$_3$). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 206.4 (CO), 175.74 (CO), 173.1 (CO), 151.38 (*C*=CH), 141.40 (*C*H=CH$_2$), 141.4 (*C*H=CH$_2$), 114.9 (CH=*C*H$_2$), 114.5 (CH=*C*H$_2$), 108.31 (C=*C*H), 62.9 (C$_q$), 61.10 (*C*H$_2$CH$_3$), 60.68 (C$_q$), 56.14 (*C*H$_2$CH$_3$), 55.58 (C$_q$), 40.58 (CH$_2$), 38.06 (CH$_2$), 33.79 (CH$_2$), 30.66 (CH$_2$), 29.18 (CH$_2$), 26.63 (CH$_2$), 26.36 (2 x CH$_3$), 26.34 (CH$_2$), 26.82 (CH$_2$), 25.30 (CH$_2$), 25.08 (CH$_2$), 24.91 (CH$_2$), 24.45 (CH$_2$), 23.78 (CH$_3$), 23.44 (CH$_2$), 23.21 (CH$_3$), 22.63 (CH$_2$), 22.14 (CH$_2$), 21.98 (CH$_2$), 21.79 (CH$_2$), 21.46 (CH$_2$), 13.87 (CH$_2$*C*H$_3$), 13.18 (CH$_2$*C*H$_3$), -2.01 (3 x CH$_3$)



124



75

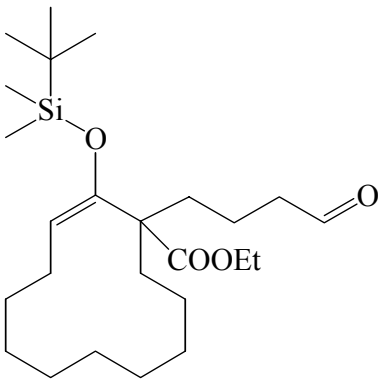
4.4.4. Hydroformylation of ethyl 1-allyl-2-(tert-butyl-dimethyl-silanoxy)-cyclododec-2-ene carboxylate

R 58 Amounts:

4.0 g	(11.0 mmol)	ethyl 1-allyl-2-(tert-butyl-dimethyl-silanox)-cyclododec-2-ene carboxylate (**123**)
15.0 mg	(1 mol %)	$[Rh(cod)Cl]_2$
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 21.

The products are then separated by column chromatography on alumina N (III), cyclohexane/ Et_2O (2:1) giving 4.1 g of ethyl 1-(4-oxo-butyl)-2-(tert-butyl-dimethyl-silanoxy)-cyclododec-2-ene carboxylate (**125**) (9.5 mmol, 87 % yield) ($C_{25}H_{46}O_4Si$, 438.71 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 9.70 (t, 1H, ^3J = 1.50 Hz, C*H*O), 4.40 (dd, 1H, ^3J = 9.7 Hz, ^3J = 1.0 Hz, CH), 4.02 (m, 2H, CH_2CH_3), 3.62 (dd, 1H, ^3J = 6.4 Hz, ^3J = 1.2 Hz, CH_2), 3.59 (dd, 1H, ^3J = 6.7 Hz, ^3J = 1.5 Hz, CH_2), 2.42 (m, 2H,CH_2), 2.20 (m, 1H, CH_2), 2.01-1.45 (m, 6H CH_2), 1.40–1.27 (m, 9H, CH_2), 1.21 (t, 3H, ^3J = 7.2 Hz, CH_2CH_3), 0.9 (s, 9H, CH_3), 0.0 (s, 6H, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 201.58 (CO), 176.67 (CO), 149.76 (*C*=CH), 108.34 (C=*C*H), 60.20 (CH_2CH_3), 55.78 (C_q), 43.76 (CH_2), 43.60 (C_q), 32.14 (CH_2), 29.13 (CH_2), 26.34 (CH_2), 25.90 (CH_3), 25.67 (CH_2), 24.80 (CH_2), 24.65 (CH_2), 24.49 (CH_2), 23.49 (CH_2), 23.35 (CH_2), 21.41 (CH_2), 21.20 (CH_2), 16.92 (CH_2), 13.76 (CH_2CH_3), -3.73 (3 x CH_3).



125

4.4.5. Enolboration /hydroformylation /aldol addition

Enolboration / hydroformylation / aldol cyclization of 2-allyl-cyclododecanone (48)

R 59: A solution of 377 mg (1.7 mmol) of 2-allyl-cyclododecanone (**48**), 0.2 ml (172 mg, 1.7 mmol) of NEt_3 in 25 ml of abs. CH_2Cl_2 is stirred for 10 min at 0°C. 4.3 mg (1 mol %) of [Rh(acac)$(CO)_2$] in anhydrous dichloromethane (20 ml), under Ar, 0.4 ml (360 mg, 1.7 mmol) of (*cy*-hex)$_2$BCl are added dropwise and the mixture is placed in an autoclave. After flushing with argon the reactor is pressurized with 10 bar carbon monoxide and 10 bar hydrogen, magnetically stirred and heated to 90 °C for 24h. Then, the autoclave is allowed to cool to room temperature. After removing the syn gas, the remaining solution is filtered through alumina using MTBE as eluent. The solvent is removed by rotary evaporation and the residue is diluted with 15 ml of MeOH and a solution of $NaHCO_3$ is added until pH=7. To the neutral solution 20 ml of H_2O_2 are added and the solution is stirred for 1h. Then, water is added and the aqueous layer is extracted three times with diethylether. The organic layer is back washed once with brine (30 ml) and dried. After removing of the solvent, the crude mixture is filtered on pad of alumina N (III), cyclohexane / Et_2O (3:1) furnishing 86 mg (0.34 mmol, 20 % yield) of 12-hydroxy-bicyclo[9.4.1]hexadecan–16-one (**50**) as a colorless solid ($C_{16}H_{30}O_2$, 252.21 g / mol). Its spectroscopic characteristics are consistent with those previously reported by C. Hollmann.

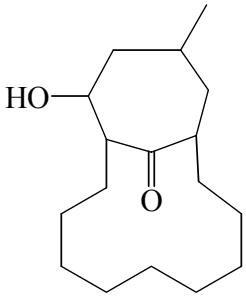
Enolboration / hydroformylation / aldol cyclization of 2-(2-methylprop-2-enyl)cyclododecanone (66)

R 60 Amounts:

400.0 mg	(1.69 mmol)	2-(2-methylprop-2-enyl)cyclododecanone (**66**)
4.3 mg	(1 mol %)	Rh(acac)$(CO)_2$
172 mg	(1.7 mmol)	NEt_3
360 mg	(1.7 mmol)	(*cy*-hex)$_2$BCl
60 ml		abs. CH_2Cl_2

Procedure: Analogously to R 59

The crude mixture is filtered through a pad of alumina N (III) using cyclohexane / Et_2O (2:1) to furnish 0.3 g of a mixture of β-ketoester **66** and 12-hydroxy-14-methyl-16-oxo-bicyclo[9.4.1]hexadecane (**97**) ($C_{17}H_{30}O_2$, 266.41 g / mol) in a ratio of 1:2.48 calculated by ^{1}HNMR (from CH=C/ C*H*OH). **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.78 (s, 1H, C*H*H=C), 4.67 (s, 1H, CH*H*=C), 3.45 (m, 1H, CH), 3.43 (m, 1H, CH), 2.72 (m, 1H, CH), 2.40 (m, 5H, CH), 1.83 (m, 4H, CH), 1.67-1.46 (m, approx. 16H, CH_2), 1.63 (s, 3H, CH_2), 1.20 (m, approx. 11H, CH_2), 1.34 (m, approx. 12H, CH_2), 0.86 (m, 3H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 215.65, 214.83 (CO), 142.92 (*C*=CH), 112.09 (C=*C*H), 70.33 (CH), 49.91 (CH), 40.29 (CH_2), 39.61 (CH_2), 38.46 (CH_2), 38.05 (CH_2), 37.85 (CH_2), 36.96, 36.80 (CH_2), 35.24 (CH_2), 30.74 (CH_2), 30.45 (CH_2), 30.05 (CH_2), 27.30, 27.12 (CH), 26.20 (CH_2), 25.64 (CH_2), 25.32 (CH_2), 24.63 (CH_2), 24.48 (CH_2), 24.11 (CH_2), 24.04 (CH_2), 23.69 (CH_2), 23.41 (CH_2), 22.60 (CH_2), 22.46 (CH), 22.11 (CH_2), 21.79 (CH_2), 20.04, 19.90 (CH).



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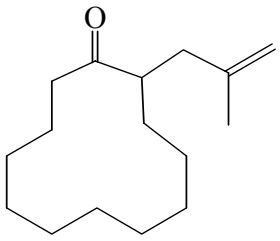


66

Enolboration / hydroformylation / aldol cyclization of ethyl 1-allyl-2-oxo-cyclododecane carboxylate (74)

R 61 Amounts:

500.0 mg	(1.7 mmol)	ethyl 1-allyl-2-oxo-cyclododecane carboxylate (**74**)
4.3 mg	(1 mol %)	$Rh(acac)(CO)_2$
172.0 mg	(1.7 mmol)	NEt_3
100.0 mg	(1.7 mmol)	$(cy\text{-hex})_2BCl$
20.0 ml		abs. CH_2Cl_2

Procedure: Analogously to R 59.

The crude mixture is filtered through a pad of alumina N (III) using cyclohexane / Et_2O (2:1) to furnish 480 mg of a mixture of ethyl 12-hydroxy-16-oxo-

bicyclo[9.4.1]hexadecan carboxylate (**81**) ($C_{19}H_{30}O_3$, 324.21 g / mol) (75% yield calculated by NMR-analysis) as a single diastereoisomers (detected by NMR-analysis) and ethyl 2-oxo-1-(4-oxo-butyl)-cyclododecane carboxylate (**80**) ($C_{19}H_{32}O_4$, 324.45 g / mol), (25% yield calculated by NMR-analysis). Its spectroscopic data are consistent with those reported in R 23.

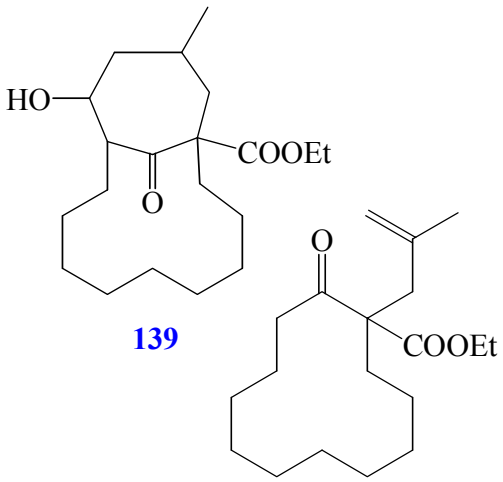
Enolboration / hydroformylation / aldol cyclization of 1-(2-methyl-allyl)-ethyl 2-oxo-cyclododecane carboxylate (75)

R 62 Amounts:

0.5 g	(1.7 mmol)	ethyl 1-(2-methyl-prop-2-enyl)-2-oxo-cyclododecane carboxylate (**75**)
4.3 mg	(1 mol %)	$Rh(acac)(CO)_2$
172 mg	(1.7 mmol)	NEt_3
100 mg	(1.7 mmol)	$(cy\text{-hex})_2BCl$
20 ml		abs. CH_2Cl_2

Procedure: Analogously to R 59.

The crude mixture is filtered through a pad of alumina N (III) using cyclohexane / Et_2O (2:1) to furnish 0.3 g of a mixture of β-ketoester **75** and ethyl 12-hydroxy-14-methyl-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**139**) ($C_{20}H_{34}O_4$, 338.49 g / mol) in a ratio of 1: 2 calculated by ^{1}HNMR (from CH=C/ C*H*OH).



139 **75**

Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.78 (d, 1H, C*H*H=C, J_{gem} = 1.5 Hz), 4.67 (s, 1H, CH*H*=C), 4.13 (q, 2H, ^3J = 7.2 Hz, *C*H_2CH$_3$), 4.09 (q, 2H, ^3J = 7.2 Hz, *C*H_2CH$_3$), 3.45 (m, 1H, CH), 2.92-2.86 (m, 2H, CH_2), 2.60 (s, 3H, CH_2), 2.06 (m, 5H, CH_2), 2.03 (m, 6H, CH_2), 1.5 (s, 6H, CH_2), 1.49 (m, 4H, CH_2), 1.34 (m, approx. 18H, CH_2), 1.19 (t, 3H, ^3J = 7.2 Hz, CH_2*C*H_3), 0.86 (m, 6H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 206.80, 206.53 (CO), 173.18, 169.83 (CO), 141.30 (*C*=CH),

114.57 (C=*C*H), 70.19 (CH), 63.03, 62.83 (C_q), 61.17, 61.10 (*C*$H_2$$CH_3$), 57.34 (CH) 38.24, 37.98 (CH_2), 35.33, 33.72 (CH_2), 29.57, 29.08 (CH_2), 26.66, 26.54 (CH_2), 26.26 (CH_2), 25.34, 25.31 (CH_2), 24.04 (CH_2), 24.35 (CH_2), 23.35 (CH_2), 23.14 (CH), 22.54 (CH_2), 22.13, 22.04 (CH_2), 21.93, 21.82 (CH_2), 21.38 (CH_2), 19.06 (CH_2), 13.93, 13.79 (CH_2*C*H_3).

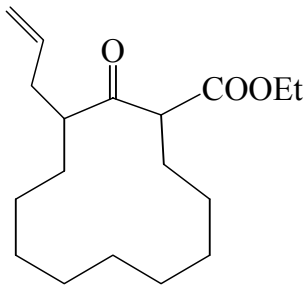
Preparation of ethyl 3-allyl-2-oxo-cyclododecane carboxylate (140)

R 63 Amounts:

10.0 g (67 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
5.3 g (73.7 mmol)	3-bromo-1-butene (**63**)
8.0 g (134 mmol)	*n*-BuLi
13.4 g (134 mmol)	diisopropylamine
150 ml	abs. THF

Procedure: Analogously to R 2

After removing of the solvent and distillation of the resulting crude mixture under reduced pressure (3 x 10^{-2} mbar) at 125 °C gives 17 g (58.3 mmol, 87 % yield) ethyl 3-allyl-2-oxo-cyclododecane carboxylate (**140**) ($C_{18}H_{30}O_3$, 294.43 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1.8 calculated by ^{1}HNMR (from CH_2CH_3).as colorless crystals. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 5.74 (ddd, 1H, ^{3}J = 17.2 Hz, ^{3}J = 10.2 Hz, ^{3}J = 6.7 Hz, C*H*=CH_2), 4.99 (dd, 1H, ^{3}J = 17.2 Hz, J_{gem} = 1.75 Hz, CH=C*H*H), 4.93 (dd, 1H, ^{3}J = 10.2 Hz, J_{gem} = 1.5 Hz, CH=CH*H*), 4.12 (q, 2H, ^{3}J = 6.9 Hz, *C*$H_2$$CH_3$), 3.97 (dd, 1H, ^{3}J = 11.4 Hz, ^{3}J = 3.2 Hz, CH), 3.71 (dd, 1H, ^{3}J = 9.7 Hz, ^{3}J = 4.7 Hz, CH), 2.90 (m, 1H, CH), 2.28 (m, 2H, CH_2), 2.01-1.81 (m, 4H, CH_2), 1.64-1.52 (m, 3H, CH_2), 1.21 (t, 3H, ^{3}J = 6.7 Hz, CH_2CH_3), 1.40-1.26 (m, 9H, CH_2), 1.14-0.88 (m, 4H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 215.88, 207.21 (CO), 169.79 (CO), 138.31, 137.73 (*C*H=CH_2), 114.04, 114.67 (CH=*C*H_2), 61.25, 61.22 (*C*$H_2$$CH_3$), 60.20 ($C_q$), 53.91, 54.43 (CH), 50.52, 49.59 (CH), 31.35, 31.29 (CH_2), 27.85 (CH_2), 27.72, 27.59 (CH_2), 26.80, 26.70 (CH_2), 26.22, 26.17 (CH_2), 23.62 (CH_2), 23.21, 23.17 (CH_2), 21.95 (CH_2), 20.42 (CH_2), 14.09, 14.02 (CH_2*C*H_3). **IR**



140

(KBr/film): $\tilde{\nu}$ [cm^{-1}] = 3076 (w), 2930 (s), 2865 (s), 1743 (s), 1712 (s), 1673 (m), 1640 (m), 1469 (m), 1445 (m), 1258 (m), 1159 (m), 1029 (m), 915 (m).

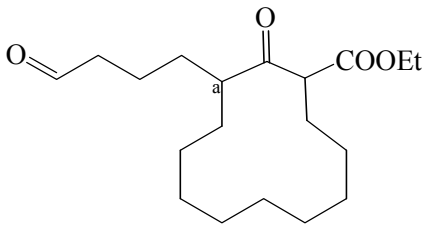
Enolboration / hydroformylation / aldol cyclization of ethyl 3-allyl-2-oxo-cyclododecane carboxylate (140)

R 64 Amounts:

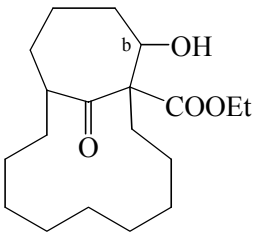
0.5 g (1.7 mmol)	ethyl 3-allyl-2-oxo-cyclododecane carboxylate (**140**)
4.3 mg (1 mol %)	$Rh(acac)(CO)_2$
172 mg (1.7 mmol)	NEt_3
100 mg (1.7 mmol)	$(cy\text{-hex})_2BCl$
20 ml	abs. CH_2Cl_2

Procedure: Analogously to R 59.

The crude mixture is filtered through a pad of alumina N (III) using cyclohexane / Et_2O (2:1) to furnish mixture of ethyl 15-hydroxy-16-oxo-bicyclo[9.4.1]hexadecan carboxylate (**142**) ($C_{19}H_{32}O_4$, 324.43 g / mol) (58% NMR-yield from CH_a and CH_b signals) and ethyl 2-oxo-3-(4-oxo-butyl)-cyclododecane carboxylate (**141**) ($C_{19}H_{32}O_4$, 324.43 g / mol). The compound **141** is present as a mixture of two diastereoisomers in a ratio of 1:6.2 (from NMR analysis from CHO signals).



141



142

Spectroscopic data of mixture of 141 (as a mixture of diastereoisomers) and **142: ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm]** = 9.71, 9.66 (t, 1H, ^3J = 1.5 Hz, CHO), 4.21 (q, 2H, ^3J = 6.9 Hz, CH_2CH_3), 4.10 (q, 2H, ^3J = 7.2 Hz, CH_2CH_3), 3.96 (dd, 2H, ^3J = 11.7 Hz, ^3J = 3.2 Hz, CH_a), 3.89 (d, 1H, ^3J = 10.7 Hz, CH_b), 2.90–2.86 (m, 2H, CH_2), 2.81–2.75 (m, 2H, CH_2), 2.41–2.24 (m, 6H), 2.20–1.95 (m, 7H, CH_2), 1.89–1.70 (m, 6H), 1.69–1.47 (m, 6H), 1.34–1.17 (m, 2H, CH_2), 1.28 (t, 3H, ^3J = 7.2 Hz, $CH_2C\mathit{H}_3$), 1.23 (t, 3H, ^3J = 6.9 Hz, $CH_2\mathit{CH}_3$), 1.07-0.86

(m, 6H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 208.71, 207.00 (CO), 202.27 (CHO), 172.49, 169.80 (CO), 79.89 (CH), 69.22 (C_q), 61.33, 61.04 (CH_2CH_3), 53.68, 51.27, 44.11, 33.93 (CH), 37.29 (CH_2), 27.98 (CH_2), 27.93 (CH_2), 27.33 (CH_2), 27.27 (CH_2), 26.83 (CH_2), 26.68 (CH_2), 26.27 (CH_2), 26.17 (CH_2), 26.05 (CH_2), 23.78 (CH_2), 23.49 (CH_2), 23.49 (CH_2), 23.43 (CH_2), 23.18 (CH_2), 22.39 (CH_2), 22.31 (CH_2), 21.90 (CH_2), 20.82 (CH_2), 20.21 (CH_2), 19.99 (CH_2), 14.09, 14.04 (CH_2CH_3). **IR (KBr/film), $\tilde{\nu}$ [cm^{-1}]** = 3524 (s), 2931 (s), 2865 (s), 1736 (s), 1710 (s), 1469 (m), 1445 (s), 1246 (m), 1226 (m), 1176 (w), 1126 (m), 1097 (m), 1073 (m), 734 (m). **LR-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 1.75), 306 (4.52), 278 (6.58), 254 (16.96), 209 (7.58), 109 (16.94), 95 (33.12), 81 (40.29), 55 (100), 29 (65.77), 18 (3.35). **HR-MS (EI, 70 eV):** Calcd.: 324.2301, Found: 324.2324.

4.5. Sequential Michael addition / aldol reaction

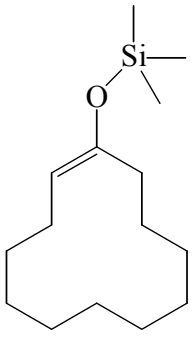
4.5.1. Stepwise Michael addition / aldol reaction of cyclododecanone derivatives

4.5.1.1. Preparation of substituted 3-(2-oxo-cyclododecyl)propanal

Preparation of cyclododec-1-enyloxy-trimethyl-silane (165)

R 65: To a mixture of 30.0 ml of N,N-dimethylformammide containing 25.0 ml (122 g, 198.0 mmol) TMSCl (**103**), 2.3 g (99.0 mmol) of Mg-turnings, a solution of 3.0 g (16.5 mmol) of cyclododecanone (**11**) in 15 ml of DMF is added dropwise for a period of 1 hour. The suspension is stirred at 5-7 °C on cooling with a water bath and stirred over night (18 h). Then, the solvent is removed under reduced pressure and the residue is dissolved in pentane and filtered on a short pad of alumina N (III) using pentane as eluent. The organic layer is washed with 40 ml of an aqueous solution of $NaHCO_3$ (3 x 30 ml), dried over $MgSO_4$. After removal of the solvent, no product is obtained and only starting material is recovered.

R 66: A solution of 4.1 g (28.0 mmol) of NaI in 30.0 ml of acetontrile is slowly added to a mixture of 3.0 g (16.5 mmol) of cyclododecanone (**11**), 3.9 ml (2.8 g, 28.0 mmol) of NEt_3 and 3.4 ml (3.05 g, 28.0 mmol) of TMSCl (**103**) at RT. An exothermic reaction occurred with concomitant formation of a white precipitate (Et_3NHI), while the acetonitrile solution turns brownish. The stirring is maintained for a period of 12 h. Then, 30 ml of cold pentane and ice-water are successively added. After decantation, the aqueous phase is extracted with pentane and the organic layer is washed with ice-water (2 x 30 ml), dried over $MgSO_4$ and distilled under reduced pressure (3 x 10^{-2} mbar) at 90°C giving 1.5 g (6.3 mmol, 38 % yield) of cyclododec-1-enyloxy-trimethyl-silane (**165**) ($C_{15}H_{30}OSi$, 254.49 g / mol) as a yellow oil. **Spectroscopic data:** **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.50 (t, 1H, ^3J = 8.0 Hz, ^3J = 7.7 Hz, C*H*=C), 2.40 (m, 4H, CH), 2.0 (m, 2H, CH_2), 1.82 (m, 3H, CH_2), 1.61 (m, 5H, CH_2), 1.21 (m, 6H, CH_2), 0.10 (s, 9H, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 151.249 (C_q), 108.77 (*C*H=C), 40.21 (CH), 27.77 (CH_2), 27.22



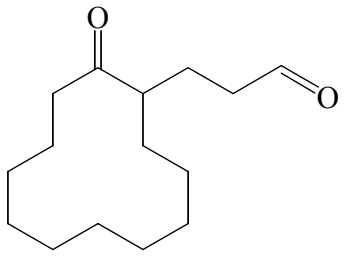
165

(CH_2), 24.63 (CH_2), 24.49 (CH_2), 24.36 (CH_2), 24.19 (CH_2), 24.08 (CH_2), 23.78 (CH_2), 22.44 (CH_2), 0.29 (3 x CH_3).

R 67: A solution of 47.0 ml (7.5 g, 118 mmol) of *n*-butyllithium in *n*-hexane (2.5 M) is added dropwise over a period of 30 min. to a cold (-78°C) solution of 18.1 ml (13.0 g, 118.0 mmol) of freshly distilled diisopropylamine in 25.0 ml of abs. THF. After 20 min., a solution of 20.0 g (109.0 mmol) of cyclododecanone (**11**) in 50 ml of abs. THF is added and the mixture is stirred for 30 min. Then, 25.7 ml (22.7 g, 185.0 mmol) of TMSCl (**103**) in 30 ml of abs. THF is added dropwise. The reaction mixture is maintained at -78°C for 45 min. and gradually warmed to room temperature. Then, after 6 hours, the aqueous layer is extracted (3 x 40 ml) with Et_2O. The organic layer is washed once with brine, filtered and dried over $MgSO_4$. The solvent is removed in vacuum giving a crude mixture. Distillation of the resulting mixture under reduced pressure (3 x 10^{-2} mbar) at 90°C gives 21.5 g (85 mmol, 78 % yield) of cyclododec-1-enyloxy-trimethyl-silane (**165**) ($C_{15}H_{30}OSi$, 254.49 g / mol) as a colorless oil. **Spectroscopic data** are consistent with those reported in R 66.

Preparation of 3-(2-oxo-cyclododecyl)propanal (145)

R 68: To a solution of 5.0 g (20.0 mmol) of cyclododec-1-enyloxy-trimethyl-silane (**165**) in 40 ml of abs. CH_2Cl_2 at -78°C is added slowly over a period 1 hour a solution of 2.2 g of acrolein (**166**) (40 mmol) in 60.0 ml of abs. CH_2Cl_2, under argon. The resulting solution is stirred for 8 hours at -78°C, washed with a solution of $NaHCO_3$ and extracted with diethylether (3 x 30 ml). The combined extracts are dried on $MgSO_4$ and concentrated under vacuum. The organic layer is separated and washed with a solution of Na_2CO_3. The combined organic phases are dried and the crude mixture is purified by bulb to bulb distillation at 85°C (4 x 10^{-2} mbar) furnishing 3.7 g (15.6 mmol, 78 % yield) 3-(2-oxo-cyclododecyl)propanal (**145**) ($C_{15}H_{26}O_2$, 238.37 g / mol) as a colorless liquid. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 9.64



145

(t, 1H, ^{3}J = 1.2 Hz, CHO), 3.30 (dd, 2H, ^{3}J = 6.7 Hz, ^{3}J = 6.5 Hz, CH_2), 2.62 (dd, 2H, ^{3}J = 9.54 Hz, ^{3}J = 3.26 Hz, CH_2), 2.55 (m, 1H, CH_2), 2.36–2.33 (m, 3H, CH_2), 2.32-2.27 (m, 4H, CH_2), 2.25 (dd, 2H, ^{3}J = 8.0 Hz, ^{3}J = 3.5 Hz, CH_2), 2.20 (dd, 1H, CH_2), 1.90 (m, 2H, CH_2), 1.63-1.53 (m, 4H, CH_2), 1.28-1.03 (m, 4H, CH_2), 0.88 (m, 1H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 213.49 (CO), 201.52 (CO), 50.557 (CH), 41.59 (CH_2), 37.23 (CH_2), 26.109 (CH_2), 25.85 (CH_2), 24.08 (CH_2), 23.76 (CH_2), 23.31 (CH_2), 22.92 (CH_2), 22.369 (CH_2), 21.97 (CH_2), 21.71 (CH_2), 21.58 (CH_2).

R 69: To a solution of 5.0 g (20.0 mmol) of 4-cyclododec-1-en-1-yl-morpholine (**70**) in 40 ml of abs. dioxane at 90°C, a solution of 21.0 g of acrolein (**166**) (250.0 mmol) in 60.0 ml of abs. dioxane is added slowly over 1 hour, under argon. The resulting solution is stirred for 66 hours at reflux. After cooling, 10 ml of HCl (conc.) is added and stirred for further 6 hours. The organic layer is separated and washed with a solution of Na_2CO_3. The organic phases are dried and the crude mixture is purified by bulb to bulb distillation at 45°C (4 x 10^{-2} mbar). Cyclododecanone (**11**) is recovered.

R 70 Amounts:

5.0 g	(20.0 mmol)	4-cyclododec-1-en-1-yl-morpholine (**70**)
21.0 g	(250.0 mmol)	acrolein (**166**)
50 ml		abs. MeOH

Procedure: Analogously to R 69, room temperature, 25 hours.
Cyclododecanone (**11**) is recovered.

R 71 Amounts:

5.0 g	(20.0 mmol)	4-cyclododec-1-en-1-yl-morpholine (**70**)
21.0 g	(250.0 mmol)	acrolein (**166**)
50.0 ml		abs. MeOH

Procedure: Analogously to R 69, 80 °C, 25 hours.
Cyclododecanone (**11**) is recovered.

R 72 Amounts:

5.0 g (20 mmol)	4-cyclododec-1-en-1-yl-morpholine (**70**)
21.0 g (250.0 mmol)	acrolein (**166**)
50 ml	abs. Et_2O

Procedure: Analogously to R 69, 0°C, 25 hours.

The crude mixture is purified by bulb to bulb distillation at 85°C (4 x 10^{-2} mbar) giving 4.6 g (19.2 mmol, 96 % yield) of 3-(2-oxo-cyclododecyl)propanal (**145**) ($C_{15}H_{26}O_2$, 238.37 g / mol) as a colorless liquid. **Spectroscopic data** are consistent with those reported in R 68.

4.5.1.2. Aldol reactions of substituted 3-(2-oxo-cyclododecyl)propanal

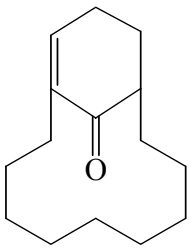
Preparation of bicyclo[9.3.1]pentadec-11-en-15-one (167)

R 73 Amounts:

1.0 g (3.4 mmol)	3-(2-oxo-cyclododecyl)propanaldehyde (**145**)
1.6 g (10.7 mmol)	DBU
80.0 ml	EtOH

Procedure: Analogously to R 39, 16 hours, room temperature.

The crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (3:1) as eluent. 540 mg (2.4 mmol, 72 % yield) of bicyclo[9.3.1]pentadec-11-en-15-one (**167**) ($C_{15}H_{24}O$, 220.35 g / mol) are isolated as a white solid. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.32 (d, 1H, ^3J = 4.2 Hz, CH), 2.79 (dd, 1H, ^3J = 13.0 Hz, ^3J = 1.5 Hz, CH), 2.39 (m, 2H, CH), 2.27 (m, 2H, CH_2), 2.03 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.55 (dd, 1H, ^3J = 13.0 Hz, ^3J = 2.2 Hz, CH), 1.43-1.01 (m, 11H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 204.44 (CO), 142.79 (CH), 137.20 (C_q), 47.21 (CH), 40.49 (CH_2), 30.66 (CH_2), 28.50 (CH_2), 27.42 (CH_2), 26.20 (CH_2), 26.10 (CH_2), 23.42 (CH_2), 22.67 (CH_2), 22.47 (CH_2), 22.20 (CH_2), 21.78 (CH_2). **LR-MS (EI, 70 eV): m/z (%)** = 220 (M^+, 30.15), 153 (33.12), 136 (20.15), 105 (11.47), 81 (6.85), 67 (36.98), 55 (18.86), 41 (28.59), 29 (17.28). **HR-MS (EI, 70 eV)**: Calcd. 220.1827, Found:



167

220.1806. **Elemental Analysis**: Calcd. % C 81.76, % H 10.98 Found: % C 80.5 % H 11.03.

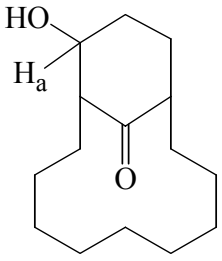
Preparation of 12-hydroxy-bicyclo[9.3.1]pentadecan-15-one (168) and bicyclo[9.3.1]pentadec-11-en-15-one (167)

R 74 Amounts:

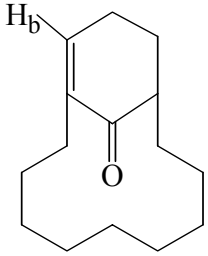
1.0 g (3.4 mmol)	3-(2-oxo-cyclododecyl)propanaldehyde (**145**)
70 ml	HCl (7N)
80 ml	dioxane

Procedure: Analogously to R 37, 16 hours, room temperature.

The crude mixture consists of compounds 12-hydroxy-bicyclo[9.3.1]pentadecan-15-one (**168**) and bicyclo[9.3.1]pentadec-11-en-15-one (**167**) in a ratio of 1:1 detected by ^{1}H-NMR (ratio calculated with respect to the H_a and H_b). The crude mixture is separated by column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) to give 430 mg (1.8 mmol, 53 % yield) of **168** ($C_{15}H_{26}O_2$, 238.37 g / mol) as brown oil and 320 mg (1.4 mmol, 42 % yield) of **167** ($C_{15}H_{24}O$, 220.35 g / mol) as a colorless oil. The compound **168** is present as a mixture of two diastereoisomers in a ratio of 1: 2.38 as detected by ^{1}H-NMR (ratio calculated with respect to the CHOH). 160 mg (0.7 mmol, 20 % yield) of minor diastereisomer is isolated by recrystallization from Et_2O.



168



167

Spectroscopic data of the minor diastereoisomer: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.91 (m, 1H, C*H*OH), 2.90 (dd, 1H, ^{3}J = 5.2 Hz, ^{3}J = 2.7 Hz, CH), 2.65 (dd, 1H, ^{3}J = 5.2 Hz, ^{3}J = 3.2 Hz, CH), 1.95-1.86 (m, 5H, CH), 1.82-1.77 (m, 1H, CH_2), 1.66-1.59 (m, 1H, CH), 1.50-1.11 (m, 14H, CH), 1.08-1.01 (m, 1H, CH), 0.96-0.86 (m, 1H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 214.78 (CO), 72.92 (CH), 60.26 (CH), 42.18 (CH), 30.02 (CH_2), 29.13 (CH_2), 26.92 (CH_2), 26.14 (CH_2), 25.54 (CH_2), 22.69 (CH_2), 22.56 (2 x CH_2), 22.24 (CH_2), 22.14 (CH_2), 22.04 (CH_2).

Spectroscopic data of **167** are consistent with those reported in R 73

4.5.2. Stepwise Michael addition / aldol addition of β-ketoester

4.5.2.1. Michael addition

Preparation of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (171)

R 75: To a mixture of 2.0 g (7.88 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) and 10.0 g of Al_2O_3 is added 0.6 ml (0.4 g 7.88 mmol) of acrolein (**166**). The mixture is stirred for 20 hours, then, filtered through a short pad of alumina N (III). After removing of solvent the residue is distilled under vacuum 110°C (4 x 10^{-2} mbar) and starting material is recovered.

R 76: To a mixture of 5.0 g (20.0 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) in 20ml THF 2.1 g (20.0 mmol) of Na_2CO_3 and a solution of 1.4 g (20 mmol) of acrolein (**166**) in 10 ml of abs. THF is added. The mixture is stirred at RT for 24 h. Then, the mixture is poured in water, and 30 ml of HCl are added. The organic phase is separated and the aqueous layer is extracted with Et_2O (3 x 30 ml). The combined organic extracts are dried over $MgSO_4$. After removing of the solvent the residue is distilled under vacuum (120°C, 1.4 10^{-1} mbar) and starting material is recovered.

R 77: To a mixture of 3.0 g (12 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) in 20 ml THF and 3.7 g (11.81 mmol) of piperidine, a solution of 1.0 ml (0.8 g, 12 mmol) of acrolein (**166**) in 10 ml of abs. THF is added. The mixture is stirred at RT for 72 h. Then, the mixture is poured in 30 ml of water and 10 ml of HCl (conc.) are added. The organic phase is separated and the aqueous layer is extracted with Et_2O (3 x 30 ml). The combined organic extracts are dried over $MgSO_4$. After removing of the solvent the residue is distilled under vacuum (110°C, 1.4 10^{-1} mbar) and starting material is recovered.

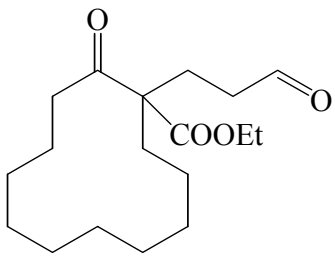
R 78 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
2.0 g (11.8 mmol)	molecular sieves
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	toluene

Procedure: Analogously to R 75, 12 hours, refluxing toluene

After removing of solvent the residue is distilled under vacuum 120°C (4 x 10^{-2} mbar), 10 % conversion in compound **171** is detected by GC-analysis.

R 79: To a mixture of 15.0 g (60.0 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) and 0.9 ml (60 mg, 6.0 mmol) of NEt_3 in 60 ml DMF a solution of 8 ml (60.0 mmol) of acrolein (**166**) in 20 ml of DMF is added. The mixture is stirred at RT for 20 h. Then, the mixture is poured in 40 ml of water and 10 ml of HCl (conc.) are added.



171

The organic phase is separated and the aqueous layer is extracted with Et_2O (3 x 30 ml). The combined organic extracts are dried over $MgSO_4$. After removing of solvent the residue is distilled under vacuum (130°C, 1.4x10^{-1} mbar) giving 15.4 g (50 mmol, 83 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**) ($C_{18}H_{30}O_4$, 310.43 g / mol) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]**: 9.63 (t, 1H, ^{3}J = 1.7 Hz, C*H*O), 4.09 (q, 2H, ^{3}J = 7.0 Hz, C*H*$_2$CH$_3$), 2.80 (m, 1H, CH), 2.24 (m, 4H, CH_2), 2.00 (m, 2H, CH_2), 1.70 (dd, 2H, ^{3}J = 13.5 Hz, ^{3}J = 6.0 Hz, CH), 1.23 (t, 3H, ^{3}J = 6.9 Hz, CH_2C*H*$_3$), 1.24-1.13 (m, approx. 13H, CH_2), 0.79 (m, 2H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 206.43 (CO), 200.92 (CO), 172.21 (CO), 62.36 (C_q), 61.32 (*C*H$_2$CH$_3$), 38.79 (CH_2), 34.12 (CH_2), 29.53 (CH_2), 29.31 (CH_2), 26.37 (CH_2), 26.19 (CH_2), 23.36 (CH_2), 22.54 (CH_2), 21.87 (CH_2), 21.73 (CH_2), 21.39 (CH_2), 18.76 (CH_2), 13.86 (CH_2*C*H$_3$).

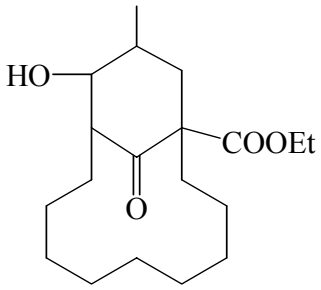
Preparation of ethyl 12-hydroxy-13-methyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (175)

R 80 Amounts:

2.0 g (7.87 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
6.0 mg (0.78 mmol)	NEt_3
0.8 g (15.74 mmol)	methacrolein (**169**)
50 ml	DMF

Procedure: Analogously to R 79

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to obtain 1.5 g (4.8 mmol, 61 % yield) of ethyl 12-hydroxy-13-methyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as a mixture of diastereoisomers in a ratio of 1:1:1 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3) as colorless crystals. **Spectroscopic data: ^{1}HNMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.10 (q, 2H, ^{3}J = 7.0 Hz, CH_2CH_3), 3.6 (m, 1H, CH), 3.39 (dd, 1H, ^{3}J = 7.0 Hz, ^{3}J = 3.5 Hz, CH), 2.90 (m, 1H, CH), 2.47 (m, 1H, CH_2), 1.90 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 2.18-1.81 (m, 5H, CH_2), 1.64-1.33 (m, 6H, CH_2), 1.34 (m, approx. 5H, CH_2), 1.19 (t, 3H, ^{3}J = 7.0 Hz, CH_2CH_3), 0.89, 087, 0.83 (d, 9H, ^{3}J = 3.5 Hz, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 210.57, 210.48, 209.45 (CO), 172.64, 172.64 (CO), 73.84, 72.38, 71.61 (CH), 66.08, 65.97, 65.65 (CH_2CH_3), 60.68, 60.64, 60.55 (C_q), 49.82, 49.06, 47.57 (CH), 38.50, 38.87, 38.38 (CH_2), 37.24, 37.59 (CH), 32.97 (CH_2), 26.00 (CH_2), 25.96, 25.91 (CH_2), 24.86, 24.79 (CH_2), 22.23, 22.16 (CH_2), 22.06, 22.01 (CH_2), 21.77, 21.82 (CH_2), 21.36 (CH_2), 19.60 (CH_2), 15.98, 16.05, 16.08 (CH_3), 14.02 (CH_2CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3503 (s), 2937 (s), 1739 (s), 1703 (s), 1470 (m), 1427 (s), 1250 (m), 1122 (m).



175

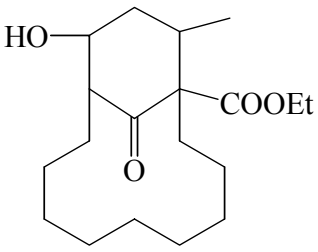
Preparation of ethyl 14-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (176)

R 81 Amounts:

1.5 g (6.0 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
6.0 mg (0.6 mmol)	NEt_3
0.66 g (12.0 mmol)	crotonic aldehyde (**170**)
50 ml	DMF

Procedure: Analogously to R 79

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to furnish 1.0 g (3.24 mmol, 54 % yield) of ethyl 14-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**176**) ($C_{19}H_{32}O_4$, 324.45 g/ mol) as a mixture of diastereoisomers in a ratio of 1 (**DS1**): 1.4 (**DS2**): 1.1 (**DS3**) detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3) as a colorless crystal. A mixture of two diastereoisomers is isolated in a ratio of 1 (**DS2**) : 7 (**DS3**) detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3) after recristallization from Et_2O. **Spectroscopic data** of a mixture of **DS2** and **DS3**: **Spectroscopic data**: **^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 4.08 (q, 2H, ^{3}J = 7.2 Hz, CH_2CH_3), 3.7 (m, 1H, CH), 2.95 (m, 1H, CH), 2.50 (dd, 1H, ^{3}J = 6.9 Hz, ^{3}J = 2.4 Hz, CH), 1.90 (m, 3H, CH_2), 1.70 (m, 1H, CH_2), 1.58-1.42 (m, 6H, CH_2), 1.254 (m, approx. 14H, CH_2), 1.19 (t, 3H, ^{3}J = 7.2 Hz, CH_2CH_3), 0.92, 0.88 (d, 4H, ^{3}J = 6.9 Hz, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 210.29 (CO), 170.66 (CO), 72.74, 71.87 (CH), 66.70, 66.78 (C_q), 60.42 (CH_2CH_3), 49.92 (CH), 38.58, 38.67 (CH_2), 37.38, 37.57 (CH), 33.46 (CH_2), 26.13 (CH_2), 26.08 (CH_2), 25.00 (CH_2), 22.28 (CH_2), 22.25 (CH_2), 21.93 (CH_2), 21.52 (CH_2), 19.75, 19.81 (CH_2), 16.10 (CH_3), 14.16 (CH_2CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3503 (s), 2937 (s), 1739 (s), 1703 (s), 1470 (m), 1427 (s), 1250 (m), 1122 (m).



176

4.5.2.2. Intramolecular aldol addition of 1,4-dicarbonyl compounds

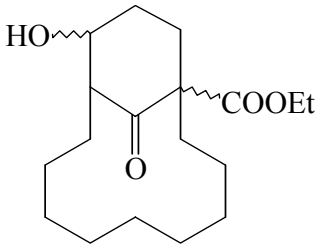
Preparation of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (174)

R 82 Amounts:

1.0 g (3.4 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**)
70 ml	HCl (7N)
80 ml	dioxane

Procedure: Analogously to R 37, 20 hours, room temperature.

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to obtain 885 mg (2.8 mmol, 82 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g/ mol) as a mixture of diastereoisomers in a ratio of 1:1.6 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_2CH_3) as a colorless crystal. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.12 (q, 2H, ^{3}J = 7.2 Hz, C*H*$_2$CH$_3$), 4.08 (q, 2H, ^{3}J = 7.2 Hz, C*H*$_2$CH$_3$), 3.45 (m, 1H, CH), 3.09 (d, 1H, ^{3}J = 4.9 Hz, C*H*OH), 2.75 (dd, 1H, ^{3}J = 10.4 Hz, ^{3}J = 1.2 Hz, CH), 2.18 (dd, ^{3}J = 13.4 Hz, ^{3}J = 4.2 Hz, 1H, CH), 2.10 (m, 2H, CH_2), 1.96 (s, 1H, OH), 1.85-1.70 (m, 6H, CH_2), 1.32-1.03 (m, approx. 17H, CH_2), 1.22 (t, 3H, ^{3}J = 7.2 Hz, CH_2CH_3), 1.20 (t, 3H, ^{3}J = 7.2 Hz, CH_2CH_3), 0.86 (m, 1H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 209.46, 208.45 (CO), 172.67, 172.56 (CO), 75.56, 73.43 (CH), 62.36, 61.57 (C_q), 60.70, 60.65 (*C*H$_2$CH$_3$), 53.60, 49.66 (CH), 32.46, 32.06 (CH_2), 31.33, 30.95 (CH_2), 28.83 (CH_2), 26.88, 26.72 (CH_2), 25.81, 25.78 (CH_2), 25.03 (CH_2), 22.94, 22.88 (CH_2), 22.83 (CH_2), 22.48, 22.37 (CH_2), 21.99 (CH_2), 21.06, 21.00 (CH_2), 13.98, 13.95 (CH$_2$*C*H$_3$). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 3503 (s), 2937 (s), 1739 (s), 1703 (s), 1470 (m), 1427 (s), 1250 (m), 1122 (m). **LR-MS (EI, 70 eV): m/z (%)** = 310 (M^+, 10), 292 (43), 263 (27), 219 (35), 207 (32), 123 (58), 109 (96), 95 (98), 81 (72), 55 (45). **HR-MS (EI, 70 eV)**: Calcd. 310.2144, Found 310.2140. **Elemental Analysis:** Calcd. % C 69.64, % H 9.74, Found % C 69.7, % H 9.9



174

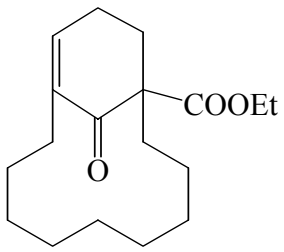
Preparation of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (177)

R 83 Amounts:

1.0 g	(3.4 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**)
0.5 mg	(3.8l mmol)	$BF_3 \cdot OEt_2$
80 ml		CH_2Cl_2

Procedure: Analogously to R 37, 24 hours, room temperature

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to obtain 804 mg (2.7 mmol, 81 % yield) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 292.41 g / mol). **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.43 (d, 1H, ^3J = 3.5 Hz, CH), 4.12 (q, 2H, ^3J = 7.0 Hz, CH_2CH_3), 2.80 (m, 1H, CH), 2.61-2.33 (m, 4H, CH_2), 1.95-1.65 (m, 7H, CH_2), 1.58 (dd, ^3J = 13.0 Hz, ^3J = 2.7 Hz, 2H, CH_2), 1.19 (t, 3H, ^3J = 7.0 Hz, CH_2CH_3), 1.14 (m, approx. 7H, CH_2), 0.86 (m, 1H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 197.55 (CO), 172.88 (CO), 143.86 (C_q), 137.29 (CH), 60.53 (CH_2CH_3), 57.80 (C_q), 32.28 (CH_2), 30.81 (CH_2), 29.12 (CH_2), 26.52 (CH_2), 25.98 (CH_2), 22.85 (CH_2), 22.47 (CH_2), 22.40 (CH_2), 22.19 (CH_2), 21.80 (CH_2), 19.07 (CH_2), 13.98 (CH_2CH_3). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 2937 (s), 1735 (s), 1672 (s), 1469 (m), 1432 (s), 1347 (m), 1252 (m), 1182 (m), 1097 (m), 1027 (m). **LR-MS (EI, 70 eV): m/z (%)** = 292 (M^+, 2.62), 219 (100), 149 (2.34), 136 (3.44), 105 (7.73), 81 (22.55), 67 (16.39), 55 (19.72), 41 (11.49), 29 (32.91). **HR-MS (EI, 70 eV)**: Calcd. 292.2038, Found 292.2027.



177

R 84 Amounts:

1.0 g	(3.4 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**)
590.0 mg	(3.8l mmol)	NaOH
80 ml		EtOH

Procedure: Analogously to R 79, 24 hours, refluxing ethanol

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to obtain 614 mg (2.1 mmol, 86 % yield) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 292.20 g / mol). **Spectroscopic data** are consistent with those reported in R 83.

R 85 Amounts:

1.0 g (3.4 mmol)	ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**)
590 mg (3.8l mmol)	NaOH
80 ml	EtOH

Procedure: Analogously to R 79, 72 hours, refluxing ethanol

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to furnish 725 mg (3.3 mmol, 97 % yield) of bicyclo[9.3.1]-pentadec-11-en-15-one (**167**) ($C_{15}H_{24}O$, 220.35 g / mol) as a white solid. **Spectroscopic data** are consistent with those reported in R 73.

4.5.3. One-Pot Michael addition / aldol cyclisation

Preparation of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (174)

R 86: To a mixture of 2.0 g (7.88 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) and 1.6 g (11.81 mmol) K_2CO_3 in 70 ml of EtOH, 0.6 ml 0.4 g (7.88 mmol) of acrolein (**166**) is added. The mixture is stirred at RT for 18 hours. Then, the mixture is filtered through a short pad of alumina. After removing of the solvent, the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.5 g (4.8 mmol, 61 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g / mol) are isolated as a colorless crystal. **Spectroscopic data** are consistent with those reported in R 82.

R 87 **Amounts:**

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.8 mol)	K_2CO_3
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 86, 72 hours, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to obtain 1.4 g (4.5 mmol, 58 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1 detected by ^{1}HNMR (calculated by respect to C*H*OH). **Spectroscopic data** are consistent with those reported in R 82.

R 88 **Amounts:**

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 86, 18 hours, refluxing EtOH.

After removing of the solvent, the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.3 g (4.4 mmol, 56 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g / mol) are obtained as a mixture of two diastereoisomers in a ratio of 1:1.09 detected by ^{1}HNMR (calculated by respect to C*H*OH). **Spectroscopic data** are consistent with those reported in R 82.

R 89 **Amounts:**

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.8 mol)	K_2CO_3
0.4 g (7.88 mmol)	acrolein (**166**)

50 ml	EtOH

Procedure: Analogously to R 86, 72 hours, refluxing EtOH.

After removing of the solvent, the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.2 g (5.2 mmol, 67 % yield) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 291.42 g / mol) are isolated. **Spectroscopic data** are consistent with those reported in R 83.

R 90 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	acetone

Procedure: Analogously to R 86, 18 hours, room temperature.

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (5:1) as eluent to obtain 1.9 g (6.1 mmol, 78 % yield) of ethyl 2-oxo-1-(3-oxo-propyl)cyclododecane carboxylate (**171**) ($C_{18}H_{30}O_4$, 310.43 g / mol) as a colorless oil. **Spectroscopic data** are consistent with those reported in R 79.

R 91 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	acetone

Procedure: Analogously to R 86, 72 hours, room temperature.

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to give 1.6 mg (5.2 mmol, 67 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g / mol) are obtained. **Spectroscopic data** are consistent with those reported in R 82.

R 92 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	EtOH

Procedure: Analogously to R 86, 18 hours, room temperature.

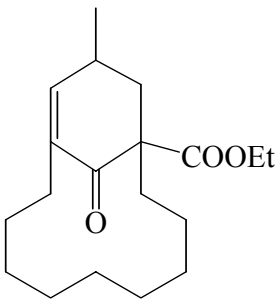
After removing of the solvent, the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.5 g (4.5 mmol, 58 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{19}H_{32}O_4$, 324.45 g / mol) are obtained as a colorless crystal. **Spectroscopic data** are consistent with those reported in R 80.

R 93 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	EtOH

Procedure: Analogously to R 86, 72 hours, room temperature.

After removing of the solvent the crude mixture contains a mixture of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{19}H_{32}O_4$, 324.45 g / mol) and methyl 15-oxo-13-methyl-bicyclo[9.3.1]pentadec-11-ene carboxylate (**182**) ($C_{19}H_{30}O_3$, 306.44 g / mol). The products are separated by chromatography using alumina N (III) and cyclohexane / Et_2O (5:1) as eluent to give 0.76 g (2.3 mmol, 30 % yield) of compound **175** as a mixture of two diastereoisomers in a ratio of 1:1.33 detected by ^{1}HNMR analysis (calculated with respect to the CH_3) and 0.86 g (2.7 mmol, 35 % yield) of methyl 15-oxo-13-methyl-bicyclo[9.3.1]pentadec-11-ene carboxylate (**182**).



182

Spectroscopic data of compound **175** are consistent with those reported in R 80.

Spectroscopic data of ethyl 13-methyl-15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**182**) are assigned by the most significant signals: **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.67 (s, 1H, CH) **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 201.54 (CO), 143.01 (C_q), 137.49 (CH)**.**

R 94 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	EtOH

Procedure: Analogously to R 86, 18 hours, refluxing ethanol

After removing of the solvent the residue is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent, to give 1.2 g (3.4 mmol, 43 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{18}H_{31}O_4$, 324.45 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1.68:1.37 detected by NMR analysis (ratio calculated with respect to the CH_3), as colorless crystal. **Spectroscopic data** are consistent with those reported in R 80

R 95 Amounts:

2.0 g (7.88 mmol.)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	EtOH

Procedure: Analogously to R 86, 72 hours, refluxing ethanol

After removing of the solvent a crude mixture of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) (37.5 % ^{1}HNMR-yield calculated with respect to the CH=C / CHO) ($C_{19}H_{32}O_4$, 324.24 g / mol) and methyl 15-oxo-13-methyl-bicyclo[9.3.1]pentadec-11-ene carboxylate (**182**) (62 % ^{1}HNMR-yield calculated with respect to the CH=C / CHO) ($C_{19}H_{30}O_3$, 306.42 g / mol) is obtained. Compound **175** is present as a mixture of two diastereoisomers in a ratio of 1:1 detected by ^{1}HNMR

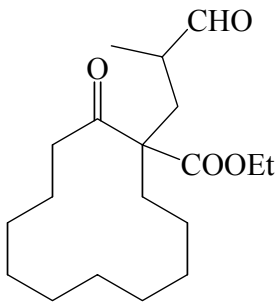
analysis (calculated with respect to the CH_3). **Spectroscopic data** are consistent with those reported in R 93.

R 96 Amounts:

2.0 g (7.88 mmol.)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)
50.0 ml	acetone

Procedure: Analogously to R 90, 18 hours, room temperature.

After removing of the solvent the residue is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (5:1) as eluent, to give 2.1 g (6.6 mmol, 85% yield) of ethyl 1-(2-methyl-3-oxo-propyl) 2-oxo-cyclododecane carboxylate (**172**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as mixture of diastereoisomers in a ratio of 1:1.6 detected by ^{1}HNMR analysis (ratio calculated with respect to CHO) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]**: 9.63 (d, 1H, ^3J = 3.0 Hz, C*H*O), 4.09 (q, 2H, ^3J = 7.2 Hz, CH_2CH$_3$), 2.80 (m, 1H, CH), 2.24-1.90 (m, 18H, CH_2), 1.23 (m, 2H, CH_2), 1.21 (t, 3H, ^3J = 7.2 Hz, CH_2CH_3), 1.02, 0.99 (d, 6H, ^3J = 7.0 Hz, CH_3), 0.79 (m, 4H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 206.83, 206.55 (CO), 201.79, 201.38 (CO), 171.31, 171.21 (CO), 61.17, 61.13 (C_q), 61.07, 61.00 (CH_2CH_3), 48.53 (CH_2), 45.97 (CH), 38.23 (CH_2), 34.23, 35.03 (CH_2), 29.52, 29.20 (CH_2), 28.13 (CH), 29.92 (CH_2), 26.68, 26.60 (CH_2), 26.42, 26.36 (CH_2), 25.26 (CH_2), 24.94 (CH_2), 23.92, 23.96 (CH_2), 22.19 (CH_2), 23.34, 23.38 (CH_2), 22.38 (CH_2), 21.89, 21.84 (CH_2), 18.66, 18.24 (CH_2), 17.14 (CH_3), 14.01, 13.89 (CH_2CH_3)



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R 97 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	methacrolein (**169**)

50 ml	acetone

Procedure: Analogously to R 86, 72 hours, room temperature.

After removing of the solvent a mixture of ethyl 1-(2-methyl-3-oxo-propyl) 2-oxo-cyclododecane carboxylate (**172**) ($C_{19}H_{32}O_4$, 324.45 g / mol) and ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{19}H_{32}O_4$, 324.45 g / mol) is obtained The products are then separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) to give 1.5 g (4.8 mmol, 61 % yield) of **175** as a mixture of diastereoisomers in a ratio of 1:2:1 detected by ^{1}HNMR (ratio calculated with respect to the CH_3) as colorless crystal and 0.8 g (2.6 mmol, 33 % yield) of **172** are isolated. **Spectroscopic data** of compound **172** are consistent with those reported in R 96. **Spectroscopic data** of compound **175** are consistent with those reported in R 80.

R 98 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.8 mol)	K_2CO_3
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	EtOH

Procedure: Analogously to R 86, 18 hours, room temperature.

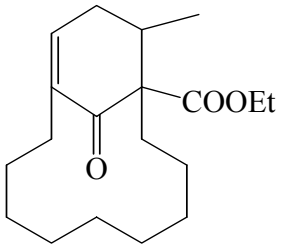
After removing of the solvent, the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent. 1.3 g (4. 1 mmol, 53 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**176**) ($C_{19}H_{32}O_4$, 324.245 g / mol) as a mixture of two diastereoisomers in a ratio of 1:1.15 detected by ^{1}HNMR (ratio calculated with respect to the CH_3) as a colorless crystal. **Spectroscopic data** are consistent with those reported in R 81.

R 99 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.8 mol)	K_2CO_3
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	EtOH

Procedure: Analogously to R 86, 72 hours, refluxing EtOH.

After removing of the solvent the product is isolated by column chromatography on alumina N (III), cyclohexane/ Et_2O (2:1) furnishing 1.9 g (6.0 mmol, 76 % yield) of ethyl 14-methyl-15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**183**) ($C_{19}H_{30}O_3$, 306.42 g / mol). **Spectroscopic data ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.43 (d, 1H, ^{3}J = 4.0 Hz, CH), 4.14 (q, 2H, ^{3}J = 7.0 Hz, C*H*$_2$CH$_3$), 2.86 (m, 1H, CH_2), 2.60 (m, 1H, CH_2), 2.40 (m, 1H, CH_2), 2.34 (m, 1H, CH_2), 2.20 (m, 1H, CH_2), 1.98 (m, 1H, CH_2), 1.65 (m, 2H, CH_2), 1.23 (m, 7H, CH_2), 1.19 (t, 3H, ^{3}J = 7.0 Hz, CH_2C*H*$_3$), 0.95 (d, 3H, ^{3}J = 7.0 Hz, CH_3), 0.86 (m, 3H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 196.39 (CO), 171.33 (CO), 142.07 (CH), 137.96 (C_q), 61.32 (C_q), 60.47 (*C*H_2CH$_3$), 35.47 (CH), 31.59 (CH_2), 30.72 (CH_2), 30.39 (CH), 27.84 (CH_2), 26.39 (CH_2), 24.14 (CH_2), 23.72 (CH_2), 23.40 (CH_2), 22.75 (CH_2), 21.17 (CH_2), 17.12 (CH_3), 14.19 (CH_2*C*H$_3$). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 2937 (s), 1735 (s), 1672 (s), 1469 (m), 1432 (s), 1347 (m), 1252 (m), 1182 (m), 1097 (m), 1027 (m).



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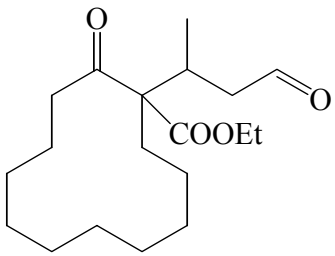
R 100 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	acetone

Procedure: Analogously to R 86, 18 h, room temperature.

After removing of the solvent the product is isolated by column chromatography on alumina N (III), cyclohexane/ Et_2O (2:1) furnishing, 2.1 mg (6.6 mmol, 84 % yield) of 1-(1-methyl-3-oxo-propyl)-ethyl 2-oxo-cyclododecane carboxylate (**173**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as mixture of diastereoisomers in a ratio of 1:2.8 detected by ^{1}HNMR analysis (ratio calculated with respect to CHO) as a colorless oil. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]:** 9.69 (t, 1H, ^{3}J = 1.5 Hz, C*H*O), 4.19 (q, 2H, ^{3}J =



173

7.2 Hz, C*H*$_2$CH$_3$), 3.69 (m, 1H, CH), 2.77-2.61 (m, 2H, CH$_2$), 2.56-2.40 (m, 3H, CH$_2$), 2.07-1.80 (m, 4H, CH$_2$), 1.27-1.20 (m, approx. 13H, CH$_2$),1.16 (t, 3H, ^{3}J = 7.2 Hz, CH$_2$C*H*$_3$), 0.91, 0.88 (d, 3H, ^{3}J = 6.9 Hz, CH$_3$), 0.86 (m, 3H, CH$_2$). **^{13}C-NMR (100 MHz, CDCl$_3$): δ [ppm]** = 206.96, 206.79 (CO), 201.99, 201.58 (CO), 169.81, 169.50 (CO), 65.83, 66.25 (C$_q$), 61.11, 61.16 (*C*H$_2$CH$_3$), 48.68 (CH$_2$), 46.03 (CH), 40.25 (CH$_2$), 29.26, 29.24 (CH$_2$), 28.24 (CH), 26.41, 26.47 (CH$_2$), 25.32 (CH$_2$), 24.99 (CH$_2$), 24.00, 23.65 (CH$_2$), 23.38, 23.21 (CH$_2$), 21.89, 21.79 (CH$_2$), 18.70, 18.28 (CH$_2$), 17.21 (CH$_3$), 14.02, 13.97 (CH$_2$*C*H$_3$).

R 101 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	K_2CO_3
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	acetone

Procedure: Analogously to R 86, 72 hours, room temperature.

After removing of the solvent the residue is filtered on pad of alumina N (III) using cyclohexane/ Et$_2$O (2:1) as eluent to give 1.4 g (4.5 mmol, 57 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**176**) ($C_{19}H_{32}O_4$, 324.24 g / mol) as a colorless crystal. **Spectroscopic data** are consistent with those reported in R 81.

R 102 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 77, 18 hours, room temperature

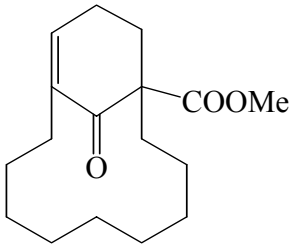
The product is isolated by column chromatography on alumina N (III), cyclohexane/ Et$_2$O (2:1) giving 1.4 g (4.9 mmol, 63 % yield) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 291.42 g / mol). **Spectroscopic data** are consistent with those reported in R 83.

R 103 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	MeOH

Procedure: Analogously to R 77, 72 hours, room temperature.

The crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent furnishing 1.5 g (5.6 mmol, 72 %) of methyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**184**) ($C_{17}H_{26}O_3$, 278.38 g / mol).



184

Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.43 (d, 1H, ^3J = 3.7 Hz, CH), 3.6 (s, 3H, CH_3), 2.85 (m, 1H, CH_2) 2.60-2.57 (m, 4H, CH_2), 1.95-1.92 (m, 1H, CH_2), 1.82-1.69 (m, 5H, CH_2), 1.58 (dd, 2H, ^3J = 12.5 Hz, ^3J = 3.5 Hz, CH_2), 1.14 (m, approx. 8H, CH_2), 0.86 (m, 1H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 197.66 (CO), 172.52 (CO), 143.97 (C_q), 137.43 (*C*H=C), 58.10 (C_q), 51.89 (CH_3), 32.40 (CH_2), 30.87 (CH_2), 29.292 (CH_2), 26.62 (CH_2), 26.10 (CH_2), 23.00 (CH_2), 22.60 (CH_2), 22.51 (CH_2), 22.31 (CH_2), 21.96 (CH_2), 20.01 (CH_2). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 2937 (s), 1735 (s), 1672 (s), 1469 (m), 1432 (s), 1347 (m), 1252 (m), 1182 (m), 1097 (m), 1027 (m).

R 104 Amounts:

2.0 g (7.88mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 77, 18 hours, refluxing ethanol

The crude mixture is separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) giving 414 mg (1.4 mmol, 18 %) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 292.20 g / mol). 1.0 g (4.9 mmol, 63 % yield) of bicyclo[9.3.1]pentadec-11-en-15-one (**167**) ($C_{15}H_{24}O$, 220.35 g /

mol) as a white solid. **Spectroscopic data** of **177** are consistent with those in R 83. **Spectroscopic data** of **167** are consistent with those reported in R 73.

R 105 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 77, 72 hours, refluxing ethanol.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent, to give 121 mg (0.55 mmol, 7 % yield) of bicyclo[9.3.1]pentadec-11-en-15-one (**167**) ($C_{15}H_{24}O$, 220.35 g / mol) as a white solid. **Spectroscopic data** are consistent with those reported in R 73.

R 106 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	EtOH

Procedure: Analogously to R 77, 18 hours, room temperature

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to furnish 550 mg (1.9 mmol, 23 % yield) of ethyl 14-methyl-15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**183**) ($C_{19}H_{30}O_3$, 306.42 g / mol). **Spectroscopic data** are consistent with those reported in R 99.

R 107 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	EtOH

Procedure: Analogously to R 77, 72 hours, room temperature.

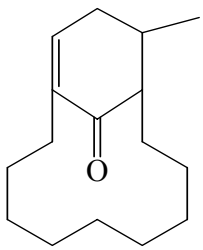
After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent, to obtain 1.7 g (5.6 mmol, 71 % yield) of ethyl 14-methyl-15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**183**) ($C_{19}H_{30}O_3$, 306.42 g / mol). **Spectroscopic data** are consistent with those reported in R 99.

R 108 Amounts:

2.0	g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6	g (11.81 mmol)	NaOH
0.4	g (7.88 mmol)	crotonic aldehyde (**170**)
50ml		EtOH

Procedure: Analogously to R 77, 18 hours, refluxing ethanol.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to give 940 mg (4.0 mmol, 51 % yield) of 14-methyl-bicyclo[9.3.1]pentadecan-11-en-15-one (**185**) ($C_{16}H_{26}O$, 234.20 g / mol).



185

Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.25 (m, 1H, CH), 2.85-2.80 (m, 1H, CH_2), 2.75-2.67 (m, 1H, CH_2), 2.45-2.42 (m, 2H, CH_2), 2.13-2.09 (m, 2H, CH_2), 2.03-1.97 (m, 1H, CH_2), 1.72-1.66 (m, 2H, CH_2), 1.70-1.67 (m, 1H, CH_2), 1.65 (dd, 3H, ^3J = 12.8 Hz, ^3J = 2.5 Hz, CH_2), 1.38-1.08 (m, approx. 7H, CH_2), 0.98 (m, 3H, ^3J = 7.2 Hz, CH_3), 0.81 (m, 3H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 204.38 (CO), 142.40 (CH), 136.83 (C_q), 54.97 (CH), 40.34 (CH), 34.67 (CH), 29.91 (CH_2), 26.34 (CH_2), 24.70 (CH_2), 24.18 (CH_2), 22.84 (CH_2), 22.82 (CH_2), 22.42 (CH_2), 22.28 (CH_2), 21.94 (CH_2), 19.97 (CH_3). **Elemental Analysis**: Calcd. % C 81.99, % H 11.18, Found % C 81.8, % H 11.4.

R 109 Amounts:

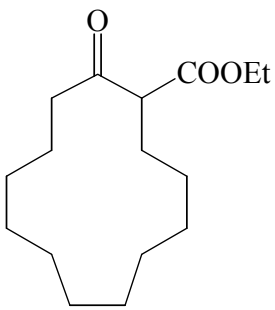
2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.6 g (11.81 mmol)	NaOH
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	EtOH

Procedure: Analogously to R 77, 72 hours, refluxing ethanol.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to give 0.3 g (1.6 mmol, 21 % yield) of 14-methyl-bicyclo[9.3.1]-pentadecan-11-en-15-one (**185**) ($C_{16}H_{26}O$, 234.20 g / mol) are isolated. **Spectroscopic data** are consistent with those reported in R 108.

Preparation of ethyl 2-oxo-cyclotridecane carboxylate (186)

R 110: 4.11 ml (4.61 g, 40.5 mmol)of boron trifluorid etherate is added to a solution of 5.0 g (27.0 mmol) of cyclododecanone (**11**) in dry 40 ml of diethylether at 0°C. A solution of 5.25 ml (5.75 g, 40.5 mmol) ethyl diazoacetate (**187**) (40.5 mmol) in 20 ml of dry diethylether is then added over a period of 15 min, and the resulting solution is stirred at room temperature under an argon atmosphere. When the reaction is completed, it is cooled to 0°C and neutralized with 40 ml of saturated aqueous sodium bicarbonate solution. The resulting mixture is extracted with chloroform (3 x 30 ml). The combined extracts are washed with saturated aqueous sodium chloride solution, dried, and concentrated. After removing of solvent the residue is distilled under vacuum 120°C, $1.4x10^{-1}$ mbar. 6.5 g (24.3 mmol, 90 % yield) of ethyl 2-oxo-cyclotridecane carboxylate (**186**) ($C_{16}H_{30}O_3$, 267.34 g / mol) are isolated. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.11 (q, 2H, ^3J = 6.9 Hz, CH_2CH_3), 3.50 (dd, 2H, ^3J = 3.7 Hz, ^3J = 2.4 Hz, CH), 2.65 (m, 3H, CH_2), 2.57 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 1.80 (m, 5H, CH_2), 1.60 (m, 2H, CH_2), 1.25 (m, approx. 9H, CH_2), 1.19 (t, 3H, ^3J = 6.9 Hz, CH_2CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 206.81 (CO), 169.82 (CO), 61.13 (CH_2CH_3), 58.15 (CH), 41.16 (CH_2), 27.62 (CH_2), 26.27 (CH_2), 25.96 (CH_2), 25.37 (CH_2), 25.15 (CH_2), 24.83 (CH_2), 24.27 (CH_2), 24.16 (CH_2), 23.04 (CH_2), 22.63 (CH_2), 13.99



186

(CH_2CH_3). **IR (KBr/film): $\tilde{\nu}$ [cm^{-1}]** = 2999 (s), 2992 (s), 2937 (s), 2928 (s), 1741 (s), 1705 (s), 1471 (m), 1427 (s), 1250 (m), 1128 (m).

R 111 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	acrolein (**166**)
50ml	EtOH

Procedure: Analogously to R 77, 18 h, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (3:1) as eluent to give 1.7 g (5.6 mmol, 72 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{18}H_{30}O_4$, 310.42 g / mol) as a brown oil as a mixture of two diastereoisomers in a ratio of 1:1.8 (detected by NMR). 0.7 g (2.5 mmol, 32 % yield) of compound **174** as a colorless crystal is obtained as a single diastereoisomer, by recrystallization from Et_2O. **Spectroscopic data** are consistent with those reported in R 82.

R 112 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	acrolein (**166**)
50.0 ml	EtOH

Procedure: Analogously to R 77, 18 hours, refluxing ethanol.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent, to give 940 mg (3.2 mmol, 41 %) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 291.42 g / mol). **Spectroscopic data** are consistent with those in R 83.

R 113 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	acrolein (**166**)
50.0 ml	EtOH

Procedure: Analogously to R 77, 72 hours, refluxing ethanol.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent to give 1.6 g (5.7 mmol, 73 %) of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 291.42 g / mol). **Spectroscopic data** are consistent with those in R 83.

Preparation of methyl 12-hydroxy-13-methyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (188)

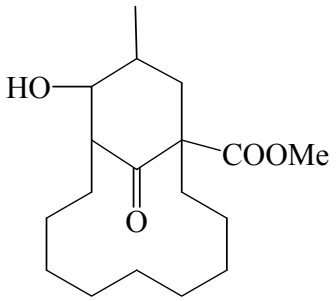
R 114 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	MeOH

Procedure: Analogously to R 77, 18 h, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to give 255 mg (0.78 mmol, 10 % yield) of 12-hydroxy-13-methyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**175**) ($C_{19}H_{32}O_4$, 324.45 g / mol) and 1.7 g (5.6 mmol, 71 % yield) of methyl 13-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**188**) ($C_{18}H_{30}O_4$, 310.42 g / mol). Compound **188** is obtained as a mixture of diastereoisomer in a ratio of 1:1.5 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3). 0.9 g (2.9 mmol, 37 % yield) of **188** are isolated as a single diastereoisomer by recrystallization from Et_2O. **Spectroscopic data:** **^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.76 (m, 1H, ^{3}J = 5.7 Hz, CH), 3.71 (s, 3H, CH_3), 3.11 (dd, 2H, ^{3}J = 5.9 Hz, ^{3}J = 2.4 Hz, CH), 2.15-1.86 (m, 8H, CH_2), 1.74-1.65 (m, 2H, CH_2), 1.59-1.52 (m, 1H, CH_2), 1.36-1.03 (m approx. 12H, CH_2), 1.16, 1.10 (d, 3H, ^{3}J = 6.7 Hz, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 210.16 (CO), 171.082

(CO), 80.47 (CH), 61.34 (C_q), 51.97 (CH), 46.84 (CH_3 / CH), 41.18 (CH_2), 36.90 (CH / CH_3), 35.15 (CH_2), 26.17 (CH_2), 26.070 (CH_2), 22.92 (CH_2), 22.625 (CH_2), 22.36 (CH_2), 21.96 (CH_2), 21.81 (CH), 20.40 (CH_2), 20.04 (CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3514 (s), 2942 (s), 2915 (s), 2864 (s), 1739 (s), 1703 (s), 1470 (m), 1433 (m), 1310 (m), 1298 (m), 1073 (m), 1063 (m), 969 (m), 878 (m), 819 (m), 784 (m). **LR-MS (EI, 70 eV): m/z (%)** = 310 (M+, 2.78), 292 (43), 205 (7.20), 123 (4.34), 109 (8.40), 95 (13.15), 81 (26.06), 67 (28.43), 55 (44.81), 41 (61.57), 28 (38.47), 18 (100). **HR-MS (EI, 70 eV)**: Calcd 310.2144, Found 310.2140. **Elemental Analysis**: Calcd. % C 69.64, % H 9.74, Found % C 69.7, % H 9.8%.



188

Preparation of methyl 12-hydroxy-14-methyl-15-oxo-bicyclo[9.3.1]pentadecan-1-carboxyl (189)

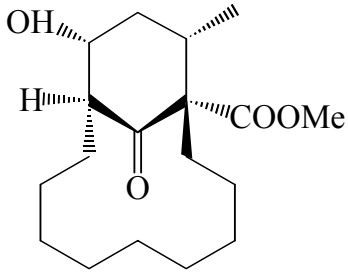
R 115 Amounts:

2.0 g (7.88mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	MeOH

Procedure: Analogously to R 77, 18 hours, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent to give 1.8 g (5.7 mmol, 73 % yield) of methyl 12-hydroxy-14-methyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**189**) ($C_{18}H_{30}O_4$, 310.42 g / mol) as a mixture of diastereoisomer in a ratio of 1:1.33 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3). 1.3 g (4.4 mmol, 62 % yield) of **189** are isolated as a single diastereoisomer by recrystallization from Et_2O. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 3.74 (m, 1H, CHOH), 3.66 (s, 3H, CH_3), 2.95 (m, 2H, CH_2/CH), 2.50 (m, 3H, CH_2), 2.30 (d, 2H, ^3J = 3.4 Hz, CH_2), 2.12 (m, 4H, CH_2), 1.90 (m, 1H, CH_2), 1.70–1.42 (m, 2H, CH_2), 1.29-1.14 (m, approx. 9H, CH_2), 1.16, 1.12 (d, 3H, ^3J = 6.9 Hz, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 211.91 (CO), 172.72 (CO), 74.16 (CH), 67.85 (C_q), 51.42 (CH), 52.87 (CH), 40.01 (CH_2),

38.89 (CH), 34.62 (CH_2), 27.57 (CH_2), 26.44 (CH_2), 23.88 (CH_2), 23.77 (CH_2), 23.70 (CH_2), 22.99 (CH_2), 21.20 (CH_2), 20.04 (CH_2), 17.66 (CH). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3514 (s), 2942 (s), 2915 (s), 2864 (s), 1739 (s), 1703 (s), 1470 (m), 1433 (m), 1310 (m), 1298 (m), 1073 (m), 1063 (m), 969 (m), 878 (m), 819 (m), 784 (m). **LR-MS (EI, 70 eV): m/z (%)** = 310 (M^+, 2.78), 251 (9.6), 236 (19.03), 222 (2.21), 208 (4.04), 180 (1.59), 166 (1.58), 152 (3.61), 124 (7.51), 110 (9.85), 96 (19.25), 82 (36.71), 68 (22.16), 55 (44.81), 41 (61.57), 29 (27.42), 18 (100). **HR-MS (EI, 70 eV)**: Calcd. 310.2144, Found 310.2140. **Elemental Analysis**: Calcd. % C 69.64, % H 9.74, Found % C 69.7, % H 9.9.



189

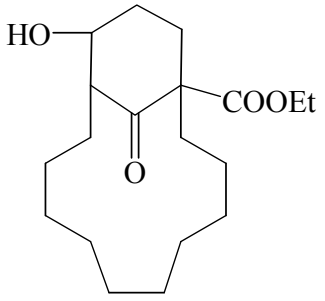
Preparation of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]hexadecan carboxylate (190)

R 116 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclotridecane carboxylate (**186**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	acrolein (**166**)
50 ml	EtOH

Procedure: Analogously to R 77, 18 hours, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane / Et_2O (2:1) as eluent giving 1.9 g (6.1 mmol, 78 % yield) of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]hexadecan carboxylate (**190**) ($C_{19}H_{32}O_4$, 324.45 g/ mol) as a mixture of two diastereoisomers in a ratio of 1:1 (detected by NMR analysis with respect to the CH_2CH_3). 0.6 g (1.8 mmol, 23 % yield) of compound **190** is isolated as a single diastereoisomer by recrystallization from Et_2O. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 4.17, 4.12 (q, 2H, ^3J = 7.2 Hz, CH_2CH_3), 3.50 (m, 1H, CH), 2.61 (m, 1H, CH_2), 2.14 (m, 3H, CH), 1.84 (m, 6H, CH_2), 1.56-1.34 (m, approx. 11H, CH_2), 1.24, 1.22 (t, 3H, ^3J = 7.2 Hz, CH_2CH_3), 1.07



190

(m, 5H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 208.02 (CO), 172.65 (CO), 73.70 (CH), 60.96 (CH_2CH_3), 60.84 (C_q), 55.25 (CH), 33.90 (CH_2), 30.70 (CH_2), 30.13 (CH_2), 29.95 (CH_2), 27.14 (CH_2), 26.88 (CH_2), 26.33 (CH_2), 25.77 (CH_2), 25.26 (CH_2), 24.85 (CH_2), 23.11 (CH_2), 22.99 (CH_2), 14.07 (CH_2CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3435 (s), 2975 (s), 2930 (s), 2861 (s), 1734 (s), 1711 (s), 1446 (m), 1380 (s), 1250 (m), 1184 (s), 1119 (m). **LR-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 9.65), 196 (7.41), 98 (9.16), 84 (45.07), 81 (30.48), 56 (50.70), 42 (20.39), 29 (84.32), 18 (43.99), 15 (6.650). **HR-MS (EI, 70 eV)**: Calcd. 324.2301, Found 324.5303.

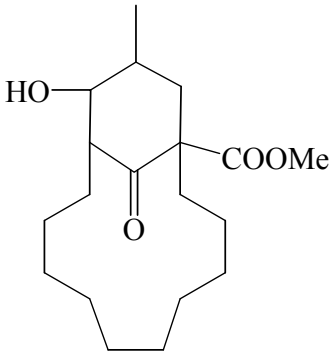
Preparation of methyl 13-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]hexadecan carboxylate (191)

R 117 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclotridecane carboxylate (**186**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	methacrolein (**169**)
50 ml	MeOH

Procedure: Analogously to R 77, 18 hours, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent giving 1.7 g (5.3 mmol, 68 % yield) of a mixture of diastereoisomers in a ratio of 1:3:8:2 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3) of methyl 12-hydroxy-13-methyl-15-oxo-bicyclo[9.3.1]hexadecan carboxylate (**191**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as colorless crystal. **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.66, 3.64 (s, 3H, CH_3), 3.55 (m, 1H, CH), 2.95 (m, 2H, CH), 2.88, 2.85 (d, 1H, ^{3}J = 5.4 Hz, CH), 2.60 (m, 5H, CH_2), 2.11-1.01 (m, approx. 18H, CH_2), 1.06, 0.95 (d, 3H, ^{3}J = 6.9 Hz, CH_3), 1.02 (m, 5H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 210.51, 208.07 (CO), 173.23, 173.14 (CO), 78.50, 76.45 (CH), 61.31, 60.87 (C_q), 54.06, 53.25, 51.92 (CH_3 / CH), 39.15, 38.38 (CH_2), 35.96



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(CH_2), 34.40 (CH_2), 35.18, 33.00 (CH), 30.08 (CH_2), 27.07 (CH_2), 26.75, 26.68 (CH_2), 26.39 (CH_2), 25.18 (CH_2), 25.67 (CH_2), 25.18 (CH_2), 23.12 (CH_2), 23.03 (CH_2), 17.81, 15.21 (CH_3). **IR (neat), $\tilde{\nu}$ [cm^{-1}]** = 3512 (s), 2928 (s), 2857 (s), 1739 (s), 1711 (s), 1459 (m), 1369 (w), 1247 (m), 1121 (s), 1055 (m). **LR-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 20.32), 306 (13.21), 82 (11.52), 68 (14.77), 54 (12.12), 41 (100), 29 (37.17), 18 (69). **HR-MS (EI, 70 eV)**: Calcd. 324.2301, Found 310.2140.

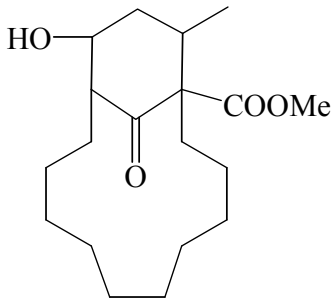
Preparation of methyl 14-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (192)

R 118 Amounts:

2.0 g (7.88 mmol)	ethyl 2-oxo-cyclotridecane carboxylate (**186**)
1.2 g (7.88 mmol)	DBU
0.4 g (7.88 mmol)	crotonic aldehyde (**170**)
50 ml	MeOH

Procedure: Analogously to R 77, 18 hours, room temperature.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent giving 1.5 g (4.8 mmol, 62 % yield) of methyl 14-methyl-12-hydroxy-15-oxo-bicyclo[9.3.1]hexadecan carboxylate (**192**) ($C_{19}H_{32}O_4$, 324.45 g / mol) as a mixture of two diastereoisomers in a of ratio of 1:1.37 detected by ^{1}HNMR analysis (ratio calculated with respect to CH_3). **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.73, 3.66 (s, 3H, CH_3), 3.69 (m, 1H, CH), 2.78 (m, 2H, CH), 2.58 (m, 3H, CH_2), 2.23 (m, 2H, CH_2), 2.62 – 2.36 (m, 4H, CH_2), 2.04-1.57 (m, 4H, CH_2), 1.45 (m, 2H, CH_2), 0.87 (d, 3H, ^{3}J = 1.9 Hz, CH_3), 0.80 (d, 3H, ^{3}J = 2.7 Hz, CH_3). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 209.27, 208.05 (CO), 171.08 (CO), 72.22, 71.34 (CH), 65.81, 65.46 (C_q), 54.56, 53.56(CH_3 / CH), 52.03, 51.56 (CH / CH_3), 38.83 (CH_2), 38.22 (CH_2), 33.99 (CH_2), 33.09 (CH_2), 33.82, 30.84 (CH), 28.36 (CH_2), 27.11 (CH_2), 26.84 (CH_2), 26.77, 26.66 (CH_2), 26.57 (CH_2), 26.33 (CH_2), 25.79, 25.65 (CH_2), 25.04 (CH_2), 24.91 (CH_2), 23.06 (CH_2), 22.79 (CH_2), 16.10, 15.99 (CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3512 (s), 2928 (s), 2857



192

(s), 1739 (s), 1711 (s), 1459 (m), 1369 (w), 1247 (m), 1121 (s), 1055 (m). **LR-MS (EI, 70 eV): m/z (%)** = 324 (M^+, 3.68), 98 (9.36), 84 (61.45), 70 (5.78), 59 (18.32), 31 (100), 29 (74), 18 (22.69), 15 (7.77). **HR-MS (EI, 70 eV)**: Calcd. 324.2301, Found 324.2283.

R 119: To a 50 ml of dry EtOH, 360 mg (16.0 mmol) of Na is added slowly under stirred at 0°C. The suspension is stirred until Na is completely dissolved. Then, carefully a solution of 4.0 g (15 mmol) of ethyl 2-oxo-cyclododecane carboxylate (**72**) is added, the solution is stirred for 1 h and, finally, a solution of 2.0 ml (0.8 g 15 mmol) of acrolein (**166**) is added. The whole solution is, then, stirred at RT for 18 h. A solution of 40 ml of acetic acid is added until Na is completely reacted and the excess of acetic acid is removed with a solution of 50 ml of sodium carbonate. The organic layer is separated and the aqueous phase is extracted with diethylether (3 x 30 ml). The combined organic layers are dried over anhydrous $MgSO_4$ and the solvent is removed in vacuum. A mixture of ethyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**) ($C_{19}H_{32}O_4$, 324.24 g / mol) and ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) ($C_{18}H_{28}O_3$, 292.20 g / mol) is obtained in a ratio of 1.6:1 detected by NMR. The products are separated by column chromatography on alumina N (III), cyclohexane / Et_2O (2:1) giving 2.7 g (8.4 mmol, 56 % yield) of compound **174** and 1.3 g (4.5 mmol, 30 % yield) of compound **177**.

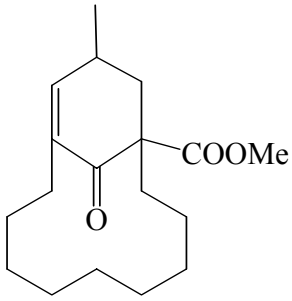
Spectroscopic data of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**174**) are consistent with those reported in R 82. **Spectroscopic data** of ethyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**177**) are consistent with those reported in R 83.

R 120 Amounts:

4.0 g (15.0 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
360 mg (15.0 mmol)	Na
0.8 g (15.0 mmol)	methacrolein (**169**)
50 ml	abs. MeOH

Procedure: Analogously to R 119, 18 hours, room temperature.

After removing of the solvent the crude mixture is consistent of methyl 12-hydroxy-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**188**) ($C_{19}H_{32}O_4$, 310.45 g / mol) and methyl 15-oxo-13-methyl-bicyclo[9.3.1]pentadec-11-ene carboxylate (**193**) ($C_{18}H_{28}O_3$, 292.20 g / mol) in 54 and 46% yield, respectively (NMR-calculated with respect to the CH_3). **Spectroscopic data of** methyl 13-methyl-15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**193**) are assigned by the most significant signals: **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.63 (s, 1H, CH) **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 201.54 (CO), 143.01 (C_q), 137.49 (CH).



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Spectroscopic data of compound **188** are consistent with those reported in R 114

R 121 Amounts:

4.0 g (15.0 mmol)	ethyl 2-oxo-cyclododecane carboxylate (**72**)
360 mg (15.0 mmol)	Na
0.8 g (15.0 mmol)	crotonic aldehyde (**170**)
50 ml	abs. EtOH

Procedure: Analogously to R 119, 18 hours, room temperature.

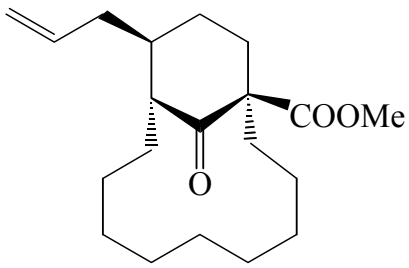
After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (2:1) as eluent giving 2.9 g (10.2 mmol, 68 % yield) of ethyl 15-oxo-13-methyl-bicyclo[9.3.1]pentadec-11-ene carboxylate (**183**) ($C_{18}H_{28}O_3$, 292.20 g / mol). **Spectroscopic data** are consistent with those reported in R 99.

4.6. Preparation of tricyclic compounds starting from bicyclic compounds

4.6.1. Preparation of starting material

Preparation of methyl 12-allyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (197)

R 122: To a solution of 1.6 g (6.55 mmol) of methyl 15-oxo-bicyclo[9.3.1]pentadec-11-ene carboxylate (**184**) in 30 ml of dry dichloromethane under argon is added a solution of 0.7 ml $TiCl_4$ (**101**) (1.2 g, 6.55 mmol) in 20 ml of abs dichloromethane dropwise with a syringe. After additional stirring for 30 min., 1.23 ml of allyltrimethylsilane (**62**) (0.8 g, 7.8 mmol) in 15 ml of abs. dichloromethane is added from a dropping funnel at –78°C and the mixture is stirred for 16 hours. 50 ml of water and, under stirring, carefully, a solution of sodiumhydrogenocarbonate is added to the mixture which is subsequently extracted with diethylether (3 x 30 ml). The organic layer is washed with water, dried over $MgSO_4$ and concentrated at reduced pressure. The residue is subjected to silica gel column chromatography using as eluent a solution of cyclohexane - diethylether (10:1) yielding 2.0 g (6.2 mmol, 96 % yield) of methyl 12-allyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**197**) ($C_{20}H_{32}O_3$, 320.49 g / mol).



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Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.74 (ddd, 1H, ^3J = 16.3 Hz, ^3J = 10.2 Hz, ^3J = 7.2 Hz, C*H*=CH_2), 4.99 (m, 2H, CH=C*H*$_2$), 3.67 (m, 1H, CH), 3.71 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 2.15 (m, 4H, CH_2), 1.96 (m, 6H, CH_2), 1.60 (m, 5H, CH_2), 1.36-1.26 (m, approx. 3H, CH_2), 0.80 (m, 5H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 211.38 (CO), 174.22 (CO), 135.96 (*C*H=CH_2), 116.70 (CH=*C*H$_2$), 61.18 (C_q), 55.11 (CH_3 / CH), 52.03 (CH_3 / CH), 41.43 (CH_3 / CH), 38.10 (CH_2), 36.40 (CH_2), 31.79 (CH_2), 30.12 (CH_2), 26.36 (CH_2), 25.73 (CH_2), 24.18 (CH_2), 23.05 (CH_2), 21.91 (CH_2), 21.49 (CH), 20.48 (CH_2), 20.19 (CH_2). **IR (KBr): $\tilde{\nu}$ [cm^{-1}]** = 3034 (w), 2942 (s), 2915 (s), 2864 (s), 1739 (s), 1703 (s), 1470 (m), 1433 (m), 1310 (m), 1298 (m), 1073 (m), 1063 (m), 969 (m), 878 (m), 819 (m), 784 (m).

Conversion of methyl 12-enyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (200).

R 123: 14.7 ml of vinyl bromide (**198**) (0.8g, 11.7 mmol) in 30 ml THF are stirred at –10°C under Argon. 0.8 g of CuI (11.7 mmol) is added to the slurry in one portion. After 30 min. at –10°C, the mixture is cooled at –78°C. 4 g (11.7 mmol) of methyl 12-enyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate **(184)** in 30 ml of dry THF are added dropwise over 30 min. to the reaction mixture. The cooling bath is removed and the mixture reaction is warmed to the room temperature. The reaction mixture is added to 100 ml of a mixture of saturated ammonium chloride:ammonium hydroxide (9:1) and 200 ml of cyclohexane. The aqueous layer is separated and extracted with cyclohexane (3 x 30 ml). The organic layer are individually washed with 9:1 mixture of saturated ammonium chloride:ammonium hydroxide until the aqueous phase is no longer blue. The organic layers are then washed with 40 ml of water and 30 ml of brine, combined and dried over $MgSO_4$. The residue is purified by silica gel chromatography using as a solvent a mixture of cyclohexane-diethylether (10:1). Products derived from decomposition are recovered.

R 124 Amounts:

1.0 g (4.5 mmol)	bicyclo[9.3.1]pentadec-11-en-15-one (**167**)
0.8 g (9.13 mmol)	vinylmagnesiumchloride (**198**)
0.8 g (4.50 mmol)	CuI
50 ml	abs. THF

Procedure: Analogously to R 123

After removing of the solvent, 8% conversion of compound **167** is detected by GC-analysis.

4.6.2. Tandem hydroformylation / aldol addition.

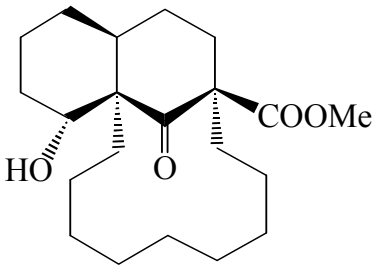
Preparation of methyl 18-hydroxy-19-oxo-tricyclo[9.7.1.0$^{1.14}$]nonadecan-11-carboxylate (201).

R 125 Amounts:

2.0 g (6.25 mmol)	methyl 12-allyl-15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**197**)
20.1 mg (1 mmol %)	$Rh(acac)(CO)_2$
16.3 mg (4 mmol %)	BIPHEPHOS (**16**)
24.7 mg (5 mmol %)	*p*-TsOH
50 ml	abs. CH_2Cl_2

Procedure: Analogously to R 18.

After removing of the solvent the crude mixture is filtered on pad of alumina N (III) using cyclohexane/ Et_2O (10:1) as eluent giving 946 mg (2.6 mmol, 43 % yield) of methyl 18-hxdroxy-19-oxo-tricyclo[9.7.1.0$^{1.14}$]nonadecan-11-carboxylate (**201**) ($C_{21}H_{34}O_4$, 350.491 g / mol). **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.1 (s, 1H, OH), 3.71 (s, 3H, CH_3), 2.4 (m, 3H, CH), 2.15 (m, 8H, CH_2), 2.10 (d, 2H, ^3J = 4.2 Hz, CH_2), 1.96-1.36 (m, approx. 9H, CH_2), 1.26-1.15 (m, approx. 8H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 210.16 (CO), 174.61 (CO), 67.52 (CH), 61.08 (C_q), 60.82 (C_q), 52.81 (CH), 38.31 (CH), 32.73 (CH_2), 30.07 (CH_2), 28.45 (CH_2), 27.51 (CH_2), 27.48 (CH_2), 26.78 (CH_2), 26.78 (CH_2), 23.74 (CH_2), 23.66 (CH_2), 23.60 (CH_2), 23.46 (CH_2), 23.22 (CH_2), 23.14 (CH_2), 19.77 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3514 (s), 2942 (s), 2915 (s), 2864 (s), 1739 (s), 1703 (s), 1470 (m), 1433 (m), 1310 (m), 1298 (m), 1073 (m), 1063 (m), 969 (m), 878 (m), 819 (m), 784 (m). **Elemental analysis**: Calcd. % C 71.96, % H 9.78, Found % C 72.0, % H 10.3.



201

4.7. Fragmentation reaction and rings expansion methods

4.7.1. Baeyer-Villiger oxidation

Oxidation of 12-hydroxy-bicyclo[9.4.1]pentadecan-16-one (50)

R 126: A solution of 1.0 g (3.96 mmol) of 12-hydroxy-bicyclo[9.4.1]pentadecan-16-one (**50**) in abs. chloroform is added to a solution of 0.84 g (7.56 mmol) of *m*-chloroperbenzoic acid (**212**) in 30 ml of abs. $CHCl_3$. The reaction mixture is heated at 0°C for 16 hours. Then, the mixture is cooled in ice-water; the solvent is removed under vacuum on a rotary evaporator. The residue is taken up in 50 ml of Et_2O, washed three times with 20 ml of aqueous K_2CO_3 and once with brine solution. After drying and removing of the solvent, the white crystalline starting material is recovered.

R 127 Amounts

1.0 g	(3.96 mmol)	12-hydroxy-bicyclo[9.41]hexadecane-16-one (**50**)
0.84 g	(7.56 mmol)	*m*-CPBA (**212**)
3.0 g	(29.0 mmol)	$NaHCO_3$
30 ml		abs. $CHCl_3$

Procedure: Analogously to R 126, 20°C, 18h.
Starting material is recovered.

Preparation of bicyclo[9.4.1]hexadec-12-en-16-one (96)

R 128: 1.0 g (3.96 mmol) of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) is dissolved in 40 ml of toluene and 20 ml of H_2SO_4 (98%) are added dropwise at a moderate rate with mechanical stirred. The mixture is stirred at room temperature for 20 hours. The brown resulting suspension is poured onto cracked ice and the mixture is treated with a solution of Na_2CO_3. The organic extracted with diethylether are dried over $MgSO_4$ and the solvent is removed under reduced pressure. Filtration on alumina N (III), cyclohexane / Et_2O (5:1) purifies the crude product. 140 mg (0.6 mmol, 15 % yield) of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.38 g / mol) as a white

solid compound are obtained. Its spectroscopic characteristics are consistent with those reported in R 39.

R 129: 1.2 g (4.7 mmol) of 12-hydroxy bicyclo[9.4.1]hexadecan-16-one (**50**) is dissolved in 40 ml of toluene and 6.5 g (32.9 mmol) of *p*-TsOH are added. The mixture is stirred at room temperature for 20 hours. The reaction mixture is treated with 30 ml of a solution of Na_2CO_3. The organic extracted with diethylether are dried over $MgSO_4$ and the solvent is removed under reduced pressure. Filtration on alumina N (III), cyclohexane / Et_2O (5:1) purifies the crude mixture. 384 mg (1.6 mmol, 35 % yield) of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.42 g / mol) as a white solid compound are obtained. Its spectroscopic characteristics are consistent with those reported in R 39.

R 130: 1.0 g (3.96 mmol) of 12-hydroxy bicyclo[9.4.1]hexadecan-16-one (**50**) is dissolved in 50 ml of pyridine. The solution is cooled in an ice bath and stirred magnetically while 3.3 ml (5.3 g, 44 mmol) of thionyl chloride is added dropwise at a slow rate. The mixture is stirred for 12 hours as it warmed to ambient temperature. The brown resulting suspension is poured onto ice-water and the mixture is acidified with 20 ml of cold mixture of HCl (20 %). The organic extracted are dried over $MgSO_4$ and the solvent is removed under reduced pressure. By GC analysis only 25 % conversion in bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.42 g / mol) is observed. Its spectroscopic characteristics are consistent with those reported in R 39.

R 131: 0.5 g (1.93 mmol) of 12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**) is dissolved in 80 ml of toluene and 1.82 g (1.93 mmol) $CuSO_4$ / silica (the catalyst is prepared from a mixture of one part of copper (II) sulfate pentahydrate and three parts of silica gel (by being dried at 240°C for 1 hour gel) is added. The mixture is heated at reflux with stirring for 20 hours. After cooling, the catalyst is removed by filtration. The solvent is removed under reduced pressure and starting material is recovered.

R 132: 0.54 g (3.8 mmol) of P_2O_5 is placed in a flask containing 30 ml of abs. toluene under Argon. 0.5 g (1.93 mmol) of 12-hydroxy bicyclo[9.4.1]hexadecan-16-one (**50**) is dissolved in 80 ml of toluene and the solution is added dropwise at a moderate rate with mechanical stirred. The mixture is heated at reflux for 18 hours. The P_2O_5 formed a dark, viscous deposit on the walls of the flask. The mixture is cooled to room temperature and filtered through alumina N (III). After removing of the solvent on the rotary evaporator, a mixture of the two isomers are, then, purified by column chromatography on alumina N (III), cyclohexane / Et_2O (5:1) 649 mg (2.7 mmol, 73 % yield) of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.42 g / mol) is observed. Its spectroscopic characteristics are consistent with those reported in R 39.

R 133: Amounts

0.5 g	(1.93 mmol)	12-hydroxybicyclo[9.4.1]hexadecan-16-one (**50**)
0.54 g	(3.8 mmol)	DBU
50 ml		EtOH

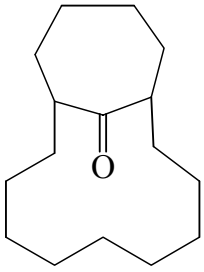
Procedure: Analogously to R27, 16 hours, refluxing EtOH.

After removing of the solvent by rotary evaporator, the crude mixture of the two isomers are then purified by column chromatography on alumina N (III), cyclohexane/ Et_2O (5:1). 383 mg (1.6 mmol, 85 %) of bicyclo[9.4.1]hexadec-12-en-16-one (**96**) ($C_{16}H_{26}O$, 234.42 g / mol) is observed. Its spectroscopic characteristics are consistent with those reported in R 39.

Preparation of bicyclo[9.4.1]hexadecan-16-one (215)

R 134: A solution of 1.2 g (8.5 mmol) of bicyclo[9.4.1]hexadecan-12-ene-16-one (**96**) in ethylacetate is hydrogenated over 300 mg Pd - C (10 % mmol) at room temperature and atmospheric pressure. The uptake of hydrogen ceased after 18 hours. The mixture is filtered from catalyst. Evaporation of the solvent furnish 1.3 g (5.4 mmol, 64 % yield) of bicyclo[9.4.1]hexadecan-16-one (**215**) ($C_{16}H_{28}O$, 236.40 g / mol) as a white solid. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 2.93-2.86 (dd, 2H, ^3J = 11.80 Hz, ^3J = 2.76 Hz, CH), 2.24 (m, 3H, CH_2), 1.90 (m, 4H, CH_2),

1.70 (m, 4H, CH_2), 1.60-1.51 (m, 4H, CH_2), 1.25 (m, 8H, CH_2), 0.8 (m, 3H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 218.70 (CO), 55.58 (CH), 44.57 (CH), 35.90 (CH_2), 32.12 (CH_2), 31.64 (CH_2), 31.60 (CH_2), 30.58 (CH_2), 27.27 (CH_2), 26.86 (CH_2), 26.10 (CH_2), 24.24 (CH_2), 23.70 (CH_2), 23.05 (CH_2), 21.73 (CH_2), 21.63 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 2927 (s), 2858 (s), 1708 (s), 1632 (w), 1604 (w), 1138 (w), 729 (m). **LR-MS (EI, 70 eV): m/z (%)** = 236 (M^+, 18), 207 (100), 191 (17), 179 (15), 147 (25), 119 (18), 98 (40), 73 (58), 67 (25), 55 (38).



215

Attempted oxidation of bicyclo[9.4.1]hexadecan-16-one (215)

R 135: 1.0 ml (1.1 g, 15.0 mmol) of peracetic acid (**217**) is added to a cooled solution of 1.0 g (4.6 mmol) of bicyclo[9.4.1]hexadecan-16-one (**215**) in dichloromethane containing 0.6 g of $NaHCO_3$. The resulting mixture is stirred at 0°C for 10 hours, washed with 30 ml of a solution of saturated aqueous $NaHSO_3$, The organic extracted with diethylether are dried over $MgSO_4$. After removing of the solvent, starting material is recovered.

R 136 Amounts:

0.8 g (3.38 mmol)	bicyclo[9.4.1]hexadecan-16-one (**215**)
0.77 g (4.56 mmol)	*m*-CPBA (**212**)
43 mg (0.4 mmol)	$NaHCO_3$
30 ml	abs. $CHCl_3$

Procedure: Analogously to R 126, 20 hours, room temperature.
After removing of the solvent, starting material is recovered.

R 137 Amounts:

0.8 g (3.38 mmol)	bicyclo[9.4.1]hexadecan-16-one (**215**)
0.77 g (4.56 mmol)	*m*-CPBA (**212**)

43 mg (0.4 mmol)	$NaHCO_3$
30 ml	abs. $CHCl_3$

Procedure: Analogously to R 126, 48 hours, refluxing.

After removing of the solvent, starting material is recovered.

R 138 Amounts:

1.0 g	(4.6 mmol)	bicyclo[9.4.1]hexadecan-16-one (**215**)
2.0 g	(27.4 mmol)	peracetic acid (**217**)
0.4 g	(3.0 mmol)	$BF_3 \cdot OEt_2$
30 ml		abs. CH_3CCl_3

Procedure: Analogously to R 126, 5 days, 50°C.

After removing of the solvent, starting material is recovered.

Baeyer Villiger of bicyclo[9.3.1]pentadecane derivatives

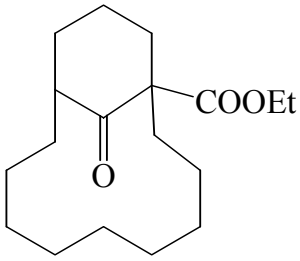
Preparation of ethyl 15-oxo-bicyclo[9.3.1]pentadecan carboxylate (219)

R 139 Amounts:

1.0 g	(4.27 mmol)	ethyl bicyclo[9.3.1]pentadecan-11-ene-15-one-carboxylate (**177**)
300 mg		Pd / C
50 ml		EtOAc

Procedure: Analogously to R 134

Evaporation of solvent furnish 0.9 g (3.1 mmol, 74 % yield) ethyl 15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**219**) ($C_{18}H_{28}O_3$, 294.42 g / mol) in a ratio of 1:1 detected ^{1}HNMR (ratio calculated with respect to CH_2CH_3) as a white solid compound. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.11, 4.09 (q, 2H, ^3J = 7.0 Hz, CH_2CH_3), 2.80 (dd, 1H, ^3J = 12.0 Hz, ^3J = 3.51 Hz, CH), 2.43-2.40 (m, 1H, CH_2), 2.38-2.34 (dd, 1H, ^3J = 11.5 Hz, ^3J = 3.5 Hz, CH*H*), 2.36-2.34 (dd, 1H, ^3J = 9.0 Hz, ^3J = 2.5 Hz, C*H*H), 1.97 (ddd, 4H, ^3J =



219

12.5 Hz, ^3J = 5.7 Hz, ^3J = 5.0 Hz, CH), 1.80 (m, 3H, CH), 2.03-1.91 (m, 3H, CH_2), 1.88-1.58 (m, 4H, CH_2), 1.45-1.05 (m, 4H, CH_2), 1.20, 1.19 (t, 3H, ^3J = 7.0 Hz, CH_2CH_3), 0.86 (m, 3H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 211.10 (CO), 173.64 (CO), 61.72 (C_q), 60.71 (CH_2CH_3), 52.15, 49.88 (CH), 40.27, 39.64 (CH_2), 36.09 (CH_2), 35.68 (CH_2), 32.30 (CH_2), 30.64 (CH_2), 28.27 (CH_2), 26.34, 26.36, (CH_2), 26.91, 25.78 (CH_2), 24.32 (CH_2), 23.12 (CH_2), 21.39 (CH_2), 20.26, 20.24 (CH_2), 17.33 (CH_2), 14.12 (CH_2CH_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 2929 (s), 2865 (s), 1735 (s), 1697 (s), 1469 (m), 1445 (s), 1240 (m), 1178 (m), 1152 (w), 1121 (w). **LR-MS (EI, 70 eV): m/z (%)** = 294 (M^+, 92.32), 220 (33.85), 170 (100), 122 (11.77), 95 (23.34), 81 (30.72), 55 (81.02), 41 (90.91), 29 (31.91). **HR-MS (EI, 70eV):** Calcd. 294.2195, Found 294.2169.

R 140 Amounts:

1.0 g (1.26 mmol)	ethyl 15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**219**)
0.9 g (9.2 mmol)	$NaHCO_3$
300 mg	*m*-CPBA (**212**)
20 ml	abs. $CHCl_3$

Procedure: Analogously to R 127.

Starting material is recovered.

Preparation of bicyclo[9.3.1]pentadecan-16-one (218)

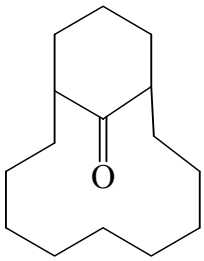
R 141 Amounts:

2.2 g (10.0 mmol)	bicyclo[9.3.1]pentadec-1-(14)-en-15-one (**167**)
300.0 mg	Pd / C
50 ml	EtOAc

Procedure: Analogously to R 134

Evaporation of the solvent furnished 2.1 g (9.6 mmol, 96 % yield) of bicyclo[9.3.1]pentadecan-15-one (**218**) ($C_{15}H_{26}O$, 222.36 g / mol) as a white solid. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 2.80 (dd, 1H, ^3J = 11.8 Hz, ^3J = 3.5 Hz, CH), 1.97 (m, 4H, CH), 1.98-1.94 (m, 1H, CH), 1.90-1.82 (m, 2H,

CH_2), 1.77-1.64 (m, 3H, CH_2), 1.38-1.31 (m, 4H, CH_2), 1.45-1.05 (m, 3H, CH_2), 1.28-1.06 (m, 8H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 216.12 (CO), 52.22, 50.88 (CH), 39.69 (2 x CH_2), 33.23 (CH_2), 32.58 (CH_2), 28.32 (2 x CH_2), 26.87, 26.42 (CH_2), 25.97, 25.84 (CH_2), 24.75, 24.49 (CH_2), 22.69, 22.44 (CH_2), 21.21 (2 x CH_2), 16.84 (CH_2). **LR-MS (EI, 70 eV): m/z (%)** = 222 (M^+, 16.71), 96 (6.21), 81 (15.95), 67 (29.79), 55 (62.14), 41 (100), 29 (33.06).



218

HR-MS (EI, 70 eV): Calcd. 222.1984, Found 222.1987. **Elemental analysis:** Calcd. % C 81.02, % H 11.79, Found % C 81.0, % H 11.9.

R 142 Amounts:

1.0 g	(4.54 mmol)	bicyclo[9.3.1]pentadecan-16-one (**218**)
1.5 g	(9.0 mmol)	*m*-CPBA (**212**)
70.0 mg	(0.4 mmol)	Na_2CO_3

Procedure: Analogously to R 127

Starting material is recovered.

4.7.2. Fragmentation reaction under acetalization conditions

Attempted conversion of 3-(2-oxo-cyclododecyl)propanal (145)

R 143 Amounts

1.0 g	(3.8 mmol)	3-(2-oxocyclododecyl)propanal (**145**)
1 ml	(26 mmol)	$BF_3{\cdot}OEt_2$
3.27ml	(19 mmol)	Ethylene glicol
80 ml		EtOH

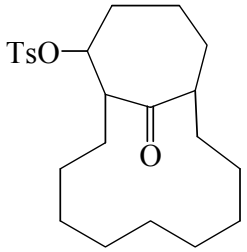
Procedure: Analogously to R 138, 16 hours, room temperature.

Column chromatography on alumina N (III), cyclohexane / Et_2O (3:1) purify the product **168** giving 636 mg (2.4 mmol, 63 % yield) of 12-hydroxybicyclo[9.3.1]pentadecan-16-one (**168**) ($C_{15}H_{26}O_2$, 238.37 g / mol) as a white solid. Spectroscopic data are consistent with R 74

4.7.3. Grob fragmentation

Preparation of 16-oxo-bicyclo[9.4.1]hexadec-2-yl-4-methylbenzenesulfonate (238)

R 144: A solution of 3.0 g (11.6 mmol) of 12-hydroxy-bicyclo[9.4.1]hexadecan-16-one (**50**) in 30 ml dry of dichlomethane is added to 3.0 ml (2.1 g, 21.0 mmol) of triethylamine in 20 ml of dichloromethane at 0°C. The mixture is treated with a solution of 2.0 g (10.2 mmol) of tosylchloride (**237**) over a period of 20 min. The solution is stirred for 72 h at room temperature, then diluted with CH_2Cl_2, washed with cold water, 10 ml of a solution of HCl (10 %), saturated with a solution of Na_2CO_3, and brine. The organic layer is separated, the aqueous phase is extracted with Et_2O (3 x 30 ml), dried over $MgSO_4$ and the solvent is removed under reduced pressure. Recrystallisation from cyclohexane gives 4.1 g (10.1 mmol, 87 % yield) of 16-oxo-bicyclo[9.4.1]hexadec-2-yl-4-methylbenzenesulfonate (**238**) as a white solid ($C_{23}H_{34}O_4S$, 406.58 g / mol).



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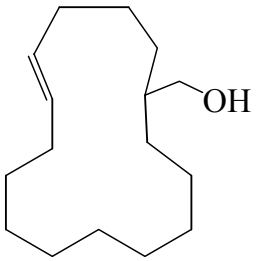
Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.93 (d, 1H, ^{3}J = 8.5 Hz, CH), 7.83 (d, 1H, ^{3}J = 8.2 Hz, CH), 7.42 (d, 1H, ^{3}J = 8.2 Hz, CH), 7.39 (d, 1H, ^{3}J = 8.2 Hz, CH), 4.64 (d, 1H, ^{3}J = 9.2 Hz, CH), 2.79 (dd, 1H, ^{3}J = 11.8 Hz, ^{3}J = 2.52 Hz, CH), 2.51 (s, 3H, CH_3), 1.98 (m, 1H, CH_2), 1.78-1.71 (m, 2H, CH_2), 1.62-1.48 (m, 4H, CH_2), 1.41-1.10 (m, approx. 11H, CH_2) 1.08-0.95 (m, 6H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 214.31 (CO), 144.96 (CH), 146.78 (CH), 130.20 (CH), 129.84 (CH), 127.75 (CH), 127.02 (CH), 85.37 (CH), 61.33 (CH), 46.17 (CH), 36.48 (CH_2), 34.30 (CH_2), 31.66 (CH_2), 27.70 (CH), 27.26 (CH_2), 26.63 (CH_2), 26.42 (CH_2), 23.90 (CH_2), 23.53 (CH_2), 22.35 (CH_2), 21.80 (CH_3), 21.63 (CH_2), 21.43 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3047 (w), 2928 (s), 2898 (s), 2862 (s), 2846 (s), 2364 (w), 1930 (w), 1702 (s), 1595 (m), 1469 (m), 1369 (s), 1191 (s), 1174 (s), 1093 (m), 964 (m), 814 (s), 668 (s), 553 (s). **LR-MS (EI, 70 eV): m/z (%)** = 190 (M-189), 91 (100), 63 (8.84), 39 (9.50), 27 (2.01).

Preparation of 1-cyclopentadec-5-enyl-methanol (239)

R 145: A solution of 2.0 g (6.0 mmol) of toluene-4-sulfonic acid-16-oxo-bicyclo[9.4.1]hexadec-12-yl-ester (**238**) in 25 ml of THF is treated with 0.8 g (21 mmol) of $LiAlH_4$. The resulting suspension is heated at reflux for 16 hours, and then cooled. 100 ml of water (carefully) is added, and then HCl (conc.) is added until a clear solution is obtained. The solution is extracted with Et_2O (3 x 30 ml). The combined ether layers are dried over $MgSO_4$, the solvent removed to leave a crude product. Recrystallization from cyclohexane yielded 1.2 g (5.2 mmol, 88 % yield) cyclopentadec-5-en-1-ylmethanol (**239**) ($C_{16}H_{30}O$, 238.41 g / mol).

Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 5.32 (ddd, 2H, ^3J = 5.2 Hz, ^3J = 2.7 Hz, ^3J = 2.5 Hz, CH), 3.51 (dd, 1H, ^3J = 10.5 Hz , ^3J = 4.7 Hz, CH*H*), 3.43 (dd, 1H, ^3J = 10.5 Hz , ^3J = 6.2 Hz, C*H*H), 2.10-2.00 (m, 4H, CH_2), 1.95-1.880 (m, 4H, CH_2), 1.51-1.11 (m, approx. 18H, CH_2). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 131.31 (*C*H), 130.85 (*C*H), 66.00 (CH_2), 39.46 (CH), 31.66 (CH_2), 31.56 (CH_2), 29.86 (CH_2), 28.09 (CH_2), 27.89 (CH_2), 27.07 (CH_2), 26.90 (CH_2), 26.90 (3 x CH_2), 26.15 (CH_2), 25.37 (CH_2). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3338 (bs), 2928, (s), 2861 (s), 1468 (s), 1443 (s), 1260 (s), 1021 (s), 799 (s). **LR-MS (EI, 70 eV): m/z (%)** = 238 (M^+, 29.96), 220 (52.66), 136 (26.13), 122 (11.94), 108 (17.81), 94 (46.65), 80 (97.29), 66 (7.70), 55 (100). **HR-MS (EI, 70 eV):** Calcd. 238.2297, Found: 239.4309.

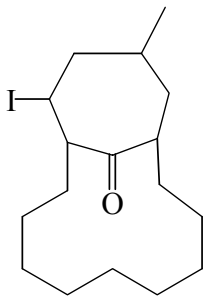


239

Preparation of 12-iodo-14-methylbicyclo[9.4.1]hexadecan-16-one (241)

R 146: To 50 ml of dry dichloromethane are added in order: 2.0 g (11.2 mmol) of triphenylphosphine, 0.7 g (11.2 mmol) of imidazole and 2.8 g (11.2 mmol) of iodine (**240**). A solution of 2.0 g (7.51 mmol) of 12-hydroxy-14-methyl-bicyclo[9.4.1]hexadecan-16-one (**97**) in dry dichloromethane is added and the mixture is stirred at room temperature under for 18 hours. When the reaction is completed, most of the solvent is removed under vacuum and the product is purified by passing it through a column silica gel with pentane as solvent and combining the fractions containing the product. After removing of solvent 2.4 g (6.3 mmol, 85 % yield) of 12-iodo-14-

methylbicyclo[9.4.1]hexadecan-16-one ($C_{17}H_{29}IO$, 376.31 g / mol) (**241**). The crystalline product is obtained without further purification. **Spectroscopic data: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 4.47 (m, 1H, CH_2), 2.50 (m, 1H, CH), 3.15-2.80 (m, 2H, CH), 2.74-2.640 (m, 1H, CH), 2.46-2.34 (m, 2H, CH), 2.30 (m, 1H, CH_2), 2.29-1.01 (m, approx. 20H, CH_2), 0.97 (d, 3H, ^{3}J = 6.7 Hz, CH_3). **^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 211.08 (CO), 53.85 (CH), 51.46 (CH_2), 48.18 (CH), 40.55 (CH_2), 40.47 (CH), 32.91 (CH_2), 31.98 (CH_2), 30.075 (CH), 27.44 (CH_2), 26.631 (CH_2), 24.33 (CH_3), 24.220 (CH_2), 23.28 (CH_2), 22.28 (CH_2), 21.70 (CH_2), 21.57 (CH_2) **IR (neat): ṽ [cm^{-1}]** = 2940 (s), 2924 (s), 2904 (s), 2862 (s), 1697 (s), 1468 (m), 1255 (m). **LR-MS (EI, 70 eV): m/z (%)** = 249 (M^+-I, 100), 231 (3.65), 175 (1.20), 149 (3.73), 135 (6.23), 109 (10.7), 95 (16.50), 83 (19.84), 69 (21.80), 55 (25.93), 41 (14.57), 29 (2.82). **Elemental analysis** for $C_{17}H_{30}OI$: Calcd. % C: 54.26, % H: 7.77, Found: % C: 54.7, % H: 7.9.



241

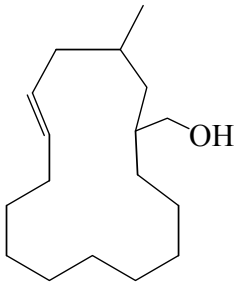
Preparation of (3-methylcyclopentadec-5-en-1-yl)methanol (242)

R 147 Amounts:

1.0 g	(2.3 mmol)	12-iodo-14-methyl-bicyclo[9.4.1]hexadecan-16-one (**241**).
0.8 g	(21.0 mmol)	$LiAlH_4$
30.0 ml		abs. THF

Procedure: Analogously to R 145

After removing of the solvent the crude mixture is consistent of 12-iodo-14-methylbicyclo[9.4.1]hexadecan-16-one ($C_{17}H_{29}IO$, 376.31 g / mol) (**241**) and (3-methylcyclopentadec-5-en-1-yl)methanol (**242**) ($C_{17}H_{32}O$, 252.43 g / mol) in a ratio of 2: 1 (NMR-calculated with respect to the CH=C*H* / C*H*-I). **Spectroscopic data of** (3-Methylcyclopentadec-5-en-1-yl)methanol (**242**) ($C_{17}H_{32}O$, 252.43 g / mol) are assigned by the most significant signals: **^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm]** = 6.32 (m, 2H, CH=CH).**^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm]** = 131.73



242

(*C*H=CH), 128.88 (CH=*C*H), 66.13 (CH_2), 37.93, (CH), **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 3440 (s), 2929 (s), 2857 (s), 1047 (m), 967 (m).

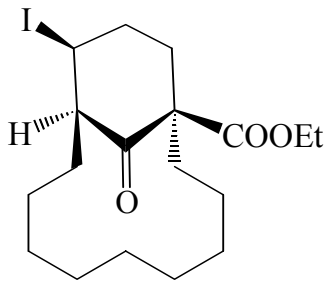
Preparation of ethyl 15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (243)

R 148 Amounts:

4.0 g	(13.0 mmol)	ethyl 15-oxo-bicyclo[9.3.1]pentadecan carboxylate (**174**)
5.4 g	(20.0 mmol)	PPh_3
1.3 g	(2.0 mmol)	Imidazole
5.0 g	(11.2 mmol)	I_2 (**240**)
30.0 ml		abs. CH_2Cl_2

Procedure: Analogously to R 146

After completion of the reaction most of the solvent ie removed under vacuum and the product is isolated by passing it through a column of silica gel with pentane as eluent, followed by three washings. Combining the fractions and evaporation of the solvent gave, without further purification, 4.8 g (11.6 mmol, 85 % yield) of ethyl 15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (**243**) ($C_{18}H_{29}IO_3$, 420.12 g / mol) as a colorless crystal.



243

Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 4.62 (m, 1H, CH), 4.20 (q, 2H, ^3J = 6.4 Hz, CH_2CH_3), 2.90 (dd, 2H, ^3J = 12.9 Hz, ^3J = 4.4 Hz, CH_2), 2.70 (m, 2H, CH_2), 2.36 (m, 4H, CH_2), 2.16 (m, 1H, CH_2), 1.40 (m, 1H, CH_2), 1.25 (m, approx. 10 H, CH_2), 1.23 (t, 3H, ^3J = 6.4 Hz, CH_2CH_3), 0.98 (m, 3H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 205.87 (CO), 171.98 (CO), 61.69 (C_q), 60.43 (*C*H_2CH_3), 49.51 (CH), 39.62 (CH), 34.58 (CH), 32.87 (CH_2), 31.97 (CH_2), 30.31 (CH_2), 26.89 (CH_2), 25.82 (CH_2), 23.27 (CH_2), 22.69 (CH_2), 22.53 (CH_2), 21.40 (CH_2), 20.62 (CH_2), 14.07 (CH_2*C*H_3). **IR (neat): $\tilde{\nu}$ [cm^{-1}]** = 2927 (s), 2867 (s), 1745 (s), 1711 (s), 1468 (m), 1437 (m), 1366 (m), 1279 (m), 1208 (m). **HR-MS (FAB): m/z (%)** = 421.23 $[M+H]^+$. **LR-MS (EI, 70 eV): m/z (%)**: 293 (100), 247 (50.39), 219 (45.70), 109 (23.36), 95 (44.94), 81 (37.65), 67 (47.10), 55 (42.79), 41 (55.97), 29 (45.11). **HR-MS (EI 70 eV):** Calcd. 420.1161,

Found 421.1270. **Elemental analysis**: Calcd. % C 51.43, % H 6.95, Found % C 51.5, % H 6.9.

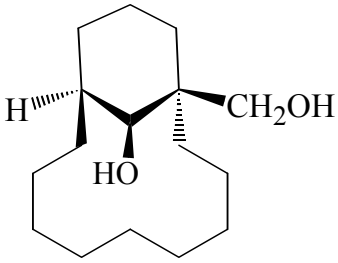
Preparation of 1-hydroxymethyl-bicyclo[9.3.1]pentadecane-15-ol (244)

R 149 Amounts:

1.6 g	(3.8 mmol)	ethyl 15-oxo-12-iodo-bicyclo[9.3.1]pentadecan carboxylate (**243**)
2.8 g	(7.62 mmol)	$LiAlH_4$
30 ml		abs. THF

Procedure: Analogously to R 147

After removing of the solvent 564 mg (2.22 mmol, 75 % yield) of 1-(hydroxymethyl)bicyclo[9.3.1]pentadecan-15-ol (**244**) are obtained without further purification ($C_{16}H_{30}O_2$, 254.22 g / mol). **Spectroscopic data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm]** = 3.75 (d, 1H, ^3J = 10.7 Hz), 3.48 (t, 2H, ^3J = 11.2 Hz, CH_2), 2.72 (s, O*H*), 2.25 (m, 3H, CH_2), 2.00–1.88 (m, 8H, CH_2), 1.78–1.54 (m, 4H, CH_2), 1.51–1.37 (m, 4H, CH_2), 1.26–1.09 (m, 2H, CH_2), 0.98-0.88 (m, 4H, CH_2). **^{13}C-NMR (125 MHz, $CDCl_3$): δ [ppm]** = 82.72 (CHOH), 72.13 (CH_2OH), 43.10 (CH_2), 34.87 (CH_2), 34.32 (CH), 33.18 (CH_2), 29.97 (CH_2), 29.85 (CH_2), 27.41 (CH_2), 25.79 (CH_2), 24.20 (CH_2), 23.56 (CH_2), 22.66 (CH_2), 22.05 (CH_2), 21.09 (CH_2), 19.84 (CH_2). **IR (neat): ṽ [cm^{-1}]** = 3265 (s), 2927 (s), 2917 (s), 2852 (s), 1473 (m), 1463 (m), 1086 (m), 1050 (m), 1019 (m). **LR-MS (EI, 70 eV): m/z (%)** = 236 (M-H_2O, 100), 218 (8.38), 205 (24.48), 109 (13.68), 95 (22.97), 81 (23.83), 67 (20.27), 55 (28.25), 41 (33.05), 29 (8.08).



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