Mark David Keränen

Sequential Hydroformylation / Aldol Reactions:

Stereochemical Control Towards the Synthesis of the Labdane Diterpenoid Forskolin and Related Terpenoid Natural Products


Coleus forskohlii

Sequential Hydroformylation/Aldol Reactions: Stereochemical Control Towards the Synthesis of the Labdane Diterpenoid Forskolin and Related Terpenoid Natural Products

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Mark David Keränen
aus Ely, Minnesota
Vermilion Iron Range

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Co-referee:	*Prof. Dr. Norbert Krause*
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Index of abbreviations and symbols

abs.	absolute, dry
Ac	acetyl
acac	acetylacetonato
Bn	benzyl
Bp	boiling point
Br	broad (FTIR)
Bu	butyl
Bz	benzoyl
cod	cyclooctadienyl
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet (NMR)
dd	doublet of doublets (NMR)
ddd	doublet of a doublet of doublets (NMR)
δ	delta (NMR shift designator)
DMF	dimethylformamide
dq	doublet of quartets (NMR)
dr	diastereomeric ratio
dt	doublet of triplets (NMR)
ee	enantioexcess
EI	Electron impact (MS)
ESI	Electrospray ionisation (MS)
Et	ethyl
eV	electronvolt (MS)
FTIR	Fourier-Transform infrared spectroscopy
GC	gas chromatography
Hz	Hertz
i-	*iso*
J	NMR coupling constant (Hz)

LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
m	multiplet (NMR)
M^+	Molecular peak (MS)
Me	methyl
mp	melting point
MS	Mass spectroscopy
n-	normal
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect (NMR)
NOESY	Nuclear Overhauser effect spectroscopy
p	total pressure
Ph	phenyl
ppm	parts per million (NMR)
Pr	propyl
q	quartet (NMR)
rac	racemic
RT	room temperature
s	singlet (NMR)
t	time, triplet (NMR)
t	tertiary
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Tf	triflate
Ts	tosyl

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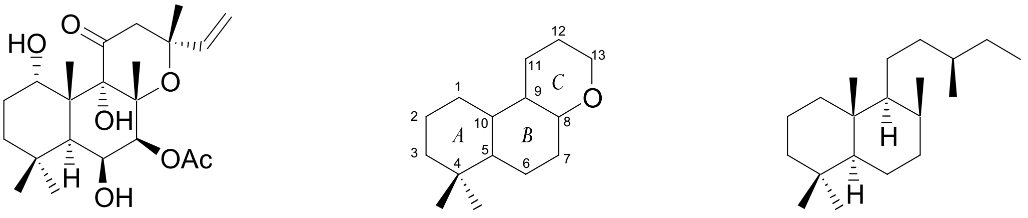
"Twenty years of schooling and they put you on the day shift."

- Bob Dylan, Subterranean Homesick Blues

For Uta and Matti

1 INTRODUCTION

The labdane diterpenoid forskolin (**1**) isolated from the methanolic extract of the roots of the Indian herb *Coleus forskohlii*[1] in 1977, has been responsible for an enormous amount of synthetic interest over the past two decades.[2] Long before it was identified as the principal biologically active constituent, its parent herb was mentioned in ancient Hindu medicinal texts as a treatment for several health-related complaints. It was later shown that its eight chiral centers and high degree of oxygenation (Scheme 1) lend not only to its structural complexity but to its wide range of interesting physiological activities stemming from its being a potent stimulator of adenylate cyclase in various human tissues.[3] Forskolin's synthetic history[4] also serves as a shining example for illustrating one of the major problems associated with the total synthesis of terpenoid natural products in general: the persistent reliance upon Diels-Alder methodologies to construct 6-membered ring moieties and the long linear routes that result from the necessary step-by-step installation of the remaining functionality in a stereoselective fashion.



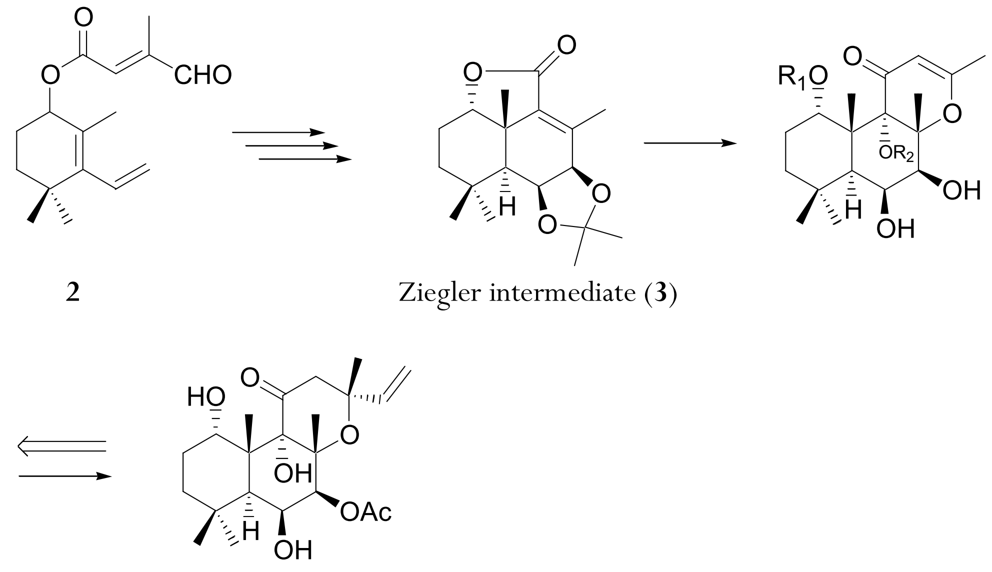
forskolin (**1**) forskolin numbering labdane

Scheme 1: *Structure and numbering scheme of forskolin and its parent diterpene labdane.*

While indeed many approaches to this challenging target were attempted, another striking similarity between the successful total syntheses exists in the fact that they both proceed through a common advanced intermediate, 1,1,6,8,8,9c-hexamethyl-1,2,3,3a,6a,9a,9b,9c-octahydro-4,7,9-trioxa-cyclopenta[*e*]acenaphthylen-5-one (**3**), which is commonly known as the Ziegler intermediate in credit to the group who first recognized its potential as a useful synthon, albeit as part of an ultimately unsuccessful synthesis.[2a] The convergence of these independently investigated synthetic routes upon a single intermediate clearly points to a lack of general strategies with which to successfully approach such a molecule.

Ziegler carried out the construction of his intermediate via an intramolecular Diels-Alder approach from diene **2** (Scheme 2). Attachment of the dienophile tether allowed for the Diels-

Alder reaction to take place affording only one cycloaddition diastereoisomer. This adduct is transformed in several steps to **3**, through which all subsequent total syntheses proceeded. Attachment of the *C*-ring and conjugate addition of the C-13 vinyl group would allow for the completion of the natural product. **Ziegler**, however, did not elaborate further on his intermediate in this initial report, and subsequently reported a synthesis based upon a degradation product of forskolin.[5] This fact also points to another major problem that was a direct effect of the dependence on a Diels-Alder route to construct the *AB*-decalin system - namely that the installation of the pyranone *C*-ring would prove to be no easy task. In all cases, the synthesis of the *C*-ring required more steps to accomplish than the construction of the rest of the molecule as a whole.



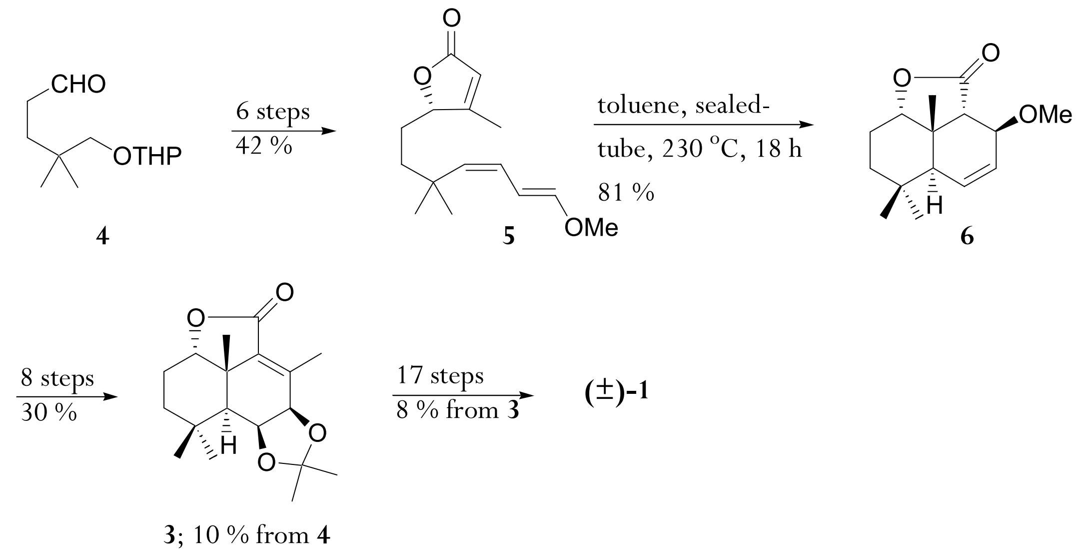
2

Ziegler intermediate (**3**)

1

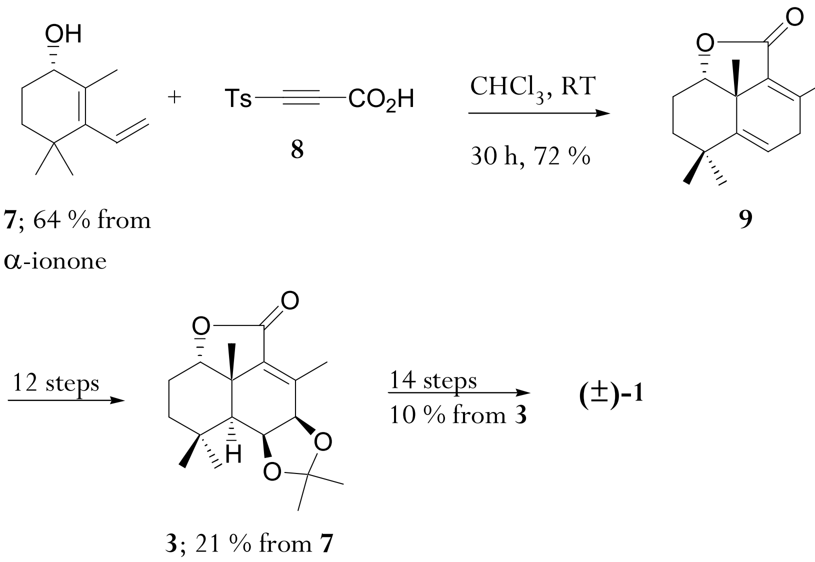
Scheme 2: *Ziegler's route to forskolin as envisioned through key intermediate 3.*

The first successful total synthesis came as a result of the work of **Ikegami.**[6] He constructed in his approach a more complicated but equally straightforward intramolecular Diels-Alder system **5** from aldehyde **4**, which proceeds from the resulting decalin **6** in eight steps to afford the Ziegler intermediate **3** in 10 % overall yield for the sequence. An involved linear sequence is then followed which installs the *C*-ring pyranone system in 14 steps and 8 % yield from **3** (Scheme 3).



Scheme 3: ***Ikegami*** *total synthesis of forskolin.*

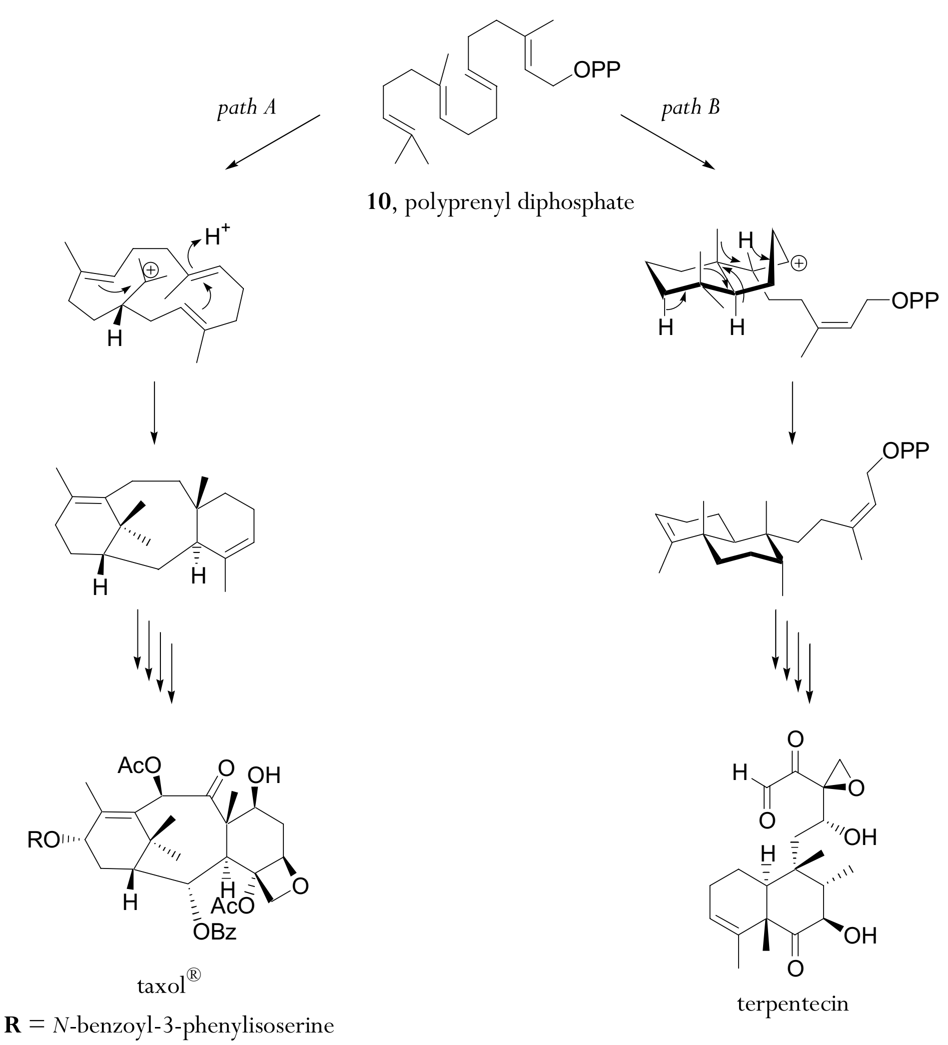
In the **Corey**[7] total synthesis, a Diels-Alder reaction takes place early on between acetylene **8** and diene **7** - similar to **2** but obtained in optically pure form from α-ionone - to provide lactone **9** in 72 % yield.



Scheme 4: ***Corey*** *total synthesis of forskolin.*

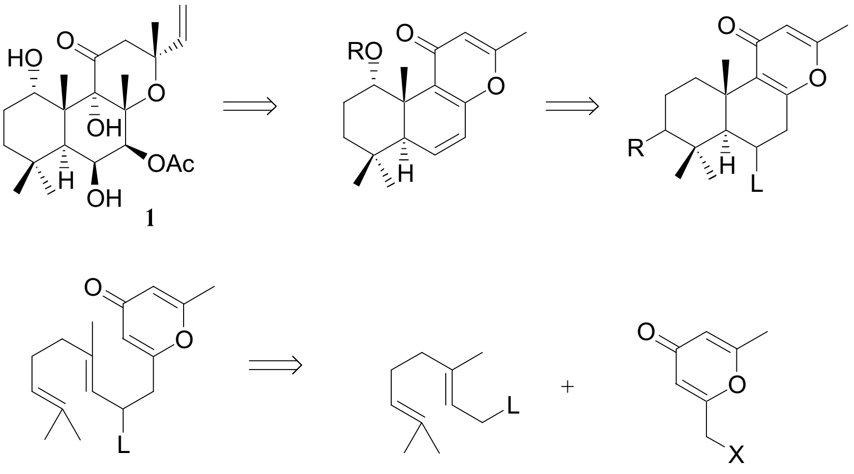
This decalin system is further elaborated in twelve high-yielding steps to afford **3** in 21 % from **7**. Following another long linear sequence similar to **Ikegami**, the *C*-ring is constructed to afford forskolin in a 10 % yield from **3** (Scheme 4).

Subsequent to these initial total syntheses, activity surrounding forskolin and the Ziegler intermediate did not subside.[8] There have been a number of reported formal syntheses of forskolin aside from Ziegler's initial attempt that have resulted in yet more methods of construction of this same intermediate, and once again nearly all proceed via Diels-Alder routes.[2d,9] While one could no doubt devote a large amount of time surveying the synthetic routes to this challenging molecule, it is the intention herein to point out the prevalent use of Diels-Alder and related cyclization reactions to construct such molecules. While this methodology for the construction of the *AB*-ring system has resulted in three successful total syntheses of forskolin, this happened only after the completion of long, involved synthetic routes to install the pyranone *C*-ring. Such routes not only drastically lower the overall yield of a synthesis, but make the entire method less attractive to those wishing to reproduce the synthesis or produce a larger amount of the compound, which is the reason why one chooses to pursue a synthetic route as opposed to isolation of the natural product from its biological source. Other approaches have used advanced intermediates that have been synthesized via other methods[10], some involving the use of other natural products, namely carbohydrates[9,11], as building blocks or entry points into the synthesis. While these sequences tend to be shorter and perhaps even higher yielding on average, they are only accomplished by the removal, reversal or in some cases destruction of a large number of the stereocenters already present in the chiral starting material. When considering the construction of terpenoid natural products, it can be useful to consider the way in which Nature herself accomplishes this task, via initiating a reaction cascade that results in the sequential stereocontrolled construction of C-C & C-O bonds. The cyclization reactions resulting in the biosynthesis of a given terpene framework are catalyzed by enzymes known as terpene cyclases.[12] Several genes encoding terpene cyclases have been identified, and much work has gone into the elucidation of the most likely mechanisms with which these enzymes accomplish their chemistry.[13] These cyclases can act upon a single polyprenyl diphosphate **10**, producing after subsequent oxidations, dehydrations, hydrogenations or acylations an astounding number of terpenoids with incredible structural diversity, ranging from taxol®,[14] to terpentecin[15] (Scheme 5).



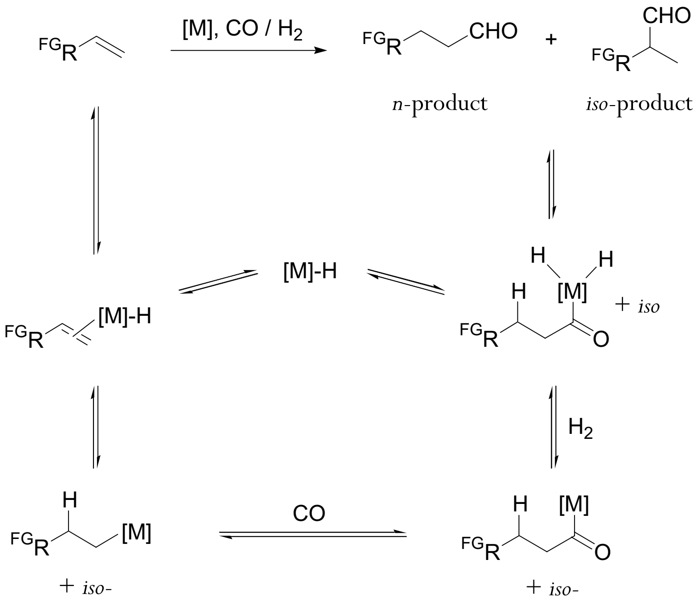
Scheme 5: Biosynthesis of structurally unrelated terpenoids from a single polyprenyl diphosphate.

From these observations, it can be seen that when planning an approach to such complex molecules, it is advisable to mimic as closely as possible the efficiency by which their biosynthesis proceeds - emphasizing the sequential formation of structural elements in a stereoselective and atom economical fashion from simple, readily-obtainable starting materials. One prominent example of this is the polyene cyclization strategy explored by **Kim**.[16] In this work, an advanced substrate is constructed which is envisioned to undergo cyclization via a biomimetic pathway, providing access to the entire forskolin framework in one step (Scheme 6).



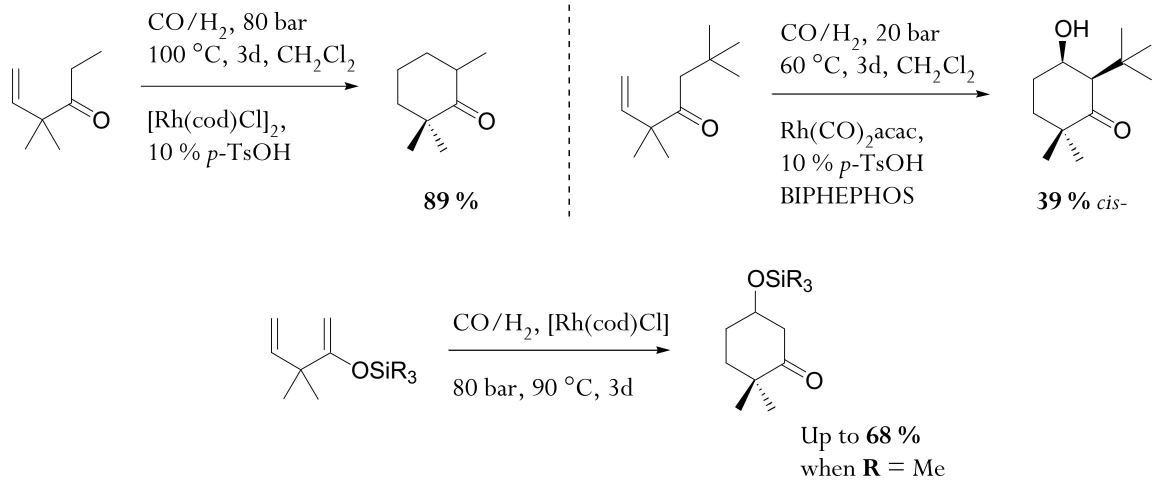
Scheme 6: *Biomimetic polyene-cyclization strategy envisioned by* **Kim** *as a means of access to the forskolin system.*

Another biomimetic approach to be explored in detail in this work will involve the use of hydroformylation/aldol reaction sequences to approach in a stereoselective fashion the complex carbon skeleton of forskolin and related terpenoids from the appropriate olefin-containing precursors. As viewed under the definition put forth by **Trost**[17], hydroformylation - or the late transition-metal-catalyzed addition of CO and H_2 across an unsaturated carbon-carbon bond discovered in 1938 by **Roelen**[18] - is a prototype of an atom economical reaction. The process requires only a catalytic amount of metal (rhodium is the most active and selective) and all atoms present in the starting material remain in the product (Scheme 7).



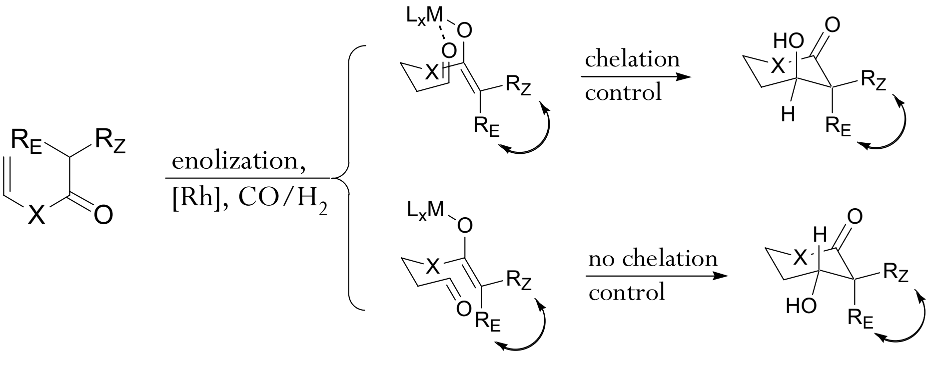
Scheme 7: *Hydroformylation of olefins and representative mechanistic steps.*

In spite of these attractive aspects, this industrially important process has not found wide usage in organic synthesis[19] because of one prominent setback, the difficulty to control all aspects of selectivity during the reaction.[20] Hydroformylation results in the formation of a new C-C and a new C-H bond, each of which could result in the formation of a new stereocenter. The aldehyde functionality that is introduced also can allow for the further elaboration of the carbon skeleton though subsequent transformations. While notable advances have been reported in the area of research focusing solely on the hydroformylation step (*n*-selectivity mediated by ligands, diastereoselective[21] and enantioselective[22] examples) sequential reactions that take advantage of a reactive aldehyde group generated under relatively mild conditions are quite seldom indeed.[23] Among these, even less-frequently encountered types of sequential reaction partners to hydroformylation are those involving C-nucleophiles, specifically those involved in aldol processes. While aldol products have frequently been observed as by products of hydroformylation processes run at the industrial scale, there are very few reported examples that exploit the full range of reactivity available in this transformation. The main reason for this fact is that when considering a sequential hydroformylation/aldol reaction, several more factors come into play that make the transformation not an easy one to approach in a straightforward fashion. To accomplish this transformation in a stereoselective manner, a way must be found to generate an enolate of either a *E*(O)- or *Z*(O)-configuration while allowing for a controlled delivery of the aldehyde to this enolate under hydroformylation conditions that provide exceptionally high *n*- : *iso*-selectivities. In this almost completely unexplored area, preliminary work has shown that this sequential reaction could be performed effectively on β,γ-unsaturated ketones under mild acid-catalysis and where a rhodium-catalyzed hydroformylation/Mukaiyama aldol addition of the corresponding pre-formed silyl enol ethers was also reported (Scheme 8).[24] While the stereochemical aspect of the reaction was interesting in the fact that only the *cis*-diastereoisomer was observed, the conditions did not prove to be extendable to ketones that would allow further elaboration subsequent to cyclization. As stated, some initial trials were conducted involving the silyl enol ethers generated from the same ketones used in the acid-catalyzed reactions.



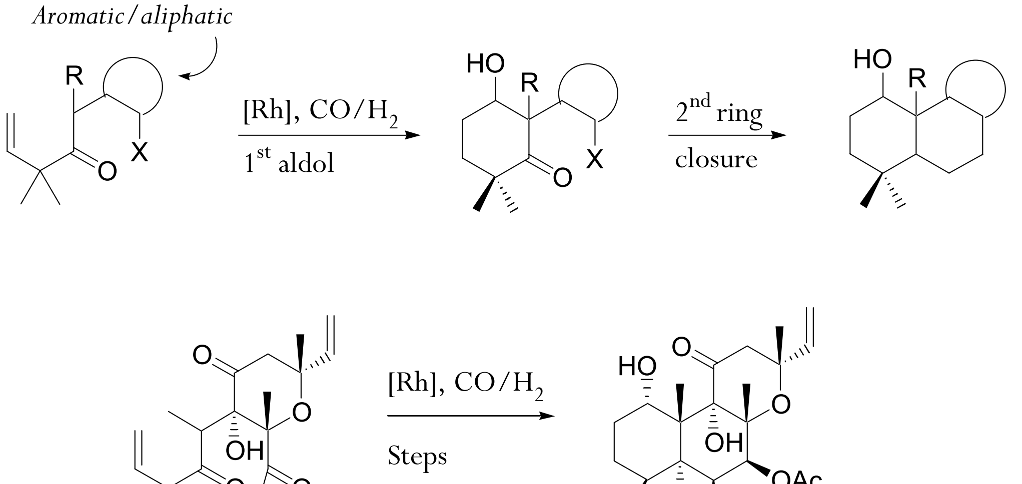
Scheme 8: *Acid- & rhodium-catalyzed sequential hydroformylation/aldol-Mukaiyama aldol reactions.*

This reaction proved to be effective in other types of substrates to afford a new general method of obtaining these types of aldol adducts in a one-pot procedure in good yields. However, investigations into the stereochemical nuances of this particular transformation were not conducted, and information into the nature of enolate geometry and direction of the aldehyde through chelation or non-chelation control remains to be unravelled (Scheme 9).



Scheme 9: *Transition state models of the intramolecular hydroformylation/aldol addition illustrating the effects of enolization geometries and chelation control.*

The goal of this work is to put forth a thorough investigation into the variables mentioned above, focusing on parameters such as enolate geometry and chelation in the Mukaiyama systems while exploring new in-situ methods that allow for the same stereocontrolled transformation to take place in a completely regio- and stereoselective fashion, offering complementary methods to obtain the corresponding aldol adducts in the context of constructing systems applicable to the synthesis of terpenoid natural products and analogs. Of great interest are the β-hydroxycycloalkanone moieties possessing an adjacent α-stereocenter, possibly incorporating in more advanced substrates the lattice of terpenoid natural products into a hydroformylation precursor. The general concept is to begin with various α′-substituted-β,γ-unsaturated ketones with which to single out the individual variables mentioned above while holding the other variables as constant as possible. Successes observed with these simpler compounds can greatly advance the application of this methodology towards the synthesis of various types of terpenes, while allowing for a complete understanding of the process, resulting in an optimization of the reaction as a whole and ultimately leading toward a completely regio-, chemo- and stereoselective one-pot process. In extension of the monocyclic compounds, a precursor that would allow for the study of both cyclization steps needed to construct a complete tricyclic skeleton is thought to be obtainable directly from compounds such as those in Scheme 10, where subsequent to the initial hydroformylation and aldol addition, the final *B*-ring closure can take place via a variety of methods to afford terpenoids or analogs.



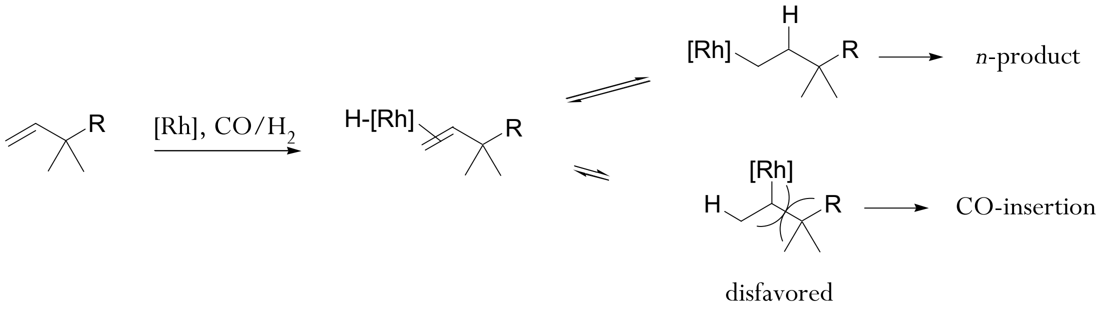
1

Scheme 10: *Construction of the complete forskolin system and related terpenoid ring systems via sequential hydroformylation/aldol addition.*

2 THEORY

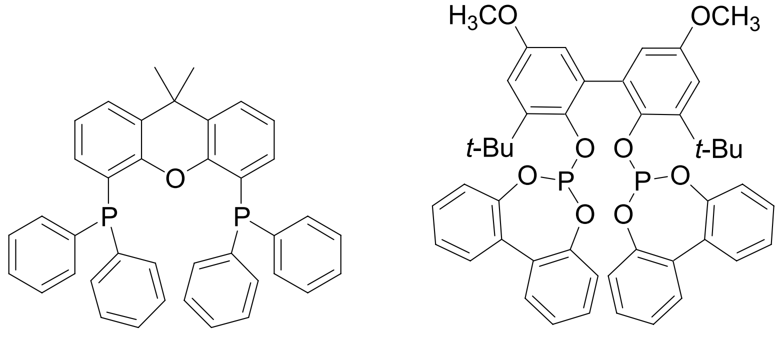
2.1 *n*-Selective hydroformylation: BIPHEPHOS and XANTPHOS

As the initial step in the sequential hydroformylation/aldol addition reaction, hydroformylation must be performed in a regioselective fashion (selective for the *n*-product) in order to allow for the entire sequence to be of any practical use in synthesis. The appearance of regioisomers resulting from hydroformylation would only further complicate the subsequent aldol addition step, resulting in product mixtures which would involve much time and effort to separate. For these reasons, the desire to control the regioselectivity to as high a degree as possible has attracted much attention in recent years.[25] To accomplish this here, both passive and active methods were employed. Aside from being a standard structural feature of the *A*-ring components of a great many terpenoid natural products, the geminal dimethyl substitution pattern of the desired substrates has two distinct advantages when incorporated into the precursor. This substitution pattern adjacent to an olefin permits a selective *n*-hydroformylation[26] due to steric hindrance, and the quaternary carbon center also enhances cyclization reactions via the Thorpe-Ingold effect[27] while at the same time prohibiting isomerization of the olefin. For the particular substrates in this study, this steric factor accounted for the almost exclusive production of *n*-hydroformylation products (Scheme 11).



Scheme 11: *Regioselective n-hydroformylation directed by a quaternary center.*

When an adjacent quaternary center is not present, we must rely on another method to direct the hydroformylation. Instead of incorporating the steric bulk into the substrate, the use of large chelating ligands has become a standard practice in many forms of transition metal catalysis. In the case of hydroformylation, several ligands have been evaluated which result in extremely high *n- : iso-*selectivities dependent largely on the bite angle to rhodium generated upon chelation. The ligands that have been employed by our workgroup after many trials and evaluations are the phosphite ligand BIPHEPHOS and the more recently-discovered phosphine ligand XANTPHOS (Scheme 12).



XANTPHOS
n- : iso-
53 : 1 for 1-octene

BIPHEPHOS
n- : iso-
>40 : 1 in general cases

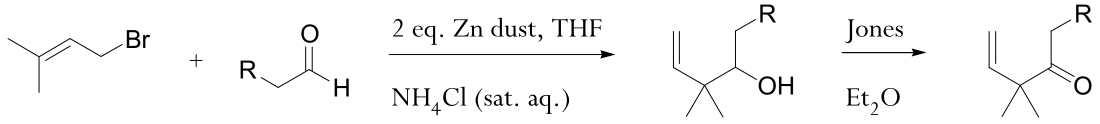
Scheme 12: *Structures of the ligands XANTPHOS and BIPHEPHOS.*

Both of these bidentate ligands work on the principle that in the presence of an excess amount of the chelating ligand, the catalyst will remain sufficiently large enough through the reaction process to direct the key insertion of the acylmetal-hydride at the *n*-position of the olefin. One of the first examples using BIPHEPHOS in hydroformylation was reported by **Buchwald**[28], whereby it was determined that in general BIPHEPHOS was able to affect regioselectivities on the order of > 40 : 1 *n- : iso-*aldehydes in a wide variety of substrates. A particular benefit to the use of BIPHEPHOS is that it lowers the activation barrier of the reaction, allowing for hydroformylation to take place at lower temperatures than would normally be possible. This is particularly attractive when desiring to perform the reaction on compounds containing labile or temperature-sensitive groups. A problem present in the use of BIPHEPHOS lies only in that when attempting to perform some selected tandem reactions in the presence of amines, or on temperatures higher than 70-80 °C, some ligand decomposition is observed, and will be discussed in detail later. For these reasons it was necessary to explore other ligands which would afford high regioselectivities while remaining compatible with a wide variety of reagents and temperatures.

Meeting these requirements is the phosphine ligand XANTPHOS. The activity of an entire range of ligands based on the xanthene skeleton has been investigated by **van Leeuwen**[21a, c] and XANTPHOS was found to afford excellent regioselectivities on the olefins tested, for example 53 : 1 in the case of 1-octene, using higher temperatures than those tolerated by BIPHEPHOS. While a relatively small amount of compounds were tested, and it remained to be seen whether XANTPHOS could tolerate a combination of reagents such as amines, acids and the like, the ligand seemed a worthwhile choice while it lacked the phosphite structure which most likely made BIPHEPHOS prone to degradation and decomposition under harsher conditions. The experiments where these ligands were employed in and the results thereof will be discussed in due course.

2.2 Preparation of β,γ-unsaturated terpenoid *A*-ring precursors

The appropriate precursors and model compounds with which to begin a study of methods of sequential hydroformylation/aldol addition reactions can be prepared via a variety of methods. Among the most general and effective to produce unsaturated ketones bearing an alkyl substituent is the two step sequence of Zn(0) mediated aldehyde addition reported by **Wilson**[29] followed by Jones oxidation[30] of the resulting homoallylic alcohol in ether to cleanly afford the desired unsaturated ketones 3,3-dimethyl-pent-4-en-2-one (**11**) and 4,4-dimethyl-hex-5-en-3-one (**12**) in 33 % and 72 % respectively after Kugelrohr distillation (Scheme 13).

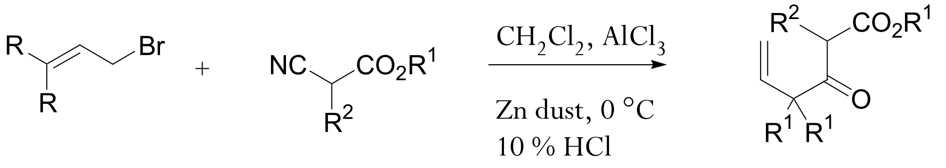


11, 33 %, R = H
12, 72 %, R = CH_3

yields over 2 steps

Scheme 13: *Preparation of alkyl substituted β,γ-unsaturated ketone starting materials.*

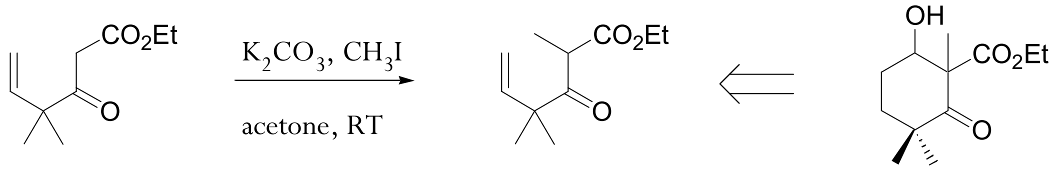
To prepare the ketoesters necessary to install functionality resembling that of the labdane terpenoids, another method similar to the one described above was used. Using a method described by **Hiyashi** and co-workers[31], cyanoacetic acid esters were treated with Zn(0) in the presence of prenyl or allyl bromide and $AlCl_3$ before being worked up by the addition of 10 % HCl to give ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**), *t*-butyl 4,4-dimethyl-3-oxo-hex-5-enoate (**14**) and *t*-butyl 3-oxo-hex-5-enoate (**15**) in one step (Scheme 14).



13, R = Me, R^1 = Et, R^2 = H, 61 %,
13a, R^2 = Me, 85 % (see below)
14, R = Me, R^1 = *t*-Bu, R^2 = Me, 48 %
15, R = H, R^1 = *t*-Bu, R^2 = Me, 66 %

Scheme 14: *Zn and Al-mediated Barbier-type allyllation of cyanoesters.*

The β-ketoester **13** could be subsequently alkylated with methyl iodide and K_2CO_3 in acetone to afford ethyl 2,4,4-trimethyl-3-oxo-hex-5-enoic acid methyl (**13a**) in 85 % (Scheme 15). This compound is a particularly interesting precursor in the fact that it possesses all of the functionality necessary to construct the *A*-ring of forskolin and allow for further elaboration towards the natural product by way of the carboxyl group adjacent to the quaternary center. The stereocontrolled formation of a quaternary center is one of the main obstacles present en route to these types of molecules, and an efficient method to obtain large amounts of this compound was a requirement of this study.



13 **13a,** 85 % forskolin A-ring analog

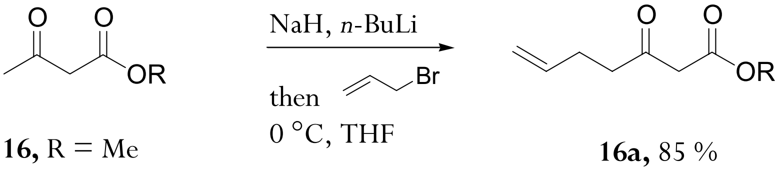
Scheme 15: *Methylation to afford a forskolin A-ring precursor* ***13a****.*

2.3 Preparation of model substrates

2.3.1 "Linear" ketoesters

A number of other compounds needed to be prepared in order to test the particular nuances of a sequential hydroformylation/aldol addition reaction sequence. As this area is almost completely unexplored, a large number of variables must be investigated and optimized before a successful transfer of the conditions can be applied toward the synthesis of a natural product. As this work is based upon the success of a hydroformylation reaction being carried out in a regioselective fashion in the presence of any number and type of reagents or reactive intermediates (enolates, etc.) a variety of substrates should be constructed in order to show the versatility and generality of any new process. For this reason, a number of substrates were synthesized which would allow for investigation of the key components of the reaction sequence – the regioselective hydroformylation step, the generation of enolates from esters as well as ketoesters and ketones, the regioselective aldol addition, the formation of a quaternary center and the optimization of all of these variables in a one-pot method.

Beginning with the regioselective hydroformylation step, a number of derivatives of acetoacetates were prepared which would allow for the investigation of this through the use of different ligands under different cyclization conditions. Beginning with acetoacetates **16**-**18**, (**18** was prepared by the method of **Doyle**[32] from diketene, (–)-menthol and NaOAc in 86 % yield) a regioselective allylation took place using a method described **Weiler**[33] and further applied by **Kende**[34] and **Stork**[35] in which the ketoester is first deprotonated with NaH before formation of the more reactive lithium enolate via addition of *n*-BuLi. Treatment with allyl bromide results in clean formation of the "linear" 3-oxo-hept-6-enoic acid ketoesters **16a**, **17a** and **18a**, all of which were easily purified via Kugelrohr distillation at 60-70 °C @1 mbar (Scheme 16).

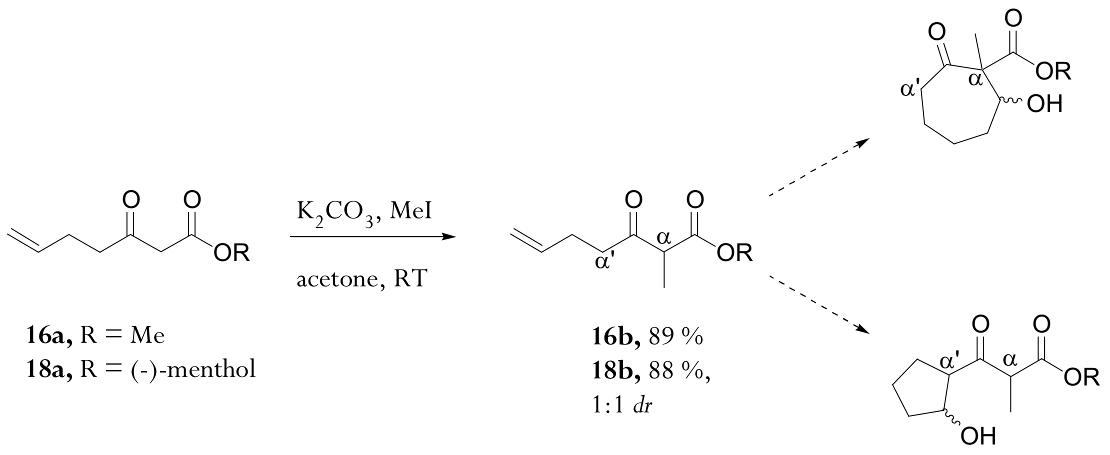


16, R = Me
17, R = *t*-Bu
18, R = (-)-menthol,
86 % from diketene

16a, 85 %
17a, 48 %
18a, 54 %

Scheme 16: *Regioselective allylation to give "linear" ketoesters.*

Compounds **16a** and **18a** were regioselectively methylated using **Stork's**[30] procedure to give the ketoesters methyl 2-methyl-3-oxo-hept-6-enoate (**16b**) in 89 % yield and (–)-menthyl 2-methyl-3-oxo-hept-6-enoate (**18b**) in 88 % yield, which uniquely allow for the testing of quaternary center formation and 7-membered ring formation at the inherently more reactive α-center as opposed to 5-membered ring formation as the result of aldol addition at the less hindered and less reactive α′-center (Scheme 17). The presence of the chiral ester will also allow for testing the possibility of obtaining asymmetric induction in the aldol addition reaction.



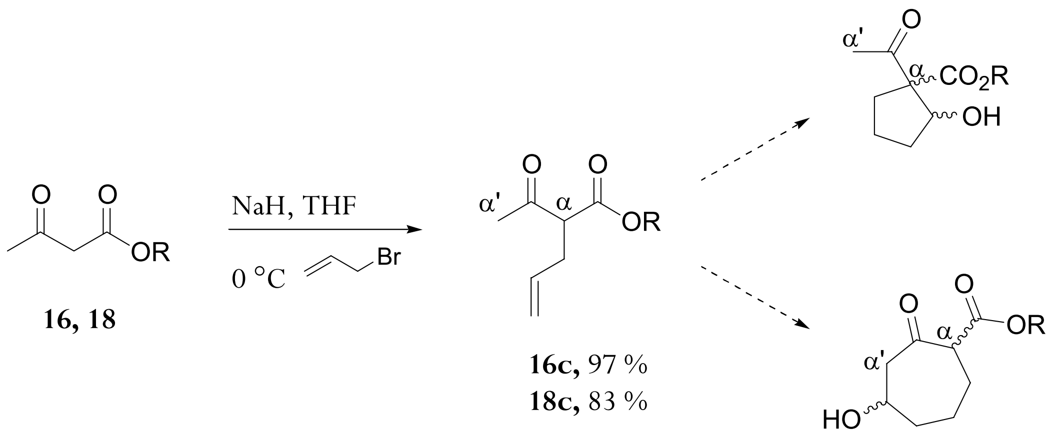
16a, R = Me
18a, R = (-)-menthol

16b, 89 %
18b, 88 %,
1:1 *dr*

Scheme 17: *Regioselective methylation of ketoesters to test propensity of quaternary center formation.*

2.3.2 "Branched" ketoesters

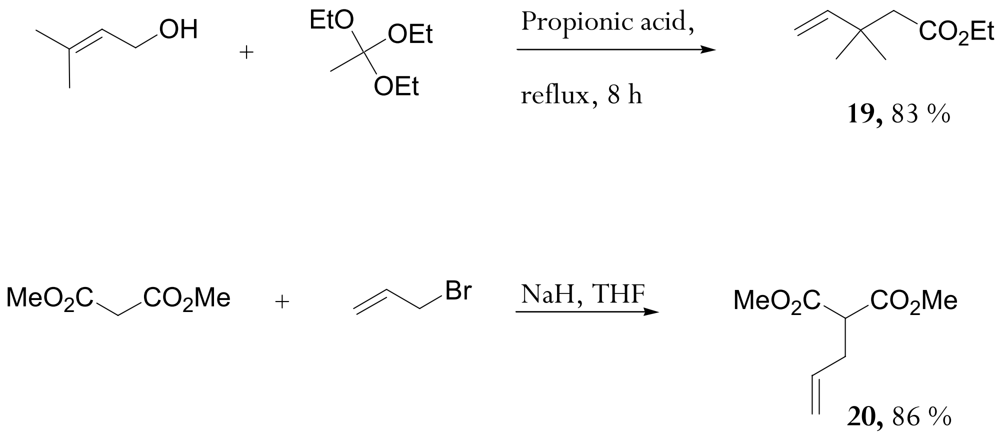
This cyclization could also be tested further by performing the alkylation in the α–position, which is accomplished by addition of the allyl bromide subsequent to deprotonation with NaH. Two "branched" ketoesters methyl 2-acetyl-pent-4-enoate (**16c**) and (–)-menthyl 2-acetyl-pent-4-enoate (**18c**) were constructed as well from the parent acetoacetates **16** and **18**, with esters of different steric demand and chirality once again being employed to determine whether or not this plays a role in determining the stereochemical outcome of any possible aldol addition which takes place. These compounds are able to undergo aldol addition subsequent to hydroformylation to construct a 5-membered ring bearing a quaternary center or, as in the linear cases, addition to the less hindered α′-center affording a 7-membered ring carbocycles (Scheme 18).



Scheme 18: Allylation of acetoacetates to produce "branched" ketoesters.

2.4 Preparation of unsaturated esters

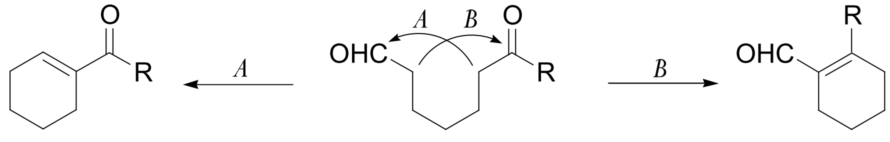
In addition to these ketoesters, the unsaturated esters ethyl 3,3-dimethyl-pent-4-enoate (**19**) and dimethyl allyl malonate (**20**) were also prepared, in order to further investigate the reactivity of the ester enolate under various conditions (Scheme 19). Ester **19** was prepared in 83 % yield via the method of **Hudlicky**[36] by refluxing ethyl orthoacetate with 3-methyl-but-2-en-1-ol for 8 h in the presence of a catalytic amount of propionic acid. Malonate ester **20** was made in 86 % yield via an analogous fashion to the many ketoesters prepared above, by alkylation with allyl bromide and NaH in THF after a procedure reported by **Denis**.[37]



*Scheme 19: Preparation of unsaturated esters **19** and **20**.*

2.5 Sequential hydroformylation/acid-catalyzed aldol reactions

In the past decades, much has been learned in the area of intramolecular aldol reactions involving ketoaldehydes.[38] While stepwise reactions subsequent to the generation of the aldehyde can be run in the presence of strong mineral acids such as HCl and H_2SO_4, these catalysts are too harsh for performing the reaction in an autoclave, and are almost always useless when enolizable aldehydes such as those obtained from olefins in hydroformylation (such as **21**) are used due to the problem of chemoselectivity in the condensation (Scheme 20).



21

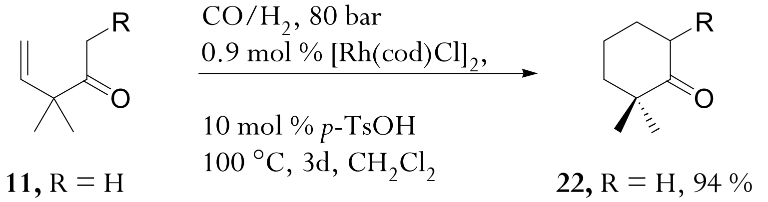
Scheme 20: *Chemoselectivity in the intramolecular aldol condensation of ketoaldehyde* ***21****.*

Base catalysis can be employed to solve problems of chemoselectivity in some systems through the generation of enamines from the reactive aldehydes[39], but is most often times incompatible in combination with a transition-metal catalyzed hydroformylation. Mild conditions are necessary to stop the reaction after the aldol addition stage, resulting in retention of the maximum amount of oxygen functionality. Through explorations conducted in this workgroup it has been determined that *p*-toluenesulfonic acid (*p*-TsOH) in amounts ranging from 5 – 10 mol % is the most suitable catalyst for accomplishing this transformation in a one-pot fashion subsequent to hydroformylation.[24a]

2.5.1 Investigations with β,γ-unsaturated ketones

As alluded to in the introduction, a great deal of work has already been carried out in the area of affecting aldol reactions subsequent to hydroformylation in the presence of acid catalysis. In the context of compounds lending themselves to use in the synthesis of terpenes, the following reactivities were observed. It has previously been reported[24a,b] that ketones 3,3-dimethyl-pent-4-en-2-one (**11**) and 4,4-dimethyl-hex-5-en-3-one (**12**), when hydroformylated with the $[Rh(cod)Cl]_2$ catalyst in the presence of 10 mol % *p*-TsOH, using the relatively harsh conditions of 80 bar CO/H_2, 100 °C for 3 d, the reaction proceeds through the aldol condensation step.

The resulting enone of is hydrogenated in the autoclave to produce the corresponding methylcyclohexanones **22** and **23** in 94 % and 89 % yield, respectively (Scheme 21).

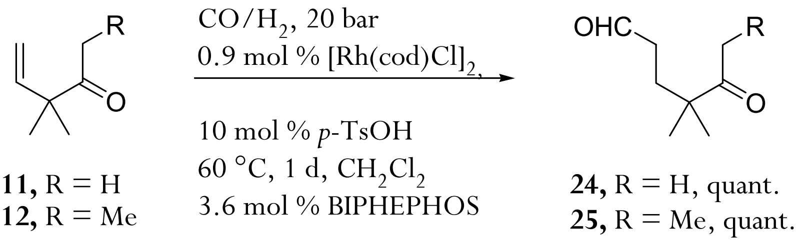


11, R = H
12, R = Me

22, R = H, 94 %
23, R = Me, 89 %

Scheme 21: *Reported hydroformylation/acid-catalyzed aldol condensation affording methylcyclohexanones.*

While this scenario established the connectivity desired in the form of a cyclohexanone, the amount of oxygen functionality and stereochemical information lost in the transformation under these conditions makes the acid-catalyzed reaction unsuitable for application to the synthesis of forskolin. The first logical step in proceeding from these results was to attempt to make the conditions milder in the hope that the condensation/hydrogenation steps could be suppressed, so that the product of aldol addition - the β-hydroxy cyclohexanone - could be isolated. As it had been observed that hydroformylation could be performed under much milder conditions when the ligand BIPHEPHOS was employed, hydroformylation was performed in the presence of 4 mass eq. of BIPHEPHOS in relation to the catalyst, reducing the reaction pressure, temperature and time. Unfortunately, only the products of hydroformylation 4,4-dimethyl-5-oxo-hexanal (**24**) and 4,4-dimethyl-5-oxo-heptanal (**25**) were observed in quantitative yields, and none of the desired aldol addition products were detected (Scheme 22).



11, R = H
12, R = Me

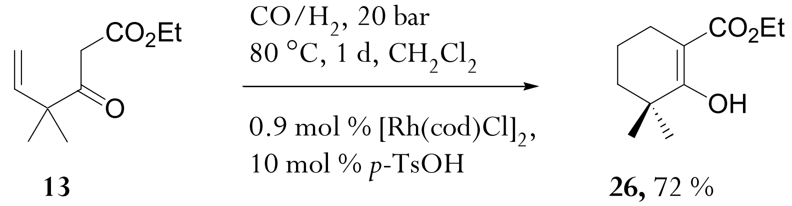
24, R = H, quant.
25, R = Me, quant.

Scheme 22: *Attempts to suppress the aldol condensation/hydrogenation sequence via addition of BIPHEPHOS and use of mild hydroformylation conditions.*

2.5.2 Investigations of β,γ-unsaturated ketoesters

2.5.2a Formation of non-quaternary centers

As the unsaturated ketones were not able to afford the desired aldol adducts, further studies were performed using the ketoesters, which would allow for the further elaboration of the product via the ester functionality. In the case of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**), hydroformylation in the presence *or absence* of 10 mol % *p*-TsOH under mild conditions resulted in the observation of the hydrogenated products the result of Knoevenagel condensation at the highly-activated α-position, namely ethyl 2-hydroxy-3,3-dimethyl-cyclohex-1-enecarboxylate (**26**) in 72 % yield as a 62:38 mixture of *enol-* and *keto-*tautomers (Scheme 23).

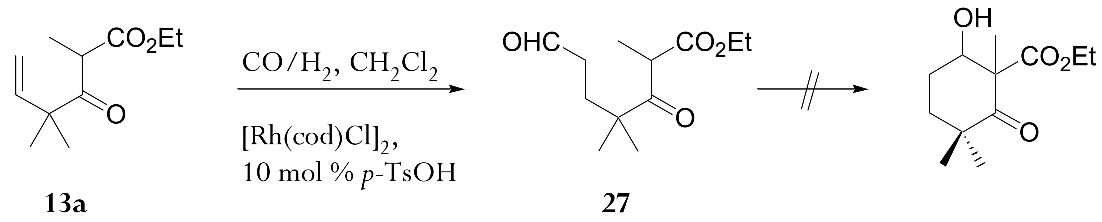


Scheme 23: *Hydroformylation of ketoester* ***13****.*

These results were encouraging, as they provided the first insight into the reactivity of the ketoester functionality towards the synthesis of 6-membered rings. While they also proceeded through the aldol condensation and subsequent hydrogenation, the fact that these particular ketoesters underwent cyclization so readily led us to explore the formation of a quaternary center under acid-catalyzed conditions.

2.5.2b Formation of quaternary centers

The presence of a quaternary center in the products would satisfy two main goals, namely the suppression of elimination and hydrogenation resulting in a loss of oxygenation, and the structural requirement necessary to allow for construction of an *A*-ring building block of forskolin. With retention of the hydroxy functions, a variable that would be introduced for the first time in these studies is that of stereochemistry, and whether or not the aldol adducts could be synthesized in a stereocontrolled manner. Investigations proceeded with α-methyl ketoester **13a** (Scheme 24).



13a **27**

Time (d)	Temp (°C)	Ligand	Yield of **27**
1	60	BIPHEPHOS	quant.
2	90	None	86 %

Scheme 24: *Attempts at formation of a quaternary center via acid catalysis.*

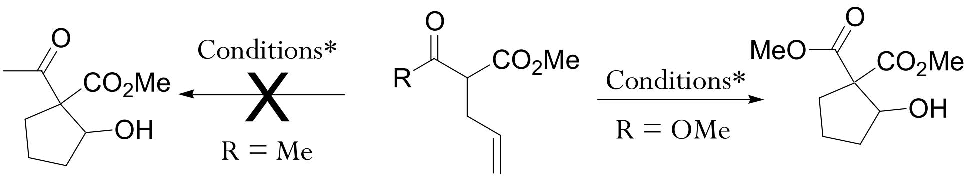
Once again, several interesting conclusions can be drawn from the results summarized above. Under both mild and harsh conditions, ketoester **13a** reacted to give only the product of hydroformylation 2,4,4-trimethyl-3,7-dioxo-heptanoic acid ethyl ester (**27**) in quantitative yield. As **27** was isolated in excellent yield, the failure to observe intramolecular aldol adducts cannot be attributed to decomposition or unwanted side reactions. It seems, rather, as if the tendency for the high reactivity towards cyclization of these particular ketoesters is not the case when additional α-substitution is present in the starting material. Nonetheless, although the presence of the methyl group does not present an extremely large steric or electronic bias, the lack of reactivity in the presence or absence of ligand even under harsh conditions shows that cyclization and quaternary center formation to construct a labdane *A*-ring system simply cannot be accomplished using this methodology. A number of other model substrates were tested which confirmed this trend, along with providing more insight into the lack of selectivity involved in the acid catalyzed process.

2.6 Investigation of regioselective ring closure/quaternary center formation

2.6.1 "Branched" ketoesters

Proceeding with the "branched" ketoesters bearing an α-allyl substituent, another limitation of aldol reactions promoted by acid catalysis was observed, namely that when employing compounds that possess more than one electrophilic component and/or enolizable site, a lack of selectivity can arise due to competing cross condensation pathways. While ketoester **13a** possesses only one strongly preferred aldol addition pathway resulting from attack of the ketoester enolate on the aldehyde generated during hydroformylation, this is not the case in the substitution patterns of acetoacetates that are not blocked to other reaction pathways.

While it has been previously observed[24a] that dimethyl allyl malonate (**20**) affords dimethyl 2-hydroxy-cyclopentane-1,1-dicarboxylate (**28**) in 69 % yield when hydroformylated in the presence of 5 mol % *p*-TsOH and BIPHEPHOS, this method fails when compounds bearing multiple electrophilic components and/or enolizable sites are employed (Scheme 25). For example, hydroformylation of methyl 2-acetyl-pent-4-enoate (**16c**) in the presence of 5 mol % *p*-TsOH and BIPHEPHOS/XANTPHOS results, even under mild conditions (60 °C, 20 bar CO/H_2), in a nearly intractable mixture of products of various ring sizes resulting from cross-condensations between the multiple electrophilic components and enolizable sites present in the compound. A regiocontrolled formation of the cyclopentanol is not possible under these conditions, and it is clear that another means of selective activation/enolization is necessary.



28, 69 %

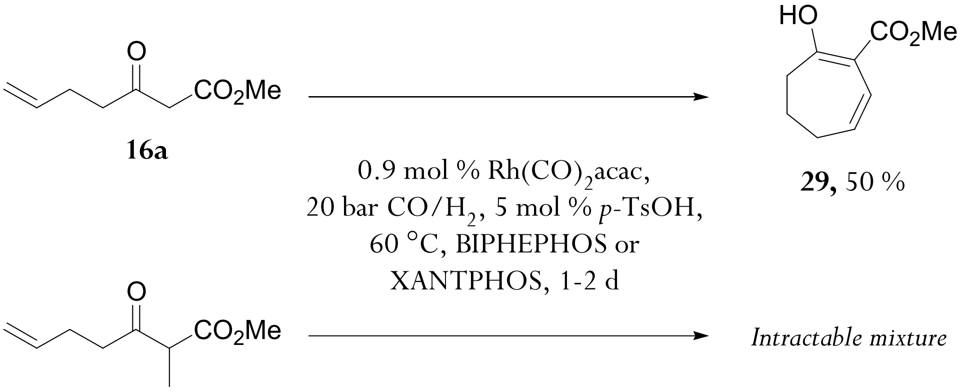
16c, R = Me
20, R = OMe

**Conditions:* 0.9 mol % Rh(CO)$_2$acac,
20 bar CO/H_2, 5 mol % *p*-TsOH, 60 °C, BIPHEPHOS or XANTPHOS

Scheme 25: *Limitations of acid catalysis when cross-condensation pathways are possible.*

2.6.2 "Linear" ketoesters

The same holds true for the "linear" unsaturated ketoesters. Hydroformylation of **16a** run in the presence of *p*-TsOH under mild conditions gives the product of Knoevenagel condensation which equilibrates to the conjugated enol-tautomer[40], methyl 2-hydroxy-cyclohepta-1,6-dienecarboxylate (**29**) in 50 % yield. An investigation of the same compounds bearing α-substitution (**16b**) under identical reaction conditions results in the observation of an intractable mixture (Scheme 26). Although no olefin was observed remaining in the reaction mixture, this shows once again that no strong preference exists for a selective aldol reaction in this type of compound.



16a

0.9 mol % $Rh(CO)_2acac$,
20 bar CO/H_2, 5 mol % *p*-TsOH,
60 °C, BIPHEPHOS or
XANTPHOS, 1-2 d

29, 50 %

Intractable mixture

16b

Scheme 26: *Differences in reactivity accounted for by the presence of α-substitution.*

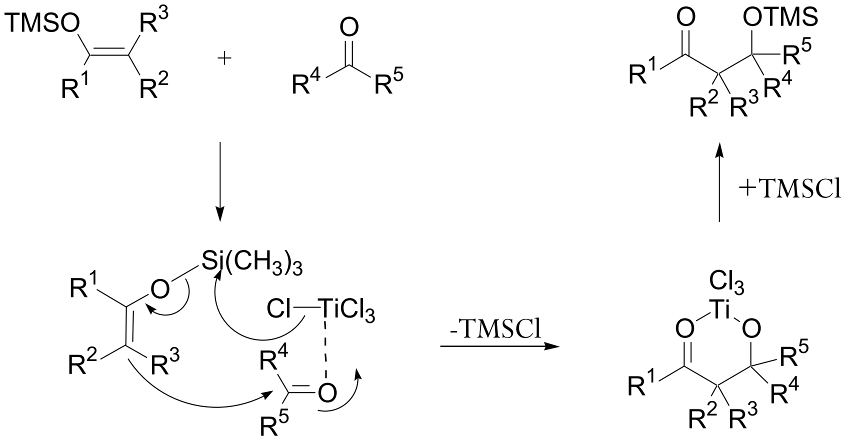
2.7 Summary

It can be concluded from these investigations that although it has been proven to be effective in catalyzing the aldol addition/condensation reactions of a number of substrates in tandem with hydroformylation, the use of acid catalysis has shown itself to be less than effective when one desires to use the reaction to provide access to terpenoid ring systems. While the basic cyclohexanone connectivity can indeed be established, the loss of the hydroxy group due to the reaction proceeding through the aldol condensation step combined with the lack of reactivity in the formation of quaternary centers are two major drawbacks of this methodology. Another method of activation is necessary when one desires to explore the stereochemical elements of this sequential transformation. Early successes in the area of sequential hydroformylation/Mukaiyama aldol addition suggested that this was a route to explore.

2.8 Sequential hydroformylation/Mukaiyama aldol addition

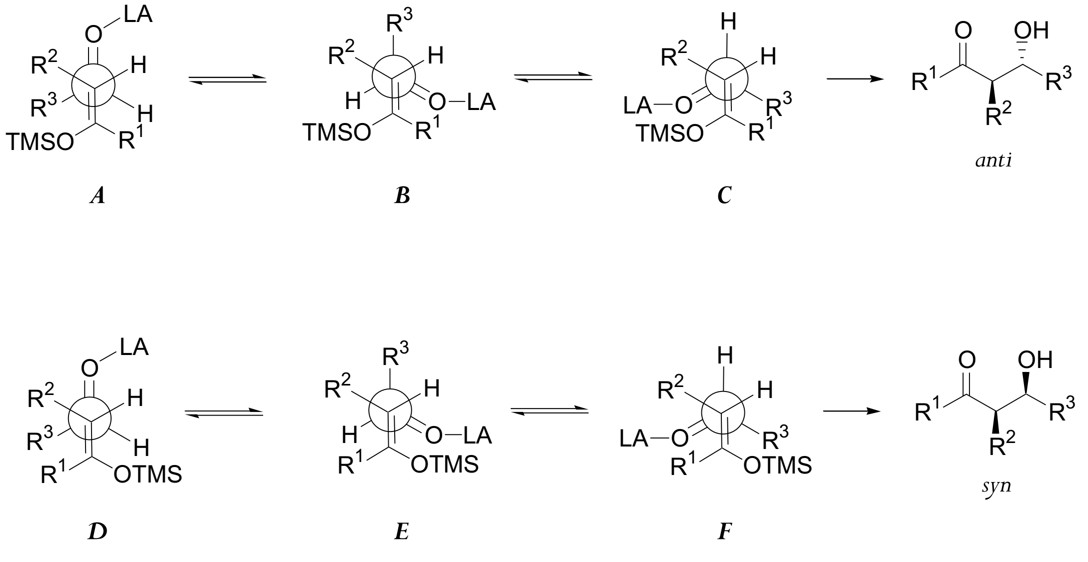
2.8.1 The transition metal-mediated Mukaiyama aldol additon

The addition of a normally inert silyl enol ether functionality to the carbonyl group of a ketone or aldehyde under the activation of metal salts was first reported in 1973 by **Mukaiyama**[41a] and immediately thereafter by **House**[42] (Scheme 27).



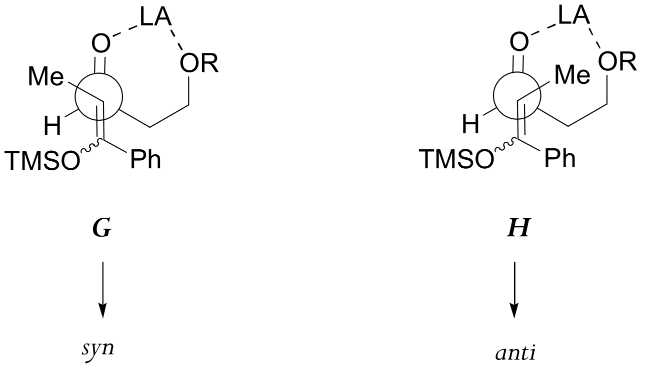
Scheme 27: The Mukaiyama aldol addition reaction of enolsilanes with aldehydes or ketones.

In this transformation, the carbonyl group of the electrophile was activated so strongly by the addition of metal salts - especially $TiCl_4$ - to the mixture that preformed silyl enol ethers of various types were able to act as nucleophiles, adding smoothly to the carbonyl group under very mild conditions (-78 C, CH_2Cl_2). This discovery represented one of the most significant advances in aldol chemistry in that it dealt with two key problems: the suppression of the aldol condensation reaction, since the silyl group was transferred to the alkoxide anion generated upon addition; and the use of enolizable aldehydes was now permitted, as cross condensation pathways were now eliminated by being able to perform the reaction in the presence of a stable, preformed enolate equivalent. With these long-standing problems aside, the reaction enabled a much wider variety of functionality to be tolerated, and as a direct result of the retention of oxygen functionality in the production of β-silyloxy ketones, the issue of simple stereoselection[43] in the addition was introduced, as two prochiral compounds - the enolsilane and the carbonyl compound - are used that produce a diastereomeric pair of aldol adducts. It was not until about ten years later that investigations into the stereochemical aspects of the reaction were started[44], and while the mechanism of the reaction has not yet been fully explained, a few important facts have been established. The most important detail that has been confirmed is that transmetalation does not occur in the reaction, which rules out the involvement of transition metal enolates in the process. The Lewis acids only role appears to be coordination to the carbonyl compound, which leads to its activation.[45] As different conditions, reagents and enolates can be used, a different mechanistic picture and other transition state assemblies were proposed to be involved for each different scenario. Further evidence for this mechanistic complexity was that the stereochemical outcome could not be explained via traditional closed transition states represented by Zimmerman-Traxler models.[46] Initial theoretical studies[47] presented that the "classic" Mukaiyama reaction takes place via an acyclic open transition state[48] mediated by a *monodentate* Ti-species, a concept that is still held to be true to this day (Scheme 28). The proposed open model assumes that the main determining force in the outcome of the reaction is the dipolar repulsion present between the uncomplexed ionic oxygens in the system. It is important to clarify that initially no stereochemical advantage had been observed for this addition, but by a careful choosing of substrates (aldehyde, silyl enol ether or silyl ketene acetal), a sufficient control of the diastereoselectivity could be obtained.



Scheme 28: *Open transition state assemblies accounting for Mukaiyama aldol addition stereoselectivities.*

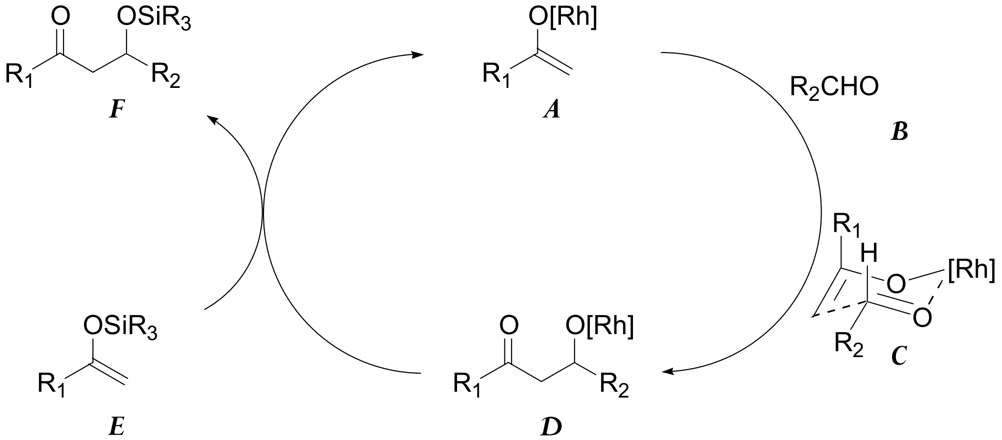
Via this analysis, three of the following transition states - ***B**, **C*** and ***E*** - can be excluded immediately on the basis of the steric repulsion and/or the unfavorable dipole-dipole interaction between R_1 and the Lewis acid. Reasonable *anti*-selectivities could be observed, independent of the enolate geometry, when R_1 is large and R_2 is very small, as transition structures ***D*** and ***F*** are disfavored compared to ***A***. In contrast to this, when R_2 is replaced by a larger group, the transition states ***A*** and ***F*** are now disfavored when compared to ***D*** via repulsive interactions between R_2 and R_3. This results in a *syn*-selective addition *irrespective of the double bond geometry* of the enolsilane. By using aldehydes capable of intramolecular chelation, a trend toward high *syn*-selective reactions was observed, as transition state ***H*** is disfavored due to the repulsive interactions present (Scheme 29).



Scheme 29: *syn-Selectivity when using aldehydes capable of chelation.*

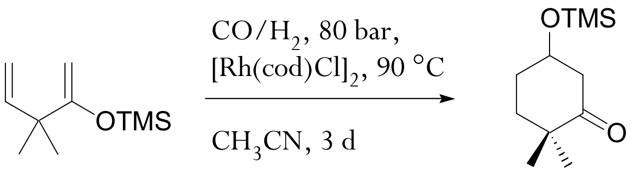
2.8.2 The rhodium-catalyzed Mukaiyama aldol addition

In contrast to these initial results, where stereochemical outcomes were determined largely by steric factors and were more or less independent of the enolate geometry, a notable advancement was made when catalytic versions of the reaction were developed. Especially of interest in the context of these studies are the versions meditated by rhodium complexes, as it would be possible to affect two processes - hydroformylation and aldol addition - through the use of a single Rh-catalyst. The first rhodium-catalyzed variant of the Mukaiyama addition was reported in 1986 by **Matsuda**.[49] These initial studies showed that the cationic rhodium complexes such as $[Rh(cod)(dppb)]PF_6$ and $[Rh(cod)(dppb)]ClO_4$ along with the neutral complex $Rh_4(CO)_{12}$ effect the intermolecular addition of enolsilanes to aldehydes under relatively harsh conditions (benzene, 100 °C) in up to 83 % yield with low diastereoselectivities (up to 56:44). In the classic cases mediated by stoichiometric amounts of Lewis acids, where transmetalation was determined not to take place, the catalytic variants of this reaction were thought to proceed via a transition-metal enolate. An improvement upon this initial procedure was reported in the following year by **Reetz**[50], where the reaction was conducted at room temperature by employing a cationic rhodium(I)diphosphine complex in CH_2Cl_2. **Reetz** also suspected a rhodium enolate to be a key player in the transformation, but this was not confirmed experimentally until work done by **Heathcock**[51] elucidated the entire catalytic cycle (Scheme 30).



Scheme 30: *Cycle of the rhodium(I)-catalyzed Mukaiyama aldol addition.*

In this cycle, the rhodium enolate ***A*** formed via transmetalation of the enolsilane adds to the aldehyde ***B*** resulting in the formation of a rhodium aldolate ***D***. A transfer of the silyl moiety from another enolsilane ***E*** results in the formation of the final adduct ***F*** along with regeneration of the reactive rhodium enolate. Notable in this cycle is the fact that the addition to the rhodium enolate that produces ***D*** can take place via a closed, highly ordered Zimmermann-Traxler transition state assembly ***C***, where a high degree of stereoselectivity can be incorporated into the reaction by using enolsilanes of a fixed geometry. Initial experiments done in this workgroup have shown that indeed this connectivity can be established to synthesize β-silyloxy-cyclohexanones from the enol ethers generated from the β,γ-unsaturated ketones we have used in the scenarios involving acid catalysis. A wide range of yields were obtained, with the best case being represented by the TMS silyl enol ether of 3,3-dimethyl-pent-4-en-2-one (**11**) reacting to give β-silyloxy-cyclohexanone **30** in 72 % yield (Scheme 31).



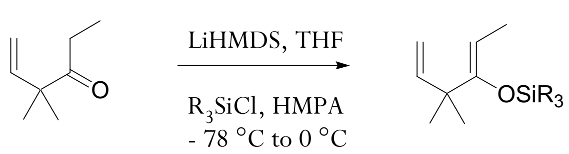
(±)-**30,** 72 %

Scheme 31: *Sequential hydroformylation/Mukaiyama aldol addition to afford cyclohexanone* ***30****.*

One of the trends that was able to be concluded from these initial results what that the TMS group seemed to be the best choice in terms of combining the best possible yield with the best possible degree of silyl transfer to the product. The most interesting aspect of this transformation was not investigated in these initial studies, however, and that is the variable of stereochemical control in the sequence. To investigate this, a number of enolsilanes were prepared from the materials used to investigate the reaction under acid catalysis and exposed to hydroformylation conditions.

2.9 Preparation of β,γ-unsaturated enolsilanes of ketones

For initial investigations into the stereochemical properties of the sequential transformation, a number of enolsilanes were prepared. As the simplest derivative, 4,4-dimethyl-hex-5-en-3-one (**12**) was subjected to standard conditions known to afford the *Z*(O)-enolsilanes **28**-**30** in good yields.[52] Three different silyl moieties were employed to test whether or not this also played a role in the stereochemical outcome of the reaction (Scheme 32).

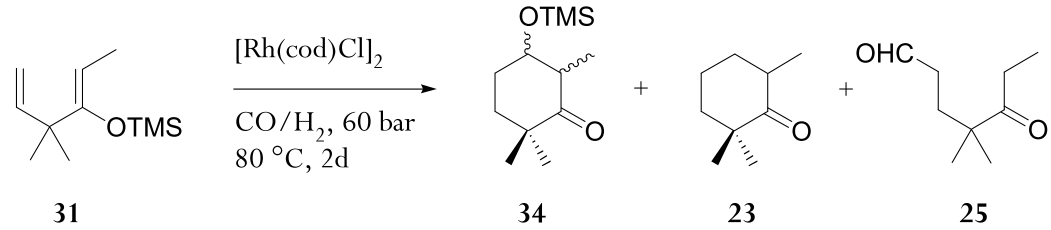


12 **31**-**33**

Silyl chloride	Yield
TMSCl	**31,** 86 %
DPMSCl	**32,** 77 %
TBSCl	**33,** 38 %

Scheme 32: *Stereoselective preparation of Z(O)-enolsilanes.*

Investigations began with (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-trimethylsilane (**31**), which was hydroformylated under standard conditions to evaluate the behavior of this compound toward the Mukaiyama aldol addition. Initial results were not nearly as encouraging as what was observed in the case of the unsubstituted enolsilanes. A variety of products were observed upon filtration of the crude reaction mixture through a small pad of alumina, which was developed to be the standard workup procedure for reactions of this type, as under neutral conditions there is a minimal chance for any type of product decomposition or retro-aldol type reactions to occur. Upon analysis of the reaction mixture, two products could be seen, in small amounts, which were the result of aldol addition processes. The desired product 2,2,6-trimethyl-5-trimethylsilanyloxy-cyclohexanone (**34**) was observed in small amounts along with large amounts of 2,2,6-trimethylcyclohexanone **23** (Scheme 33). The cyclic products amounted to the minority of the yield, the rest of which was accounted for by the product of hydroformylation and desilylation, ketoaldehyde **25**. As only dry solvents and reaction conditions were used, the observation of such a product cannot be attributed to the presence of water in the reaction mixture. It is possible that in the case of the these particular substrates, the TMS-enolsilane is too labile under the reaction conditions, and the silyl enol ether is transmetalated and collapses before an appreciable degree of hydroformylation can occur for the enolate to react with.



Product ratios determined by ^{1}H-NMR

Solvent	34	:	23	:	25
dioxane	1	:	1.2	:	2.5
CH_2Cl_2	1	:	1	:	2
MeCN	1	:	1.2	:	2

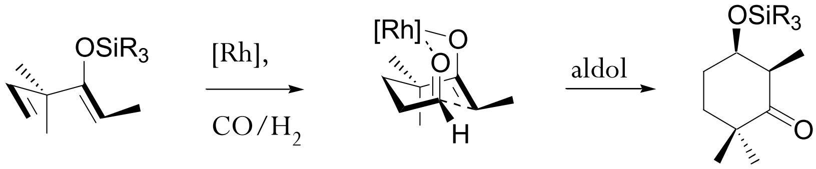
Scheme 33: *Identifiable products upon hydroformylation/aldol-reaction of enolsilane* ***31***.

Lability of the enolsilane most likely accounts for the observance of **23** in the reaction mixture. This product is the result of aldol addition with failure of the silyl transfer to take place, or possibly an in-situ deprotection, which could take place in the presence of the tetracarbonylrhodium hydride species which effects the hydroformylation, as they are known to possess a reasonable degree of acidic character[53] (Scheme 34).

$$[\mathrm{Rh(cod)Cl}]_2 \xrightarrow[\text{- (cod)}]{\mathrm{CO}} [\mathrm{Rh(CO)_2Cl}]_2 \xrightarrow[\text{- HCl}]{\mathrm{CO/H_2}} \mathrm{HRh(CO)_4}$$

Scheme 34: *Generation of an acidic rhodium hydride species - HRh(CO)$_4$ - during hydroformylation.*

That it was now possible to retain the oxygen functionality in the products through the use of this methodology what remained to be done was to improve the conversion and yield of the reaction towards the Mukaiyama product, which could then be analyzed as to determine the stereochemistry of the reaction. From an analysis of the Zimmermann-Traxler transition states that govern the assembly of the Mukaiyama products subsequent to hydroformylation, a clear stereochemical preference exists. As the enolsilane is fixed in a *Z*(O)-geometry via silylation of the lithium enolate, a closed transition state that proceeds via chelation-controlled delivery and addition of the aldehyde should be selective for a product bearing *cis*-stereochemistry (Scheme 35).

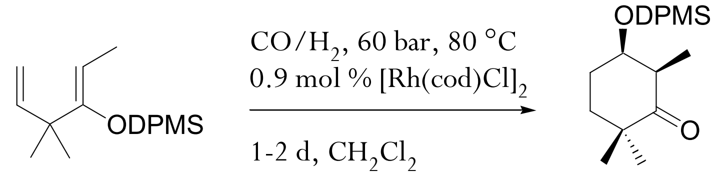


Scheme 35: *Transition state governing the intramolecular Mukaiyama aldol addition of Z(O)-enolsilanes.*

Upon hydroformylation and transmetalation to the rhodium enolate, the aldol addition is allowed to proceed, assisted by chelation to rhodium, which results in the production of the *cis*-aldol adduct. As this is an intramolecular aldol addition, the degree of *cis*-diastereoselectivity is affected by two factors - the degree of chelation control present in the addition, and the retention of the enolate geometry during the transmetalation step. In the hydroformylation of

31, the complicated mixture of products made any analysis of their stereochemistry impossible, and the investigations proceeded with the remaining enolsilanes **32** and **33**.

DPMS-enol ether **32** was hydroformylated under various conditions, in order to study the degree of silyl transfer to the product, as well as confirm the stereochemistry of the addition. As can be seen in Scheme 36, a large degree of improvement in the amount of silyl transfer was observed upon reaction of the more robust diphenyl methyl-enolsilane. The only cyclized product observed upon analysis of the reaction mixture was 5-(diphenyl methyl-silanyloxy)-2,2,6-trimethyl-cyclohexanone (**35**), which could be obtained in up to 72 % yield in a 2.1:1 *cis-* : *trans*-ratio, as determined by ^{1}H-NMR and ^{13}C-NMR. This result was encouraging as it supported the theory that the degree of silyl transfer would be improved when a more robust group was employed in the reaction. As stated, it could also be seen that the Mukaiyama aldol addition proceeded with a small degree of *cis*-stereoselectivity. This lower-than-expected amount of selectivity could be explained by steric factors.

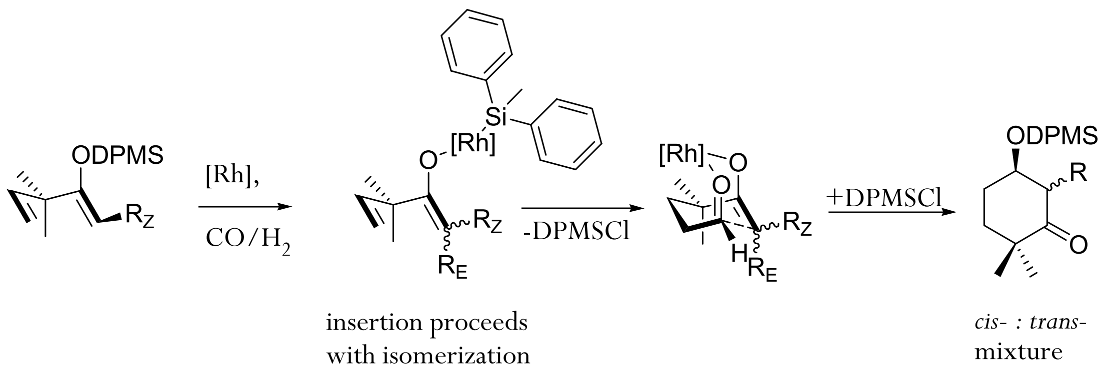


32

(±)-**35**,
up to 72 %
2.1 : 1
cis- : trans-

Scheme 36: *Hydroformylation/aldol addition of diphenyl methyl-enolsilane* **32**.

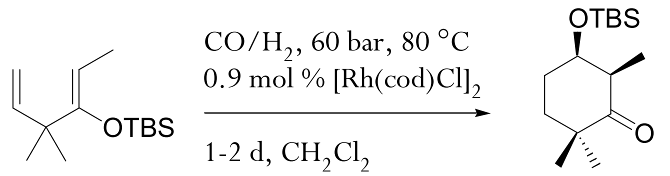
In the transmetalation of the enolsilane by the active Rh-catalyst en route to the Mukaiyama addition product, the steric bulk of the silyl group could play a role in the ability of the enolsilane to retain its *Z*(O)-configuration. In the presence of a large group such as the diphenylmethyl silyl group, the transmetalation could proceed with an inversion of the double bond to a *E*(O)-configuration (Scheme 37).



Scheme 37: *Isomerization of sterically-demanding enolsilanes under hydroformylation conditions.*

Upon insertion of the Rh(I)-species into the Si-O bond, a group as large as DPMS could effectively push the substituent on the enolsilane into a *E*(O)-position, allowing for transmetalation to take place resulting in a mixture of *Z*(O)- and *E*(O)-enolsilanes. These can then proceed through the Mukaiyama aldol reaction, resulting in the production of a mixture of *cis-* and *trans*-aldol products. Although these results were promising, it was clear that a silyl group of moderate size should be employed, and that perhaps the TBS-enolsilane would result in an improvement of the stereoselectivity.

Hydroformylation of enolsilane **33** under the standard conditions resulted in the production of 5-(*tert*-butyl-dimethyl-silanyloxy)-2,2,6-trimethyl-cyclohexanone (**36**) in up to 59 % yield and 4:1 diastereoselectivity as determined by NMR (Scheme 38).



33

(±)-**36**,
up to 59 %
4 : 1
cis- : trans-

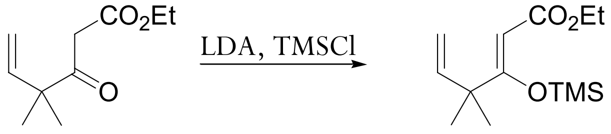
Scheme 38: *Hydroformylation/aldol addition of tert-butyl dimethyl-enolsilane 33.*

As can be seen from this result, the slightly smaller TBS group allows for the cyclization to proceed in a slightly lower overall yield, but with markedly improved diastereoselectivity. This result represents a synthetically useful variant of this reaction in terms of yield and stereoselectivity, resulting in β-silanoxy-α-methyl cyclohexanones possessing a *cis*-configuration. These products could prove useful when constructing stereodefined analogs of the forskolin *A*-ring system, as it possessed this β-hydroxy-α-methyl cyclohexanone functionality. Further elaboration towards the natural product is easier, however, when a functional group other than methyl is present in the α-position.

2.10 Preparation of β,γ-unsaturated enolsilanes of ketoesters

2.10.1 Formation of non-quaternary centers

For this reason, the TMS-silyl enol ether of α-unsubstituted ketoester **13** was synthesized via treatment with LDA and TMSCl to afford ethyl 4,4-dimethyl-3-trimethylsilanyloxy-hexa-2,5-dienoate (**37**) in 80 % yield (Scheme 39).

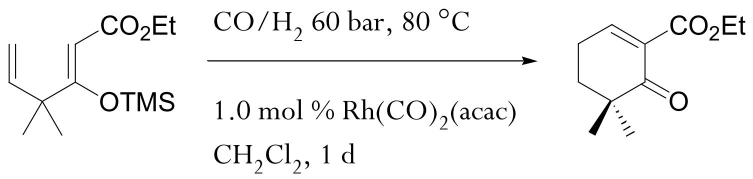


13 **37,** 80 %

Scheme 39: *Synthesis of silyl enol ethers of α-unsubstituted ketoesters.*

With this class of compound, the cyclization could be tested on the highly-activated ketoester functionality, to determine whether or not the Knoevenagel condensation/hydrogenation sequence seen in the acid-catalyzed variant could be suppressed.

Upon hydroformylation of **37**, a surprising result was observed. Upon workup, only one product could be observed, the enone ethyl 5,5-dimethyl-6-oxo-cyclohex-1-enecarboxylate (**38**) resulting from Knoevenagel condensation on the aldehyde generated through hydroformylation in nearly quantitative yield. This electron-deficient enone was resistant to hydrogenation under the hydroformylation conditions, and represents yet another type of functionality obtainable from these compounds (Scheme 40).



37

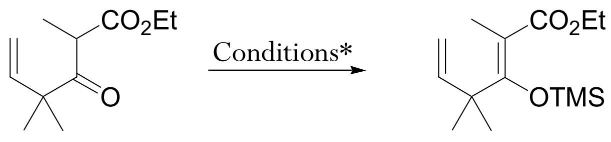
38, 97 %

Scheme 40: *Hydroformylation/Knoevenagel reaction of* ***37****.*

This product can also be seen as a useful building block towards the forskolin *A*-ring system. The required hydroxy group at C-1 could be installed via manipulation of the enone double bond, with addition to the remaining carbonyl groups allowing for elaboration towards the natural product. It now remained to test whether or not the quaternary carbon center present in the *AB*-ring fusion of the natural product could be constructed with use of this methodology. Also, in the presence of the quaternary center, the elimination of water should be suppressed, which would allow for the retention of the required C-1 oxygen function in this step.

2.10.2 Formation of quaternary centers

Unfortunately, the synthesis of a tetrasubstituted enolsilane proved to be unsuccessful. The large amount of steric hindrance present in **13a** no doubt suppresses the enolization of the keto-functionality (Scheme 41).



13a

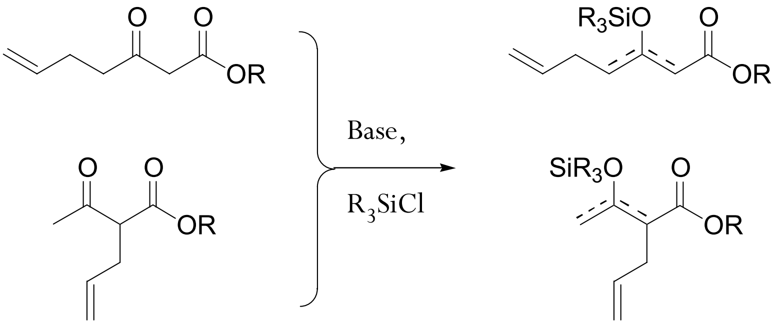
not obtainable

**Conditions:* 1. LDA, TMSCl
2. LiHMDS, TMSCl
3. Et_3N, TMSCl, reflux
4. $NaNH_2$, TMSCl

Scheme 41: *Attempts at the synthesis of tetrasubstituted carboethoxy-enolsilanes from* ***13a****.*

2.11 Investigation of model substrates

The investigation of a sequential hydroformylation/Mukaiyama aldol addition on the model substrates used to determine the scope and selectivity of the acid-catalyzed variant of this methodology provided much less information in this case. The failure to obtain enolization of compounds such as **13a** has already shown a limitation of the reaction towards certain types of sterically demanding unsaturated compounds, but it proved necessary that enolsilation be directed towards the desired position, as mixtures of silyl enol ethers arise when there are possibilities to generate more than one possible enolsilane (Scheme 42).



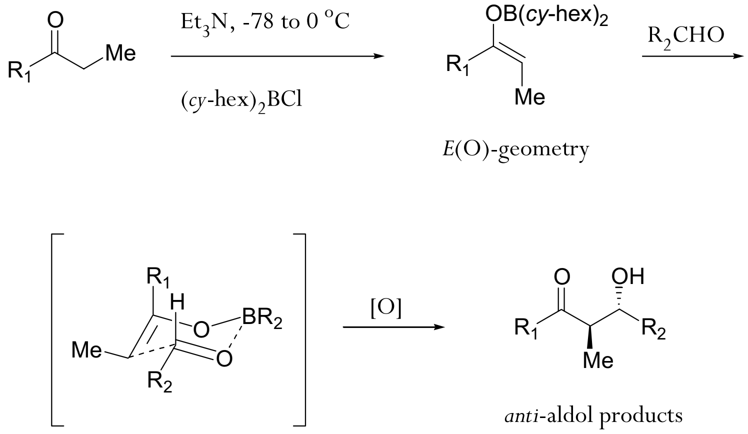
Scheme 42: *Regioselectivity problems with enolsilation in substrates bearing multiple enolizable sites.*

2.12 Summary

Despite this drawback of not being able to obtain a tetrasubstituted enolsilane to evaluate quaternary center formation, other positive results have come about through the use of sequential hydroformylation/Mukaiyama aldol addition reactions of various types of enolsilanes. First, a stereoselective synthesis of forskolin *A*-ring analogs in the form of α-methyl-β-silanoxy cyclohexanones is made possible through the use of the enolsilanes of substituted γ,δ-unsaturated ketones, offering substituted cyclohexanones bearing *cis*-stereochemistry in synthetically useful yields and diastereoselectivities. Performing the same reaction on γ,δ-unsaturated ketoesters results in the formation of enones, which is also a useful when viewed in the context of application towards labdane diterpenoids. However, the inability to obtain compounds with quaternary carbon centers through this methodology is a problem that needs to be addressed through the exploration of other methods of enolization/activation toward aldol addition.

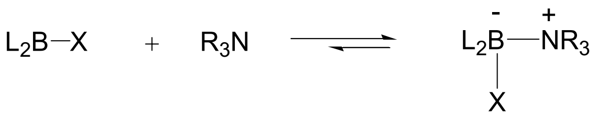
2.13 Sequential enolboration/hydroformylation/aldol addition[54]

In considering a process that would allow for the synthesis of advanced, stereodefined intermediates en route to the forskolin system using hydroformylation, another method commonly used in stereoselective aldol addition chemistry was explored. It is well-known that dialkylboron enolates afford some of the highest degrees of selectivity in intermolecular aldol addition.[55] Crucial to these high selectivities is the ability for a large degree of retention of the enolate geometry and the delivery of the aldehyde to that enolate via a chelation-controlled addition mechanism, governed by the highly-ordered Zimmermann-Traxler transition state model. Seminal work performed mainly on thioesters by **Mukaiyama**, **Masamune** and **Evans**[56], and later refined and applied to exceptionally high degrees of stereoselectivity in the context of general systems by **Brown**[57], found that enolboration had a very strong preference for an *E*(O)-geometry when performed with certain combinations of amine bases and dialkylboron halides, which translated to a preference for *anti*-aldol products following oxidative workup to remove boron chelates (Scheme 43).



Scheme 43: *Stereoselective E(O)-enolboration and subsequent diastereoselective anti-aldol addition.*

In more detailed examinations of this reaction, it was found that the dependence of the stereoselectivity on the base and boron halide chosen stemmed from the complexation reaction that takes place upon mixing the reagent pair prior to the addition of any carbonyl compound (Scheme 44).



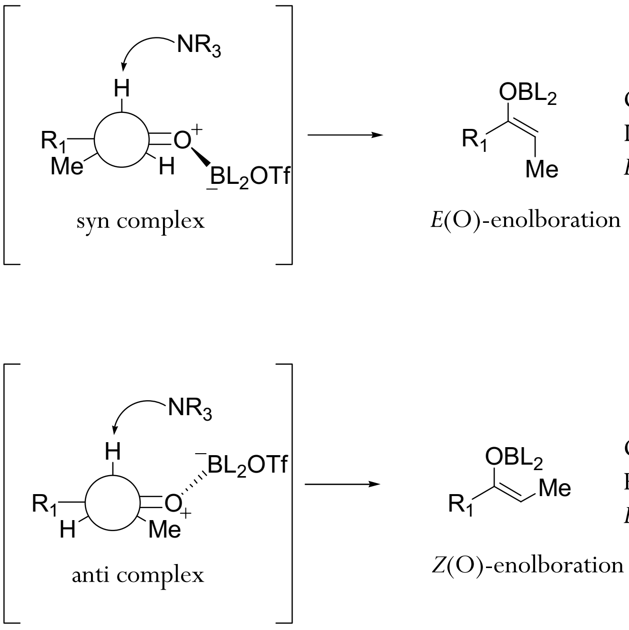
$$L_2B{-}X \; + \; R_3N \rightleftharpoons L_2\overset{-}{\underset{\displaystyle X}{B}}{-}\overset{+}{N}R_3$$

Complexation affinity: py > DABCO > DBU >> Et_3N, EtN*i*-Pr_2

Enolboration reactivity: EtN*i*-Pr_2, Et_3N >> DBU > DABCO > py

Scheme 44: *Complexation affinity of dialklboron halides with amines related to enolboration reactivity.*

It was observed, logically, that the stronger the affinity for complexation was, the reagent mixture was less reactive in the enolboration reaction due to the decreased tendency for the complex to under go the necessary dissociation during enolboration. Upon inspection of the mechanism as suggested by **Evans**[58], some generalizations can be made regarding the stereoselectivity of the enolboration, but also a rather usual exception to the rule was noticed (Scheme 45).



Generally preferred when L and NR_3 are large
L = *c*y-hex, NR_3 = Et_3N
E(O) : *Z*(O) = 81 : 19

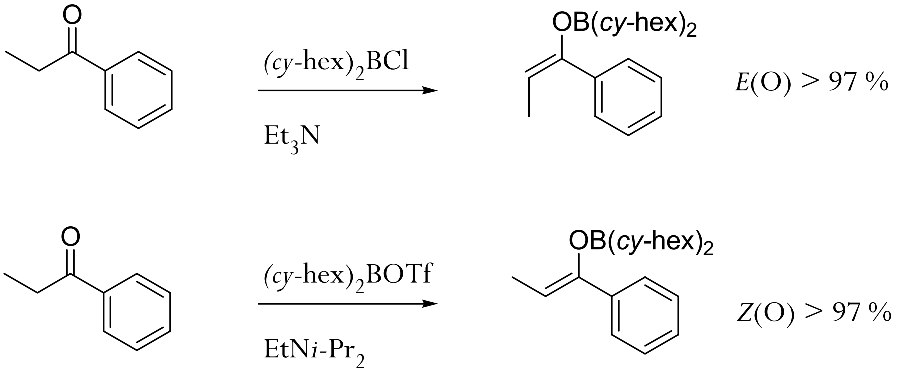
Generally preferred when L and NR_3 are small
Exception: L = *n*-Bu, NR_3 = EtN*i*-Pr
E(O) : *Z*(O) = 1 : >99

Scheme 45: *Stereoselective enolboration using dialkylboron triflates.*

For the most part, the relationship between amine size (relating directly to complexation affinity) and the ligand size on boron is a good guide for predicting the type and degree of stereocontrol in the enolboration. Small amines together with small (acyclic) alkyl groups on boron favor the formation of the *anti*-complex (see Scheme 45) resulting in formation of a

Z(O)-boron enolate after deprotonation. When more sterically demanding amines and boron halides are employed, the *anti*-complex formation is disfavored, and the *syn*-complex resulting in high proportions of *E*(O)-enolates after deprotonation predominates in solution. The notable exception mentioned above is what one observes when employing dialkylboron triflates in combination with sterically hindered bases such as Hünig's base. Contrary to what one would expect from the previous data, an overwhelmingly stereoselective *Z*(O)-enolboration takes place, indicating that another variable must be at play which determines the stereochemistry of this process.

Brown[59], in extending his work into the realm of stereoselective enolboration of ketones, noticed a similar trend when a number of boron triflates were employed. Regardless of the base used, the *Z*(O)-enolboration pathway was favored. Simply switching to the corresponding boron chloride resulted in the observation of the expected *E*(O)-enolate, and in general, Et_3N provided the optimum selectivities in conjunction with this reagent (Scheme 46).



Scheme 46: *Subtle leaving group affects in the enolboration of ketones: optimum reagent combinations for stereoselective E(O)- and Z(O)-enolboration.*

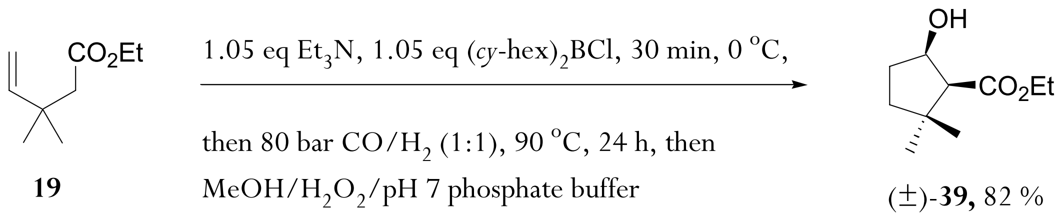
It was assumed as the result of these investigations that the leaving group present in the dialkylboron reagent played a very significant role (relating to complexation affinity) in determining whether a *syn*- or *anti*-deprotonation complex was formed, and thus determining the stereoselectivity in the enolboration process as a whole. Perhaps the synthetically most important results of Brown's detailed and thorough investigations were the discovery of the reagent combinations that afforded the desired stereoselectivities in the enolboration of a wide variety of carbonyl functionalities, be it esters, ketones or aldehydes.

Far and away the most significant findings came in the discovery of a method to generate an *E*(O)-enolate in a stereoselective fashion, and retain that geometry through a pericyclic transition state[60], incorporating it into the formation of anti-aldol addition products. This methodology allowed for the production of stereodefined aldol stereochemistry, which was before only accessible in low stereoselectivities, at best deviating only slightly from the 1:1 mixtures obtained from employing completely unselective aldol addition techniques.

Upon inspection of the stereochemistry present in the forskolin *A*-ring system, it was clear that we required the opposite stereochemistry than what was obtained through the sequential hydroformylation/Mukaiyama aldol addition reactions that were investigated earlier. Also, the failure to construct the quaternary center present in the *A*-ring system through any previously known means of activation towards aldol addition paired with the hydroformylation reaction was impetus to explore this methodology in the context of encorporating it into a three-component reaction cascade which would, if successful, result in the stereoselective production of intramolecular aldol addition products, subsequent to the initial enolboration and following hydroformylation reactions. As a cascade reaction is only as effective as its least efficient component, it was necessary to be able to fully examine and optimize the conditions needed for each individual reaction step to proceed in the presence of the other required reagents. In beginning this analysis, the conditions surrounding the enolboration were examined. Several of the model substrates constructed for these purposes proved ideal for this.

2.13.1 Enolboration/hydroformylation/aldol addition of unsaturated esters

Although only a few applications exist, enolboration has been proven to proceed very efficiently with esters[61], and several of these were chosen as test substrates in investigating the effectiveness of enolboration under the hydroformylation conditions. An astounding result was observed upon testing the first substrate for this reaction, monoester **19**, in that the reaction proceeded in a completely diastereoselective fashion to produce *cis*-ethyl 5-hydroxy-2,2-dimethyl-cyclopentanecarboxylate (**39**) in 82 % isolated yield (Scheme 47).

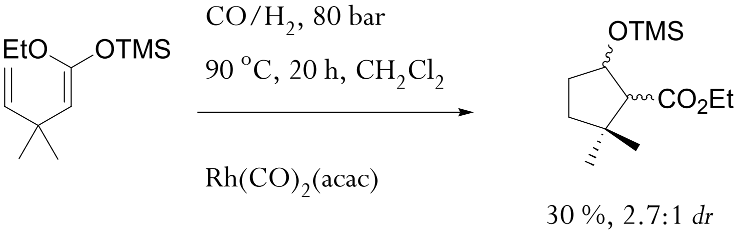


19

(±)-**39,** 82 %
only *cis*-

Scheme 47: *Sequential enolboration/hydroformylation/aldol addition of unsaturated ester* ***19.***

This represents a significant advancement in terms of both yield and stereoselectivity upon a previously reported result[24a] where the analogous TMS-analog of **39** was produced as a 2.7:1 mixture of undetermined diastereomers from the corresponding silyl ketene acetal (Scheme 48).



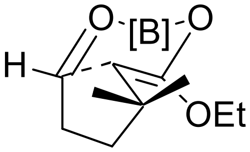
Scheme 48: *Previously reported production of the TMS-analog of* ***39*** *via hydroformylation/Mukaiyama addition.*

A step-by-step walkthrough of the reaction procedure is at this point helpful in understanding the mechanistic details of this new cascade process. Initially, the reaction is performed in an analogous fashion to the intermolecular variant of enolboration. Working under Schlenk conditions using an argon atmosphere, a slight excess (1.05 eq each) of Et$_3$N and (*cy*-hex)$_2$BCl are allowed to proceed through a short complexation phase of approximately 15 minutes before the carbonyl compound is added to the reaction mixture. The enolboration is then allowed to stir for 30-45 minutes before the mixture is syringed into an argon-flushed autoclave containing 10-15 mL of CH$_2$Cl$_2$ and the hydroformylation catalyst. The autoclave is then sealed and subjected to the required pressure, temperature and reaction time. Upon cooling to RT, the crude mixture is removed from the autoclave and concentrated under reduced pressure. This crude solid residue consisting of boron chelates and ammonium salt is dissolved in a small amount of MeOH (25 mL) before 2 mL of a pH 7 phosphate buffer solution and 1 mL of 30 % H$_2$O$_2$ is added. The regulation of the pH at neutral conditions is essential for the successful isolation of these aldol products which are the result of potentially reversible processes. Treatment of most products with strong acid or base results in either the formation of retro-aldol products or in product decomposition.

A few additional things should be said regarding some particular nuances of this reaction cascade. Both the [Rh(cod)Cl]$_2$ and Rh(CO)$_2$(acac) catalysts perform well in this sequence, with the only factor speaking in favor of one or the other is if the hydroformylation is performed in the presence of ligands directing *n*-hydroformylation. When ligands are required to accomplish a regioselective hydroformylation, the process tends to favor the use of the

$Rh(CO)_2(acac)$ catalyst in terms of isolated yield and conversion of starting material, while the $[Rh(cod)Cl]_2$ dimer is normally employed under conditions where the use of ligands is not required, which will be discussed in due course.

Returning to the observed stereoselectivity in the aldol addition of unsaturated ester **19**, a detailed discussion of the stereochemical variables surrounding the enolboration an aldol addition is helpful. The production of the *cis*-product in this case was confirmed upon inspection of the ^{1}H-NMR coupling constants and in direct comparison to the known *cis*-ethyl 2-hydroxy-cyclopentanecarboxylate, which was synthesized via a Rh-catalyzed Reformatsky reaction of the corresponding α-bromo ester in lower diastereoselectivity.[62] In this case, however, the *E*(O)-enolboration proceeded with complete diastereoselectivity, which allowed for delivery of the aldehyde generated through hydroformylation to the enolate via chelation control, proceeding through a highly-ordered Zimmermann-Traxler transition state, resulting in the cis-β-hydroxy ester **39** (Scheme 49). Also noteworthy from this transformation is the demonstration that the (cy-hex)$_2$BCl/Et$_3$N reagent system was effective in the enolboration of an ester functionality.[63] While indeed not applicable generally to ester functions, in this particular example the enolboration proceeds under the sequential reaction conditions and undergoes aldol addition with a high degree of selectivity.



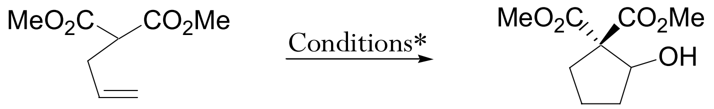
Scheme 49: *Proposed transition state assembly responsible for the production of ester **39**.*

This initial example represents the ideal combination of all three components of the reaction cascade proceeding in high stereoselectivities to afford the reaction product in high yields, which bodes well for the application of this new method for the synthesis of β-hydroxy carbocyclic compounds from easily-obtained acyclic olefins as starting materials. The fact that this is an intramolecular reaction cascade allows for a high degree of chelation-control and selectivity is allowed for with the aldehyde essentially “tethered” to the enolate. A good deal of optimization went into this process to result in the consistent production of the aldol addition adducts in good yields and selectivities. Granted, the optimum reagent concentrations needed to perform the enolboration have already been established in the literature, and the reaction variables of temperature and pressure necessary to affect the hydroformylation are more or less fixed, a certain amount of variation can be observed upon modification of the oxidative workup conditions. The standard method involving the use of hydrogen peroxide was found to be adequate for all substrates when the oxidation was allowed to proceed in dilute concentrations (0.01 M) with a small amount of 30 % H_2O_2 (1 mL) in solution, and it was found to be necessary to hold the pH of the workup at pH 7 to avoid retro-aldol reactions from taking place. Although the intermolecular versions of aldol addition are usually exposed for shorter time periods to greater concentrations of peroxide, the method involving lower concentration and longer time was found to greatly improve the yield and to some extent the stereoselectivity of this process. An even milder method of oxidation was found by **Evans**[a] to be very effective in the workup of products sensitive to over-oxidation, such as thioesters. It was shown that the oxidant MoO_5•py•HMPT[64] (MoOPH) was ideal for the workup of such sensitive compounds, but as none of the products dealt with here were sensitive to any further oxidation, the considerably more expensive molybdenum complex was not tested as a workup method.

Moving on to test the methodology on the highly-activated malonate system **20** resulted in the acquisition of a good deal more information useful to understanding the limits of this cascade. Based on the result observed in the conversion of ester **19**, it was assumed that enolboration would proceed well with this substrate, and therefore it was used to evaluate the prospect of using ligands under these conditions to direct for a regioselective hydroformylation, which after aldol addition would result in the formation of a quaternary center bearing a high degree of neighboring functionality.

When exposing **20** to the reaction conditions in the presence of *n*-directing ligands, a more drastic difference was observed. Upon trials of this sequential transformation using BIPHEPHOS to test whether the reaction can be performed at lower temperature and pressure, it was observed that in best cases a low conversion of starting material was observed, or as in most cases, an intractable mixture was observed upon oxidative workup of the reaction. The reasons for the complete incompatibility of BIPHEPHOS with these reaction conditions is not exactly known, but the presence of ligand decomposition products suggests perhaps the instability of the phosphite ligand to the presence of a tertiary amine or quaternary ammonium salts at the required reaction temperatures. Fortunately, this problem was solved through the use of XANTPHOS (2 eq. to catalyst), which provided exceptional *n*-selectivities in the sequence, in which only aldol addition products were observed.

In the conversion of **20**, the corresponding dimethyl 2-hydroxy-cyclopentane-1,1-dicarboxylate (**40**) was observed as the sole product in 51 % yield (Scheme 50).



20 **40,** 51 %

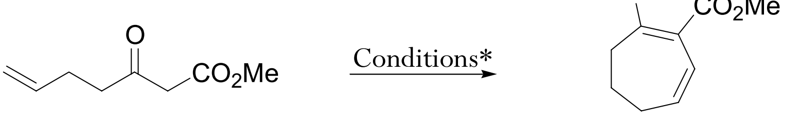
**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % Rh(CO)$_2$(acac), 1.8 mol % XANTPHOS, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 50: *Enolboration/hydroformylation/aldol addition of malonate **20**.*

While the yield is slightly lower than that reported from the use of hydroformylation in the presence of acid catalysis[24a], this particular result is important for several reasons. For one, it represents the first example of the we achieved nonetheless the goals that we desired to with this particular compound, namely that it was shown that the cascade reaction could be performed in the presence of ligands needed for *n*-selective hydroformylation, and that under these conditions a quaternary carbon center could be formed. This allowed for the potential to produce quaternary centers in a diastereoselective fashion when unsymmetrical esters are used, or also when the reactive center is present in the form of a ketoester.

2.13.2 Enolboration/hydroformylation/aldol addition of unsaturated ketoesters

When applying the optimized reaction conditions to ketoesters, several interesting results were obtained. The α-unsubstituted ketoester **16a**, when exposed to the reaction conditions afforded unsaturated diene methyl 2-hydroxy-cyclohepta-1,6-dienecarboxylate (**29**) in 82 % yield (Scheme 51).



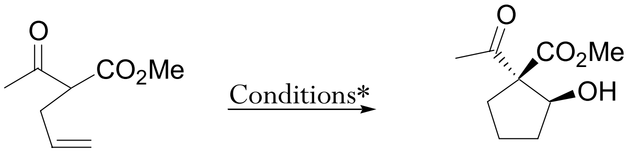
16a **29,** 82 %

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % Rh(CO)$_2$(acac), 1.8 mol % XANTPHOS, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 51: *Conversion of the α-unsubstituted ketoester **16a**.*

The elimination of water is such a driving force in the conversion of these compounds that even under the relatively mild conditions of sequential enolboration/hydroformylation/aldol addition the β-hydroxy function cannot be retained. More encouraging results were observed, however, when the reaction was performed on ketoesters possessing a second α-substituent, which allow for the production of carbocycles bearing quaternary carbon centers in a diastereoselective fashion, a process that was not able to be performed using prior methods of sequential hydroformylation/aldol addition because of chemoselectivity problems (see Scheme 25, p. 22).

Testing whether the same protocol was successful with ketoester **16c** was performed next. After oxidative workup, the fragrant and volatile methyl 1-acetyl-2-hydroxy-cyclopentane-carboxylate (**41**) was isolated as the sole product in 50 % yield as a 1.6:1 mixture of diastereomers as detected by NMR (Scheme 52).



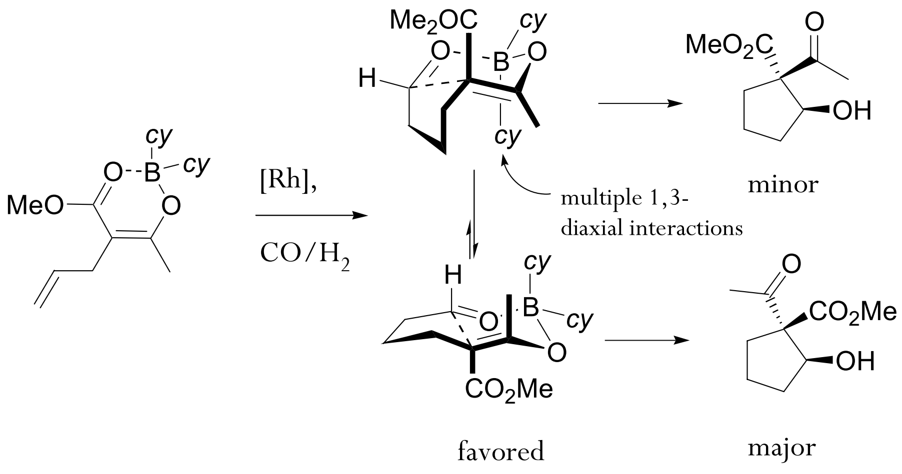
16c

41, 50 %,
1.6:1 *dr*

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % Rh(CO)$_2$(acac),
1.8 mol % XANTPHOS, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

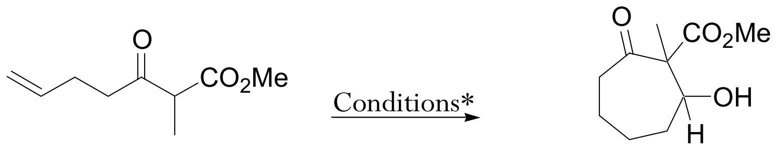
Scheme 52: *Regio- and diastereoselectivity in the enolboration/hydroformylation/aldol additon of* ***16c****.*

Several key observations can be made upon inspection of this result. The absence of the seven-membered ring adduct showed that under the conditions chosen, the enolboration does indeed proceed with complete regioselectivity to form the α,α-disubstituted boron enolate. Additionally, this method of chelation-controlled enolboration paired with hydroformylation is accompanied by a small but significant degree of diastereoselectivity in the aldol addition. As depicted below, the amount of 1,3-diaxial interactions leading to the minor diastereoisomer is reduced in the ring-flipped chair transition state affording the major diastereoisomers (Scheme 53).



Scheme 53: Transition states responsible for the observed diastereoselectivity in five-membered ring formation.

Next, the generation of a seven-membered ring system was attempted with the conversion of ketoester **16b**. When subjected to the reaction sequence, methyl 2-hydroxy-1-methyl-7-oxo-cycloheptane-carboxylate (**42**) as the sole product in 89 % yield as a 6:1 mixture of diastereoisomers (Scheme 54).



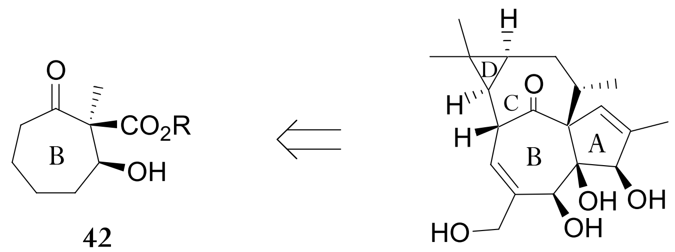
16b

42, 89 %,
6:1 *dr*

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % Rh(CO)$_2$(acac),
1.8 mol % XANTPHOS, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 54: Regio- and diastereoselectivity in the enolboration/hydroformylation/aldol additon of ***16b****.*

The suitability of this method to form functionalized cycloheptanones bearing quaternary centers in the α–position with high yields and diastereoselectivities is particularly attractive, since methods leading to highly substituted and stereodefined seven-membered rings are much less commonplace. Compound **42**, or analogs thereof could prove useful in constructing the central *B*-ring of ingenol, a compound that was only recently synthesized despite a great deal of effort over the past two decades (Scheme 55).

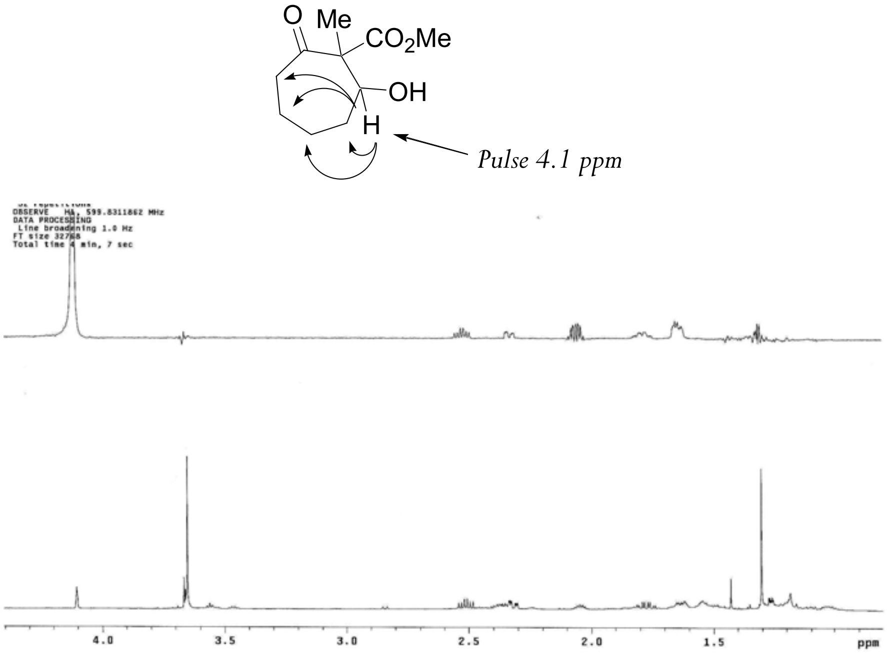


42

ingenol

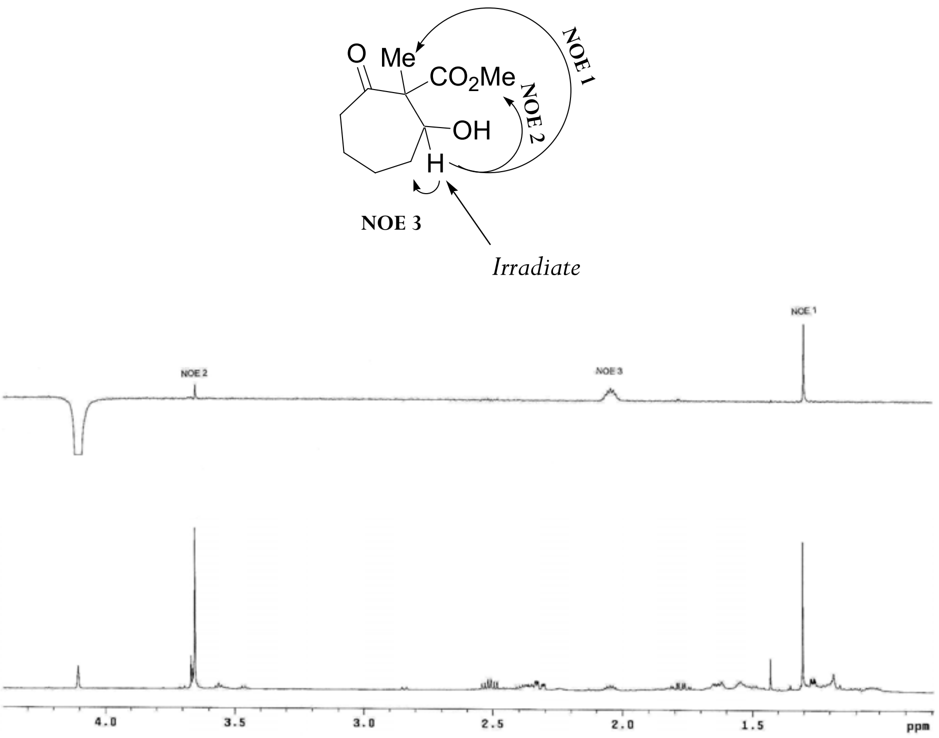
Scheme 55: *Compound* ***42*** *as a retron of the central B-ring cycloheptanone of ingenol.*

The high diastereoselectivity observed in the conversion of **16b** allows for the relative configuration of the two stereogenic centers present in cycloheptanone **42** to be determined. This was accomplished with the aid of 1D gradient TOCSY (Total COrrelation SpectroscopY) and NOE NMR experiments. Upon inspection of the TOSCY spectrum, where the $R_2C(\boldsymbol{H})OH$ resonance of the alcohol carbon is enhanced through the application of a localized pulse, one can see that the proton in question has either through-space or coupling interactions with nearly every residue present in the ring system, and does not interact with the "external" residues of the ester or methyl group (Scheme 56). This phenomenon clearly confirms the existence of a cyclic structure, and it remained now to determine the stereochemical outcome of the aldol addition.



Scheme 56: *TOCSY spectra of* ***42*** *with irradiation of* $R_2C(\mathbf{H})OH$ *resonance at 4.1 ppm.*

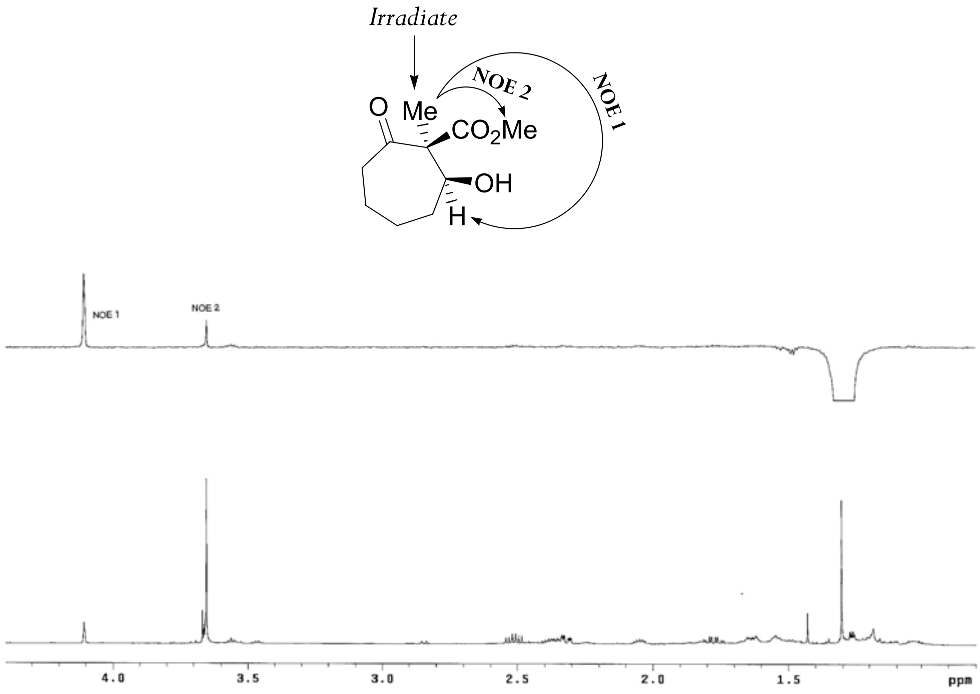
To solve this problem, 1D NOE spectra were performed, irradiating three residues on the molecule that should undeniably confirm the stereochemical relationship between the two adjacent stereocenters. The first irradiation was performed upon the same $R_2C(\boldsymbol{H})OH$ resonance as was the TOCSY experiment (Scheme 57).



Scheme 57: *1D NOE showing irradiation at 4.1 ppm.*

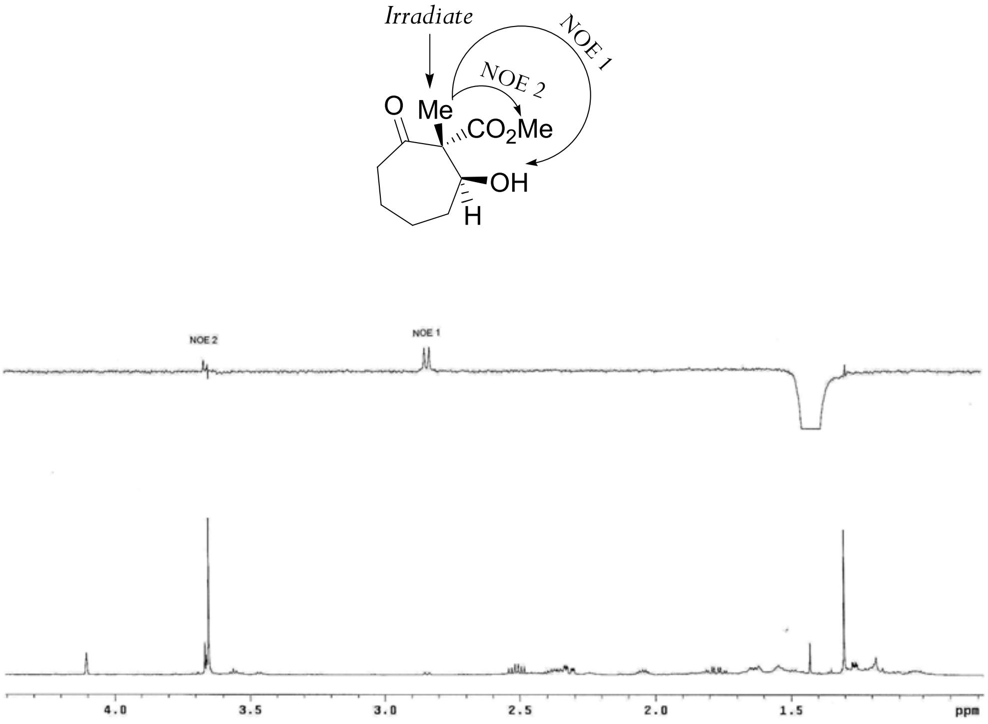
From this, one could see the presence of three NOE´s. Aside from the expected NOE to the adjacent methylene residue (NOE 3), two other through-space interactions could be seen. First, the presence of a strong NOE to the ester residue was observed (NOE 1), followed by a less-intense NOE to the methyl group on the same carbon as the ester (NOE 2). While not confirming the stereochemical relationship, this result further confirms the presence of the cycloheptanone as a mixture of diastereoisomers. Definitive information regarding the relative configuration was obtained by irradiating the two structural elements (methyl & carbomethyoxy groups) present in the quaternary carbon center.

Upon irradiation of the α-methyl group present in the major diastereoisomer, some key information regarding the stereochemical preference of the aldol addition of such β-ketoesters was obtained (Scheme 58). Upon inspection of the observed NOE´s, it can be concluded that the methyl group in question bears a *cis*-relationship to the proton on the carbon bearing the alcohol residue, as a strong through-space interaction is observed for these resonances (NOE 1). The other interaction (NOE 2) is the result of the interaction present between the two groups present in the quaternary center.



***Scheme 58**: Irradiation of the α-methyl group of the major diastereoisomers showing a cis-relationship to the adjacent proton.*

With this evidence in hand, it was left now to further confirm this stereochemistry by irradiating the resonance at 1.42 ppm representing the α-methyl group of the minor diastereoisomer. As shown in Scheme 57, the minor diastereoisomer also exhibits two diagnostic NOE′s. A small NOE can be seen, as expected, to the methyl ester on the same carbon (NOE 2), but particularly telling is the appearance of an NOE to the hydroxyl group, which is clearly resolved as a broad doublet at 2.84 ppm in the 600 MHz field strength used to perform the experiments.



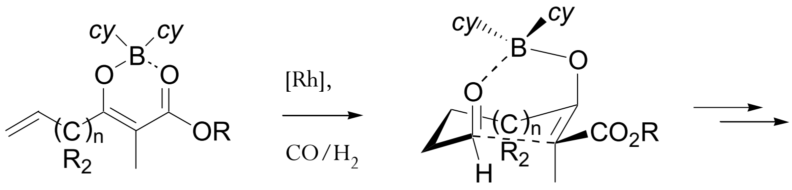
Scheme 59: *Irradiation of the α-methyl group of the minor diastereoisomers showing a cis-relationship to the hydroxyl group.*

These two results clearly confirm the relative configuration of the two contiguous stereogenic centers. The major diastereoisomer possesses a *cis*-hydroxyester configuration, while the minor bears a *trans*-configuration of the same two groups (Scheme 60).

major diastereoisomer minor diastereoisomer

Scheme 60: *Relative configurations of the diastereoisomers produced in the conversion of* ***16b.***

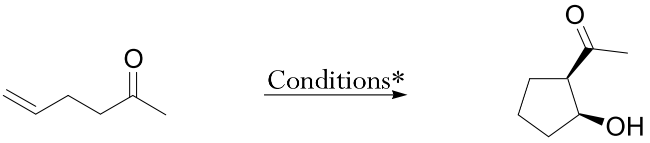
These results are important for several reasons. Besides providing a confirmation of the stereochemistry of the aldol addition step of the cascade reaction via the employment of various NMR techniques, it results in a clear transition-state picture that is complimentary to that which was hypothesized to govern the formation of the 5-membered rings reported earlier, namely that the enolate geometry here again is determined by chelation during the enolboration prior to hydroformylation. After hydroformylation, chelation switches from the ester group to the aldehyde, resulting in a rigid bicyclic transition state through which the aldol addition proceeds (Scheme 61).



Scheme 61: *Transition state assembly governing the production of carbocycles from "linear" ketoesters.*

2.13.3 Unsaturated ketones in five-membered ring formation

Testing the reaction conditions on commercially available hex-5-en-2-one (**43**) also provided an encouraging result when considering whether or not the methodology could be extended well to the production of labdane diterpenoid natural products. Upon exposure of **43** to the reaction conditions, 1-(2-hydroxy-cyclopentyl)-ethanone (**44**) was produced in 82 % yield and 2:1 ratio of diastereoisomers (Scheme 62). This bode well for the extension of the methodology to the construction of the corresponding six-membered ring systems applicable to the construction of the labdane *A*-ring systems.



43

44, 82 %
2:1 *dr*

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 62: *Conversion of **43** resulting in 1-(2-hydroxy-cyclopentyl)-ethanone (**44**).*

2.14 Summary

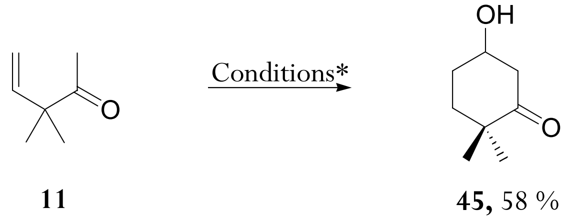
Perhaps the most important revelation to arise out of these investigations on the sequential enolboration/hydroformylation/aldol additions of various β-ketoesters is that the production of the *cis*-hydroxyester (*trans*-hydroxyalkyl/carboxyl) configuration is preferred due to the chelation control present during the enolboration. This is the precise stereochemical relationship that is present in the forskolin *A*-ring system, and as is evident in the introductory discussions of the pioneering total syntheses, a good deal of effort was expended in order to obtain this functionality in the sequence, and in both syntheses the stereocenters were set with Diels-Alder reactions. **Ikegami**, in his synthesis, was required to synthesize another starting material possessing the opposite double bond geometry, which after cyclization gave the desired *trans*-relationship. The **Corey** synthesis employs an inversion strategy consisting of oxidation followed by stereoselective reduction to offer the configuration present in forskolin, the opposite of what was obtained from the Diels-Alder ring closure. What remained to be carried out was to apply this reaction cascade to the previously discussed *A*-ring building block ketones and ketoesters, rationalizing that the stereoselectivity observed in the model substrates would transfer to the formation of the six-ring adducts, offering direct, stereoselective access to the forskolin *A*-ring system in one step.

2.15 Sequential enolboration/hydroformylation/aldol addition in the production of forskolin *A*-ring building blocks

2.15.1 Unsaturated ketones

An exploration of this reaction cascade towards the production of substituted cyclohexane systems was conducted next. Of great interest were the unsaturated ketones **11** and **12**, as they provide ideal substrates to study whether or not the elimination of water as the result of an aldol condensation step could be suppressed, and in the case of **12**, if the aldol addition could be performed in a stereoselective fashion. As the effectiveness of the (*cy*-hex)$_2$BCl/Et$_3$N reagent pair is optimal in the stereoselective enolboration of ketones, it was decided to test if the elimination of water could be suppressed. For this, ketone **11** is an ideal substrate, as the free β-hydroxy aldol adduct is not obtainable by any of the previously mentioned methods of sequential hydroformylation/aldol addition, and is moreover not described in the literature as a known compound despite its relatively low structural complexity.

Upon conversion of **11** under the standard reaction conditions used in the cascade, 5-hydroxy-2,2-dimethyl-cyclohexanone (**45**) was obtained in 58 % yield after oxidative workup (Scheme 63).

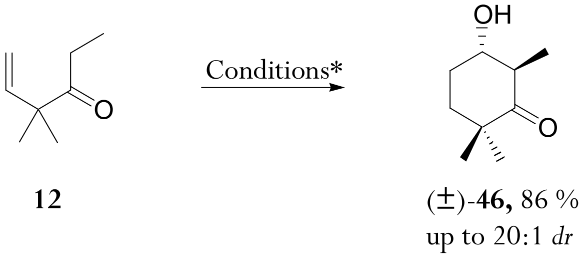


*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 63: *Production of 5-hydroxy-2,2-dimethyl-cyclohexanone (45) via sequential enolboration/ hydroformylation/aldol addition.*

Although the reaction was successful, purification via chromatography or bulb-to-bulb distillation was difficult due to this compounds tendency to rapidly undergo a retro-aldol reaction, as evidenced by the observation of the acyclic ketoaldehyde **24** after any and all attempts at purification. Nonetheless, the introduction of distilled olefin and a careful, brief oxidative workup results in samples of the β-hydroxy cyclohexanone in purity high enough to satisfy combustion analysis.

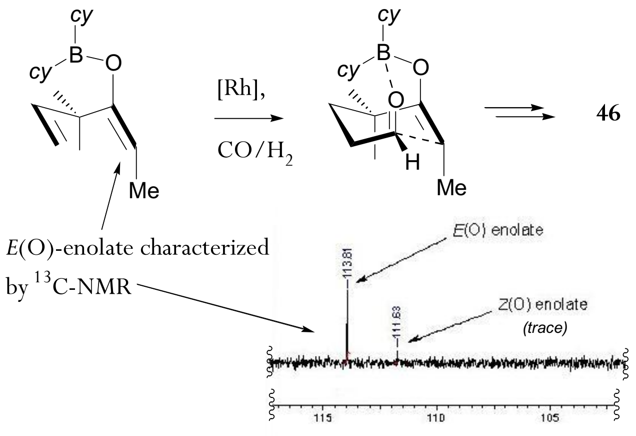
Moving on to ketone **12**, its conversion proceeded under standard conditions to afford *trans*-5-hydroxy-2,2,6-trimethylcyclohexanone (**46**) in excellent diastereoselectivity (up to 20:1 *dr*) in 86 % yield (Scheme 64). The *trans*-stereochemistry was easily established via inspection of the ^{1}H-NMR coupling constants present in the product. As the diastereoselectivity in this reaction exceeds many examples of intermolecular aldol additions, some further investigations were carried out in order to quantify this diastereoselectivity.



*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 64: *Highly diastereoselective production of trans-5-hydroxy-2,2,6-trimethylcyclohexanone (46).*

A likely transition state assembly governing this highly diastereoselective reaction sequence can be seen in Scheme 65. The results observed after the aldol addition suggest that the enolate proceeds through the aldol addition with a high degree of chelation control and retention of its geometry. Additionally, experimental evidence was gathered in the form of a ^{13}C-NMR experiment to confirm the stereoselective production of an *E*(O)-boron enolate. To accomplish this, the enolboration was carried out at 0 °C in $CDCl_3$ using the standard reagent concentrations and reaction times. As the α-enolate protons are indistinguishable in the ^{1}H-NMR of the enolate, the ^{13}C-NMR was inspected. Looking in the olefinic region (see the cutout in Scheme 65) one can clearly differentiate the peaks of the enolates generated in-situ.[65] In the spectrum measured at 15 °C, the nearly exclusive presence of the *E*(O)-enolate can be easily seen at 113.8 ppm, relative to the trace amount of *Z*(O)-enolate resembling little more than background noise at 111.6 ppm.



Scheme 65: *Proposed transition state assembly and ^{13}C-NMR of the in-situ generated enolate resulting in the production of* ***46****.*

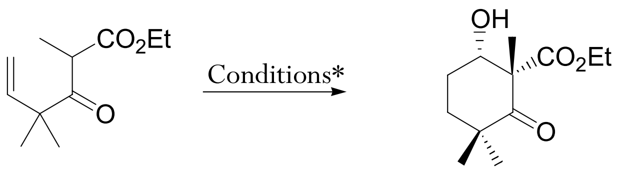
Compound **46** is not as prone to the retro-aldol addition and the purification problems that were observed in conversion of **45**, and true-to-fashion for this reaction cascade, analytically pure substances could be obtained directly from the autoclave with no or minimal purification after oxidative workup.

Having now obtained high levels of diastereoselectivity in the sequential enolboration/ hydroformylation/aldol addition of ketones - in addition to the previously mentioned examples involving esters and ketoesters – it now remained to pursue a synthesis of the forskolin *A*-ring via this methodology - with ketoesters **13** and **13a** functioning as the starting substrates.

2.15.2 Unsaturated ketoesters and the synthesis of the forskolin *A*-ring

Having demonstrated the utility of this new cascade reaction in the construction of carbocycles of different ring sizes and varying degrees of stereoselectivity from acyclic unsaturated ketones, ketoesters and esters, it remained to apply this reaction sequence towards the synthesis of the forskolin *A*-ring system.

A direct, one-step, one-pot stereoselective synthesis of ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexanecarboxylate (**47**) – a building block possessing all of the stereochemical information present in the *A*-ring of forskolin – was achieved by subjecting ketoester **13a** to the standard reaction conditions in 82 % yield as a 2.5:1 mixture of diastereomers as detected by NMR (Scheme 66).



13a

(±)-**47,** 82 %
2.5 : 1 *dr*

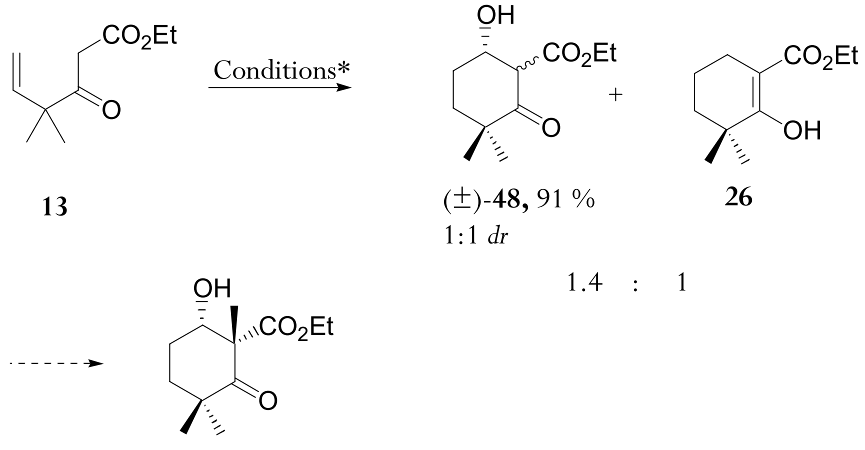
**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 66: *Stereoselective synthesis of the forskolin A-ring via sequential enolboration/ hydroformylation/aldol addition.*

Potential functions needed to elaborate this structure to the natural product are available in the form of the ketone and ester groups on the ring. A possible explanation for the lower degree of diastereoselectivity observed in this addition can be found by considering the large amount of steric hindrance presence in this compound. The addition to produce a cyclohexanone bearing α- and α′-quaternary carbon centers is a greatly-hindered process, and some equilibration of the enolate due to slow aldol addition, or more likely, a lesser degree of chelation control in the delivery of the aldehyde to the enolate in this congested atmosphere is likely the cause of the lower diastereoselectivity.

In order to improve the stereoselectivity in the construction of the *A*-ring system, it could be useful to construct the ring system without the presence of the quaternary center, and install this later through a stereoselective alkylation from the less-hindered face of the cyclic ketoester.

In order to test the possibility for constructing such a compound, we applied the standard reaction conditions to α-unsubstituted ketoester **13**. Upon oxidative workup, the cyclic ketoester was obtained as an rapidly-equilibrating mixture of diastereoisomers resulting in a 1:1 final mixture of ethyl 6-hydroxy-3,3-dimethyl-2-oxo-cyclohexane-carboxylate (**48**) in 91 % yield in a 1.4:1 mixture together with product **26**, the *enol- : keto*-tautomer mixture observed in the acid catalyzed scenario (Scheme 67).



13

(±)-**48,** 91 %
1:1 *dr*

26

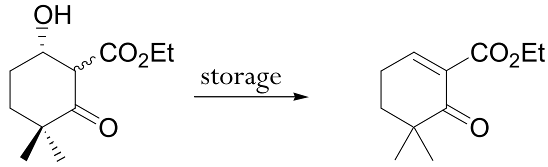
1.4 : 1

47

*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60 bar), 80 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 67: *Conversion of ketoester **13** and planned stereoselective alkylation reaction.*

Unfortunately, **48** could not be utilized "as is" as an entry point to the forskolin *A*-ring system, as it possessed a strong tendency to eliminate water even when stored frozen in benzene to afford enone **38**, which was obtained through the sequential Mukaiyama strategy (Scheme 68).



(±)-**48**

38

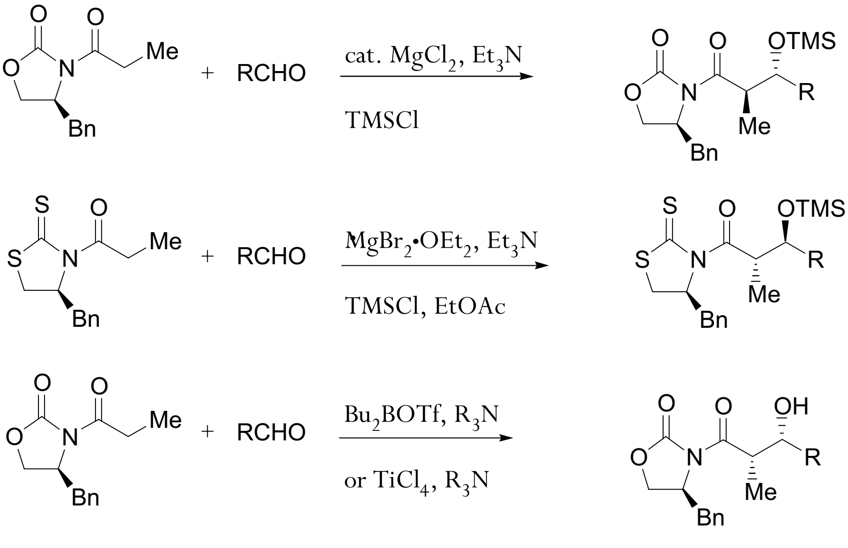
Scheme 68: *Loss of water observed over time upon storage of β-ketoester **48**.*

2.16 Summary

Using a sequential enolboration/hydroformylation/aldol addition reaction cascade, a large number of very useful carbocycles consisting of 5-, 6- and 7-membered ring systems with or without quaternary carbon centers can be constructed in a regio- and diastereoselective fashion. Among these compounds, several can be used as building blocks in the stereoselective synthesis of terpenoid natural products. Most notably, the *A*-ring of forskolin can be stereoselectively constructed in one-step from an easily-obtained acyclic ketoester, allowing for further elaboration towards the natural product via the remaining ketoester functionality. This sequential reaction has resulted in the first reported examples of successful monoester and malonate enolborations using the (*cy*-hex)$_2$BCl/Et$_3$N reagent pair under the cascade reaction conditions. Also, the reaction has proved to be effective when using ketones and ketoesters as starting materials, allowing access to a variety of aldol adducts not obtainable via other methods.

2.17 Asymmetric induction in the sequential enolboration/hydroformylation/ aldol addition reaction cascade

Asymmetric induction during aldol addition provided by the directing effects of chiral moieties present on the same molecule was extensively investigated by **Evans**[66] and others in the form of chiral oxazolidine and more recently thiazolidinethione[67] units, which have been shown to undergo extremely selective additions, offering rapid access to chiral propionate aldols, glycine aldols[68] and similar natural product units (Scheme 69).



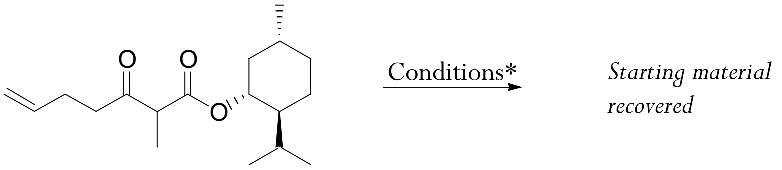
Scheme 69: *Evans' chiral oxazoladinone and thiazolidinethiones and available stereoselectivities.*

Although these methods present effective solutions to the problem of obtaining enantiopure aldol adducts, they present a problem in that the chiral unit must be removed subsequently, and that they do not always provide high general degrees of enantioselectivity with varied types of substrates.[69]

A great deal of simplification can be introduced into this approach through the use of chiral ester moieties. In boron aldol chemistry, this area was until recently unexplored presumably because of the previously mentioned disbelief as to the reactivity of esters under the commonly used enolboration conditions. Initial work has shown, however, that indeed quite good selectivities can be observed upon the enolboration/aldol addition of chiral propionate esters.[70] Given the high degrees of stereoselectivity observed in the sequential enolboration/ hydroformylation/aldol addition of unsaturated carbonyl compounds, the prospect of obtaining asymmetric induction in the aldol addition via the introduction of chiral enolates - or additionally in the case of ketoesters and esters, the introduction of chiral ester moieties or auxiliaries - was a promising possibility. Studies began with the chiral (–)-menthol esters **18b** and **18c**, the syntheses of which were reported earlier.

2.17.1 Sequential enolboration/hydroformylation/aldol addition of chiral β-ketoesters

An initial test was performed with the "linear" ester **18b**. Upon exposure to the standard conditions for the cascade reaction, no cyclization products were observed. Upon inspection of the product isolated after oxidative workup, starting material was recovered in full (Scheme 70).

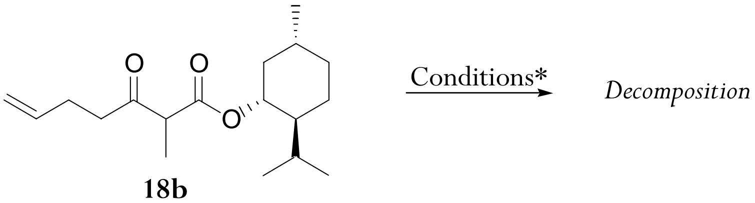


18b

*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, 0.9 mol % [Rh(cod)Cl]$_2$, 1.8 mol % XANTPHOS, CO/H$_2$ (60 bar), 80 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 70: *Attempted conversion of ketoester* ***18b*** *to afford chiral aldol adducts.*

Upon hydroformylation under mild conditions over an extended period of time with a catalytic amount of a chelating Lewis acid (10 % $ZnBr_2$), only decomposition was observed (Scheme 71).

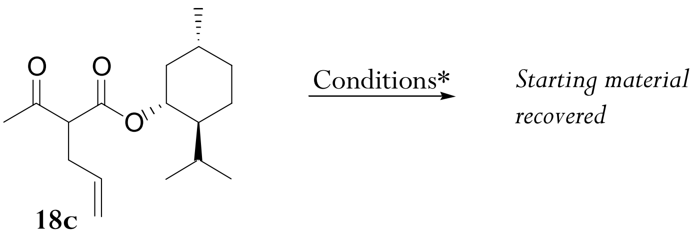


18b

**Conditions:* 0.9 mol % $[Rh(cod)Cl]_2$, 1.8 mol % XANTPHOS, 10 mol % $ZnBr_2$, CO/H_2 (40 bar), 70 °C, 3 d.

Scheme 71: *Attempted conversion of **18b** in the presence of a catalytic amount of $ZnBr_2$.*

In an analogous fashion, the conversion of "branched" ketoester **18c** resulted in a similar observation. Under the standard reaction conditions, no amount of cyclic product or hydroformylation could be observed upon analysis of the reaction mixture (Scheme 72).



18c

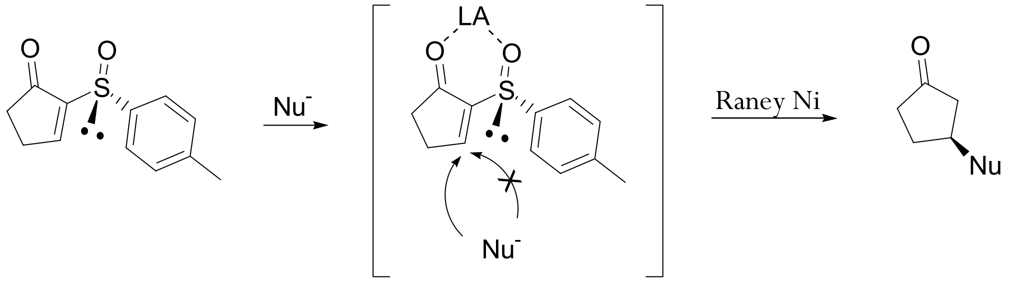
**Conditions:* $(cy\text{-hex})_2BCl$, Et_3N, 0 °C, 0.9 mol % $[Rh(cod)Cl]_2$, 1.8 mol % XANTPHOS, CO/H_2 (60 bar), 80 °C, then $MeOH/H_2O_2$/pH 7.

Scheme 72: *Conversion of "branched" ketoester **18c** under the cascade reaction conditions.*

This example seemed particularly resistant to hydroformylation, perhaps due to steric effects as the result of the large menthol moiety in a 1,3-fashion to the olefin and desired center of cyclization. With the lack of success observed in the attempts at obtaining optically pure aldol adducts through the sequential enolboration/hydroformylation/aldol addition of various unsaturated β-ketoesters, the introduction of another type of chiral auxiliary was attempted in the form of enantiopure sulfoxides.

2.17.2 An α-chiral sulfoxide as a directing group for enantioselective aldol addition

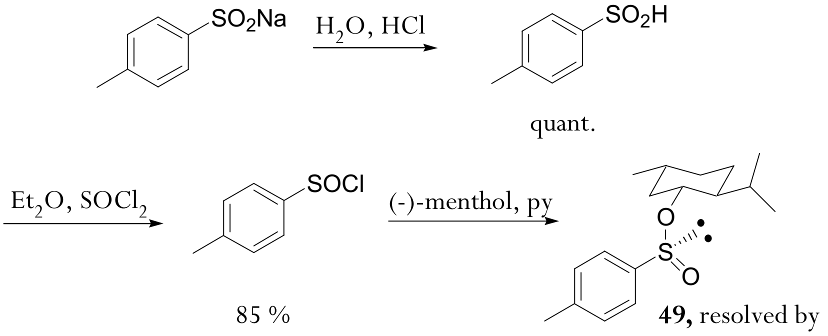
Chiral sulfoxides are known to afford exceptionally high degrees of enantioselectivity in Micheal-type addition reactions[71] when performed in the presence of a chelating Lewis acid (Scheme 73).



Scheme 73: *Enantioselective Michael-type addition mediated by a chiral sulfoxide.*

Examples involving the application of such a directing group in aldol addition are surprisingly few. One can envision a similar scenario as with the 1,4-additions taking place, with the enantiofacial selectivity being determined by the presence or absence of chelation control in the reaction. Aside from providing the asymmetric induction, the sulfoxide would additionally activate the adjacent carbon center towards aldol addition.

Preparation of the chiral sulfinates used to install the sulfoxides is general and straightforward. Following the short, high-yielding three-step synthesis of (–)-(*S*)-*p*-toluolsulfinate-(1*R*, 2*S*, 4*R*)menthylester (**49**), the final resolution is easily accomplished by cold Et_2O filtration, as only one antipode is present in the solid phase at 0 °C (Scheme 74).

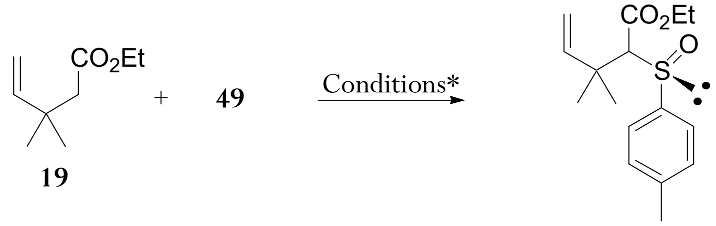


49, resolved by filtration

Scheme 74: *Preparation of* (–)-(*S*)-*p*-toluolsulfinate-(1*R*, 2*S*, 4*R*)menthylester (**49**).

The introduction of a chiral sulfoxide into a carbon framework is usually accomplished via transmetalation of olefinic bromides to generate the corresponding vinyllithium in situ, which is then added to a solution of the chiral menthyl ester. In the case of aldol substrates that do not possess any α,β-unsaturation which allows for the use of a metal-halogen exchange strategy, it was envisioned that the chiral unit could be installed via the use of standard enolate alkylation techniques, employing non-nucleophilic bases such as LDA and LiHMDS.

In the case of ester enolates, namely various Li-enolates of **19**, the introduction of the *p*-toluene sulfoxide unit to produce **50** was unsuccessful regardless of the reaction conditions used. At best, low conversions of < 5% could be observed upon inspection of the crude reaction mixture, but in nearly all cases, both starting materials were recovered upon workup (Scheme 75).



19

50

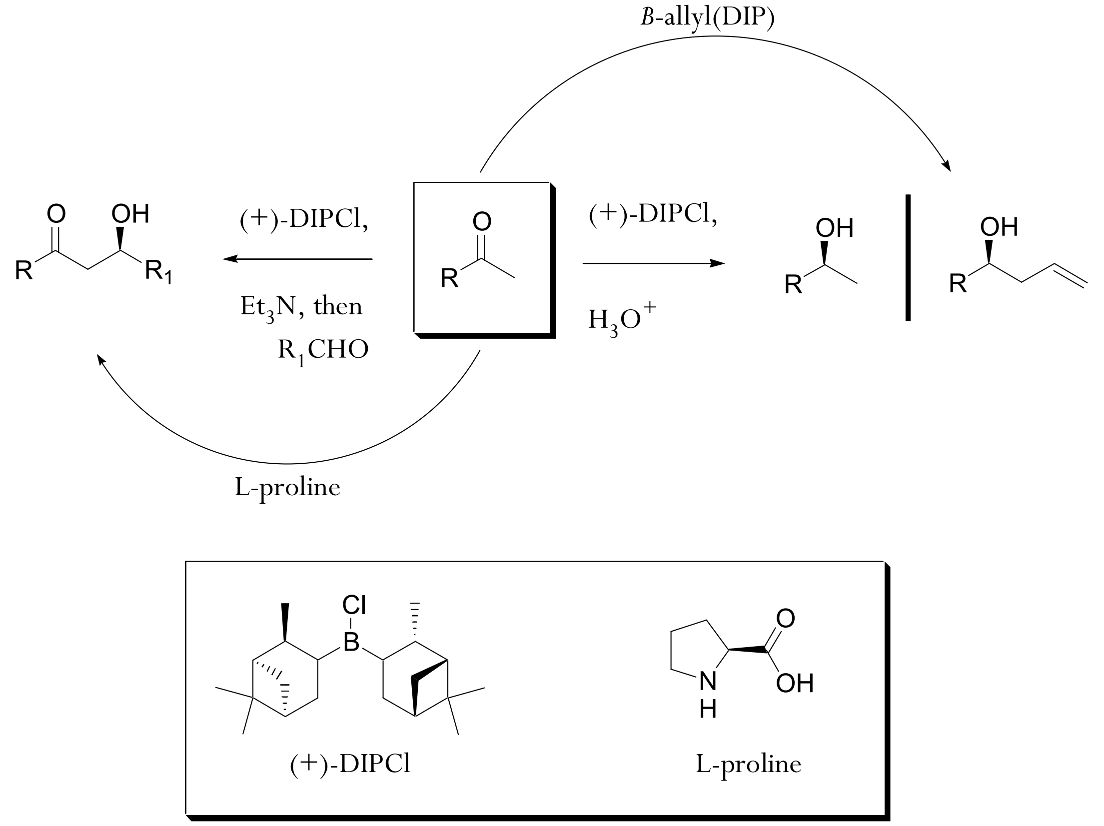
*Conditions	Yield
LDA	SM
LiHMDS	SM
i-Pr$_2$MgBr	< 5 %

Scheme 75: *Attempts at introduction of the chiral sulfoxide via alkylation of an ester enolate.*

Based upon these results an enolate alkylation strategy is not suitable for obtaining a variety of starting materials on which to test for the possibility of asymmetric induction during the aldol addition following hydroformylation. In the one case where product can be observed, the difficult separation from the menthol residue and the remaining starting materials is too difficult to warrant application of a process yielding < 5 % product. With all explorations on the introduction of chirality in the carbon framework ester and ketoester moieties giving less-than-ideal results, investigations proceeded examining the use of chiral boron enolates in the initial step of the cascade reaction.

2.17.3 Chiral enolates in the cascade reaction

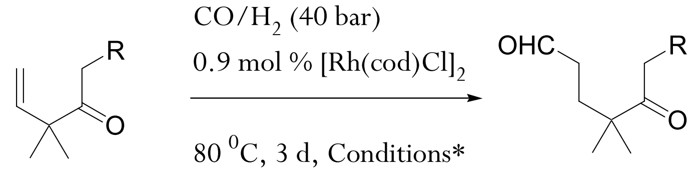
The use of chiral reagents in affecting asymmetric induction in transformations involving aldehyde functionalities has advanced greatly in recent times, mainly due to the advances made in the fields of organocatalysis involving proline-mediated enantioselective aldol addition reactions[72] and various types of α-functionalizations of aldehydes.[73,74,75] A great deal of success has also been seen with the use and development of the (±)-DIP-family of diisopinocamphenyl boron halides, which are used in asymmetric reductions,[76] allylations,[77] and aldol reactions applied to the synthesis of complex natural products[78] (Scheme 76). Both of these were envisioned as possible strategies for providing enantioselectivity in the aldol addition step of the cascade reaction.



Scheme 76: *Asymmetric reactions mediated by* L-*proline & DIP-boron reagents.*

2.17.3a Hydroformylation in the presence of L-proline catalysis

The possibility for the use of L-proline in a sequential hydroformylation/aldol addition reaction seemed very promising when one considers the prospect of simply adding a catalytic amount of a chiral reagent and performing the hydroformylation reaction with no additional constraints. Also beneficial is that fact that workup and purification are also simplified when using such a process. For these reasons, some screening was performed using unsaturated ketones **11** and **12** under various reaction conditions. Unfortunately, with variation of the solvent and catalyst concentration inline with those used for intermolecular aldol additions (DMSO, 20 mol % L-proline, 3 d), only the aldehydes **24** and **25**, resulting from hydroformylation of the olefin were observed (Scheme 77).



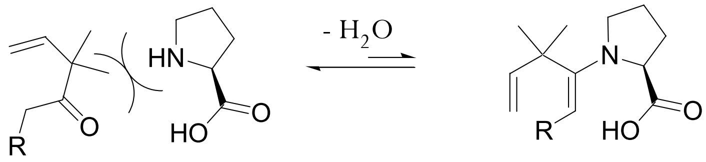
11, R = H
12, R = Me

24, R = H
25, R = Me

L-proline (mol %)	Solvent	Yield
10	$CHCl_3$	quant.
10	Dioxane	quant.
20	DMSO	quant.

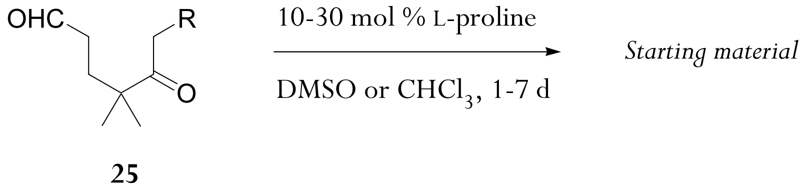
Scheme 77: *Hydroformylation of unsaturated ketones in the presence of L-proline.*

The lack of reactivity in these particular intramolecular cases probably stems from steric factors prohibiting the formation of the proline-enamine necessary to accomplish the intramolecular aldol addition (Scheme 78).



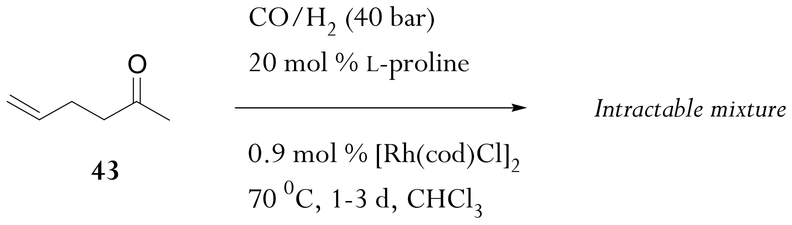
Scheme 78: *Steric hindrance in the formation of proline-enamines from ketones bearing α-quaternary centers.*

This assumption was supported by the recovery of starting materials in the attempted stepwise aldol addition reactions of the aldehydes obtained from hydroformylation. Using the accepted conditions for intermolecular proline-catalyzed addition (DMSO, 10-30 mol % amino acid) no conversion was observed after reaction times of up to 7 d (Scheme 79).



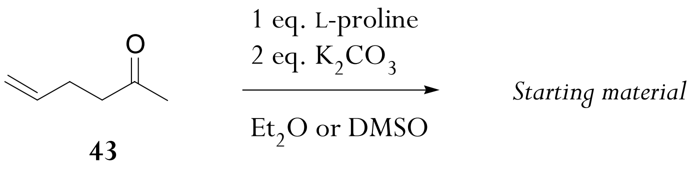
Scheme 79: *Attempted intramolecular aldol addition of ketoaldehyde* ***25****.*

When attempting to perform the tandem reaction on ketones not in possession of an α-quaternary carbon such as hex-5-en-2-one (**43**), an intractable mixture of products was isolated upon washing of the crude mixture with H_2O and extracting with Et_2O (Scheme 80).



Scheme 80: *Hydroformylation of hex-5-en-2-one (****43****) in the presence of L-proline.*

Likewise, attempts to synthesize a proline-enamine of **43** were unsuccessful. It was hoped that the enamine could be obtained via standard conditions and subjected to a hydroformylation, essentially mimicking the presence of a stoichiometric amount of L-proline in the reaction. Refluxing **43** with L-proline with K_2CO_3 in Et_2O or DMSO resulted only in the recovery of unreacted ketone (Scheme 81).



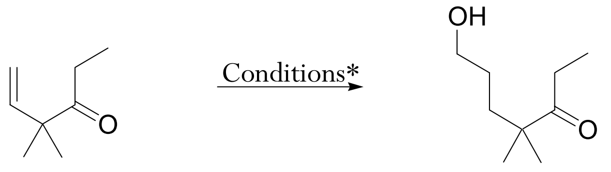
Scheme 81: *Attempted synthesis of the L-proline-enamine of* ***43****.*

Based upon these initial results, it could be inferred that carrying out hydroformylation in the presence of catalytic amounts of L-proline in order to obtain an enantioselective hydroformylation/aldol addition sequence is not an effective means by which to accomplish this goal. Investigations into the use of the chiral DIP-boron enolates were conducted next.

2.17.3b (+/–)-Diisopinocamphenylboron enolates (DIP-enolates)

As summarized in Scheme 76, the DIP-Cl[79] reagent can be used to accomplish a wide variety of asymmetric reactions, including aldol additions. The fact that this chiral reagent has been employed in enolboration and subsequent aldol additions was encouraging when considering extending its application to sequential reactions run under hydroformylation conditions.

The first experiments were performed once again with ketones **11** and **12**. Upon exposure to the standard reaction conditions used in the racemic variant, replacing (*cy*-hex)$_2$BCl with (+)-DIP-Cl or (–)-DIP-Cl in the enolboration step, a complete conversion of the starting olefin was observed upon oxidative workup. Unfortunately, a cyclic aldol product was not obtained as the result of this sequence, rather the primary alcohol 7-hydroxy-4,4-dimethyl-heptan-3-one (**51**) resulting from an in situ reduction of the aldehyde obtained from hydroformylation in essentially quantitative yield (Scheme 82).

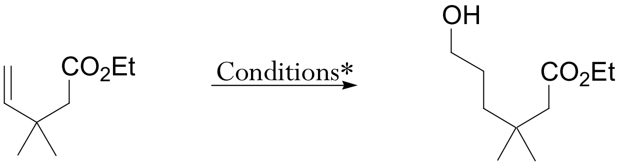


12 **51,** 96 %

**Conditions:* (+)-DIP-Cl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60 bar), 80 °C, 18h, then MeOH/H$_2$O$_2$/pH 7.

Scheme 82: *In situ aldehyde reduction in the enolboration/hydroformylation/aldol addition of* ***12*** *using (+)-DIP-Cl.*

Although this result is not the desired aldol addition product, it is interesting because it represents a net chemoselective reduction of an aldehyde in the presence of a ketone. This transformation, which could also be labelled *hydrohydroxymethylation*, is nearly impossible to accomplish with normally employed hydride reagents, and could prove very effective for the synthesis of these types of compounds, and is most likely due to the inability of the DIP-Cl reagents to perform enolboration as effectively as the less-sterically hindered (*cy*-hex)$_2$BCl reagent. Performing the same reaction on ester **19**, which afforded a completely diastereoselective aldol addition under the cascade reaction conditions, gave once again the hydrohydroxymethylation product of in situ aldehyde reduction, offering primary alcohol ethyl 6-hydroxy-3,3-dimethyl-hexanoate (**52**) in quantitative yield (Scheme 83).



19 **52,** quant.

**Conditions:* (+)-DIP-Cl, Et_3N, 0 °C, then 0.9 mol % $[Rh(cod)Cl]_2$,
CO/H_2 (60-80 bar), 90 °C, 18h, then $MeOH/H_2O_2$/pH 7.

Scheme 83: *In situ aldehyde reduction in the enolboration/hydroformylation/aldol addition of* ***19*** *with (+)-DIP-Cl.*

2.18 Summary

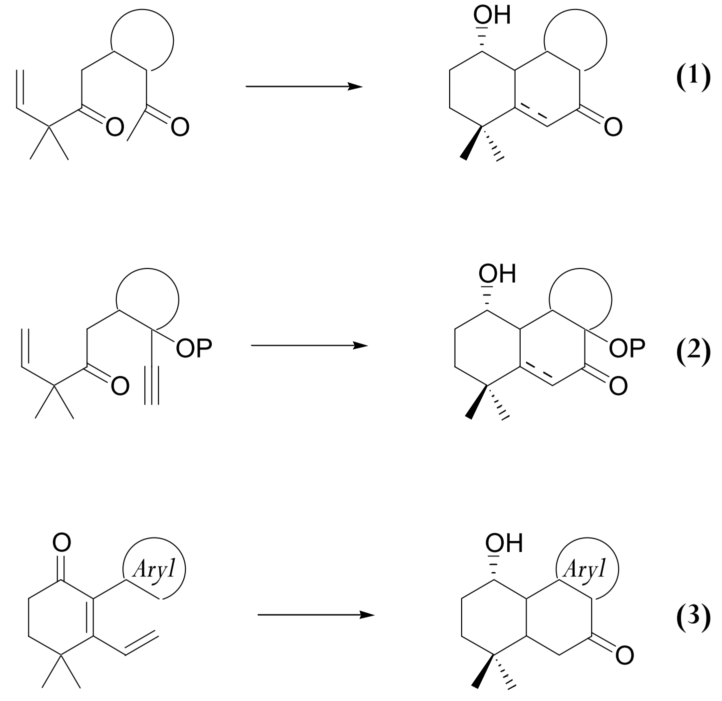
Several methods of introducing enantioselectivity into the hydroformylation/aldol addition sequence were investigated. The use of chiral esters and chiral sulfoxides incorporated into the carbon framework of the molecule proved to be unsuccessful because of problems in the reactivity of the substrates under the required conditions. In the case of the sulfoxides, low yields observed in substrate synthesis established the approach as an ineffective method with which to accomplish this goal.

Also explored were methods involving an "external control" of the enantioselectivity using either a chiral aldol catalyst in the form of L-proline, or optically pure diisopinocamphenyl boron chloride, (+)- or (–)-DIP-Cl, as a replacement of (*cy*-hex)$_2$BCl in the standard reaction conditions. In the examples involving proline catalysis, no aldol addition was observed in either the one-pot autoclave reactions or the stepwise reactions of ketoaldehydes. While the use of chiral boron enolates gave interesting results in that the sequence resulted in the formation of hydroformylation/chemoselective aldehyde reduction products in quantitative yields, no aldol addition was observed in the trials performed.

From these experiments, it was concluded that the most straightforward methods of obtaining an asymmetric variant of the sequential enolboration/hydroformylation/aldol addition cascade reaction were not successful. At this stage, the successes of the diastereoselective cascade reaction, and other methods of sequential hydroformylation/aldol addition in general, were applied to more sophisticated substrates with the ultimate goal being the rapid and efficient synthesis of polycyclic terpene skeletons from unsaturated carbonyl compounds.

2.19 Studies en route to tricyclic terpenoid natural products

As stated in the introductory chapter, the ultimate goal of this work was to establish a general route to terpene natural products of a structure resembling that of forskolin via stereoselective hydroformylation/aldol addition reaction sequences. This required the synthesis of more advanced substrates than those previously mentioned in this work that allow for the closure of the *A*- and *B*-rings present in these natural products via the introduction of an acyl group equivalent, which could be introduced via a number of methods (Scheme 84).

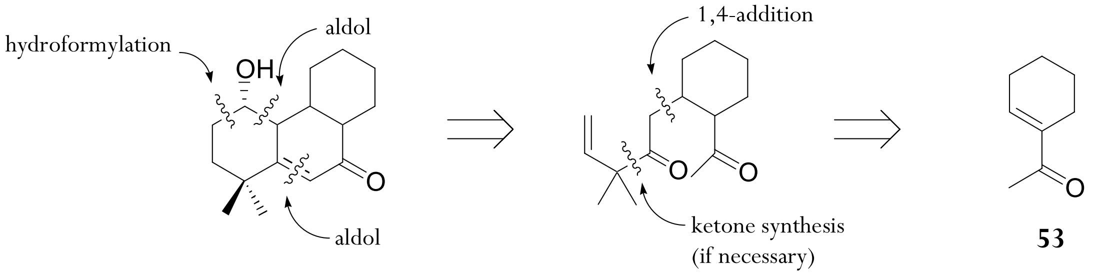


Scheme 84: *Advanced substrates resulting in the synthesis of tricyclic terpene skeletons.*

The introduction of this necessary acyl group was proposed via one of three ways. The most obvious method is to introduce an acyl group directly to an aromatic or aliphatic ring **(1)** which may or may not cause problems in the selectivity of subsequent aldol additions with another ketone present. Another commonly used equivalent can be found in the installation of an acetylenic group **(2)**, which can be later hydrated in the presence of Hg(II) salts or strong acids[80] to give the acyl functionality. A third and equally efficient strategy for the synthesis of aromatic diterpenes – a class of compounds possessing a wide range of biological activities – could be carried out by installing a vinyl group via a Grignard reaction **(3)** which could later undergo a Lewis-acid mediated cyclialkylation[81] to close the *B*-ring. A discussion of the synthesis of these advanced substrates and their application in sequential hydroformylation/aldol addition reactions follows.

2.19.1 Scenario 1 – synthesis of substrates bearing an acyl group

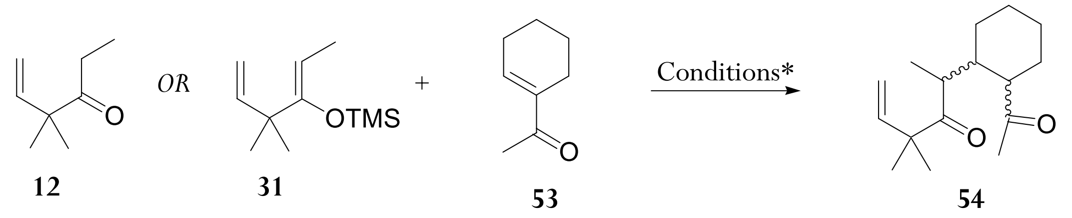
As illustrated in Scheme 81, the first of three scenarios pursued in the construction of tricyclic terpenoids involved the synthesis of saturated substrates bearing an acyl function upon which to test the effectiveness of *B*-ring closure via hydroformylation/aldol addition. To accomplish this in a straightforward fashion, a retrosynthetic analysis of the desired substrate was performed (Scheme 85).



Scheme 85: *Retrosynthetic analysis of scenario 1 products.*

By analyzing the bond formations needed to construct the desired tricyclic system, one can see that various reaction types are required. Since it is desired to test the behavior of such compounds under hydroformylation conditions, a prenyl olefin unit is needed which allows for the installation of the aldehyde. As the most direct route to this type of intermediate, several 1,4-additions of unsaturated *A*-ring precursors to the commercially available starting material 1-acetyl-1-cyclohexenone (**53**)[82] were performed.

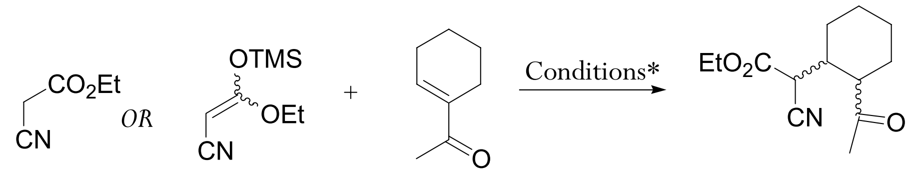
As can be seen in Scheme 86, enone **53** was very resistant to acting as a Michael acceptor even under relatively forceful conditions. Several different sets of reaction conditions were employed, and two different Michael donors were used in the form of ketone **12** and TMS-enolsilane **31**. All of the trials resulted in the observation of a complete lack of reactivity towards the desired 1,4-addition, with starting enone **53** being recovered quantitatively.



Michael donor	Conditons	Yield of **54**
12	NaOMe/MeOH	SM
12	LiHMDS	SM
12	LDA/CuCN	SM
31	$TiCl_4$	SM

Scheme 86: *Attempts at 1,4-addition to enone **53** using Michael donors **12** and **31**.*

In further attempts to obtain the desired C-C bond formation via the same 1,4-addition strategy, more nucleophilic Michael donors were used in the form of ethyl cyanoacetate (ECA) and its TMS-silyl ketene acetal 3-ethoxy-3-trimethylsilanoxy-acrylonitrile (**55**), which was synthesized from ECA via treatment with LiHMDS and TMSCl in 85 % yield (Scheme 87). It was envisioned that the required prenyl olefin unit could be installed on ethyl (2-acetyl-cyclohexyl)-cyanoacetate (**56**) via the previously employed Zn(0) and Al(III)-mediated Barbier-type addition to the nitrile, affording in one additional step the desired hydroformylation precursor.



ethyl cyano-acetate (ECA)

55, 85 % from ECA

53

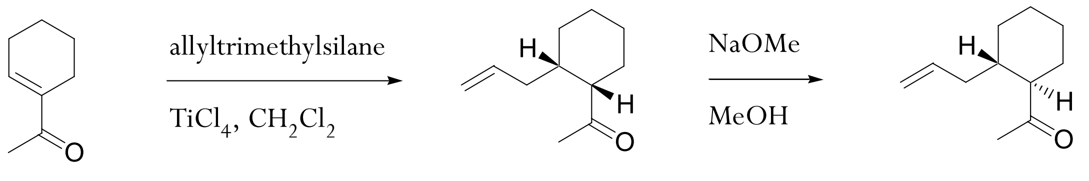
56

Michael donor	*Conditions	Yield of **56**
ECA	NaOMe/MeOH	SM
ECA	$NaNH_2$	SM
ECA	LiHMDS	SM
ECA	pyrimidine, 5 d	SM
ECA	Al_2O_3, 7 d	SM
55	$TiCl_4$	SM

Scheme 87: *Attempts at 1,4-addition to enone* **53** *using Michael donors ethyl cyanoacetate and silyl ketene acetal* **55**.

Because of the setbacks encountered in the convergent synthesis of any substrates via the Michael addition of various carbon nucleophiles which already contained the required prenyl olefin unit or allowed for its installation in one step, a variation was attempted where a simpler carbon unit could be introduced in the form of an allyl group, which could then be elaborated in a linear fashion through an ozonolysis/ketone synthesis sequence (see Scheme 85) to afford the desired hydroformylation precursors.

To begin this route, the 1,4-addition was conducted via a **Sakurai**[83] reaction reported by **Molander**[84] in which allyltrimethylsilane was added to a –78 °C solution of enone **53** and 1.2 eq. $TiCl_4$ in CH_2Cl_2 to give 1-acetyl-2-(2-propenyl)cyclohexane (**57**) as an approximately 6:1 mixture of *cis-:trans-*isomers in 65 % after purification. This product was easily epimerized with NaOMe in MeOH to afford the *trans*-product **58** as an 8:1 mixture of isomers in 85 % (Scheme 88).



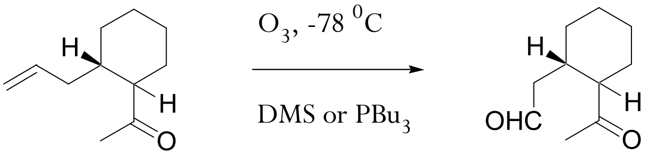
53

(±)-**57,** 65 %,
6:1 (*cis- : trans-*)

(±)-**58,** 85 %,
8:1 (*trans- : cis-*)

Scheme 88: Synthesis and epimerization of **57**.

Both unsaturated ketones were then subjected to ozonolysis conditions and workup with either DMS of PBu_3 to afford the corresponding 1,5-ketoaldehydes *cis-* and *trans*-(2-acetylcyclohexyl)-acetaldehyde (**59**) and (**60**) in quantitative yield (Scheme 89). These substrates allow for the proposed chemoselective ketone synthesis to take place by adding the prenyl unit to the aldehyde function in the presence of the neighboring ketone.

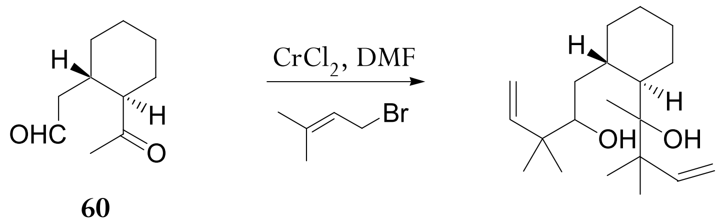


57, 58

59, *(cis-)*, quant.
60, *(trans-)*, quant.

Scheme 89: Ozonolysis of olefins **54** *and* **55** *affording1,5-ketoaldehydes.*

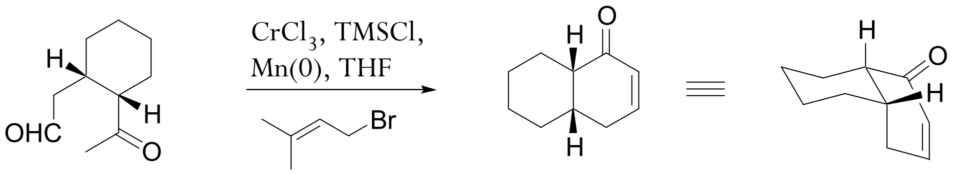
At this point, the key chemoselective carbonyl addition to the aldehyde was desired. Several variants of the **Nozaki-Hiyama-Kishi**[85] protocol of addition of allyl halides to aldehydes and ketones mediated by Cr(II) salts were available. In attempting the standard procedure with $CrCl_2$ and prenyl bromide in DMF, the product of unselective addition to both the ketone and the aldehyde were observed in the form of diprenyl-diol **61**, accounted for by the disappearance of both aldehyde and ketone moieties in the ^{13}C-NMR of the crude reaction mixture (Scheme 90).



61, major product, 82 %

Scheme 90: Unselective NHK reaction of ketoaldehyde ***60****.*

Although the original conditions were shown to proceed chemoselectively, affording addition to aldehydes when ketones were present in the same molecule, the selectivity was dependent on the $CrCl_2$ used. As chromium(II)chloride is known to be extremely hygroscopic, these reactions must be performed using Schlenk techniques to ensure the exclusion of water from the system. In the original paper itself, an alternative to the sometimes inconsistent $CrCl_2$ variant execution strategy was reported, where $CrCl_3$ salts (which are air-stable and non-hygroscopic) are reduced in situ with $LiAlH_4$, affording the reactive chromium(II)chloride species in situ. One potential problem of this strategy is that the carbonyl group, in this case the aldehyde, would potentially be reduced by the harsh hydride reagent during the reaction, resulting in low yields of the products desired. An effective solution to this problem has been reported by **Fürstner**[86], in where catalytic amounts of chromium(III)chloride effect the addition when run in the presence of stoichiometric amounts of Mn(0) as the reducing agent, which presents a neutral alternative to the harsh conditions involving $LiAlH_4$. TMSCl is also present in the reaction mixture, acting as a scavenger for alcoholate anion as the addition proceeds. The resulting TMS ethers can be hydrolyzed by the addition of water upon workup.
Tests of these conditions were carried out with ketoaldehydes **59** and **60**. In the case of the *cis*-isomer **59**, when reacted with 7 mol % $CrCl_3$, 1.7 eq. Mn(0), 2 eq. prenyl bromide and 2.5 eq. TMSCl in 3 mL THF, an interesting result was observed. Instead of giving any type of carbonyl addition products, the product of intramolecular aldol condensation *cis*-4a,5,6,7,8,8a-hexahydro-4*H*-naphthalen-1-one (**62**) was obtained in 92 % yield (Scheme 91).



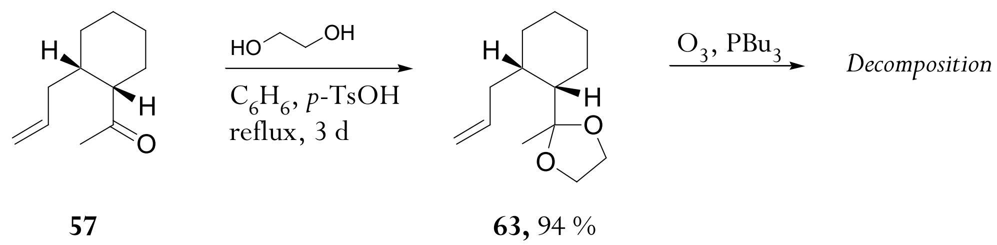
59

62, 92 %

Scheme 91: *Aldol condensation observed in leiu of the NHK reaction of* ***59****.*

The type of activation resulting in such an effective aldol addition and subsequent dehydration to afford the enone under neutral conditions is not known with certainty. However, based on results observed in the carboxylation of ketones using Et_3N and Mg halides[87] – a so-called "soft enolization" procedure – the involvement of a chromium or manganese enolate is assumed to be the driving force resulting in aldol condensation. The well-known Lewis acidity of the mixed salts generated in the NHK reaction could also affect the condensation in such an acid sensitive substrate.[88] The extension of this result into a general method of accomplishing aldol condensation under neutral conditions may warrant further investigation as a general means of accomplishing aldol condensations under completely neutral conditions. It was postulated that the failure to incorporate any of the prenyl unit into the molecule may be due to the fact the THF was used as the solvent, as the reactive prenylchromium(II) species formed in situ has a low solubility in ether solvents. DMF should also neutralize the Lewis acidity of Cr^{2+}, possibly eliminating the tendency for aldol addition to occur. Performing the same reaction with DMF as the solvent did not favor a prenylation pathway as hoped, rather, an intractable mixture of products was formed. To compound on the difficulty observed in accomplishing this addition, the results were no different when the *trans*-aldehyde **60** was subjected to the identical reaction conditions. Again, performing the reaction in DMF resulted in an intractable mixture.

A way of circumventing this issue was sought by pursuing a longer route to this type of substrate, where the competing addition reactions could be eliminated from the sequence. At first, it was envisioned that a ketalization of **57** would allow for the rest of the sequence to proceed smoothly. Indeed, ketalization using 5 mol % *p*-TsOH with benzene and ethylene glycol as the solvent under Dean-Stark conditions afforded unsaturated ketal 2-(2-allyl-cyclohexyl)-2-methyl-[1,3]dioxolane (**63**) in 94 % (Scheme 92).

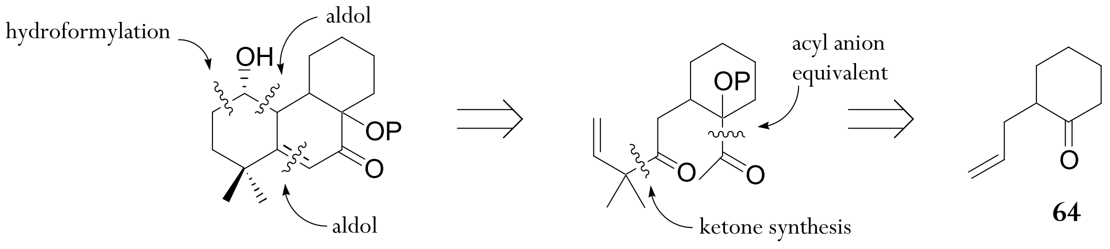


Scheme 92: Ketalization of 57 and subsequent ozonolysis.

Surprisingly, this compound decomposed upon all attempted ozonolysis reactions, affording products bearing neither the allyl side chain nor the expected aldehyde or ketal moieties. At this point, it was clear that another route to these compounds was necessary.

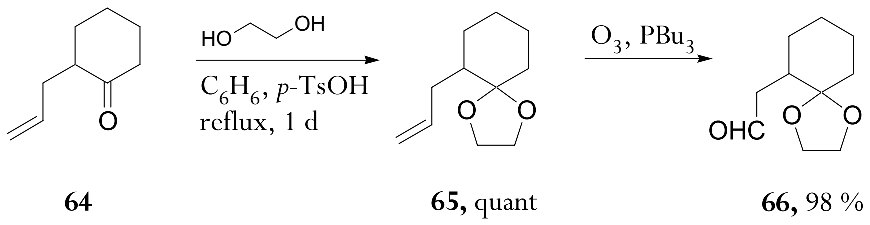
2.19.2 Scenario 2 – synthesis of substrates bearing C-8 oxidation

In order to move further in the direction of forskolin, compounds bearing analogous C-8 oxygenation could be obtained directly from 2-allyl cyclohexanone (**64**) using a strategy similar to the one previously reported, involving a series of carbonyl additions resulting ultimately in an unsaturated olefin that can undergo the hydroformylation/aldol addition sequence. The retrosynthetic analysis of this C-8 oxygenated compound can be seen in Scheme 93.



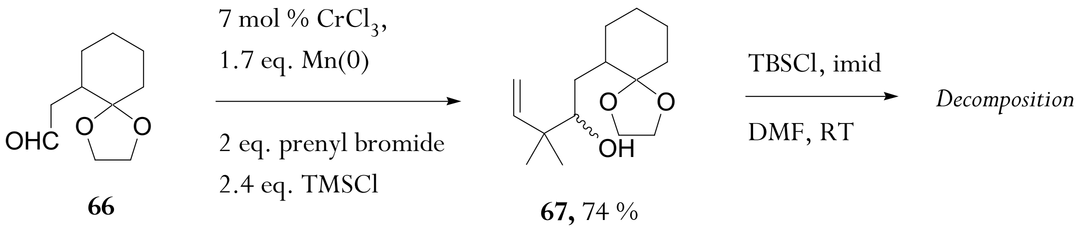
Scheme 93: Retrosynthetic analysis of C-8 oxygenated compounds.

Proceeding from **64**, which can be synthesized in multi-gram amounts via alkylation of the corresponding morpholine enamine in the presence of NaI and allyl bromide in MeCN, a ketalization was again performed to yield 6-allyl-1,4-dioxa-spiro[4.5]decane (**65**) in quantitative yield. This product, in contrast to the results obtained in the ozonolysis of related ketal **63**, proceeded smoothly through the reaction to offer (1,4-dioxa-spiro[4.5]dec-6-yl)-acetaldehyde (**66**) in excellent yield (Scheme 94).



***Scheme 94:** Ketalization of **64** and subsequent ozonolysis.*

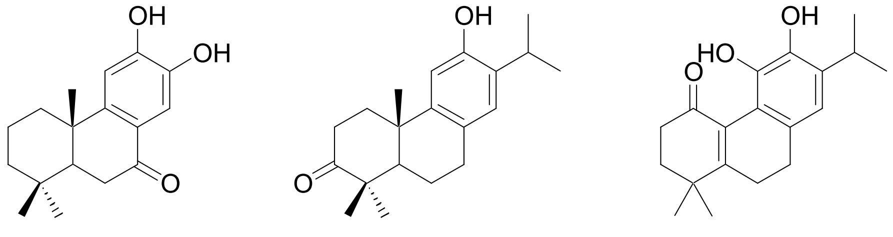
This aldehyde was then subjected to NHK-prenylation conditions to afford the homoallyl alcohol 1-(1,4-dioxa-spiro[4.5]dec-6-yl)-3,3-dimethyl-pent-4-en-2-ol (**67**) in very good yield, which could then allow for the introduction of the acyl group in the form of an acetylene unit subsequent to protection (Scheme 95). Unfortunately, attempts to carry out the necessary protection of this alcohol resulted in decomposition of the homoallylic alcohol.



***Scheme 95:** NHK reaction of aldehyde **66** and attempted TBS-protection.*

2.19.3 Scenario 3 – Aromatic terpenoids

Motivated in part by the difficulties experienced in the synthesis of the saturated substrates, it was planned to approach the synthesis of diterpenes bearing an aromatic C-ring. Such compounds have a long history in traditional medicine, primarily in Asian cultures, as they possess a wide range of biological activities ranging from sedative and tranquilizing effects[89] to finding use in the treatment of coronary disease and insomnia (Scheme 96).[90]



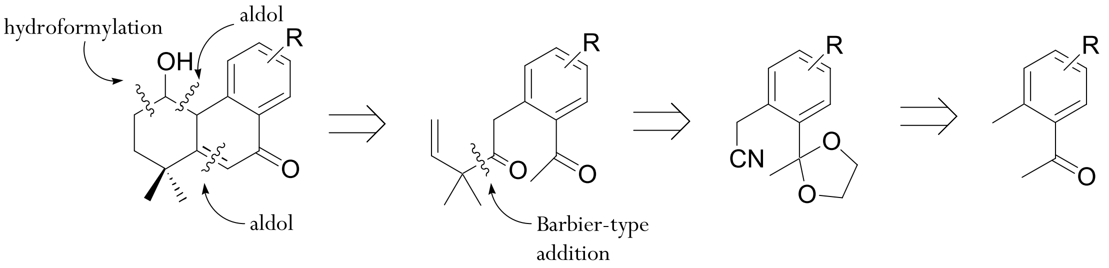
nimbidiol hinokione sageone

Scheme 96: Three biologically active aromatic diterpenes.

Approaching these compounds would simplify the construction of the desired olefin substrates, and would also aid in the subsequent hydroformylation/aldol reactions, in that both carbonyl functions have only one enolizable site. This would eliminate the possibility of a mixture of products arising from aldol additions of compounds bearing multiple enolizable sites. Such a strategy could also reduce the length of the routes to construct such natural products, while in the currently available strategies[91,92] much effort is put into the construction of the substituted *A*-ring, whereas it could be accomplished in one step with via a one-pot hydroformylation/aldol sequence.

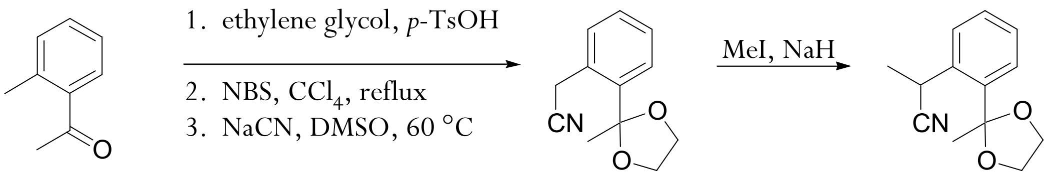
2.19.3a Acetophenones

A retrosynthetic analysis of this class of products revealed that they, too, could also be obtained from readily-available starting materials through straightforward synthetic routes (Scheme 97). Aside from the required hydroformylation and aldol reactions to close the tricyclic structure, the unsaturated olefin precursor can be constructed in one step via means of a Barbier-type addition to a nitrile, which could be synthesized from the corresponding methyl acetophenone in a three-stop sequence of ketalization, bromination and substitution with $^{-}$CN.



Scheme 97: Retrosynthetic analysis of aromatic diterpenes from acetophenones.

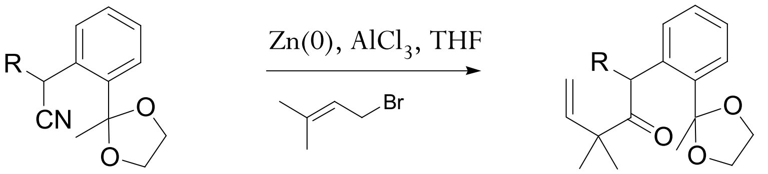
Beginning with *o*-methyl acetophenone, the cyano-ketone [2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-acetonitrile (**68**)[93] was prepared in 65 % overall yield from the corresponding ethylene ketal though benzylic bromination in CCl_4 with NBS[94] followed by reaction with NaCN[95] in DMSO at 60 °C. This product was also methylated with MeI and NaH in DMSO[96] to afford the substituted propionitrile 2-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-propionitrile (**69**) in quantitative yield (Scheme 98).



68, 58 % **69,** quant.

Scheme 98: *Synthesis of aryl nitriles **68** and **69**.*

Now, the Barbier-type addition to construct the unsaturated prenyl ketones for further reaction in the autoclave could be performed. Using the Zn(0) and $AlCl_3$ mediated coupling conditions used earlier in the prenylation of cyanoesters, ketones 3,3-dimethyl-1-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-pent-4-en-2-one (**70**) and 4,4-dimethyl-2-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-hex-5-en-3-one (**71**) were obtained in 62 % and 57 % yield, respectively (Scheme 99).

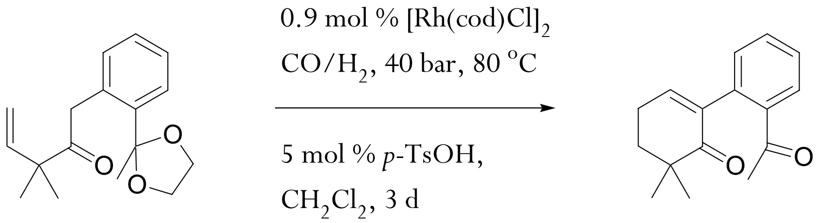


68, R = H
69, R = Me

70, 62 %, R = H
71, 57 %, R = Me

Scheme 99: *Prenylation of aromatic nitriles via Barbier-type addition mediated by activated Zn(0).*

With these two substrates in hand, they could now be subjected to sequential hydroformylation/aldol sequences to determine the ideal conditions to allow for the construction of perhydrophenanthrene diterpenes from these substrates. Studies began by investigating the method of sequential hydroformylation/acid-catalyzed aldol addition. Ketone **70**, bearing no methyl substitution at the benzylic position, was hydroformylated with 0.9 mol % $[Rh(cod)Cl]_2$ and 40 bar CO/H_2 at 80 °C in the presence of 5 mol % *p*-TsOH for a reaction time of 3 d. Upon filtration and chromatography of the crude reaction mixture, the deketalization/aldol condensation product 2-(2-acetyl-phenyl)-6,6-dimethyl-cyclohex-2-enone (**72**) was obtained as the sole product in 57 % yield (Scheme 100).

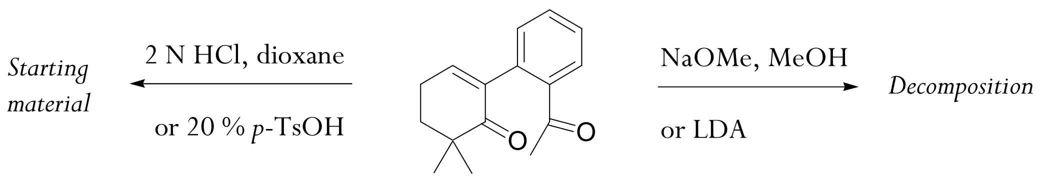


70 **72,** 57 %

Scheme 100: *Hydroformylation/aldol condensation of ketone* 70.

Despite the fact that the deketalization proceeded completely under the reaction conditions in the autoclave, a second aldol condensation to close the *B*-ring did not take place, despite the driving force of aromatization present in the system. Attempts to suppress the deketalization by shortening the reaction times, running the hydroformylation without acid present or using the sequential enolboration/hydroformylation/aldol addition cascade also resulted in styrene **72** in comparable yields.

Next, to take advantage of the fact that a separate deketalization subsequent to hydroformylation was not necessary, the final *B*-ring closure was attempted by subjecting this product to various conditions. Unfortunately, both basic and acidic conditions failed to afford the desired ring closure. Via an acidic pathway, only starting material was recovered, while basic conditions afforded complete decomposition of the reactant (Scheme 101).



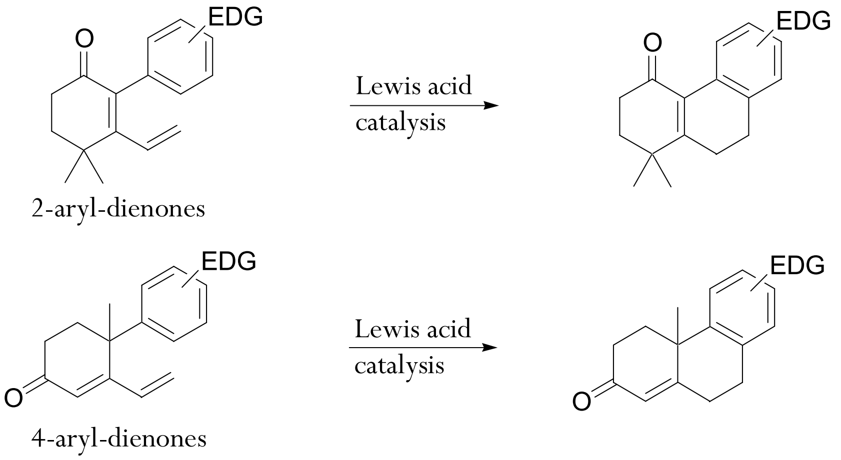
72

Scheme 101: *Attempts at B-ring closure from diketone* 72.

While not successful in affording a tricyclic system by the use of this route, the ease at which the styrene *A*-ring was constructed is a significant improvement upon current methods used to construct such products en route to the final natural products. For these reasons, a combination of a hydroformylation/cyclialkylation strategy could prove very effective in the synthesis of these natural products, and provide an alternative for approaching the forskolin *ABC*-ring system.

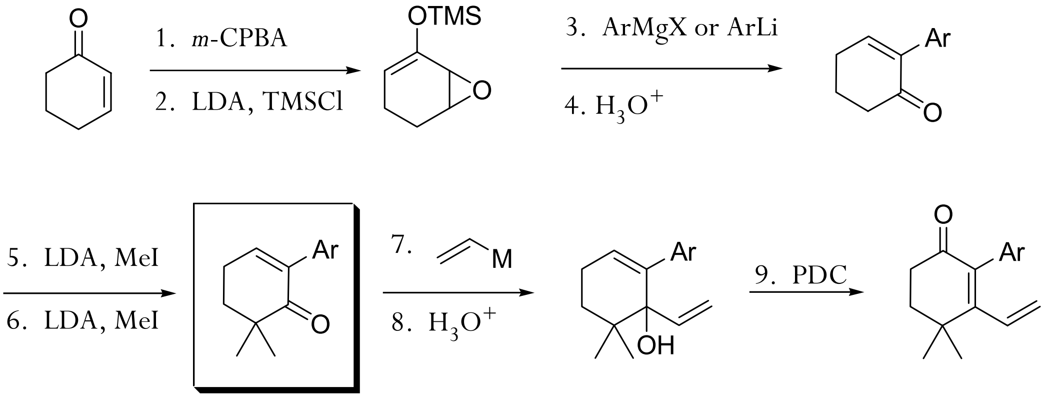
2.19.3b Hydroformylation/cyclialkylation

The intramolecular Friedel-Crafts alkylation of conjugated dienones (cyclialkylation) has been proven to be useful for the construction of tricyclic compounds bearing either an arene[97] or furan[98] *C*-ring function. The success of the arene cyclization is dependent on the presence of electron-donating groups (EDG) on the ring, most often present in the form of methoxy groups, as these are most prevalent on natural products of this type (Scheme 102).



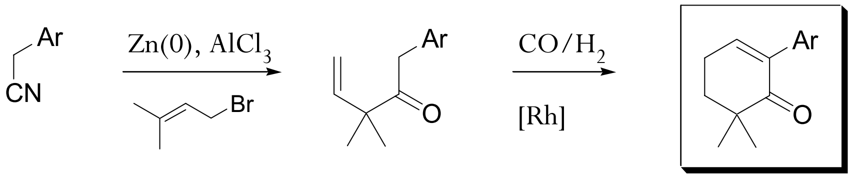
Scheme 102: *Cyclialkylation of arenes resulting in B-ring closure.*

Key to the construction of such a 6,6,6-fused unit is the synthesis of substituted 2- and 4-aryl dienones, which allow for the final cyclialkylation to take place via the addition of Lewis-acids. To date, the best method available for construction of such aryl-dienone systems is accomplished via multi-step sequences developed by **Wender**[99] and **Majetich**[100] involving alkylations and Grignard or organolithium additons followed by oxidative rearrangement with PDC[101] to give the final product (Scheme 103).



Scheme 103: ***Wender*** *synthesis of 2-aryl dienones.*

In comparison, via a hydroformylation/aldol condensation route, the intermediate 2-aryl-enone can be obtained in one step from the corresponding unsaturated ketones, which can then undergo vinyl Grignard addition and PDC oxidation to afford the cyclization precursor 2-aryl-dienone, which allows for ring closure to take place (Scheme 104).

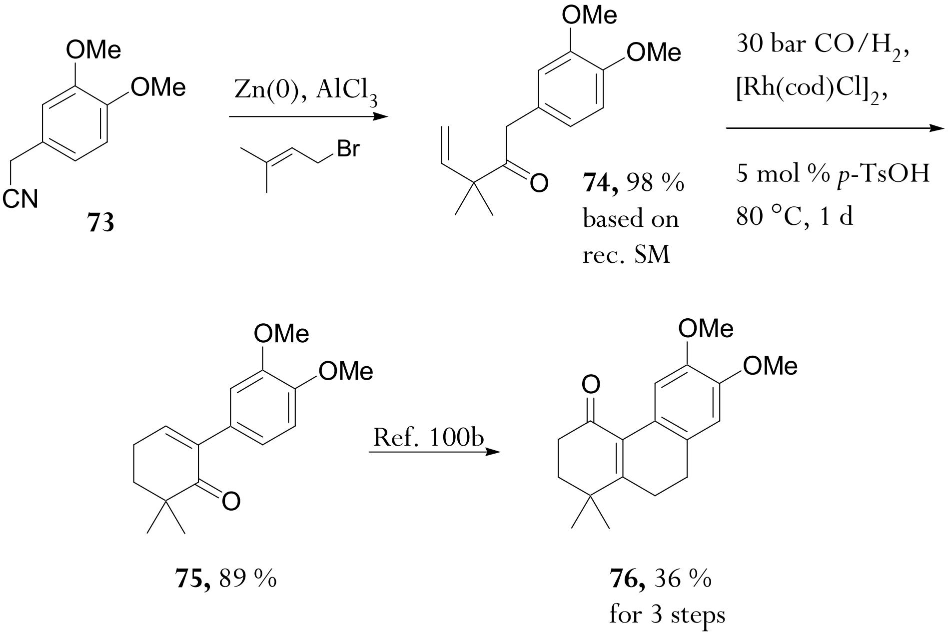


Scheme 104: *Two-step synthesis of 2-aryl-enones via hydroformylation/aldol condensation.*

With the goal of combining the rapid synthesis of 2-aryl-enones via hydroformylation with the proven method of ring closure offered by Lewis acid-catalyzed cyclialkylation, the formal synthesis of an analog of the natural product nimbidiol (see Scheme 96) was carried out.

The synthesis of this aromatic diterpenoid is shown in Scheme 105. This was accomplished by accessing the key intermediate aryldienone directly from the commercially available valeronitrile **73** via the previously used Zn(0) and aluminium-mediated alkylation with prenyl bromide to afford 1-(3,4-dimethoxyphenyl)-3,3-dimethyl-pent-4-en-2-one (**74**) in 98 % yield based on recovered starting material. This unsaturated ketone then underwent hydroformylation in the presence of *p*-TsOH catalysis to afford the desired product 2-(3,4-dimethoxyphenyl)-6,6-dimethyl-cyclohex-2-enone (**75**) in 89 % yield. Compound **75** was converted by **Majetich**[100b] to the desired nimbidiol analog 6,7-dimethoxy-1,1-dimethyl-

2,3,9,10-tetrahydro-1*H*-phenanthren-4-one (**76**) via the addition of vinyllithium, oxidation with PDC and subsequent cyclialkylation with $BF_3 \cdot OEt_2$ in 36 % yield over three steps (see Scheme 105).



Scheme 105: *Formal synthesis of the nimbidiol analog 6,7-dimethoxy-1,1-dimethyl-2,3,9,10-tetrahydro-1H-phenanthren-4-one (**76**) via hydroformylation/aldol condensation of **74**.*

The major advantage to this route can be seen immediately in the rapidity with which the key 2-aryl enone **75** is approached. While the **Majetich** route took over seven steps to accomplish, and afforded product **75** in 21 % yield, the route employing sequential hydroformylation/aldol condensation in the presence of 5 mol % p-TsOH provided this key intermediate in two steps and 87 % yield.

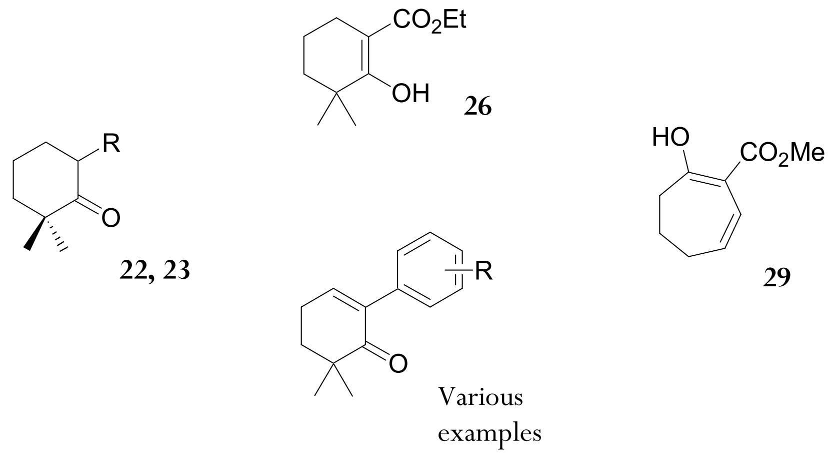
2.20 Summary

Several methods were employed in order to test the possibility of obtaining aliphatic and aromatic labdane diterpenoids through the use of sequential hydroformylation/aldol reactions. The construction of the tricyclic ring system was attempted by extending the currently available methods of accomplishing the desired aldol reaction to substrates that allow for the closure of the *B*-ring system of the terpenoid via another aldol reaction or by Lewis acid-mediated cyclialkylation. Strategies leading to the construction of substrates allowing for the construction of aliphatic diterpenes were unsuccessful due largely in part to the unselective fashion with which the desired carbonyl addition or ozonolysis reactions took place. On the other hand, two routes were explored and elaborated to allow for the construction of aromatic substrates with which to test the possibility of obtaining *B*-ring closure via an aldol reaction. While the substrate in question allowed for efficient *A*-ring closure and simultaneous deketalization under hydroformylation conditions, a second aldol reaction was not observed. The lack of reactivity towards a second aldol addition was also observed under more driving conditions employing strong acid and/or base. For this reason, the tendency of unsaturated benzylic ketones under hydroformylation/aldol conditions to produce unsaturated 2-aryl enones was used to greatly shorten the length of the sequences required to obtain the substrates needed to afford the cyclialkylation precursor. Using this strategy, a 5-step formal synthesis of an analog of the natural product nimbidiol was carried out.

3 CONCLUSION AND OUTLOOK

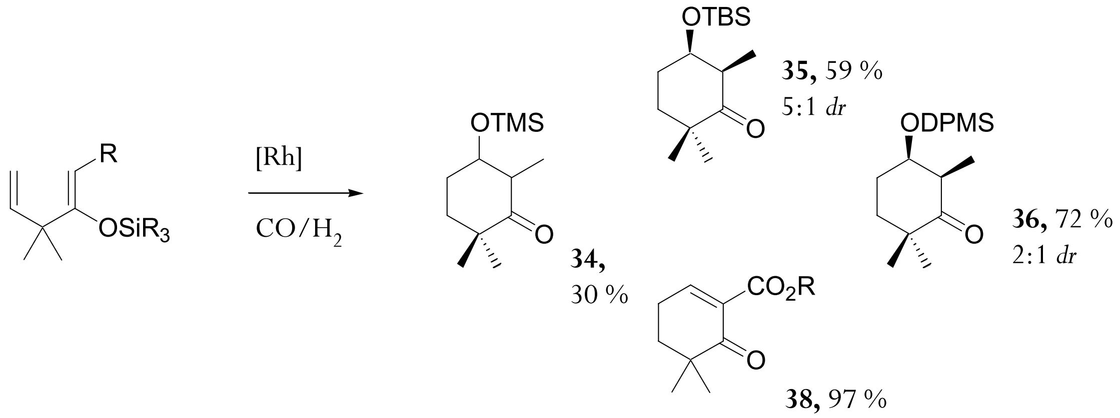
In this work, a thorough investigation of the variables involved in determining the stereochemical outcome of hydroformylation/aldol reaction sequences towards the construction of forskolin and other terpenoid natural products was conducted. The two previously-reported methods of activation towards aldol reactions under hydroformylation – acid catalyzed and Mukaiyama aldol addition – were investigated initially.

In the acid-catalyzed scenarios (Scheme 102), the reaction conditions were evaluated to observe whether of not the elimination of water and subsequent hydrogenation of the resulting enone could be somehow suppressed via the addition of BIPHEPHOS ligand and performing the reaction under much milder conditions than normal. This attempt to retain oxygenation in the aldol products was unsuccessful, as only the products of hydroformylation were observed. Attempts were made therefore on β-ketoesters which would also allow for the construction of the desired substituted cyclohexanones. For the α-unsubstituted ketoesters, a sequence of Knoevenagel condensation/hydrogenation was observed once again, resulting in the corresponding cyclohexanones, existing primarily as the more stable, conjugated *enol*-tautomers. As the a-substituted ketoesters designed to as retrons of the forskolin *A*-rings system gave no cyclization products upon hydroformylation in the presence of mild acid catalysis, the known alternative method of activation towards aldol addition under hydroformylation conditions – the sequential hydroformylation/Mukaiyama aldol addition – was explored.



Scheme 106: *Carbocyclic functionality obtainable from sequential hydroformylation/acid-catalyzed aldol reactions.*

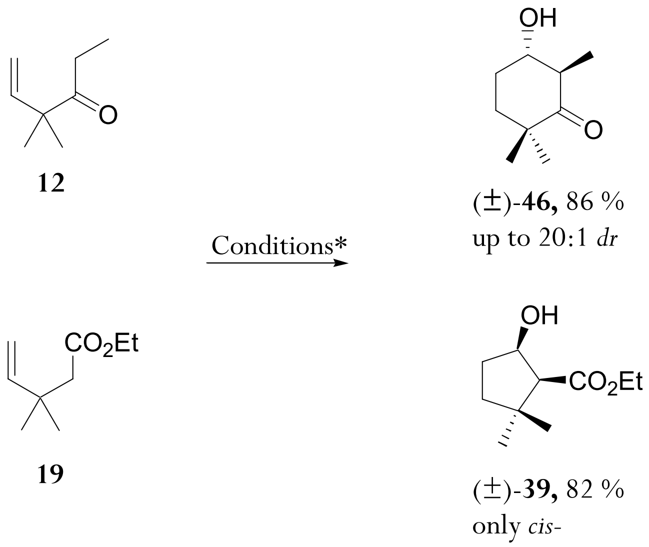
To investigate this method of sequential aldol addition in the production of forskolin *A*-ring analogs in a diastereoselective fashion, various *Z*(O)-silyl enol ethers of the ketones and ketoesters used in the initial investigations were synthesized. Much optimization of the reaction conditions was carried out, allowing for maximum transfer of the silyl moiety to the alcoholate generated from the aldol addition while keeping the diastereoselectivity up to synthetically useful levels. For the first application of the sequential hydroformylation/Mukaiyama aldol addition in the stereoselective synthesis of substituted cyclohexanones applicable to the synthesis of labdane diterpenoid natural products, the reaction proceeded in high yields and diastereoselectivities (Scheme 107). For the α-monosubstituted enolsilanes of ketoesters, a unique phenomenon was observed upon exposure to the hydroformylation conditions, namely that the enone resulting from the Knoevenagel condensation was not hydrogenated as is the norm for more electron-rich enones under the reaction conditions. This method allowed access to a new class of cyclohexanones not previously obtainable through sequential hydroformylation/aldol reactions. Once again, however, the direct construction of the complete forskolin *A*-ring system was not able to be accomplished via this methodology, as the formation of a tetrasubstituted enolsilane to allow for the construction of a quaternary center through Mukaiyama aldol addition was not successful, and another method needed to be employed to allow for the one-pot construction of stereodefined building blocks.



Scheme 107: *Terpenoid A-ring analogs synthesized by sequential hydroformylation/Mukiayama aldol addition.*

As a direct result of the shortcomings of the previously reported methods, namely the loss of oxygen functionality under acid catalysis and the failure to form the desired quaternary centers via aldol addition through both acid-catalyzed and Mukaiyama variants, a new reaction sequence was sought which would allow for these goals to be accomplished, and if possible with improved degrees of stereoselectivity and perhaps even enantioselectivity.

This was accomplished by employing a novel cascade reaction initiated by enolboration, which generated an enolate in situ, which was then free to react with aldehydes generated from olefins in an intermolecular aldol addition reaction. For a wide variety of unsaturated substrates such as ketones, ketoesters, diesters (malonates) and even in one case a monoester, the reaction resulted consistently in good-to-excellent yields. In nearly all cases, this newly-developed reaction cascade prevented the elimination of water and subsequent hydrogenation by effectively trapping the alcohol generated via aldol addition as a boron chelate, which could be hydrolyzed under very mild conditions upon workup of the crude autoclave mixture by the addition of a buffered aqueous solution of H_2O_2 and methanol. Not only was the reaction stopped at the aldol addition step, this last element in the cascade always proceeded with a significant degree of stereoselectivity. The reactions of ketone **12** and ester **19** proceeded exceedingly well for a three-component reaction cascade, with diastereomeric ratios greater than 20:1 being observed (Scheme 108).



12

(±)-**46,** 86 %
up to 20:1 *dr*

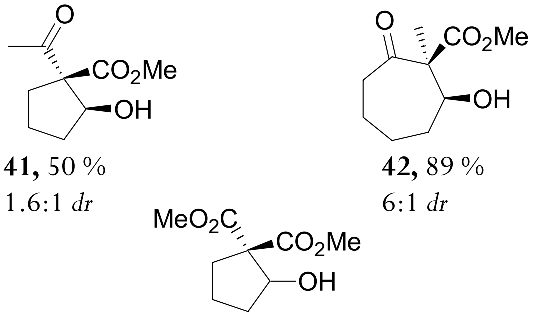
19

(±)-**39,** 82 %
only *cis-*

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 108: *Examples of highly-diastereoselective sequential enolboration/hydroformylation/aldol addition.*

Other aspects of selectivity proved to be very controllable in this reaction sequence. The use of substrates that possessed more than one enolizable site, combined with the presence of terminal olefins that did not have large directing groups to allow for a substrate-controlled *n*-selective hydroformylation proved to be no limitation for this cascade. The enolboration proceeds with such regioselectivity when performed with β–ketoesters that cyclization pathways resulting from the more sterically hindered aldol addition reaction took place in every case. Malonates were also activated towards addition, providing together with the conversion of **19** the first successful enolborations of ester functions under the cascade conditions by this reagent combination. This tendency was exploited to result in the production of highly-functionalized quaternary carbon centers in a diastereoselective fashion when performing the reaction on 1,3-carbonyl compounds bearing α-substitution. Three examples of this can be seen in Scheme 109.



41, 50 %
1.6:1 *dr*

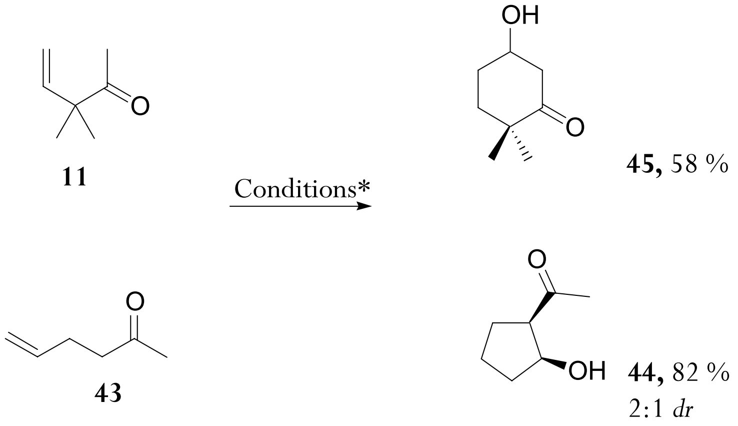
42, 89 %
6:1 *dr*

40, 51 %

Scheme 109: *Synthesis of carbocyclic quaternary carbon centers via sequential enolboration/hydroformylation/aldol-addition.*

Particularly attractive in this set of examples is the excellent yield and high diastereoselectivity with which the substituted cycloheptanone **42** is produced via this methodology. Methods to construct seven membered rings are much less common, and this result could be very useful in constructing the ring systems of other terpenoids, such as ingenol, which bears a both a central 7-membered ring and a-quaternary center.

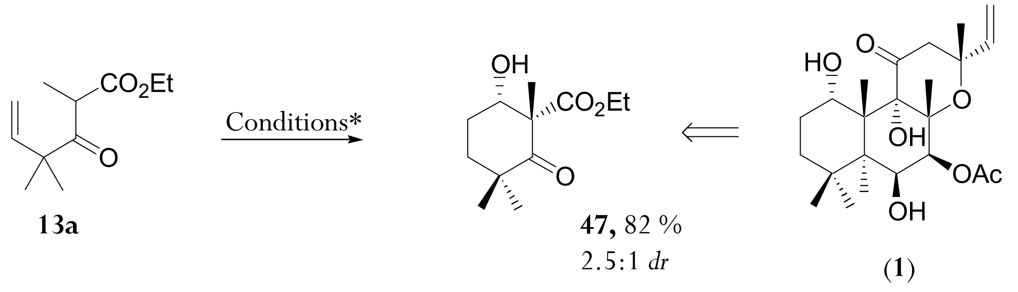
This cascade reaction, aside from being in general high-yielding, regio- and diastereoselective, and compatible with various sets of conditions needed to effect *n*-selective hydroformylation, were shown to be extremely mild and tolerant of some very sensitive functional groups resulting from the aldol addition. The conversions of ketones **11** and **43** illustrate this tendency very well. The synthesis of both of these free-alcohols through aldol addition cannot be done via other reported techniques, due to the potential for retro-aldol/hydrogenation reactions to occur, but they have proven to be accessible via sequential enolboration/ hydroformylation/aldol addition in good yields for the cascade process (Scheme 110).



*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 110: *Mild and selective enolboration/hydroformylation/aldol addition of ketones.*

One of the highlights of this method can be seen in its application to the one-pot, diastereoselective synthesis of the forskolin *A*-ring system. Upon application of the cascade reaction conditions to the α-methyl ketoester **13a**, the forskolin *A*-ring in the form of **47** was synthesized in 82 % yield and 2.5:1 *dr* (Scheme 111). Further elaboration in direction of the natural product could be conducted via use of the two carbonyl functionalities present in **47**.



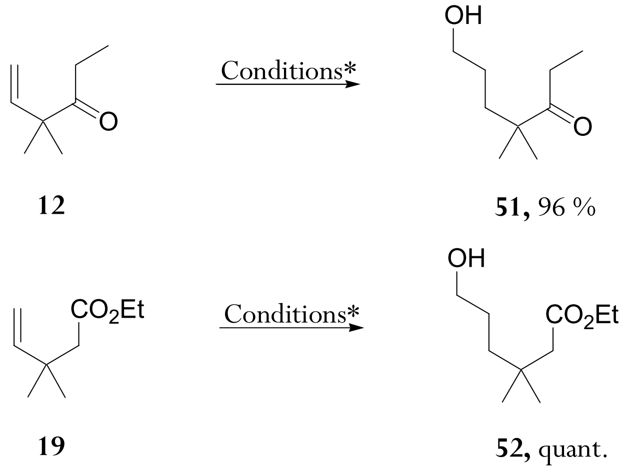
*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Scheme 111: *Stereoselective synthesis of the forskolin A-ring system.*

While the diastereoselectivity of the process is not optimum in this case, this result is far more practical and rapid than any currently available method by which to construct this system.

Especially attractive in this sequence is the avoidance of any protecting group strategies for the aldehyde or the alcohol generated from aldol addition. Notably, the boron enolate tolerates the hydroformylation conditions and reacts immediately with the aldehyde generated from the olefin unit.

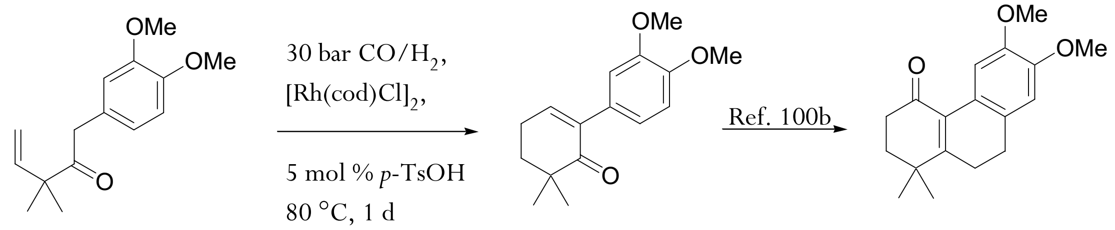
Any attempts to bring asymmetric induction into this newly-found reaction cascade were unfortunately without success. A systematic approach was taken to incorporate the chirality into the substrate itself in the form of chiral esters or sulfoxides, into the aldol catalyst in the form of L-proline, or into the enolate thorough the use of chiral DIP-boron reagents in the enolboration step. In the attempts involving the use of DIP-boron halides, an interesting result was obtained in that the products of hydroformylation/aldehyde reduction were seen in quantitative yields for both ketones and ester substrates. This sequence could be further optimized to afford a new, chemoselective method for the one carbon homologation of olefins to primary alcohols - or hydrohydroxymethylation (Scheme 112).



**Conditions:* (+)-DIP-Cl, Et_3N, 0 °C, then 0.9 mol % $[Rh(cod)Cl]_2$, CO/H_2 (60-80 bar), 80-90 °C, 18 h, then $MeOH/H_2O_2$/pH 7.

Scheme 112: *Highly-efficient hydroformylation/aldehyde reduction sequences using (+)-DIP-Cl.*

In completion of this study, the synthesis of labdane natural products and analogs of forskolin was attempted via the use of sequential hydroformylation/aldol reactions. While the aliphatic compounds constructed to resemble the forskolin system were not easily approached, and suffered from incompatibility with the routes chosen for their synthesis, a good deal of success was had exploring the use of sequential hydroformylation/aldol reactions in the synthesis of aromatic diterpenes. Using this methodology, the formal synthesis of an advanced analog of the natural product nimbidiol was accomplished in a greatly reduced number of steps than used in the one existing synthesis (Scheme 113).



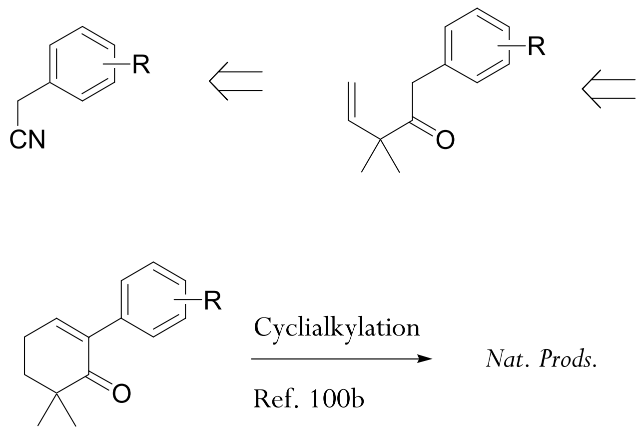
74, 98 % based on rec. SM

75, 89 %

76, 36 % for 3 steps

Scheme 113: *Formal synthesis of nimbidiol analog* ***76****.*

Using the method of sequential hydroformylation/aldol reactions, which have been demonstrated in this work and others to give the corresponding 2-aryl dienones in high yields, can offer rapid and efficient entry to a wide variety of aromatic diterpenes possessing wide ranges of biological activity. This is accomplished by the synthesis of unsaturated aryl ketones, using various nitriles, some of which are commercially available, while some are prepared through the use of short synthetic sequences (Scheme 114). The corresponding 2-aryl dienones can be converted to the natural products through Lewis-acid mediated cyclialkylation.

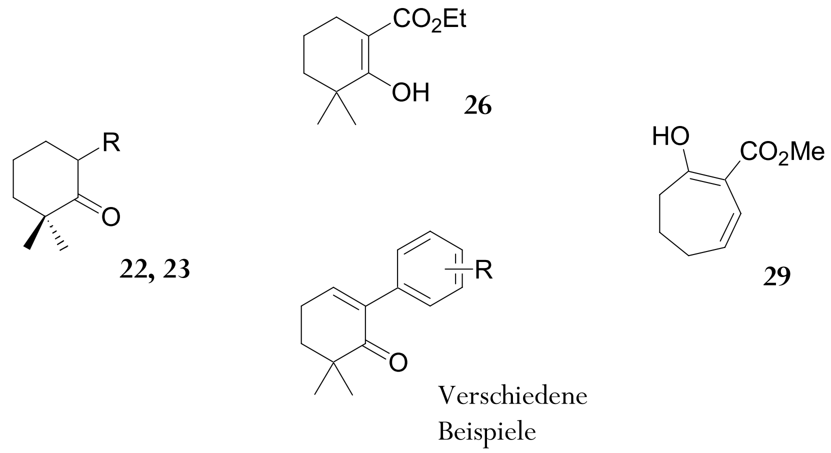


Scheme 114: *General route to aromatic diterpeniod natural products via sequential hydroformylation/aldol reactions.*

4 DEUTSCHE ZUSAMMENFASSUNG

Beschrieben in dieser Arbeit ist eine genaue und sorgfältige Untersuchung von sequenziellen Hydroformylierung/Aldol-reaktionen, die eine stereoselektive Route in Richtung des Naturstoffs Forskolin und verwandte Diterpenen erlauben. Insgesamt sind drei verschiedene Routen untersucht worden, zwei davon (die Säure-katalysierte und Mukaiyama-aldol Varianten) die schon bekannt sind, waren als erstes evaluiert im Rahmen ihrer Anwendbarkeit zur Terpensynthese.

Die säure-katalysierte Variante hat durch viele Versuche gezeigt, daß sie gut geeignet ist als eine Methode für Terpensynthese, weil durch ihre Anwendung eine Vielfalt von Verbindungen, wie die substituierten Cyclohexane, die von ungesättigten β-Ketoestern erhalten werden können, gut anwendbar als Bausteine in Terpensynthese sind (Abb. 115) .



26

22, 23

29

Verschiedene Beispiele

Abb. 115: *Bausteine erhalten durch sequenzielle hydroformzlierung/säure-katalysierte Aldol-reaktionen.*

Da die Produkte dieser Methode keine Stereozentren besitzen, weil die zu einer Aldolkondensation/Hydrierungssequenz in Gegenwart von Säuren führen, ist die zweite Methode – die Mukaiyama-aldol Methode – untersucht worden.

Um diese Methode zu untersuchen,sind verschiedene Enolsilan-derivate hergestellt worden, die eine *Z*(O)-geometrie besitzen. Nach vielen Optimierungen der Reaktionsbedingungen sind die ersten Beispiele einer stereoselektiven Hydroformylierung/Mukaiyama-aldol Sequenz zu berichten, die passende Labdanterpen-bausteine zur Verfügung stellen (Abb. 116).

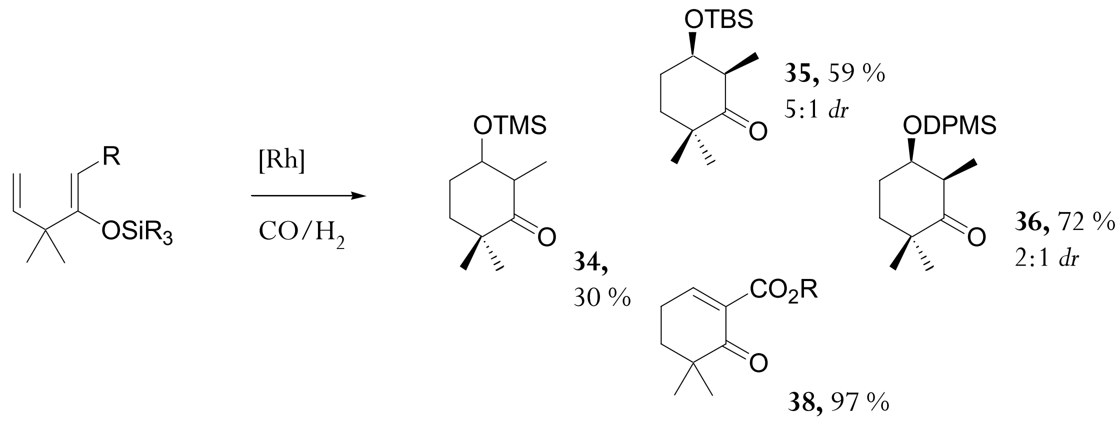
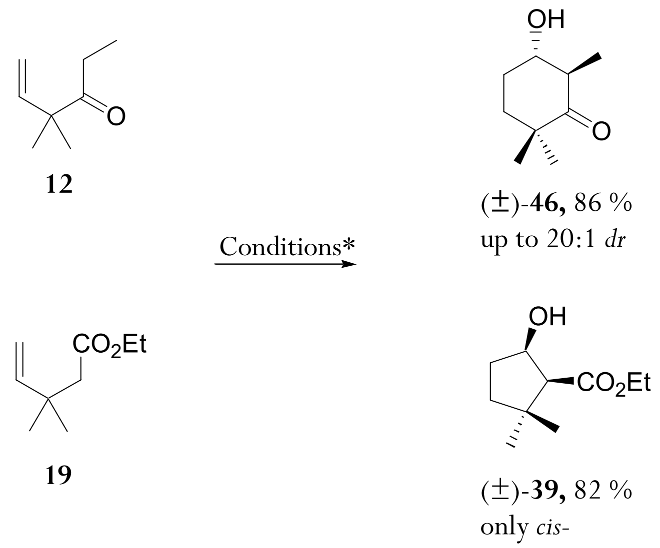


Abb. 116: *Bausteine erhalten durch sequenzielle Hydroformylierung/Mukaiyama aldol-addition.*

Da keine quaternäre Zentren durch die Mukaiyamavariante gebildet werden konnten und da der Prozess mit einer mittelmäßigen Stereoselektivität abläuft, ist eine komplett neue Methode examiniert worden, die eine sequenzielle Enolborierung/Hydroformylierung/Aldol-addition nutzt.

Durch diese Methode ist es gelungen, eine regio- und stereoselektive Enolborierung durchzuführen, und das entsprechende Enolat in-situ zu hydroformylieren. Die Boronatchelate werden oxidativ aufgearbeitet, um an die Aldolprodukte kommen zu können.

Eine Vielzahl von Verbindungen sind durch Anwendung dieser Methode, in guten bis ausgezeichneten Diastereoselektivitaten erhältlich (Abb. 117). In fast allen Fällen (Ketonen, Ketoestern und Diestern) ist die Eliminierung von Wasser unterdrückt und in einem Fall läuft die Reaktion sogar mit einem ungesättigten Monoester, die vorher immer als unreaktiv unter Enolborierungsbedingungen galt.



12

(±)-**46,** 86 %
up to 20:1 *dr*

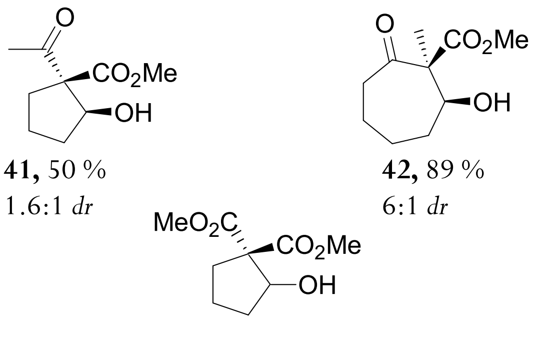
19

(±)-**39,** 82 %
only *cis*-

**Conditions:* (*cy*-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Abb. 117: *Hoch-diastereoselektive Beispiele von sequenzieller Enolborierung/Hydroformzlierung/Aldol-addition.*

Andere Aspekte der Sequenz sind gut kontrollierbar. Substrate die mehrfach enolizierbar sind oder terminale Olefine die keine Substrat-gesteuerte Hydroformylierung erlauben, sind nämlich kein Problem für diese Sequenz. Da die Enolborierung so ausgezeichnet regioselektiv mit β-Ketoestern und Malonatestern läuft, ist die regio- und diastereoselektive Synthese von substituierten quaternären Zentren möglich (Abb. 118)



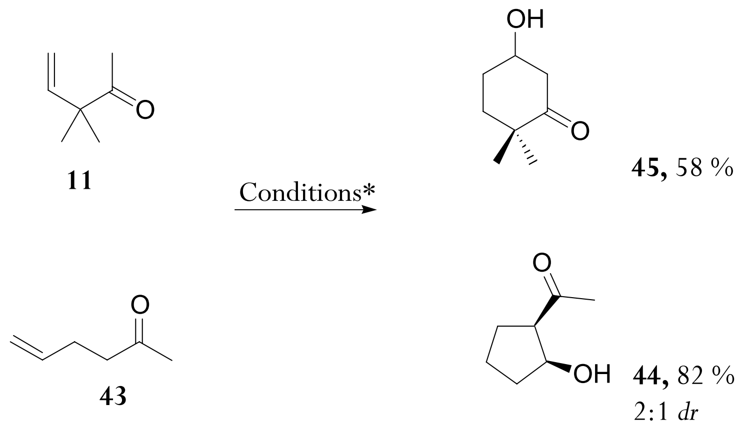
41, 50 %
1.6:1 *dr*

42, 89 %
6:1 *dr*

40, 51 %

Abb. 118: *Synthese von substituierten quaternären Zentren durch sequenzielle Enolborierung/Hydroformzlierung/Aldol-addition.*

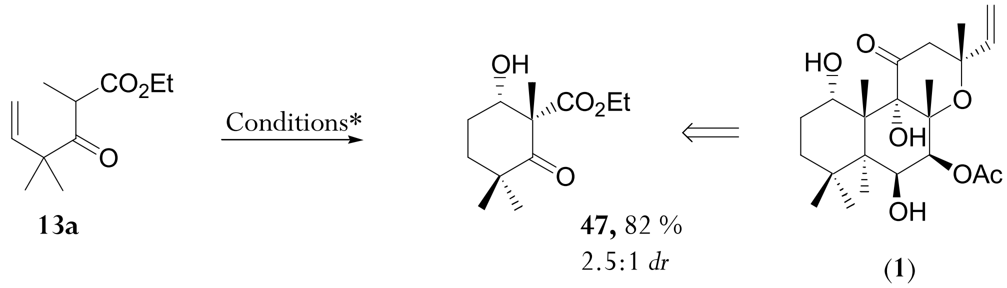
Es hat sich gezeigt, daß diese neue Methode auch sehr tolerant gegenüber empfindlichen Gruppen ist. Einige Beispiele gibt es im Abb. 119 zu sehen.



*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Abb: 119: *Milde und selektive Beispiele von sequenzieller Enolborierung/Hydroformzlierung/Aldol-addition.*

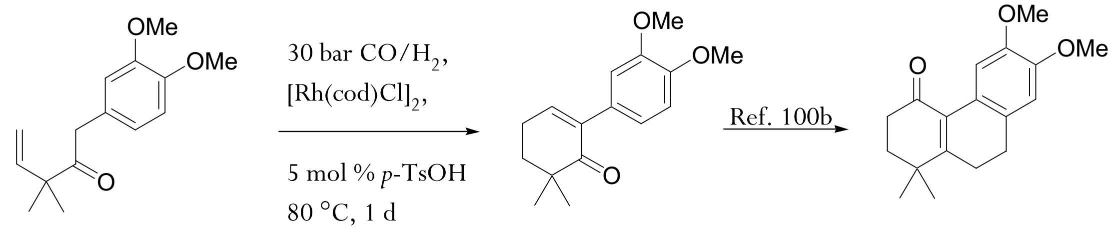
Es ist auch sogar eine "one-pot" Synthese des *A*-ring von Forskolin gelungen, die in hoher Ausbeute und mäßiger Selektivität läuft. Die verbliebenen Ester- und Ketogruppen erlauben eine passende Ausfeilung in Richtung Forskolin (Abb. 120).



*Conditions: (cy-hex)$_2$BCl, Et$_3$N, 0 °C, then 0.9 mol % [Rh(cod)Cl]$_2$, CO/H$_2$ (60-80 bar), 90 °C, then MeOH/H$_2$O$_2$/pH 7.

Abb. 120: *Stereoselektive Synthese des Forskolin A-ring Systems.*

Zum Schluß sind Methoden untersucht worden, die Zugang zur tricyclischen Terpenen erlauben. Gefunden wurde eine sequenzielle Hydroformylierung/Cyclialkylierung, die eine schnelle und effiziente Route repräsentiert. Als Beispiel dafür ist die Formalsynthese des Nimbidiol Analogs **76** durchgeführt worden (Abb. 121).



74, 98 %
based on
rec. SM

75, 89 %

76, 36 %
for 3 steps

Abb. 121: *Formalsynthese von Nimbidiol Analog* ***76****.*

5 EXPERIMENTAL

5.1 General Methods

5.1.a Reagents, solvents and synthesized catalysts/starting materials

All reagents were purchased from commercial sources and were used without further purification unless otherwise stated. THF and Et_2O were distilled over sodium metal and benzophenone, while CH_2Cl_2 and triethylamine (Et_3N) were distilled over CaH_2. When specified, advanced starting materials were synthesized using the cited literature procedures, and product identity and purity was confirmed via ^1H & ^{13}C NMR. The $[Rh(cod)Cl]_2$ catalyst used in hydroformylation was prepared via the method of **Crabtree**[102], while the $Rh(CO)_2(acac)$ hydroformylation catalyst and $RhCl_3 \cdot 3H_2O$ were donated by Degussa AG, Düsseldorf.

5.1.b Spectroscopic and analytical methods

^1H & ^{13}C NMR spectra were measured using Bruker DRX 400, 500 and Varian 600 MHz instruments. If not otherwise stated, $CDCl_3$ was used as the solvent, and both proton and carbon spectra were referenced to $CHCl_3$ (δ 7.25 and δ 77.00, respectively) as the internal standard. All coupling constants are reported in Hz. Structural and stereochemical assignment was made when necessary with the aid of $^1H,H$-COSY, $^1H,^{13}C$-COSY, 1D-GNOE, NOESY, ^1H-TOCSY and GHMBC experiments. All 1D-NMR spectra were Fourier-transformed using Bruker WINNMR software and plotted using the ACDLABS SpecMan software suite, while 2D-NMR were processed and plotted using ACDLABS 2D-NMR software package.

FTIR spectra were acquired using a Nicolet Impact 400 D spectrometer using neat compounds or thin films in $CDCl_3$ between NaCl plates.

ESI mass spectra were recorded using a TSQ Finnigan mass spectrometer, while high-resolution analytical mass spectra **HR-FABMS** and **HR-EIMS** were recorded on JEOL JMS-SX 102A and Finnigan MS 8200 spectrometers, respectively.

Optical rotations of enantiopure or enantioenriched substrates were performed using a Perkin-Elmer 341 polarimeter.

Elemental analyses were performed using a Leco CHNS-932 analyzer.

Melting points were measured using a Büchi melting point apparatus B-540 and are not corrected.

5.1.c Chromatographic/purification methods

Analytical gas chromatography was performed on a Fisons GC 9130 containing a CP-Sil-5(CB) capillary column. Detection was accomplished via a flame-ionization detector.

TLC was performed exclusively on aluminum-backed Merck F_{254} silica gel 60 plates, with the appropriate running solvents, and developed using *p*-anisaldehyde stain.

Silica gel chromatography was performed using Merck silica gel 60 (size 0.063-0.200 nm). Filtrations subsequent to hydroformylation in order to remove catalyst residue were performed with Merck alumina, neutral activity.

5.1.d Working methods

Reactions were performed in normal laboratory glassware with ground glass joints, and reactions requiring an inert atmosphere were run under positive pressure of argon.

Hydroformylations were performed in commercial autoclaves (Berghof type A, 250 mL PTFE insert) or similar house-made autoclaves (70 mL, stainless steel) using specially designed heating and stirring mantles according to the following methods:

Procedure A: *Hydroformylation.* Olefin was added along with the desired solvent to the autoclave. The mixture was stirred as the hydroformylation catalyst was added to the reaction. When necessary, BIPHEPHOS or XANTPHOS ligand (2.0 eq to catalyst) was added, and the autoclave was sealed. The vessel was pressurized to the appropriate levels of CO and H_2 ***!!CAUTION!!*** with continuous stirring. When pressurization was complete, the autoclave was heated to the appropriate reaction temperature, which was maintained for the desired reaction time, after which the autoclave was allowed to cool to RT before being depressurized and flushed once with argon. The crude reaction materials were filtered through a small plug of neutral alumina in order to remove the catalyst and/or ligand residue, and the mixture was purified via flash chromatography on silica gel or Kugelrohr distillation when necessary.

Procedure B: *Sequential hydroformylation/acid-catalyzed aldol reactions.* The unsaturated carbonyl compound was added along with the desired solvent to the autoclave. The mixture was stirred as the hydroformylation catalyst and 5-10 mol % *p*-TsOH was added to the reaction. When necessary, BIPHEPHOS or XANTPHOS ligand (2.0 eq to catalyst) was added, and the autoclave was sealed. The vessel was pressurized to the appropriate levels of CO and H_2 with continuous stirring. When pressurization was complete, the autoclave was heated to the appropriate reaction temperature, which was maintained for the desired reaction time, after which the autoclave was allowed to cool to RT before being depressurized and flushed once with argon. The crude reaction materials were filtered through a small plug of neutral alumina in order to remove the catalyst and/or ligand residue, and the mixture was purified via flash chromatography on silica gel or Kugelrohr distillation when necessary.

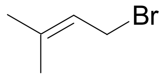
Procedure C: *Sequential hydroformylation/Mukaiyama aldol reactions.* The unsaturated enolsilane was added along with the desired solvent to the autoclave. The mixture was stirred as the hydroformylation catalyst was added to the reaction. When necessary, BIPHEPHOS or XANTPHOS ligand (2.0 eq to catalyst) was added, and the autoclave was sealed. The vessel was pressurized to the appropriate levels of CO and H_2 with continuous stirring. When pressurization was complete, the autoclave was heated to the appropriate reaction temperature, which was maintained for the desired reaction time, after which the autoclave was allowed to cool to RT before being depressurized and flushed once with argon. The crude reaction materials were filtered through a small plug of neutral alumina in order to remove the catalyst and/or ligand residue, and the mixture was purified via flash chromatography on silica gel or Kugelrohr distillation when necessary.

Procedure D: *Sequential enolboration/hydroformylation/aldol-addition reactions.* Et_3N (1.05 eq. to carbonyl compound) was pre-complexed under an argon atmosphere with (*cy*-hex)$_2$BCl (1.05 eq.) in the required amount of dry CH_2Cl_2 at 0 °C for 15 min. The unsaturated carbonyl compound in approx. 1 mL of solvent was then added slowly via syringe and the enolboration was allowed to stir for an additional 30 min. The mixture was simply transferred into the autoclave containing the hydroformylation catalyst, 10-15 mL of solvent and XANTPHOS ligand (2 eq. to catalyst) when necessary. The autoclave was then pressurized with equal pressures of CO and H_2 and heated to the desired temperature. Upon cooling the autoclave to RT, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue (~25 mL) along with 2 mL of conc. pH 7 phosphate buffer and 1 mL of 30 % H_2O_2, and the reaction was allowed to stir overnight before being extracted with ether (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 75 mL), dried and concentrated prior to further purification when necessary via flash chromatography or Kugelrohr distillation.

Procedure E: *Attempted sequential asymmetric enolboration/hydroformylation/aldol-addition reactions.* Et_3N (1.05 eq. to carbonyl compound) was pre-complexed under an argon atmosphere with (+)-DIP-Cl (1.05 eq.) in the required amount of dry CH_2Cl_2 at 0 °C for 15 min. The unsaturated carbonyl compound in approx. 1 mL of solvent was then added slowly via syringe and the enolboration was allowed to stir for an additional 30 min. The mixture was simply transferred into the autoclave containing the hydroformylation catalyst, 10-15 mL of solvent and XANTPHOS ligand (2 eq. to catalyst) when necessary. The autoclave was then pressurized with equal pressures of CO and H_2 and heated to the desired temperature. Upon cooling the autoclave to RT, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue (~25 mL) along with 2 mL of conc. pH 7 phosphate buffer and 1 mL of 30 % H_2O_2, and the reaction was allowed to stir overnight before being extracted with ether (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 75 mL), dried and concentrated prior to further purification when necessary via flash chromatography or Kugelrohr distillation.

5.2 Syntheses

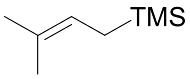
Preparation of 1-bromo-3-methyl-but-2-en (prenyl bromide)[103]



C_5H_9Br
Mol. Wt.: 149,03

86.1 g (1.0 mol) 2-methyl-3-buten-1-ol was added to 250 mL Et_2O, and stirring was maintained at RT. To this solution was added at once 400 mL of a 48 % $HBr_{(aq.)}$ solution, and thorough stirring was continued for 15 min. The reaction mixture was transferred into a separatory funnel, and the aqueous layer was removed and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed extensively with sat. aq. $NaHCO_3$ (5 x 100 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure to give 93 % (0.93 mol, 139 g) prenyl bromide as a nearly colorless liquid in need of no further purification (> 94 % pure by GC). All spectroscopic data matched that reported in the literature.

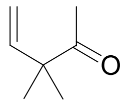
Preparation of trimethyl-(3-methyl-but-2-enyl)-silane (prenyl trimethylsilane)



$C_8H_{18}Si$
Mol. Wt.: 142,31

6.5 g (0.27 mol) Mg(0) turnings are flame dried three times and allowed to cool back to RT under and argon atmosphere before 300 mL THF and approx. 1.0 g prenyl bromide are added at once. After the reaction is initiated, the reaction is kept near RT by the aid of a water bath as 10.0 g (67.0 mmol) prenyl bromide and 6.9 mL (64.0 mmol) TMSCl were added to the reaction dropwise over the course of 30 min. The reaction mixture was allowed to stir at RT for 48 h before the thick mixture was suction filtered to remove the remaining Mg solids, and the filter cake was amply washed with THF. The filtrate was cooled to 0 °C before being quenched with 250 mL sat. aq. NH_4Cl solution. The aqueous layer is removed and is extracted with Et_2O (1 x 50 mL) before the combined organic extracts are dried over $MgSO_4$, concentrated under reduced pressure and fractionated over a Vigreux column (130-135 °C @ 760 mbar) to give 6.5 g (45.6 mmol, 68 %) pure prenyl trimethylsilane as a colorless liquid. All spectroscopic data matched that reported in the literature.

Preparation of 3,3-dimethyl-pent-4-en-2-one (11)[104]

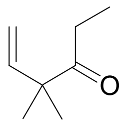


11

$C_7H_{12}O$
Mol. Wt.: 112,17

In a two-necked round-bottom flask containing 200 mL CH_2Cl_2 cooled to 0 °C was added $AlCl_3$ (13.3 g, 0.10 mol) followed by fresh distilled acetyl chloride (8.6 g, 0.11 mol) slowly via syringe under an argon atmosphere. After stirring for 30 min. the mixture was taken up in an addition funnel and dropped into a stirring mixture of prenyl trimethylsilane (14.3 g, 0.10 mol) in 100 mL CH_2Cl_2 which is cooled to -60 °C. After addition is complete, the mixture is stirred for an additional 10 min. before being poured over a mixture of ice and 100 mL sat. aq. NH_4Cl solution. The mixture is extracted with CH_2Cl_2 before being dried over $MgSO_4$, concentrated and purified by Kugelrohr distillation (70 °C @ 200 mbar) to give 8.7 g (78.0 mmol, 78 %) of 3,3-dimethyl-pent-4-en-2-one (**11**) as a colorless oil. All spectroscopic data matched that reported in the literature.

Preparation of 4,4-dimethyl-hex-5-en-3-one (12)[105]

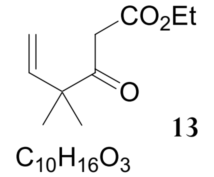


12

$C_8H_{14}O$
Mol. Wt.: 126,20

A two-necked 250 mL round-bottom flask containing a stirring mixture of 40 mL sat. aq. NH_4Cl solution and 8 mL of THF was maintained at RT using a water bath as prenyl bromide (5.8 g, 38.9 mmol) and propionaldehyde (3.0 mL, 52.0 mmol) were added to the mixture. With continued vigorous stirring, zinc dust (4.0 g, 62.0 mmol) was slowly added portion-wise to the mixture. The mixture heated up considerably upon addition of the metal, and after addition was complete the reaction was stirred for an additional 2 h, upon which the mixture was extracted with ether, dried over $MgSO_4$ and concentrated to give the crude 4,4-dimethyl-hex-5-en-3-ol, which was taken up in ether and stirred at RT as 30 mL of Jones reagent (prepared by dissolving 100.0 g sodium dichromate in 300.0 mL H_2O, followed by the addition of 1.3 mol H_2SO_4 and diluting to 500.0 mL total volume with H_2O) was dropped to the mixture over 30 min. After addition, the mixture was stirred for an additional 2 h before being extracted with ether and washed repeatedly with sat. aq. $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$ and concentrated to give 3.5 g (28 mmol) 4,4-dimethyl-hex-5-en-3-one (**12**) in 72 % as a pale yellow oil which was used in future reactions without further purification. All spectroscopic data matched that reported in the literature.

Preparation of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (13) from ethyl cyanoacetate

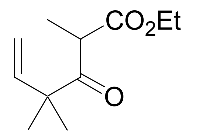


13

$C_{10}H_{16}O_3$
Mol. Wt.: 184,23

A mixture of zinc dust (19.6 g, 0.3 mol), $AlCl_3$ (4 g, 30 mmol) and ethyl cyanoacetate (10.6 mL, 90 mmol) was stirred in 200 mL of dry THF at 0 °C. After 15 min. a solution of prenyl bromide (11.53 mL, 0.1 mol) in 15 mL THF was added slowly. After addition was complete, the reaction was left to warm to RT and was stirred overnight, when 200 mL of 2 N HCl was added to the reaction mixture and stirring was continued for another 15 min. The reaction was filtered and washed with sat. aq. $NaHCO_3$ (3 x 100 mL) and brine (100 mL) before being dried, concentrated and purified by column chromatography (5:1 CH_2Cl_2/hexane) to give 11.2 g (61 %) of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**) as a pale-yellow oil. All spectroscopic data matched that reported in the literature.

Preparation of ethyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (13a)



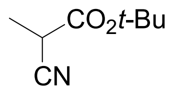
13a

$C_{11}H_{18}O_3$
Mol. Wt.: 198,26

To a stirring mixture of ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**) (1.0 g, 5.4 mmol) and CH_3I (0.3 mL, 5.4 mmol) in 15 mL of acetone at RT was added at once 0.75 g (5.4 mmol) K_2CO_3 and the mixture was stirred overnight. The mixture was then extracted with ether and washed with sat. aq. $NaHCO_3$ solution before being dried and concentrated to give 0.92 g ethyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (**13a**) (4.6 mmol, 85 %) as a yellow oil which required no further purification.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.20 (m, 6H); 1.26 (m, 6H); 3.89 (q, *J* = 6 Hz, 1H); 4.09 (q, *J* = 6 Hz, 2H); 5.21 (dd, *J* = 5, 10 Hz, 2H); 5.81 (dd, *J* = 10, 20 Hz, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 13.9, 14.8, 23.3, 46.8, 51.8, 61.1, 115.3, 141.4, 170.6, 208.6. **FTIR ($CDCl_3$ film):** 2977, 1751, 1685, 1249, 910, 743 cm^{-1}. **HR-EIMS** anal. calc. for $C_{11}H_{19}O_3$ $[M + H]^+$: 199.1334; anal. found: 199.1359.

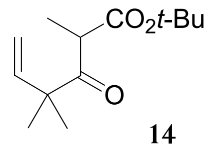
Preparation of *tert*-butyl cyano-methyl-acetate (Starting material for 14 and 15)[106]



$C_8H_{13}NO_2$
Mol. Wt.: 155,19

To a stirring solution of 84 mmol LDA in 100 mL dry THF at –78 °C was added 2.0 g (36.3 mmol) propionitrile slowly via syringe. The solution was allowed to stir for 30 min at 0 °C before being cooled again to –78 °C as 7.9 g (36.3 mmol) di-*tert*-butyl dicarbonate was added in 5 mL dry THF. The ice bath was removed, and the reaction was allowed to stir overnight, warming to RT. The reaction was quenched via the addition of 50 mL NH_4Cl solution, the aqueous layer was extracted with Et_2O (1 x 50 mL) and the combined organic extracts were dried over $MgSO_4$ before being concentrated under reduced pressure to afford 3.1 g (20.1 mmol, 55 %) *tert*-butyl cyano-methyl-acetate as a yellow oil. All spectroscopic data matched that reported in the literature.

Preparation of *tert*-butyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (14)



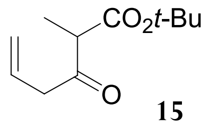
14

$C_{13}H_{22}O_3$
Mol. Wt.: 226,31

A mixture of 1.6 g zinc dust, 0.34 g $AlCl_3$ and *tert*-butyl cyano-methyl-acetate (1.0 g, 6.4 mmol) was stirred in 50 mL of dry THF at 0 °C. After 15 min. a solution of 1 mL prenyl bromide in 15 mL THF was added slowly. After addition was complete, the reaction was left to warm to RT and was stirred overnight, when 50 mL of 2 N HCl was added to the reaction mixture and stirring was continued for another 15 min. The reaction was filtered and washed with sat. aq. $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL) before being dried and concentrated to give 704 mg (3.1 mmol, 48 %) of *tert*-butyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (**14**) as a colorless oil needing no further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 6H); 1.43 (m, 9H); 1.48 (d, J = 8 Hz, 3H); 3.41 (q, J = 8 Hz, 1H); 5.16 (dd, J = 8, 20 Hz, 2H); 5.85 (dd, J = 12, 20 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 15.1, 27.6, 32.3, 47.5, 84.2, 115.0, 141.4, 165.4, 208.9. **FTIR** (neat): 2980, 2937, 1743, 1711, 1157, 848 cm^{-1}.

Preparation of *tert*-butyl 2-methyl-3-oxo-hex-5-enoate (15)



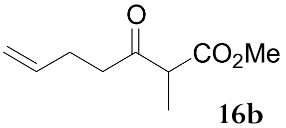
15

$C_{11}H_{18}O_3$
Mol. Wt.: 198,26

A mixture of zinc dust (1.6 g, 25.6 mmol), $AlCl_3$ (342 mg, 2.56 mmol) and *tert*-butyl cyano-methyl-acetate (1.0 g, 6.4 mmol) was stirred in 50 mL of dry THF at 0 °C. After 15 min. a solution of allyl bromide (0.61 mL, 7.0 mmol) in 15 mL THF was added slowly. After addition was complete, the reaction was left to warm to RT and was stirred overnight, when 50 mL of 2 N HCl was added to the reaction mixture and stirring was continued for another 15 min. The reaction was filtered and washed with sat. aq. $NaHCO_3$ (3 x 100 mL) and brine (100 mL) before being dried, concentrated to give 832 mg (66 %, 4.2 mmol) of *tert*-butyl 2-methyl-3-oxo-hex-5-enoate (**15**) as a colorless oil needing no further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 8 Hz, 3H); 1.36 (s, 9H); 3.22 (m, 2H); 3.39 (q, J = 8 Hz, 1H); 5.07 (m, 2H); 5.81 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 12.4, 27.63, 46.0, 53.0, 81.6, 118.8, 130.0, 169.3, 203.8. **FTIR (neat):** 2981, 2938, 1743, 1369, 1162, 846 cm^{-1}.

Preparation of methyl 2-methyl-3-oxo-hept-6-enoate (16b) via 16a



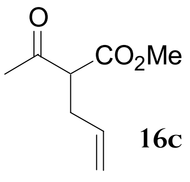
16b

$C_9H_{14}O_3$
Mol. Wt.: 170,21

(A) To a stirring mixture of 1.2 g (50 mmol) NaH in 100 mL dry THF cooled to 0 °C was added 3.48 g (30 mmol) methyl 3-oxo-butyrate via syringe. When addition was complete, the mixture was stirred for 30 min at 0 °C before 11.7 mL (50 mmol) of *n*-BuLi (2.5 M in hexane) was added over 10 min via syringe. The mixture was stirred for another 10 min before allyl bromide (3.99 g, 33 mmol) was added and the mixture was allowed to warm to RT while stirring. The reaction was then quenched via the slow addition of 100 mL sat. aq. NH_4Cl solution, extracted with Et_2O (1 x 50 mL) and washed with brine before being dried, concentrated and purified by Kugelrohr distillation to give 3.9 g methyl 3-oxo-hept-6-enoate (**16a**) (25.0 mmol, 85 %) as a pungent-smelling, light-yellow oil which was immediately taken on to the subsequent methylation reaction without purification.

(B) To a stirring RT acetone solution (20 mL) of 3.9 g methyl 3-oxo-hept-6-enoate (25.0 mmol), 0.40 mL CH_3I (6.4 mmol) and 885 mg (6.4 mmol) K_2CO_3 were added at once and the mixture was stirred overnight. The mixture was then extracted with Et_2O (1 x 50 mL) and washed with brine before being dried over $MgSO_4$ and concentrated under reduced pressure to give methyl 2-methyl-3-oxo-hept-6-enoate (**16b**) in 89 % as a light-yellow oil which required no further purification. All spectroscopic data matched that reported in the literature.

Preparation of methyl 2-acetyl-pent-4-enoate (16c)[107]

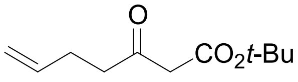


16c

$C_8H_{12}O_3$
Mol. Wt.: 156,18

To a suspension of 60 % NaH (625 mg, 26 mmol) in 75 mL dry THF at 0 °C was added via syringe methyl 3-oxo-butyrate (2.3 g, 19.8 mmol). When addition was complete, the mixture was stirred for 15 min at 0 °C before allyl bromide (2.94 g, 24 mmol) was added dropwise. After 2 h, the mixture was quenched by the slow addition of sat. aq. NH_4Cl, extracted with ether and washed with brine before being dried, concentrated and purified by Kugelrohr distillation (70 °C @ 1 mbar) to give 3.0 g methyl 2-acetyl-pent-4-enoate (**16c**) (19.2 mmol, 97 %) as a nearly colorless oil. All spectroscopic data matched that reported in the literature.

Preparation of *t*-butyl 3-oxo-hept-6-enoate (17a)

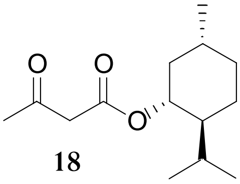


17a

$C_{11}H_{18}O_3$
Mol. Wt.: 198,26

(A) To a stirring mixture of 880 mg (20 mmol) NaH in 50 mL dry THF cooled to 0 °C was added 3.16 g (20 mmol) *t*-butyl 3-oxo-butyrate via syringe. When addition was complete, the mixture was stirred for 30 min at 0 °C before 8.4 mL of *n*-BuLi (2.5 M in hexane) was added over 10 min via syringe. The mixture was stirred for another 10 min before allyl bromide (1.9 mL, 20 mmol) was added and the mixture was allowed to warm to RT while stirring. The reaction was then quenched via the slow addition of 100 mL sat. aq. NH_4Cl solution, extracted with Et_2O (1 x 50 mL) and washed with brine before being dried, concentrated and purified by Kugelrohr distillation to give 1.9 g *t*-butyl 3-oxo-hept-6-enoate (**17a**) (9.6 mmol, 48 %) as a light-yellow oil which was immediately taken on to the subsequent methylation reaction without purification.

Preparation of (–)-menthyl 3-oxobutyrate (18)

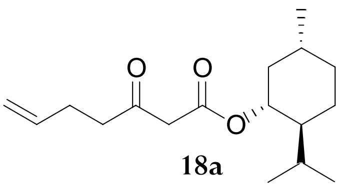


18

$C_{14}H_{24}O_3$
Mol. Wt.: 240,34

To a stirring RT solution of (–)-menthol (15 g, 9.6 mmmol) in 80 mL acetone in a 250 mL round-bottom flask was added Et_3N (1.3 mL, 9.6 mmol) followed by diketene in acetone (50 % w/w, 21 g, 126 mmol). The reaction was stirred at reflux for 2 h, allowed to cool, diluted with 1 N HCl and extracted with CH_2Cl_2 (1 x 100 mL). The organic extract was dried with $MgSO_4$ and concentrated before being purified via Kugelrohr distillation (140 °C @ 0.5 mbar) to give 21.2 g (–)-menthyl 3-oxobutyrate (**18**) (8.8 mmol, 92 %) as a colorless oil. All spectroscopic data matched that reported in the literature.

Preparation of (–)-menthyl 3-oxo-hept-6-enoate (18a)



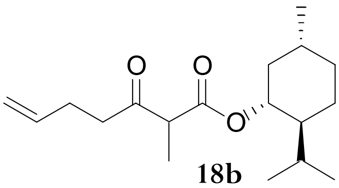
18a

$C_{17}H_{28}O_3$
Mol. Wt.: 280,40

To a stirring mixture of 700 mg (16.3 mmol) NaH in 100 mL dry THF at 0 °C was added 3 g (12.5 mmol) (–)-menthyl 3-oxo-butyrate (**18**) via syringe. When addition was complete, the mixture was stirred for 30 min at 0 °C before 5.5 mL of *n*-BuLi (2.5 M in *n*-hexane) was added slowly via syringe. The mixture was stirred for another 10 min before allyl bromide (1.6 mL, 12.5 mmol) was added and the mixture was allowed to warm to RT while stirring. The reaction was then quenched via the slow addition of 100 mL sat. aq. NH_4Cl solution, extracted with Et_2O (1 x 50 mL) and washed with brine before being dried, concentrated and purified by Kugelrohr distillation (100 °C @ 1 mbar) to give 1.9 g (6.7 mmol, 54 %) (–)-menthyl 3-oxo-hept-6-enoate (**18a**) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.72 (d, *J* = 8 Hz, 3H) 0.86 (m, 6H); 0.96 (m, 2H); 1.33 (m, 2H); 1.65-2.00 (m, 4H); 2.31 (m, 2H); 2.60 (t, *J* = 8 Hz, 2H); 3.38 (s, 2H); 4.68 (dt, *J* = 4, 8 Hz, 1H); 4.98 (dd, *J* = 16, 24 Hz, 2H); 5.75 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 16.2, 20.8, 22.0, 23.3, 26.2, 27.5, 31.4, 34.2, 40.7, 42.0, 46.9, 49.8, 75.6, 115.6, 136.6, 166.8, 202.1. **FTIR** (neat): 2956, 2870, 1730, 1715, 1239 cm^{-1}. **HR-FABMS** anal. calc. for $C_{17}H_{29}O_3$ $[M + H]^+$: 281.2116; anal. found: 281.2120.

Preparation of (–)-menthyl 2-methyl-3-oxo-hept-6-enoate (18b)



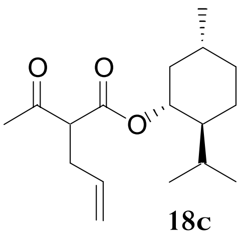
18b

$C_{18}H_{30}O_3$
Mol. Wt.: 294,43

To a stirring acetone solution (20 mL) of 956 mg (–)-menthyl 3-oxo-hept-6-enoate (3.4 mmol), 0.21 mL MeI (3.4 mmol) and 463 mg (3.4 mmol) K_2CO_3 were added at once and the mixture was stirred overnight at RT. The mixture was then extracted with Et_2O (1 x 50 mL) and washed with brine before being dried over $MgSO_4$ and concentrated under reduced pressure to give (–)-menthyl 2-methyl-3-oxo-hept-6-enoate (**18b**) in 88 % as a 1:1 mixture of diastereoisomers yellow oil which required no further purification.

1:1 Mixture of Diastereoisomers: ^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.66 (m, 3H) 0.82 (m, 6H); 0.92 (m, 2H); 1.25 (d, *J* = 8 Hz, 3H); 1.33 (m, 2H); 1.65-2.00 (m, 4H); 2.26 (m, 2H); 2.55 (m, 2H); 3.42 (m, 1H); 4.63 (dt, *J* = 4, 8 Hz, 1H); 4.91 (dd, *J* = 16, 24 Hz, 2H); 5.72 (m, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ *Diastereoisomer 1:* 12.6, 15.7, 20.6, 21.8, 22.9, 25.8, 27.4, 31.2, 33.9, 40.3, 40.4, 52.9, 75.1, 115.2, 136.6, 169.9, 204.6. δ *Diastereoisomer 2:* 12.6, 16.0, 23.1, 40.3, 53.0, 75.1. **FTIR** (neat): 2956, 2870, 1730, 1715, 1239 cm^{-1}. **HR-FABMS** anal. calc. for $C_{18}H_{31}O_3$ $[M + H]^+$: 295.2273; anal. found: 295.2250.

Preparation of (–)-menthyl 2-acetyl-pent-4-enoate (18c)

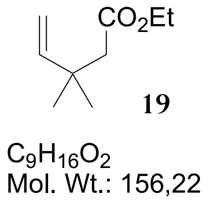


18c

$C_{17}H_{28}O_3$
Mol. Wt.: 280,40

To a suspension of 60 % NaH (625 mg, 20 mmol) in 75 mL dry THF at 0 °C was added via syringe (–)-menthyl 3-oxo-butyrate (4.8 g, 20 mmol). When addition was complete, the mixture was stirred for 15 min at 0 °C before allyl bromide (1.7 mL, 20 mmol) was added dropwise. After 2 h, the mixture was quenched by the slow addition of sat. aq. NH_4Cl, extracted with ether and washed with brine before being dried, concentrated and purified by Kugelrohr distillation (70 °C @ 1 mbar) to give 4.6 g (–)-menthyl 2-acetyl-pent-4-enoate (**18c**) (16.6 mmol, 83 %) as a nearly colorless oil. All spectroscopic data matched that reported in the literature.

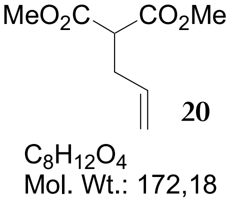
Preparation of ethyl 3,3-dimethyl-pent-4-enoate (19)



19

In a 100 mL round-bottom flask was added 4.3 g (50 mmol) 3-methyl-2-butene-1-ol, 50 mL triethylorthoacetate and 0.5 mL propionic acid with stirring. The mixture was refluxed overnight before being extracted with Et_2O (2 x 50 mL) and washed with H_2O and $NaHCO_3$ (1 x 50 mL each). The organic layer was dried over $MgSO_4$ and concentrated to give 6.5 g (83 %) of ethyl 3,3-dimethyl-pent-4-enoate (**19**) as a colorless, fragrant oil needing no further purification. All spectroscopic data matched that reported in the literature.

Preparation of dimethyl 2-allyl-malonate (20)



20

To a suspension of 11 g 60 % NaH (280 mmol) in 200 mL dry THF was added dropwise 33.0 g dimethyl malonate (250 mmol). After addition was complete, the mixture was stirred for 15 min at RT before 30.3 g allyl bromide (250 mmol) was added dropwise. After 2 h, the mixture was quenched by the slow addition of water, extracted with ether and washed with brine before being dried, concentrated and purified by flash chromatography (15:1 hexane/Et_2O) to give 37.1 g dimethyl 2-allyl-malonate (**20**) (215 mmol, 86 %) as a colorless oil. All spectroscopic data matched that reported in the literature.

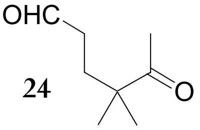
Preparation of 4,4-dimethyl-5-oxo-hexanal (24)

Amounts:	300 mg	(2.7 mmol)	3,3-dimethyl-pent-4-en-2-one (**11**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	15 mg	(10 mol %)	*p*-TsOH
	16 mg	(1.8 mol %)	BIPHEPHOS

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 20 bar CO/H_2 (1:1), 60 °C, 20 h

Yield: 379 mg **24** (2.7 mmol, quantitative yield).

The spectra matched the data reported.[24a] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.08 (s, 6H); 1.13 (t, *J* = 4 Hz, 3H); 1.23 (d, *J* = 8 Hz, 3H); 1.79 (dt, *J* = 2, 4 Hz, 2H); 2.30 (dt, *J* = 4, 8 Hz, 2H); 4.04 (q, *J* = 4 Hz, 2H); 9.67 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 14.8, 24.1, 30.7, 39.6, 46.3, 47.9, 61.3, 170.4, 201.6, 210.6.



24

$C_8H_{14}O_2$
Mol. Wt.: 142,20

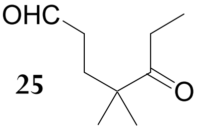
Preparation of 4,4-dimethyl-5-oxo-heptanal (25)

Amounts:	300 mg	(2.4 mmol)	3,3-dimethyl-pent-4-en-2-one (**12**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	15 mg	(10 mol %)	*p*-TsOH
	16 mg	(1.8 mol %)	BIPHEPHOS

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 20 bar CO/H_2 (1:1), 60 °C, 20 h

Yield: 373 mg **25** (2.4 mmol, quantitative yield).

The spectra matched the data reported.[24a] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.08 (s, 6H); 1.13 (t, *J* = 4 Hz, 3H); 1.23 (d, *J* = 8 Hz, 3H); 1.79 (dt, *J* = 2, 4 Hz, 2H); 2.30 (dt, *J* = 4, 8 Hz, 2H); 4.04 (q, *J* = 4 Hz, 2H); 9.67 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 14.8, 24.1, 30.7, 39.6, 46.3, 47.9, 61.3, 170.4, 201.6, 210.6.



25

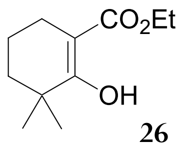
$C_9H_{16}O_2$
Mol. Wt.: 156,22

Preparation of ethyl 2-hydroxy-3,3-dimethyl-cyclohex-1-enecarboxylate (26)

Amounts:	460 mg	(2.5 mmol)	ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**)
	6 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	47 mg	(10 mol %)	*p*-TsOH

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 20 bar CO/H_2 (1:1), 80 °C, 20 h

Yield: 356 mg **25** (1.8 mmol, 72 % as a 1.6:1 mixture of *enol-:keto*-tautomers).



26

$C_{11}H_{18}O_3$
Mol. Wt.: 198,26

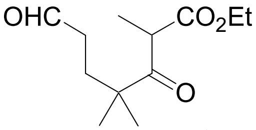
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H); 1.19 (s, 3H); 1.28 (t, *J*= 8 Hz, 3H); 1.60-1.79 (m, 6H); 3.58 (dd, *J*= 8, 12 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 14.27, 20.02, 25.41, 26.95, 36.23, 45.73, 53.77, 60.88, 173.26, 210.50. **FTIR** ($CDCl_3$) 2964, 2868, 1743, 1711, 1610, 1312, 838. **HR-EIMS** anal. calc. for $C_{11}H_{18}O$ $[M]^+$: 198.1256; anal. found: 198.1252.

Preparation of ethyl 2,4,4-trimethyl-3,7-dioxo-heptanoate (27)

Amounts:	250 mg	(1.2 mmol)	ethyl 2,4,4-dimethyl-3-oxo-hex-5-enoate (**13a**)
	4.0 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	20.0 mg	(10 mol %)	*p*-TsOH

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 90 °C, 20 h

Yield: 228 mg **27** (1.0 mmol, 86 %).



27

$C_{12}H_{20}O_4$
Mol. Wt.: 228,28

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H); 1.13 (t, *J* = 4 Hz, 3H); 1.23 (d, *J* = 8 Hz, 3H); 1.79 (dt, *J* = 2, 4 Hz, 2H); 2.30 (dt, *J* = 4, 8 Hz, 2H); 4.04 (q, *J* = 4 Hz, 2H); 9.67 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 14.8, 24.1, 30.7, 39.6, 46.3, 47.9, 61.3, 170.4, 201.6, 210.6. **FTIR** (neat): 2977, 2940, 1720, 1704, 1455, 1197, 1085. **HR-FABMS** anal. calc. for $C_{12}H_{21}O_4$ $[M + H]^+$: 229.1421, anal. found; 229.1419.

Alternate preparation of ethyl 2,4,4-trimethyl-3,7-dioxo-heptanoate (27)

Amounts:	250 mg	(1.2 mmol)	ethyl 2,4,4-dimethyl-3-oxo-hex-5-enoate (**13a**)
	4.0 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	20.0 mg	(10 mol %)	*p*-TsOH
	32.0 mg	(3.6 mol %)	BIPHEPHOS

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 60 °C, 20 h

Yield: 273 mg **27** (1.2 mmol, quantitative yield).

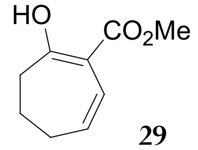
Preparation of methyl 2-hydroxy-cyclohepta-1,6-dienecarboxylate (29)

Amounts:	390 mg	(2.5 mmol)	methyl 3-oxo-hept-6-enoate (**16a**)
	8 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	20.0 mg	(5 mol %)	*p*-TsOH
	32 mg	(1.8 mol %)	XANTPHOS

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 20 bar CO/H_2 (1:1), 60 °C, 24-48 h

Yield: 210 mg **29** (1.3 mmol, 50 %) as a yellow oil needing no further purification.

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.55-1.84 (m, 4H); 2.20 (m, 2H); 2.53 (m, 2H); 3.70 (s, 3H); 5.23 (m, 1H); 5.85 (m, 1H); 12.17 (s, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 27.6, 28.2, 36.0, 52.5, 98.6, 128.4, 134.6, 170.9, 172.6.

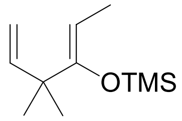


29

$C_9H_{12}O_3$
Mol. Wt.: 168,19

Preparation of (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-trimethylsilane (31)

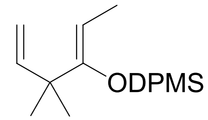
To a stirred prepared solution of LDA (4 mmol) under argon in THF at –78 °C was added 4,4-dimethyl-hex-5-en-3-one (**12**) (500 mg, 3.9 mmol) in 1 mL THF. This solution was stirred for 30 min before 0.56 mL TMSCl (4.4 mmol) was added via syringe. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring to RT. After stirring overnight, the solvent was removed and the residue was filtered through a small plug of neutral alumina with *n*-hexane to give (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-trimethylsilane (**31**) as a transparent light-yellow oil in 86 % (665 mg, 3.3 mmol). All spectral data matched that reported in the literature.



31

$C_{11}H_{22}OSi$
Mol. Wt.: 198,38

Preparation of (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-methyldiphenylsilane (32)



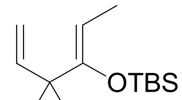
32

$C_{21}H_{26}OSi$
Mol. Wt.: 322,52

To a stirred prepared solution of LiHMDS (19.0 mmol) under argon in THF at –78 °C was added **4**,4-dimethyl-hex-5-en-3-one (**12**) (2.0 g, 16.0 mmol) in 1 mL THF. This solution was stirred for 30 min before 3.4 mL DPMSCl (16.0 mmol) was added via syringe. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring to RT. After stirring overnight, the solvent was removed and the residue was filtered through a small plug of neutral alumina with *n*-hexane to give (1-ethylidene-2,2-dimethyl-but-3-enyloxy)-methyldiphenylsilane (**32**) as a transparent light-yellow oil in 77 % (3.9 g, 12.3 mmol).

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.74 (s, 3H); 1.13 (s, 6H); 1.39 (d, *J* = 8 Hz, 3H); 4.68 (q, *J* = 8 Hz, 1H); 4.95 (dd, *J* = 1.2, 10 Hz, 2H); 5.86 (dd, *J* = 10, 17.5 Hz, 1H); 7.37 (m, 6H); 7.60 (m, 4H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ -2.5, 12.3, 25.8, 42.9, 100.1, 111.6, 127.8, 129.7, 134.4, 137.5, 146.2, 156.9.

Preparation of *t*-butyl-(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-dimethylsilane (33)



33

$C_{14}H_{28}OSi$
Mol. Wt.: 240,46

To a stirred prepared solution of LDA (8.0 mmol) under argon in THF at –78 °C was added **4**,4-dimethyl-hex-5-en-3-one (**12**) (500 mg, 4.0 mmol) in 1 mL THF. This solution was stirred for 30 min before HMPA (2 mL) and TBSCl (4.1 mmol) were added. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring to RT. After stirring an additional 2 h, the solvent was removed and the residue was filtered through a small plug of neutral alumina with *n*-hexane to give *t*-butyl-(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-dimethylsilane (**33**) as a transparent light-yellow oil in 38 % (376 mg, 1.5 mmol).

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ -0.15 (s, 6H); 0.96 (s, 9H); 1.14 (s, 6H); 1.52 (d, *J* = 8 Hz, 3H); 4.60 (q, *J* = 8 Hz, 1H); 4.95 (dd, *J* = 20, 24 Hz, 2H); 5.89 (dd, *J* = 12, 20 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ -2.81, 11.76, 19.11, 26.08, 26.44, 42.89, 98.94, 111.00, 146.88, 156.73. **FTIR** (neat): 2960, 2930, 2858, 1662, 1472, 1320, 1076, 837. **HR-EIMS** anal. calc. for $C_{14}H_{28}OSi$ $[M]^+$: 240.1909; anal. found: 240.1900.

Preparation of 5-(trimethylsilanyloxy)-2,2,6-trimethylcyclohexanone (34)

Amounts:	230 mg	(1.1 mmol)	(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-trimethylsilane (**31**)
	3 mg	(0.9 mol %)	$Rh(CO)_2(acac)$

Procedure: Procedure **C**; using 10 mL CH_2Cl_2, 40 bar CO/H_2 (1:1), 80 °C, 24 h

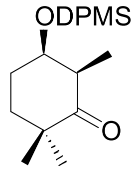
Yield: **34** was obtained as a 1:1.2:2.5 mixture with **23** and **25** as identified by NMR.

Preparation of 2,2,6-trimethyl-5-(methyl-diphenylsilanyloxy)-cyclohexanone (35)

Amounts:	190 mg	(0.59 mmol)	(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-methyldiphenylsilane (**32**)
	3.0 mg	(2.0 mol %)	$Rh(CO)_2(acac)$

Procedure: Procedure **C**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 90 °C, 24 h

Yield: 147 mg **35** (0.42 mmol, 72 %) as a 2.1:1 mixture of *cis-:trans-* diastereoisomers.



(±)-**35**

$C_{22}H_{28}O_2Si$
Mol. Wt.: 352,54

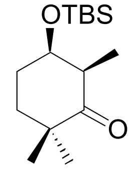
cis-diastereoisomer: ^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.76 (s, 3H); 1.12 (s, 6H); 1.10 (d, *J* = 3 Hz, 3H); 1.19 (s, 3H); 1.20 (s, 3H); 1.72-1.84 (m, 2H); 1.95-2.04 (m, 2H); 2.81 (dq, *J* = 3, 6 Hz, 1H); 3.33 (dt, *J* = 6, 10 Hz, 1H); 7.37 (m, 6H); 7.60 (m, 4H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 1.1, 13.9, 25.4, 26.2, 29.0, 34.8, 45.5, 49.5, 75.2, 127.9, 128.0, 129.8, 129.9, 134.5, 136.4.

Preparation of 5-(*t*-butyl-dimethylsilanyloxy)-2,2,6-trimethylcyclohexanone (36)

Amounts:	100 mg	(0.42 mmol)	*tert*-butyl-(1-ethylidene-2,2-dimethyl-but-3-enyloxy)-dimethylsilane
	3.0 mg	(0.9 mol %)	Rh(CO)$_2$(acac)

Procedure: Procedure **C**; using 10 mL CH$_2$Cl$_2$, 40 bar CO/H$_2$ (1:1), 80 °C, 24 h

Yield: 66.0 mg **36** (0.24 mmol, 59 %) as a 4:1 mixture of diastereoisomers.



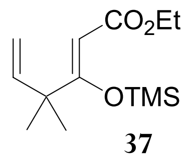
(±)-**36**

$C_{15}H_{30}O_2Si$
Mol. Wt.: 270,48

cis-diastereoisomer: ^{1}**H-NMR** (500 MHz, CDCl$_3$) δ 0.05 (s, 6H); 0.89 (s, 9H); 1.05 (d, *J* = 4 Hz, 3H); 1.13 (s, 3H); 1.18 (s, 3H); 1.74-1.81 (m, 2H); 1.98-2.08 (m, 2H); 2.78 (dq, *J* = 3, 5 Hz, 1H); 3.45 (dt, *J* = 3, 7 Hz, 1H). ^{13}**C-NMR** (125 MHz, CDCl$_3$) δ 0.97, 11.31, 16.42, 23.02, 24.28, 25.30, 25.75, 26.46, 27.29, 27.61, 27.76, 32.08, 51.22, 81.43, 212.72. **FTIR** (CDCl$_3$): 2977, 2932, 2872, 1712, 1383, 1111, 909, 734. **HR-FABMS** anal. calc. for $C_{15}H_{30}O_2Si$ $[M + H]^+$: 270.2015; anal. found: 270.2020.

Preparation of ethyl 4,4-dimethyl-3-trimethylsilanyloxy-hexa-2,5-dienoate (37)

To a stirred prepared solution of LDA (60.0 mmol) under argon in THF at –78 °C was added ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (9.2 g, 50.0 mmol) in 2 mL THF. This solution was stirred for 1 h before TMSCl (11 mL, 87.0 mmol) was added. After 10 min the cooling bath was removed and the reaction was allowed to warm with stirring overnight to RT. The solvent was removed and the residue was taken up in hexanes and filtered through alumina to give **37** (10.2 g, 40 mmol) as a yellow oil in 80 %.



37

$C_{13}H_{24}O_3Si$
Mol. Wt.: 256,41

^{1}**H-NMR** (400 MHz, CDCl$_3$) δ 0.25 (s, 9H); 1.17 (s, 6H); 1.22 (t, *J* = 8 Hz, 3H); 4.08 (q, *J* = 8 Hz, 2H); 5.05 (dd, *J* = 8, 16 Hz, 2H); 5.21 (s, 1H); 5.85 (dd, *J* = 8, 16 Hz, 1H). ^{13}**C-NMR** (100 MHz, CDCl$_3$) δ 1.16, 14.39, 25.10, 44.39, 59.01, 96.59, 112.79, 144.25, 166.11, 173.23. **FTIR** (neat): 2972, 1717, 1617, 1250, 1175, 846. **HR-EIMS** anal. calc. for $C_{13}H_{24}O_3Si$: 256.1495; anal. found: 256.1482.

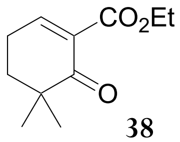
Preparation of ethyl 5,5-dimethyl-6-oxo-cyclohex-1-enecarboxylate (38)

Amounts:	500 mg	(2.1 mmol)	ethyl 4,4-dimethyl-3-trimethylsilanyloxy-hexa-2,5-dienoate (**13**)
	10.0 mg	(1.0 mol %)	$[Rh(cod)Cl]_2$

Procedure: Procedure **C**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 24 h

Yield: 365 mg **38** (2.0 mmol, 97 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 6H); 1.26 (t, *J* = 7.5 Hz, 3H); 1.82 (t, *J* = 5 Hz, 2H); 2.47 (dt, *J* = 5, 7.5 Hz, 2H); 4.19 (q, *J* = 7.5 Hz, 2H); 7.48 (t, *J* = 7.5 Hz, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 15.6, 24.7, 24.9, 25.2, 37.0, 43.3, 62.5, 133.2, 155.1, 166.7, 201.5. **FTIR** (neat): 2995, 2898, 1750, 1360, 1040. **HR-FABMS** anal. calc. for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1178; anal. found: 197.1205.



38

$C_{11}H_{16}O_3$
Mol. Wt.: 196,24

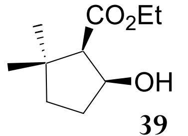
Preparation of ethyl 5-hydroxy-2,2-dimethyl-cyclopentanecarboxylate (39)

Amounts:	200 mg	(1.28 mmol)	ethyl 3,3-dimethyl-pent-4-enoate (**19**)
	6 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	1.28 mL	(1.28 mmol)	$(cy\text{-hex})_2BCl$
	0.28 mL	(1.28 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 18 h

Yield: 186 mg **39** (1.0 mmol, 82 %) as a single diastereoisomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 2H); 1.85 (m, 1H); 2.05 (m, 1H); 2.27 (m, 2H); 3.64 (s, 3H); 3.66 (s, 3H); 4.53 (t, *J* = 5 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 20.0, 30.8, 32.6, 48.9, 52.5, 64.7, 77.2, 169.3, 171.0. **FTIR** (neat): 3501 (broad), 2952, 2856, 1731,



39

$C_{10}H_{18}O_3$
Mol. Wt.: 186,25

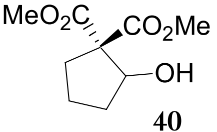
1436, 1274, 1091. **HR-FABMS** anal. calc. for $C_{10}H_{18}O_3$ $[M]^+$: 186.1256; anal. found: 186.1262.

Preparation of dimethyl 2-hydroxy-cyclopentane-1,1-dicarboxylate (40)

Amounts:	500 mg	(2.90 mmol)	dimethyl allylmalonate
	6.0 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	24.0 mg	(1.8 mol %)	XANTPHOS
	3.04 mL	(3.04 mmol)	(*cy*-hex)$_2$BCl
	0.42 mL	(3.04 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 18 h

Yield: 294 mg **40** (1.45 mmol, 51 %).



40

$C_9H_{14}O_5$
Mol. Wt.: 202,20

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.64 (m, 2H); 1.85 (m, 1H); 2.05 (m, 1H); 2.27 (m, 2H); 3.64 (s, 3H); 3.66 (s, 3H); 4.53 (t, *J* = 5 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 20.0, 30.8, 32.6, 48.9, 52.5, 64.7, 77.2, 169.3, 171.0. **FTIR** (neat): 3501 (broad), 2952, 2856, 1731, 1436, 1274, 1091. **HR-FABMS** anal. calc. for $C_9H_{15}O_5$ $[M + H]^+$: 203.0920; anal. found: 203.0910.

Alternate preparation of methyl 2-hydroxy-cyclohepta-1,6-dienecarboxylate (29)

Amounts:	188 mg	(1.2 mmol)	methyl 3-oxo-hept-6-enoate (**16a**)
	3 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	12 mg	(1.8 mol %)	XANTPHOS
	1.2 mL	(1.2 mmol)	(*cy*-hex)$_2$BCl
	0.17 mL	(1.2 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 80 bar CO/H_2 (1:1), 90 °C, 18 h

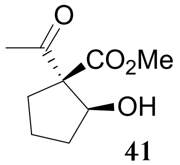
Yield: 165 mg **29** (0.9 mmol, 82 %) as a yellow oil needing no further purification.

Preparation of methyl 1-acetyl-2-hydroxy-cyclopentanecarboxylate (41)

Amounts:	250 mg	(1.60 mmol)	methyl 2-acetyl-pent-4-enoate
	4.0 mg	(0.9 mol %)	Rh(CO)$_2$(acac)
	16.0 mg	(1.8 mol %)	XANTPHOS
	1.68 mL	(1.68 mmol)	(*cy*-hex)$_2$BCl
	0.23 mL	(1.68 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 18 h

Yield: 150 mg **41** (0.80 mmol, 50 %) as a 1.6:1 mixture of volatile diastereoisomers.



41

$C_9H_{14}O_4$
Mol. Wt.: 186,21

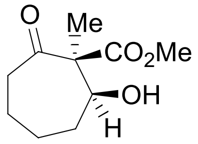
^{1}**H-NMR** (400 MHz, $CDCl_3$) *Major diastereoisomer:* δ 1.45-1.92 (m, 4H); 2.02 (m, 2H); 2.15 (s, 3H); 3.69 (s, 3H) 4.65 (t, *J* = 8 Hz, 1H). *Minor diastereoisomer:* δ 2.13 (s, 3H); 3.72 (s, 3H); 4.51 (t, *J* = 6 Hz, 1H). ^{13}**C-NMR** (100 MHz, CDCl3) *Major diastereoisomer:* δ 24.0, 25.3, 28.5, 38.3, 52.5, 66.5, 76.3, 173.6, 200.2. *Minor diastereoisomer:* δ 26.2, 52.7, 77.4. **FTIR** (neat): 3411 (broad), 2933, 2856, 1720, 1711, 1258, 1063, 733. **HR-FABMS** anal. calc. for $C_9H_{15}O_4$ [M + H]$^+$: 187.0970; anal. found: 187.0950.

Preparation of methyl 2-hydroxy-1-methyl-7-oxo-cycloheptanecarboxylate (42)

Amounts:	232 mg	(1.37 mmol)	methyl 2-methyl-3-oxo-hept-6-enoate
	3 mg	(0.9 mol %)	Rh(CO)$_2$(acac)
	15 mg	(1.8 mol %)	XANTPHOS
	1.43 mL	(1.43 mmol)	(*cy*-hex)$_2$BCl
	0.20 mL	(1.43 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 18 h

Yield: 243 mg **42** (1.2 mmol, 89 %) as a 6:1 mixture of diastereoisomers.



42

$C_{10}H_{16}O_4$
Mol. Wt.: 200,23

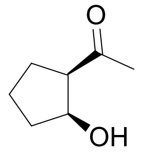
^{1}**H-NMR** (400 MHz, $CDCl_3$) *Major diastereoisomer:* δ 1.35 (s, 3H); 1.80 (dt, *J* = 4, 12 Hz, 2H); 2.49 (m, 4H); 2.55 (dt, *J* = 4, 12 Hz, 2H); 3.69 (s, 3H); 4.15 (m, 1H). *Minor diastereoisomer:* δ 1.47 (s, 3H); 3.71 (s, 3H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) *Major diastereoisomer:* δ 17.6, 25.4, 27.6, 35.4, 39.5, 52.5, 61.2, 78.9, 172.8, 207.1. *Minor diastereoisomer:* δ 17.8, 52.6. **FTIR** ($CDCl_3$): 3500 (broad), 2935, 1712, 1453, 1255, 910, 733. **HR-FABMS** anal. calc. for $C_{10}H_{17}O_4$ $[M + H]^+$: 201.1127; anal. found: 201.1112.

Preparation of 1-(2-hydroxy-cyclopentyl)-ethanone (44)

Amounts:	196 mg	(2.0 mmol)	hex-5-en-2-one (**43**)
	5 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	20 mg	(1.8 mol %)	XANTPHOS
	2.0 mL	(2.0 mmol)	(*cy*-hex)$_2$BCl
	0.27 mL	(2.0 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 80 bar CO/H_2 (1:1), 90 °C, 18 h

Yield: 223 mg **44** (1.76 mmol, 87 %) as a 2:1 mixture of diastereoisomers.



(±)-**44**

$C_7H_{12}O_2$
Mol. Wt.: 128,17

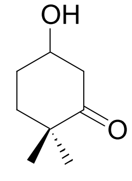
Major diastereoisomer: ^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.35-1.62 (m, 6H); 2.08 (s, 3H); 2.4 (m, 1H); 3.72 (dt, *J* = 2, 6.4 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 23.7, 24.8, 30.0, 31.7, 45.6, 70.3, 209.1. *Minor diastereoisomer:* ^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.35-1.62 (m, 6H); 2.10 (s, 3H); 2.4 (m, 1H); 3.83 (t, *J* = 6.4 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 23.7, 24.8, 30.0, 31.7, 45.6, 71.3, 209.3. **FTIR** (neat): 3408 (broad), 2925, 2867, 1710, 1244, 1063. **HR-FABMS** anal. calc. for $C_9H_{15}O_4$ $[M + H]^+$: 187.0970; anal. found: 187.0950.

Preparation of 5-hydroxy-2,2-dimethyl-cyclohexanone (45)

Amounts:	200 mg	(1.80 mmol)	3,3-dimethyl-pent-4-en-2-one (**11**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	1.89 mL	(1.89 mmol)	(*cy*-hex)$_2$BCl
	0.26 mL	(1.89 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 90 °C, 16 h

Yield: 148 mg **45** (1.04 mmol, 58 %) as a light-yellow oil.



(±)-**45**
$C_8H_{14}O_2$
Mol. Wt.: 142,20

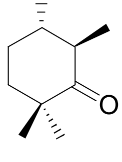
^{1}**H-NMR** (500 MHz, $CDCl_3$) δ 1.24 (s, 3H); 1.56 (s, 3H); 1.69 (m, 4H); 2.10 (d, *J* = 5 Hz, 2H); 3.58 (m, 1H). ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ 24.0, 24.1, 25.3, 26.5, 36.6, 47.2, 70.2, 214.4. **FTIR** ($CDCl_3$): 3466 (broad), 2933, 1702, 1451, 1097, 909. **Anal. calc.** for $C_8H_{14}O_2$: C, 67.6; H, 9.9; anal. found: C, 67.8; H, 10.1.

Preparation of 5-hydroxy-2,2,6-trimethylcyclohexanone (46)

Amounts:	202 mg	(1.60 mmol)	4,4-dimethyl-hex-5-en-3-one (**12**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	1.68 mL	(1.68 mmol)	(*cy*-hex)$_2$BCl
	0.23 mL	(1.68 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 90 °C, 16 h

Yield: 215 mg **46** (1.37 mmol, 86 %) as a 20:1 mixture of diastereoisomers.



(±)-**46**
$C_9H_{16}O_2$
Mol. Wt.: 156,22

^{1}**H-NMR** (500 MHz, $CDCl_3$) δ 1.07 (d, *J* = 8 Hz, 3H); 1.18-1.27 (m, 6H); 1.53 (m, 2H); 1.85 (m, 2H); 2.45 (dq, *J* = 3.5, 8 Hz, 1H); 3.57 (m, 1H). ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ 8.0, 24.0, 24.2, 24.4, 29.9, 43.7, 46.0, 70.3, 216.7. **FTIR** (neat): 3399 (broad), 2934, 1704, 1452, 1100, 972. **ESI-MS** $[M + H]^+$: 157.1. **HR-FABMS** anal. calc. for $C_9H_{17}O_2$

$[M + H]^+$: 157.1229; anal. found: 157.1220

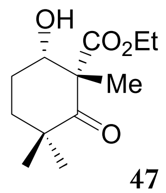
Preparation of ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexanecarboxylate (47)

Amounts:			
	50 mg	(0.25 mmol)	ethyl 2,4,4-trimethyl-3-oxo-hex-5-enoate (**13a**)
	0.6 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	3 mg	(1.8 mol %)	XANTPHOS
	0.26 mL	(0.26 mmol)	(*cy*-hex)$_2$BCl
	0.036 mL	(0.26 mmol)	triethylamine

Procedure: Procedure **D**; using 5 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 18 h

Yield: 47 mg **47** (0.205 mmol, 82 %) as a 2.5:1 mixture of diastereoisomers.

^{1}**H-NMR** (400 MHz, $CDCl_3$) *Major diastereoisomer:* δ 1.14 (m, 3H); 1.20 (t, J = 8 Hz, 3H); 1.24 (m, 3H,); 1.27 (s, 3H); 1.61-1.69 (m, 3H); 1.87 (m, 1H); 3.58 (t, J = 6 Hz, 1H); 4.10 (q, J = 8 Hz, 2H). *Minor diastereoisomer:* δ 1.29 (s, 3H); 3.95 (q, J = 8 Hz, 2H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) *Major diastereoisomer:* δ 13.9, 14.8, 24.02, 24.05, 25.4, 27.7, 48.4, 61.1, 62.8, 70.3, 170.6, 211.3. *Minor diastereoisomer:* δ 14.7, 61.3, 170.5. **FTIR** (neat): 3364 (broad), 2932, 2856, 1758, 1685, 1239, 1023. **HR-FABMS** anal. calc. for $C_{12}H_{19}O_4$ $[M - H]^+$: 227.1283; anal. found: 227.1259



47

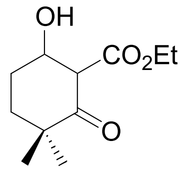
$C_{12}H_{20}O_4$
Mol. Wt.: 228,28

Preparation of ethyl 6-hydroxy-3,3-dimethyl-2-oxo-cyclohexanecarboxylate (48)

Amounts:			
	200 mg	(1.08 mmol)	ethyl 4,4-dimethyl-3-oxo-hex-5-enoate (**13**)
	4 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	1.13 mL	(1.13 mmol)	(*cy*-hex)$_2$BCl
	0.16 mL	(1.13 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 20 h

Yield: 211 mg **48** (0.98 mmol, 91 %) as a 1:1 mixture of diastereoisomers in a 1.35:1 ratio with **26**.



48

$C_{11}H_{18}O_4$
Mol. Wt.: 214,26

Diastereoisomer 1: **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 1.19 (t, *J* = 8 Hz, 3H); 1.26 (m, 3H); 1.46 (m, 3H); 1.52 (m, 2H); 1.81 (m, 2H); 3.53 (m, 2H); 4.12 (q, *J* = 8 Hz, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 14.0, 24.0, 24.7, 25.0, 28.0, 45.8, 53.7, 60.7, 70.1, 173.1, 200.1. *Diastereoisomer 2:* **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 13.9, 60.0, 176.9. **FTIR** (neat): 3400 (broad), 2932, 2856, 1731, 1650, 1610, 1454, 1254, 1030, 827. **ESI-MS** *m/z* 214.1 $[M]^+$; *2m/z* 429.1 $[M + H]^+$.

Attempted enolboration/hydroformylation/aldol addition of 18b

Amounts:	309 mg	(1.05 mmol)	(–)-menthyl 2-methyl-3-oxo-hept-6-enoate (**18b**)
	3 mg	(0.9 mol %)	$Rh(CO)_2(acac)$
	12 mg	(1.8 mol %)	XANTPHOS
	1.05 mL	(1.05 mmol)	(*cy*-hex)$_2$BCl
	0.15 mL	(1.05 mmol)	triethylamine

Procedure: Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 20 h

Yield: Starting material **18b** was recovered quantitatively.

Hydroformylation of 18b in the presence of $ZnBr_2$

Amounts:	107 mg	(0.36 mmol)	(–)-menthyl 2-methyl-3-oxo-hept-6-enoate (**18b**)
	2 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	8 mg	(1.8 mol %)	XANTPHOS
	8 mg	(10 mol %)	$ZnBr_2$

Procedure: Procedure **A**; using 10 mL CH_2Cl_2, 40 bar CO/H_2 (1:1), 70 °C, 3 d

Yield:	An intractable mixture of decomposition products was obtained upon filtration.

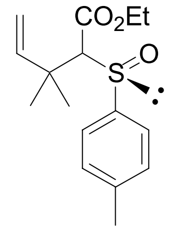
Attempted enolboration/hydroformylation/aldol addition of 18c

Amounts:	309 mg	(1.05 mmol)	(–)-menthyl 2-acetyl-pent-4-enoate (**18c**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	16 mg	(1.8 mol %)	XANTPHOS
	1.05 mL	(1.05 mmol)	$(cy\text{-hex})_2BCl$
	0.15 mL	(1.05 mmol)	triethylamine

Procedure:	Procedure **D**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 80 °C, 20 h
Yield:	Starting material **18c** was recovered quantitatively.

Preparation of (–)-ethyl 3,3-dimethyl-2-(toluene-4-sulfinyl)-pent-4-enoate (50)

To a stirred solution of **19** (4 g, 26 mmol) in 5 mL THF under argon at –78 °C was added *i*-Pr_2MgBr (26 mmol). The solution was stirred for 1 h at this temperature before **49** (6.25 g, 26 mmol) was added at once. The reaction was stirred overnight at – 40 °C. After this time the cooling bath was removed and the reaction was allowed to warm with stirring to RT, After which the solvent was removed and the residue was filtered through a small plug of neutral alumina with Et_2O to give **50** in < 5 % yield as a mixture with recovered starting material and **49** which could not be separated.



$C_{16}H_{22}O_3S$
Mol. Wt.: 294,41

Hydroformylation of 11 in the presence of L-proline

Amounts:	200 mg	(1.8 mmol)	3,3-dimethyl-pent-4-en-2-one (**11**)
	4 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	21 mg/42 mg	(10/20 mol %)	L-proline

Procedure:	Procedure **A**; using 10 mL $CHCl_3$, 40 bar CO/H_2 (1:1), 80 °C, 3 d Procedure **A**; using 10 mL dioxane, 40 bar CO/H_2 (1:1), 80 °C, 3 d

Procedure **A**; using 10 mL DMSO, 40 bar CO/H_2 (1:1), 80 °C, 3 d

Yield: Aldehyde **24** was obtained in quantitative yield from all attempts.

Hydroformylation of 12 in the presence of L-proline

Amounts:	200 mg	(1.6 mmol)	4,4-dimethyl-hex-5-en-3-one (**12**)
	3 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	9 mg/18 mg	(5/10 mol %)	L-proline

Procedure: Procedure **A**; using 10 mL $CHCl_3$, 40 bar CO/H_2 (1:1), 50 °C, 3 d
Procedure **A**; using 10 mL dioxane, 40 bar CO/H_2 (1:1), 80 °C, 3 d
Procedure **A**; using 10 mL DMSO, 40 bar CO/H_2 (1:1), 80 °C, 3 d

Yield: Aldehyde **25** was obtained in quantitative yield from all attempts.

Stepwise conversion of 25 in the presence of L-proline

Ketoaldehyde **25** (249 mg, 1.6 mmol) was dissolved in 5 mL DMSO or $CHCl_3$ and stirred at RT as L-proline (10/20/30 mol %) was added to the reaction mixture. The reaction was allowed to stir for as little as 1 d up to 7 d before being washed with H_2O (1 x 25 mL), extracted with Et_2O (1 x 50 mL), dried and concentrated to give recovered **25** in quantitative yield.

Hydroformylation of hex-5-en-2-one (43) in the presence of L-proline

Amounts:	196 mg	(2.0 mmol)	hex-5-en-2-one (**43**)
	6 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	46 mg	(20 mol %)	L-proline

Procedure: Procedure **A**; using 10 mL $CHCl_3$, 40 bar CO/H_2 (1:1), 70 °C, 1 d
Procedure **A**; using 10 mL $CHCl_3$, 40 bar CO/H_2 (1:1), 70 °C, 3 d

Yield: An intractable mixture of products was obtained in all attempts.

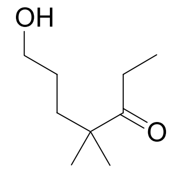
Preparation of 7-hydroxy-4,4-dimethyl-heptan-3-one (51)

Amounts:	189 mg	(1.5 mmol)	4,4-dimethyl-hex-5-en-3-one (**12**)
	3 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	490 mg	(1.5 mmol)	(+)-DIP-Cl
	0.21 mL	(1.5 mmol)	triethylamine

Procedure: Procedure **E**; using 10 mL CH_2Cl_2, 40 bar CO/H_2 (1:1), 90 °C, 18 h

Yield: 221 mg (1.4 mmol, 96 %) as a light yellow oil that was purified by silica gel chromatography ($R_f = 0.2$, 20 % Et_2O/hexanes).

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.98 (t, J = 8 Hz, 3H); 1.06 (s, 3H); 1.08 (s, 3H); 1.69 (m, 2H); 1.88 (m, 2H); 2.31 (q, J = 8 Hz, 2H); 3.54 (t, J = 4 Hz, 2H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 20.6, 27.6, 34.2, 38.8, 41.6, 62.7, 216.7.



51

$C_9H_{18}O_2$
Mol. Wt.: 158,24

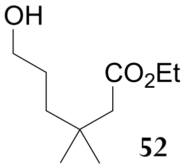
Preparation of ethyl 6-hydroxy-3,3-dimethyl-hexanoate (52)

Amounts:	300 mg	(1.9 mmol)	**19**
	3 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	641 mg	(2.0 mmol)	(+)-DIP-Cl
	0.28 mL	(2.0 mmol)	triethylamine

Procedure: Procedure **E**; using 10 mL CH_2Cl_2, 40 bar CO/H_2 (1:1), 90 °C, 18 h

Yield: 357 mg (1.9 mmol, quantitative yield) as a light yellow oil that was purified by silica gel chromatography ($R_f = 0.2$, 20 % Et_2O/hexanes).

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.04 (s, 3H); 1.05 (s, 3H); 1.17 (t, J = 8 Hz, 3H); 1.71 (m, 2H); 1.85 (m, 2H); 2.12 (s, 2H); 3.54 (t, J = 4 Hz, 2H); 4.03 (q, J = 8 Hz, 2H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 14.1, 27.1, 27.3, 27.5, 34.2, 37.8, 38.7, 45.8, 60.0, 63.2, 172.6.



52

$C_{10}H_{20}O_3$
Mol. Wt.: 188,26

Attempted 1,4-addition of 12 to 1-acetyl-1-cyclohexene (53) mediated by sodium methoxide

Amounts:	1.1 g	(8.8 mmol)	**12**
	1.2 g	(9.7 mol)	1-acetyl-1-cyclohexene (**53**)
	570 mg	(19.4 mmol)	NaOMe

Procedure: To the stirring solution of **12** and **53** in 15 mL MeOH was added NaOMe, and the reaction mixture was allowed to stir for 24 h under reflux. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of 12 to 1-acetyl-1-cyclohexene (53) mediated by LiHMDS

Amounts:	1.1 g	(8.8 mmol)	**12**
	1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
	2.0 mL	(9.7 mmol)	HMDS

Procedure: To the stirring solution of HMDS in dry THF at –78 °C was added 9.7 mmol *n*-BuLi (4.2 mL/2.5 M solution in hexane) and the reaction was allowed to stir for 30 min before **12** was added in 5 mL THF and the reaction mixture was stirred for 1 h. After this time, **53** was added via syringe and the reaction was allowed to stir overnight, warming to RT. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of 12 to 1-acetyl-1-cyclohexene (53) mediated by LDA/CuCN

Amounts:	1.1 g	(8.8 mmol)	**12**
	1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
	783 mg	(8.8 mmol)	CuCN

Procedure: To the stirring solution of LDA in dry THF at –78 °C was added **12** in 5 mL THF and the reaction mixture was stirred for 1 h. After this time, CuCN was added and the mixture assumed a dark-brown color and was stirred for 15 min before **53** was added via syringe and the reaction was allowed to stir overnight, warming to RT. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted Mukaiyama 1,4-addition of 31 to 1-acetyl-1-cyclohexene (53) mediated by $TiCl_4/Ti(Oi\text{-}Pr)_4$

Amounts:			
	1.7 g	(8.8 mmol)	**31**
	1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
	1.8 g	(9.7 mmol)	$TiCl_4$

Procedure: To a stirring solution of **53** in 10 mL dry THF at –78 °C was added via syringe $TiCl_4$ and the reaction was allowed to stir for 10 min before enolsilane **31** was added and stirred for an additional 30 min at –78 °C and then allowed to warm to RT overnight. Upon workup with $NaHCO_3$ (1 x 25 mL), extraction with Et_2O (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of ethyl cyanoacetate (ECA) to 1-acetyl-1-cyclohexene (53) mediated by sodium methoxide

Amounts:			
	1.0 g	(8.8 mmol)	ethyl cyanoacetate (**ECA**)
	1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
	570 mg	(19.4 mmol)	NaOMe

Procedure: To a stirring solution of **ECA** in abs. MeOH was added NaOMe and the reaction mixture was stirred for 1 h. After this time, **53** was added via syringe and the reaction was allowed to stir overnight at reflux. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of ethyl cyanoacetate (ECA) to 1-acetyl-1-cyclohexene (53) mediated by sodium amide

Amounts:

1.0 g	(8.8 mmol)	ethyl cyanoacetate (**ECA**)
1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
755 mg	(19.4 mmol)	$NaNH_2$

Procedure: To a stirring solution of **ECA** and **53** in 10 mL benzene was added solid $NaNH_2$ and the reaction was allowed to stir at reflux for 1 d. Upon workup with $NaHCO_3$ (1 x 25 mL), extraction with Et_2O (1 x 25 mL) and drying over $MgSO_4$ no conversion was observed, and starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of ethyl cyanoacetate (ECA) to 1-acetyl-1-cyclohexene (53) mediated by LiHMDS

Amounts:

1.0 g	(8.8 mmol)	ethyl cyanoacetate (**ECA**)
1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
2.0 mL	(9.7 mmol)	HMDS

Procedure: To the stirring solution of HMDS in dry THF at –78 °C was added 9.7 mmol *n*-BuLi (4.2 mL/2.5 M solution in hexane) and the reaction was allowed to stir for 30 min before **ECA** was added and the reaction mixture was stirred for 30 min. After this time, enone **53** was added via syringe and the reaction was allowed to stir overnight, warming to RT. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$ no conversion was observed, and starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of ethyl cyanoacetate (ECA) to 1-acetyl-1-cyclohexene (53) mediated by pyrimidine

Amounts:

1.0 g	(8.8 mmol)	ethyl cyanoacetate (**ECA**)
1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
2.6 mL	(26.4 mmol)	pyrimidine

Procedure: To a stirring solution of **ECA** and **53** was added pyrimidine via syringe and the neat reaction mixture was allowed to stir 5 d at reflux. Upon extraction with Et_2O (1 x 25 mL), washing with $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

Attempted 1,4-addition of ethyl cyanoacetate (ECA) to 1-acetyl-1-cyclohexene (53) mediated by Al_2O_3

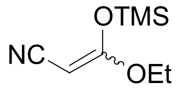
Amounts:

0.8 mL	(1.0 mmol)	ethyl cyanoacetate (**ECA**)
0.1 mL	(1.0 mmol)	1-acetyl-1-cyclohexene (**53**)
1.0 g	(26.4 mmol)	Al_2O_3

Procedure: A mixture of **ECA** and **53** was absorbed onto Al2O3 and the mixture was allowed to sit for up to 7 d, with aliquots periodically being removed, washed with Et_2O, evaporated and analyzed by GC. No conversion was observed, and starting material **53** was recovered in a quantitative yield.

Yield: 124 mg **53** (1.0 mmol, quantitative yield).

Preparation of 3-ethoxy-3-trimethylsilanyloxy-acrylonitrile (55) from ECA[108]



55
$C_8H_{15}NO_2Si$
Mol. Wt.: 185,30

To a stirring solution of 18.6 mL (88 mmol) HMDS in 50 mL dry THF at –78 °C was added 88.0 mmol *n*-BuLi (35.2 mL/2.5 M solution in hexanes) and the mixture was allowed to stir for 10 min before being warmed to 0 °C and stirred for another 45 min. The reaction mixture was cooled again to –78 °C before 5.0 g (44.0 mmol) **ECA** was added via syringe. The deprotonation was allowed to proceed for 1 h before 6.5 mL (5.3 mmol) TMSCl was added at once and the reaction mixture was warmed slowly to RT while stirring overnight. Upon quenching with sat. aq. NH_4Cl (1 x 100 mL), extraction with Et_2O (1 x 25 mL), washing with sat. aq. $NaHCO_3$ (1 x 25 mL) and drying over $MgSO_4$, 6.9 g (37.4 mmol) **55** was isolated as a light-yellow oil needing no further purification in 85 % yield. All spectra matched the data reported in the literature.

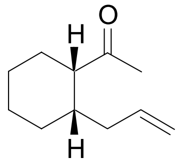
Attempted Mukaiyama 1,4-addition of 55 to 1-acetyl-1-cyclohexene (53) mediated by $TiCl_4$

Amounts:	1.6 g	(8.8 mmol)	**55**
	1.2 g	(9.7 mmol)	1-acetyl-1-cyclohexene (**53**)
	1.8 g	(9.7 mmol)	$TiCl_4$

Procedure: To a stirring solution of **53** in 10 mL dry THF at –78 °C was added via syringe $TiCl_4$ and the reaction was allowed to stir for 10 min before **55** was added and stirred for an additional 30 min at –78 °C and then allowed to warm to RT overnight. Upon workup with $NaHCO_3$ (1 x 25 mL), extraction with Et_2O (1 x 25 mL) and drying over $MgSO_4$, starting material **53** was recovered in a quantitative yield.

Yield: 1.2 g **53** (9.7 mmol, quantitative yield).

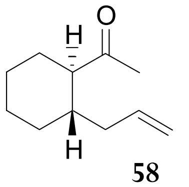
Preparation of *cis*-1-acetyl-2(2-propenyl)cyclohexane (57)



57
$C_{11}H_{18}O$
Mol. Wt.: 166,26

A solution of 3.35 g (27.0 mmol)1-acetyl-1-cyclohexene in CH_2Cl_2 (75 mL) was cooled to – 78 °C before 6.0 g (32.0 mmol) $TiCl_4$ was added via syringe. Stirring was maintained as a yellow precipitate formed, and after an additional 5 min 4.6 g (40.0 mmol) allyl trimethylsilane was added in 40 mL CH_2Cl_2. The deep-violet solution was stirred for 40 min before 50 mL H_2O was added, and the mixture was allowed to warm to RT. The aqueous layer was separated washed with Et_2O (1 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by Kugelrohr distillation (50 °C @ 0.3 mbar) to afford 1-acetyl-2(2-propenyl)cyclohexane (**57**) as an approximately 6:1 mixture of *cis-:trans-*isomers. All spectroscopic data matched that reported in the literature.

Preparation of *trans*-1-acetyl-2(2-propenyl)cyclohexane (58)

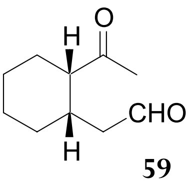


58

$C_{11}H_{18}O$
Mol. Wt.: 166,26

A solution of 500 mg NaOMe in 15 mL MeOH was stirred at RT as 1.14 g *cis*-1-acetyl-2(2-propenyl)cyclohexane was added. The mixture was stirred for 3 d before being heated under reflux for another 24 h. After cooling to RT, mixture was extracted with Et_2O and washed with 20 mL H_2O. The organic layer was dried over $MgSO_4$ and concentrated to afford 1-acetyl-2(2-propenyl)cyclohexane (**58**) as an approximately 8:1 mixture of *trans-:cis-*isomers. All spectroscopic data matched that reported in the literature.

Preparation of *cis*-(2-acetyl-cyclohexyl)-acetaldehyde (59)

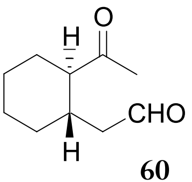


59

$C_{10}H_{16}O_2$
Mol. Wt.: 168,23

O_3 was bubbled through a -78 °C solution of 1.8 g (10.8 mmol) *cis*-1-acetyl-2(2-propenyl)cyclohexane in CH_2Cl_2/MeOH (5:1, 42 mL) containing a catalytic amount of $NaHCO_3$ (~ 30 mg) until a blue color persisted, indicating an excess of O_3 in solution. The solution was now flushed with argon until the blue color disappeared, upon which PBu_3 (3.2 g, 16.0 mmol) was added slowly by syringe. The mixture was allowed to warm to RT and stirred for another 2 h. The volatiles were removed in vacuum and the residue was chromatographed (3:1 EtOAc/hexane) to give 1.8 g (10.8 mmol, quantitative yield) *cis*-(2-acetyl-cyclohexyl)-acetaldehyde (**59**) as a clear oil. All spectroscopic data matched that reported in the literature.

Preparation of *trans*-(2-acetyl-cyclohexyl)-acetaldehyde (60)

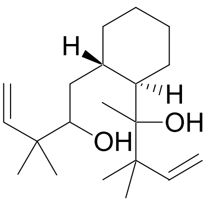


60

$C_{10}H_{16}O_2$
Mol. Wt.: 168,23

O_3 was bubbled through a -78 °C solution of 2.0 g (12.0 mmol) *trans*-1-acetyl-2(2-propenyl)cyclohexane in CH_2Cl_2/MeOH (5:1, 42 mL) containing a catalytic amount of $NaHCO_3$ (~ 30 mg) until a blue color persisted, indicating an excess of O_3 in solution. The solution was now flushed with argon until the blue color disappeared, upon which PBu_3 (3.2 g, 16.0 mmol) was added slowly by syringe. The mixture was allowed to warm to RT and stirred for another 2 h. The volatiles were removed in vacuum and the residue was chromatographed (3:1 EtOAc/hexane) to give 2.0 g (12.0 mmol, quantitative yield) *trans*-(2-acetyl-cyclohexyl)-acetaldehyde (**60**) as a clear oil. All spectroscopic data matched that reported in the literature.

Unselective NHK reaction of 57: Production of 2-[2-(2-hydroxy-3,3-dimethyl-pent-4-enyl)-cyclohexyl]-3,3-dimethyl-pent-4-en-2-ol (61)



61

$C_{20}H_{36}O_2$
Mol. Wt.: 308,50

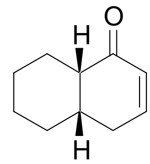
To a stirring 0 °C solution of 210 mg (1.25 mmol) *trans*-(2-acetyl-cyclohexyl)-acetaldehyde (**60**) in 5 mL DMF was added 430 mg (3.5 mmol) $CrCl_2$. To this mixture was added at once 260 mg (1.75 mmol) prenyl bromide. The reaction was allowed to stir for 30 min at 0 °C and then for 2 h at RT before being quenched by the addition of 2 mL H_2O to the mixture. The quench was stirred for 30 min before being extracted with Et_2O and concentrated to give the product of unselective *bis*-NHK coupling **61** as a yellow oil in 82 % yield.

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.95 (m, 2H); 1.03 (s, 3H); 1.25 (m, 2H); 1.39 (m, 2H); 1.59 (m, 2H); 1.71 (m, 2H); 1.77 (m, 2H); 3.28 (dt, *J* = 4, 8 Hz, 1H); 4.96 (m, 4 H); 5.88 (m, 2H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 22.7, 23.7, 26.1, 27.2, 28.6, 29.6, 34.5, 37.0, 39.8, 51.1, 57.1, 75.9, 78.5, 111.2, 111.8, 142.9, 145.6.

Preparation of 4a*S*,5,6,7,8,8a*S*-hexahydro-4*H*-naphthalen-1-one (62)

To a stirring RT solution of 30 mg (0.18 mmol) *cis*-(2-acetyl-cyclohexyl)-acetaldehyde (**59**) in 5 mL THF was added 17 mg (0.30 mmol) Mn(0) and 2 mg (0.01 mmol) anhydrous $CrCl_3$. To this mixture was added at once 53 mg (0.36 mmol) prenyl bromide followed by 0.05 mL (0.43 mmol) TMSCl. The reaction was allowed to stir for 3 h before being quenched by the addition of 2 mL H_2O to the mixture. The quench was stirred for 30 min before being extracted with Et_2O, dried over $MgSO_4$ and subjected to silica gel chromatography (R_f 0.2 in 20 % Et_2O/hexane) to afford 25 mg (0.16 mmol, 92 %) 4a*S*,5,6,7,8,8a*S*-hexahydro-4*H*-naphthalen-1-one (**62**) as a colorless solid bearing a melting point range of 62-65 °C.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.05-1.24 (m, 4H); 1.69-1.80 (m, 4H); 1.94 (dt, *J* = 3.7, 12.3 Hz, 1H); 2.11 (ddt, *J* = 2.3, 7.7, 11 Hz, 1H); 2.23 (d, *J* = 14 Hz, 1H); 2.31 (dt, *J* = 4.9, 18.8 Hz, 1H); 5.95 (dd, *J* = 2.7, 10 Hz, 1H); 6.88 (ddd, *J* = 1.9, 5.9, 10 Hz, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 25.3, 25.4, 25.6, 33.5, 33.6, 40.0, 51.0, 129.47, 148.7, 201.3. **FTIR** (neat): cm^{-1}. **HR-EIMS:** anal. calc. for $C_{10}H_{14}O$ $[M]^+$: 150.1045; anal. found: 150.1041.

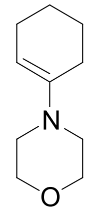


62

$C_{10}H_{14}O$
Mol. Wt.: 150,22

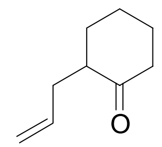
Preparation of 2-allylcyclohexanone (64)[109]

(A) To a stirring solution of 157 g morpholine and 147 g (1.5 mol) cyclohexanone in 500 mL toluene was added 10 mol % *p*-TsOH, and the reaction was allowed to reflux under Dean-Stark conditions for 2 d before being cooled to RT, extracted with Et_2O, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated under reduced pressure and distilled with the aid of a water aspirator (~ 15 mbar) to give 240 g (1.44 mol, 96 %) as a colorless oil. All spectroscopic data matched that reported in the literature.



$C_{10}H_{17}NO$
Mol. Wt.: 167,25

(B) To a stirring solution of 8 g (47.8 mmol) 4-cyclohex-1-enyl-morpholine in 50 mL MeCN was added 5.8 g (47.8 mmol) allyl bromide along with 782 mg NaI, and the mixture was held at reflux for 2.5 h. After cooling the deep-red mixture to RT, the reaction was washed with 1 N HCl (50 mL), $NaHCO_3$ (2 x 50 mL) before being extracted with Et_2O,

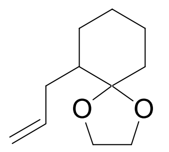


64

$C_9H_{14}O$
Mol. Wt.: 138,21

dried over $MgSO_4$ and concentrated under reduced pressure to give 5.3 g (38.3 mmol, 80 %) 2-allylcyclohexanone (**64**) as a light-yellow oil needing no further purification. All spectroscopic data matched that reported in the literature.

Preparation of 6-allyl-1,4-dioxa-spiro[4.5]decane (65)[110]

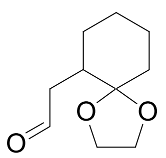


65

$C_{11}H_{18}O_2$
Mol. Wt.: 182,26

To a stirred solution of 2 g (14.4 mmol) 2-allylcylcohexanone (**64**) in 100 mL C_6H_6 and 50 mL ethylene glycol was added 150 mg *p*-TsOH, and the reaction was kept at reflux under Dean-Stark conditions for 2 d. Upon cooling to RT, the crude reaction mixture was extracted with Et_2O and subjected to silica gel chromatography (10 % Et_2O/hexanes) to afford 2.6 g (14.4 mmol, quantitative yield) **65** as a colorless oil. All spectroscopic data matched that reported in the literature.

Preparation of (1,4-dioxa-spiro[4.5]dec-6-yl)-acetaldehyde (66)



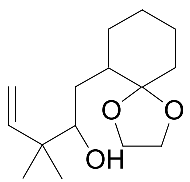
66

$C_{10}H_{16}O_3$
Mol. Wt.: 184,23

O_3 was bubbled through a -78 °C solution of 1.0 g (5.5 mmol) 6-allyl-1,4-dioxa-spiro[4.5]decane (**65**) in CH_2Cl_2/MeOH (5:1, 42 mL) containing a catalytic amount of $NaHCO_3$ (~ 30 mg) until a blue color persisted, indicating an excess of O_3 in solution. The solution was now flushed with argon until the blue color disappeared, upon which PBu_3 (1.3 mL, 5.5 mmol) was added slowly by syringe. The mixture was allowed to warm to RT and stirred for another 2 h. The volatiles were removed in vacuum and the residue was chromatographed (3:1 EtOAc/hexane) to give 990 mg (5.3 mmol, 98 %) (1,4-dioxa-spiro[4.5]dec-6-yl)-acetaldehyde (**66**) as a clear oil in need of no further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14-1.75 (m, 8H); 2.07 (m, 2H); 2.43 (dd, *J* = 4, 20 Hz, 2H); 3.70 (t, *J* = 4 Hz, 2H); 3.84 (t, *J* = 4 Hz, 2H); 9.58 (d, *J* = 4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 23.5, 24.8, 30.3, 34.4, 40.3, 44.2, 63.9, 64.6, 109.7, 201.85.

Preparation of 1-(1,4-dioxa-spiro[4.5]dec-6-yl)-3,3-dimethyl-pent-4-en-2-ol (67)

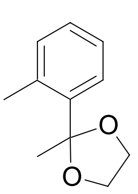


67

$C_{15}H_{26}O_3$
Mol. Wt.: 254,37

To a stirring RT solution of 100 mg (0.54 mmol) (1,4-dioxa-spiro[4.5]dec-6-yl)-acetaldehyde (**66**) in 5 mL THF was added 65 mg (0.92 mmol) Mn(0) and 6 mg (0.04 mmol) anhydrous $CrCl_3$. To this mixture was added at once 162 mg (1.1 mmol) prenyl bromide followed by 0.17 mL (1.3 mmol) TMSCl. The reaction was allowed to stir for 3 h before being quenched by the addition of 2 mL H_2O to the mixture. The quench was stirred for 30 min before being extracted with Et_2O, dried over $MgSO_4$ and concentrated to afford 102 mg (0.4 mmol, 74 %) 1-(1,4-dioxa-spiro[4.5]dec-6-yl)-3,3-dimethyl-pent-4-en-2-ol (**67**) as a colorless oil which was taken on to the following protection step without purification.

Preparation of 2-methyl-2-*o*-tolyl-[1,3]dioxolane

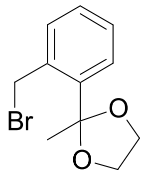


$C_{11}H_{14}O_2$
Mol. Wt.: 178,23

To a stirring solution of *o*-methyl-acetophenone (10 g, 74.5 mmol) in 150 mL C_6H_6 was added 4.57 mL (81.9 mmol) ethylene glycol and 1.42 g (10 mol %) *p*-TsOH. The mixture was allowed to reflux under Dean-Stark conditions for 24 h before being washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give 12.9 g (98 %, 73.1 mmol) 2-methyl-2-*o*-tolyl-[1,3]dioxolane as a colorless oil that needed no further purification. All spectroscopic data matched that reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H); 2.39 (s, 3H); 3.72 (t, J = 8 Hz, 2H); 4.02 (t, J = 8 Hz, 2H); 7.17 (m, 3H); 7.56 (d, J = 8 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 20.9, 26.4, 64.1, 125.7, 126.2, 128.3, 132.0, 135.7, 140.7.

Preparation of 2-(2-bromomethyl-phenyl)-2-methyl-[1,3]dioxolane

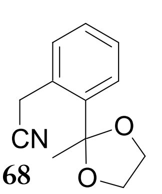


$C_{11}H_{13}BrO_2$
Mol. Wt.: 257,12

To a stirring solution of 8.1 g (45 mmol) of 2-methyl-2-*o*-tolyl-[1,3]dioxolane in 150 mL CCl_4 was added 8 g (45 mmol) *N*-bromosuccinamid (NBS) and 100 mg AIBN. The reaction was refluxed for 15 min before being quickly cooled to RT, washed with $NaHCO_3$, dried over $MgSO_4$ and concentrated to give 10.5 g (41 mmol, 91 %) as a light yellow oil that needed no further purification. All spectroscopic data matched that reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 3H); 3.76 (t, *J* = 8 Hz, 2H); 3.99 (s, 2H); 4.05 (t, *J* = 8 Hz, 2H); 7.31 (ddd, *J* = 2, 4.4, 6.8 Hz, 2H); 7.40 (dd, *J* = 4.4, 6.8 Hz, 1H); 7.60 (ddd, *J* = 2, 4.4, 6.8 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 20.0, 27.3, 64.3, 126.8, 127.2, 128.3, 128.7, 130.6, 140.9.

Preparation of [2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-acetonitrile (68)



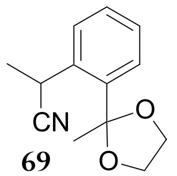
68

$C_{12}H_{13}NO_2$
Mol. Wt.: 203,24

To a stirring solution of 1.2 g (4.7 mmol) 2-(2-bromomethyl-phenyl)-2-methyl-[1,3]dioxolane in 25 mL dry DMSO was added 256 mg (5.3 mmol) NaCN and the reaction was allowed to stir between 50-60 °C for 3 h, upon which the reaction was cooled to RT before being extracted with Et_2O, washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give after silica gel chromatography (25 % Et_2O/hexanes) 588 mg (2.9 mmol, 64 %) **68** as a yellow solid possessing a melting point of 85-87 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H); 3.76 (t, *J* = 8 Hz, 2H); 4.00 (s, 2H); 4.07 (t, *J* = 8 Hz, 2H); 7.31 (ddd, *J* = 2, 4.4, 6.8 Hz, 2H); 7.42 (dd, *J* = 4.4, 6.8 Hz, 1H); 7.62 (ddd, *J* = 2, 4.4, 6.8 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 20.0, 27.3, 36.8, 64.3, 126.8, 127.4, 128.3, 128.8, 130.6, 140.9. **FTIR** ($CDCl_3$): 3063, 2972, 2892, 1714, 1195, 1036, 403. **HR-FABMS** anal. calc. for $C_{12}H_{14}O_2N$ $[M + H]^+$: 204.1025, anal. found; 204.1017.

Preparation of 2-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-propionitrile (69)



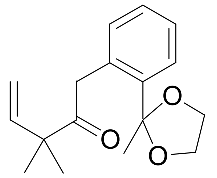
69

$C_{13}H_{15}NO_2$
Mol. Wt.: 217,26

To a stirring solution of 168 mg (3.5 mmol) NaH in 3 mL DMSO was added 386 mg (1.9 mmol) of [2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-acetonitrile (**68**) and in 0.15 mL MeI in 3 mL Et_2O. The reaction was stirred for 2 h before being cooled to 0 °C when 0.2 mL *i*-PrOH was added followed by 5 mL H_2O. The mixture was extracted with Et_2O (50 mL), washed with brine and dried over $MgSO_4$ before being concentrated to give 412 mg (1.9 mmol, quantitative yield) **69** as a yellow oil in need of no further purification.

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.58 (d, *J* = 7.2 Hz, 3 H); 1.63 (s, 3H); 3.72 (m, 2H); 4.01 (m, 2H); 4.74 (q, *J* = 7.2 Hz, 1H); 7.24 (dt, *J* = 1.6, 4.8 Hz, 1H); 7.35 (dt, *J* = 1.6, 4.8 Hz, 1H); 7.56 (ddd, *J* = 1.6, 4.8, 18.4 Hz, 2H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 21.8, 27.3, 21.8, 41.1, 64.4, 64.7, 108.9, 123.0, 126.6, 128.0, 128.9, 129.2, 135.4. **FTIR** ($CDCl_3$):. **HR-FABMS** anal. calc. for $C_{13}H_{16}O_2N$ $[M + H]^+$: 218.1181; anal. found: 218.1185.

Preparation of 3,3-dimethyl-1-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-pent-4-en-2-one (70)


$C_{17}H_{22}O_3$ **70**
Mol. Wt.: 274,35

To a stirring RT solution of [2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-acetonitrile (422 mg, 2.1 mmol) in 3 mL anhydrous THF were added zinc dust (540 mg, 4 eq.) and 470 mg (1.5 eq.) prenyl bromide to the reaction mixture. The mixture was stirred vigorously as $AlCl_3$ (112 mg, 0.4 eq.) was added at once to the reaction. Stirring was continued for 3 h, when the reaction was quenched via the addition of 5 mL $NHCl_4$ solution. The reaction was stirred for 10 min. and extracted with Et_2O (100 mL) before being washed with $NaHCO_3$ and brine (1 x 50 mL each), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (25 % Et_2O/hexanes) to afford 243 mg (42 %) **70** as a low-melting solid.

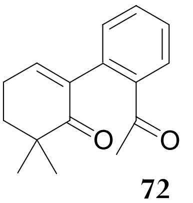
^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.01 (s, 3H); 1.26 (s, 3H); 3.53 (t, *J* = 8 Hz, 2H); 3.82 (t, *J* = 8 Hz, 2H); 5.15 (dt, *J* = 12, 28 Hz, 2H); 6.03 (dt, *J* = 8, 12 Hz, 1H); 6.89 (dd, *J* = 4, 8 Hz, 1H); 7.15 (dt, *J* = 4, 8 Hz, 2H); 7.47 (dd, *J* = 4, 8 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 24.0, 27.4, 42.9, 50.6, 64.0, 113.8, 126.2, 126.7, 127.8, 132.4, 132.7, 141.0, 143.2, 146.9, 210.42. **FTIR** (neat): 3063, 2972, 2892, 1714, 1195, 1036, 403. **HR-FABMS** anal. calc. for $C_{17}H_{23}O_3$ $[M + H]^+$: 275.1692, anal. found; 275.1670.

Preparation of 2-(2-acetyl-phenyl)-6,6-dimethyl-cyclohex-2-enone (72)

Amounts:	50 mg	(0.182 mmol)	3,3-dimethyl-1-[2-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-pent-4-en-2-one
	1 mg	(0.9 mol %)	$[Rh(cod)Cl]_2$
	3.0 mg	(10 mol %)	*p*-TsOH

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 20 bar CO/H_2 (1:1), 80 °C, 48 h

Yield: 25 mg **72** (0.103 mmol, 57 %) after silica gel chromatography (50 % Et_2O/hexanes).

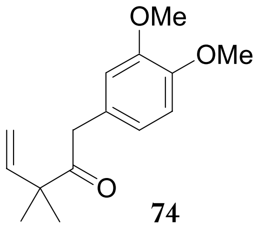


72

$C_{16}H_{18}O_2$
Mol. Wt.: 242,31

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 0.88 (s, 6H); 1.74 (t, J = 8 Hz, 2H); 2.27 (dt, J = 4, 8 Hz, 2H); 2.65 (s, 3H); 6.66 (t, J = 4 Hz, 1H); 7.47 (m, 2H); 7.77 (d, J = 4 Hz, 1H); 7.96 (d, J = 4 Hz, 1H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 19.4, 23.3, 24.1, 36.3, 36.8, 41.5, 126.9, 127.6, 128.5, 129.9, 131.28, 135.5, 147.6, 150.5, 192.5, 193.9. **HR-FABMS** anal. calc. for $C_{16}H_{18}O_2$ $[M]^+$: 242.1307, anal. found; 242.1309.

Preparation of 1-(3,4-dimethoxyphenyl)-3,3-dimethylpent-4-en-2-one (74)



74

$C_{15}H_{20}O_3$
Mol. Wt.: 248,32

To a stirring RT solution of valeronitirle (500 mg, 2.8 mmol) in 5 mL anhydrous THF were added zinc dust (550 mg, 4.0 eq.) and 600 mg (1.5 eq.) prenyl bromide to the reaction mixture. The mixture was stirred vigorously as $AlCl_3$ (112 mg, 0.4 eq.) was added at once to the reaction. Stirring was continued for 3 h, when the reaction was quenched via the addition of 5 mL $NHCl_4$ solution. The reaction was stirred for 10 min. and extracted with Et_2O (100 mL) before being washed with $NaHCO_3$ and brine (1 x 50 mL each), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (R_f = 0.6, 3:1 % EtOAc/hexanes) to afford 61 mg (9 %) 1-(3,4-dimethoxy-phenyl)-3,3-dimethyl-pent-4-en-2-one (**74**) as a fragrant light-yellow oil.

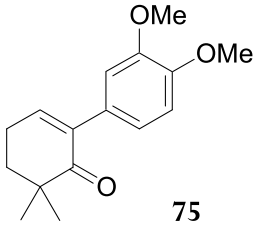
^{1}**H-NMR** (400 MHz, $CDCl_3$) δ 1.25 (s, 6H); 3.68 (s, 2H); 3.82 (s, 3H); 3.83 (s, 3H); 5.20 (dd, J = 4, 16 Hz, 2H); 5.93 (dd, J = 12, 16 Hz, 1H); 6.65-6.82 (m, 3H). ^{13}**C-NMR** (100 MHz, $CDCl_3$) δ 23.6, 43.5, 51.4, 55.9, 111.6, 112.9, 114.9, 121.7, 127.3, 147.9, 148.8, 210.4. **FTIR** (neat): 2969, 2935, 2835, 1712, 1516, 1263, 1029 cm^{-1}. **HR-FABMS** anal. calc. for $C_{15}H_{20}O_3$ $[M]^+$: 248.1412; anal. found: 248.1429.

Preparation of 2-(3,4-dimethoxyphenyl)-6,6-dimethylcyclohex-2-enone (75)

Amounts:	196 mg	(0.79 mmol)	1-(3,4-dimethoxy-phenyl)-3,3-dimethyl-pent-4-en-2-one (**74**)
	3 mg	(0.9 mol %)	Rh(CO)$_2$(acac)
	12 mg	(1.8 mol %)	XANTPHOS
	14 mg	(10 mol %)	*p*-TsOH

Procedure: Procedure **B**; using 10 mL CH_2Cl_2, 60 bar CO/H_2 (1:1), 90 °C, 18 h

Yield: 182 mg **75** (0.70 mmol, 89 %) as a thick, clear-yellow oil.



75

$C_{16}H_{20}O_3$
Mol. Wt.: 260,33

The spectroscopic data are in agreement with that reported in the literature.[100b] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 1.90 (t, *J* = 8 Hz, 2H); 2.52 (dt, *J* = 6, 8 Hz, 2H); 3.82 (s, 3H); 3.83 (s, 3H); 6.72-6.84 (m, 4H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 23.5, 24.6, 36.1, 41.4, 55.8, 55.9, 110.6, 112.4, 121.2, 128.6, 139.5, 143.3, 148.2, 203.4.

6 LITERATURE

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Curriculum Vitae

Personal information

Name: Mark David Keränen
Date of birth: 30.04.1976
Place of birth: Ely, Minnesota – USA
Familial status: Married, wife Uta and son Matti

Education

1/2001 – 7/2004	Ph.D., Fachbereich Chemie, Universität Dortmund – Dortmund, Germany
9/1998 – 10/2000	Ph.D. Candidate, University of Minnesota – Minneapolis, MN
9/1996 – 6/1998	BS Chemistry, University of Minnesota – Minneapolis, MN
9/1994 – 6/1996	AA Chemistry, Vermilion Community College – Ely, MN

Scientific employment

Assistant Professor of Chemistry. August 2004
Department of Math, Science and Technology, University of Minnesota, Crookston

Wissenschaftlicher Angestellter/Assistent, 2001-July 2004
Fachbereich Chemie, Universität Dortmund. Advisor: Prof. Dr. Peter Eilbracht

Graduate research/teaching associate, 1998-2000
University of Minnesota Dept. of Chemistry. Advisor: Prof. George O'Doherty

Undergraduate research/teaching associate, 1996-1998
University of Minnesota Dept. of Chemistry. Advisor: Prof. George O'Doherty

Chemistry lecture tutor/teaching assistant, 1995-1996
Vermilion Community College. Advisor: Mr. Philip Barker

Memberships & affiliations

American Chemical Society: Organic & Inorganic divisions, Organometallic subdivision

Honors and awards

Finalist, 1999-2000 Fulbright Russia grant competition
University of MN UROP grant winner, 1996-1998
University of MN nominee for the 1997-98 Pfizer Undergraduate Synthetic Chemistry Fellowship.