Synthesis of \((R)-\text{Muscone}\)

- Macrocycle, many degrees of freedom (freedom of rotation). Reaction are therefore rather intermolecular than intramolecular. A cycle with 15 members behaves more or less than a acyclic system.
- Variation at the configuration of C-3 influences strongly the odor character and the human olfactory threshold. R-Muscone has an extremely low threshold (0.027 ng/L) whereas S-Muscone has only a threshold of 3 ng/L and is therefore 100 times less intense than R-Muscone. R-Muscone was isolated by Walbaum in 1906 from musk pod obtained from the male musk deer \textit{Moschus moschferus}, and its structure was determined by Ruzicka in 1926.

**Dieckmann** - Working under high dilution

**Metathesis**

**Negishi coupling**

**Asymmetric Michael addition**

**Asymmetric hydrogenation**

Isomerize to the \(\alpha,\beta\) unsaturated species
Synthesis of (R)-Muscone

Starting from large cycles:

Commercially available cheap cyclic systems:

- Butadiene dimerization
- Butadiene trimerization

Fluka 98

<table>
<thead>
<tr>
<th>Compound</th>
<th>Quantity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ml</td>
<td>20 €</td>
<td></td>
</tr>
<tr>
<td>500 g</td>
<td>40 €</td>
<td></td>
</tr>
<tr>
<td>5 g</td>
<td>30 €</td>
<td></td>
</tr>
</tbody>
</table>


Alternatives have been tried as well, due to a poor yield in the elimination of the bromide.

Elimination with Sulfur:

Elimination with Selenium:

Elimination with Chiral Aminoalcohol:

More resources available at www.chemistforchrist.de
Synthesis of (R)-Muscone

Furakawa introduced Et₂Zn instead of the Zn/Cu couple. Et₂Zn is commercially available.

\[ \text{I} \quad \text{Et}_2\text{Zn} \quad \text{I} \quad \text{ZnI} + \text{EtI} \]

It's not a real carbene it is a carbenoid!

**Charette, *Synlett 1995*, 1197**

Introducing the asymmetric variant of the Simmons-Smith reaction:

**Synthesis by Mash et al., *JOC 1986*, 51, 2721**

Mash used chiral acetals to introduce a chiral center because the asymmetric version of Charette hasn't been developed at that time.
Synthesis of (R)-Muscone

More important than 1,3 diaxial repulsions in the corresponding substituted cyclohexane, due to C-O bonds being shorter than C-C bonds.

Preferred coordination

Repulsion is getting smaller because the bond holding the two moieties together has been broken.

Disfavoured coordination

Repulsion is getting greater because the bond holding the two moieties together has been transformed into a double bond.

Therefore attacking the acetal with a nucleophile will cleave the bond pointing towards us rather the bond pointing away from us.

Creation of the stereogenic center in the β-position.


More a Lithium-Enolate due to HSAB-concept

More resources available at www.chemistforchrist.de
Synthesis of (R)-Muscone

Dieckmann reaction:

\[
\begin{align*}
\text{OH} & \quad \rightarrow \quad \text{O} \quad \rightarrow \quad \text{O} \\
\text{R'} & \quad \rightarrow \quad \text{R'} \\
\end{align*}
\]

Idea: Why not link the 2 ends together by a chiral auxiliarly.

Take the same principle and apply it to the conjugated addition!

If an attack from the back should be favoured one only has to replace the ester group by an OH-group which coordinates the Me\textsubscript{2}CuLi.

What about if R' and R were connected?!

Even under high dilution conditions only the polymerized product is formed.
Synthesis of (R)-Muscone

Solution of Nicolau \textit{JOC}, 1979, 44, 4011

\begin{align*}
\text{HO} & \quad \text{PPh}_3 \\
\text{HO} & \quad \text{EtO} \quad \text{12}
\end{align*}

Try to imitate an intramolecular reaction by forming an intramolecular hydrogen bond which brings the alcohol and the ester close enough to react!

Synthesis of Oppolzer \textit{JACS}, 1993, 115, 1593

Key step in the synthesis:

Introduction to Zn-Chemistry: Chemistry of RZnX and R\textsubscript{2}Zn


1849 \textsuperscript{1}\textsuperscript{st} Zn-Organanyl synthesized by Frankland

\textit{Liebig's Ann. Chem.} 1849, 71, 171 and 213

\textsuperscript{1}\textsuperscript{st} Zn-Organanyl synthesized by Frankland

\textit{Liebig's Ann. Chem.} 1849, 71, 171 and 213

Lacking reactivity RZnX and R\textsubscript{2}Zn were soon replaced by the more reactive Grignard reagents MgX-R.
Synthesis of \((R)\)-Muscone

Reformatsky:

\[
\begin{align*}
O & \quad R \quad \text{Zn} \quad \rightarrow \quad O \\
\text{Br} & \quad R
\end{align*}
\]

This reaction cannot be done with Mg, because due to its increased reactivity it would react with itself.

More ways to synthesize R-Zn:

\[
R \quad \text{Zn}
\]

Hundsdiecker, *German patent, 1936*

Wittig *Liebig's Ann. Chem. 1967, 702, 24*

**Resurrection of Zn-Chemistry**

Negishi *JACS, 1980, 102, 3298*

Extended the scope of Zn-Chemistry to Crosscoupling reactions due to Zn-R being able to undergo transmetallations unto Palladium.

\[
\begin{align*}
R & \quad \text{Zn} \quad \text{X} \quad \text{Zn} \quad \text{Ar} \\
\text{or} & \quad \text{R} \quad \text{Al} \quad \text{Pd (cat.)} \quad \text{R} \quad \text{Ar}
\end{align*}
\]

This would be impossible to do with Grignard reagents!

**Thiele: Transmetallation with Organocopper reagents** *J. Organomet. Chem. 1968, 12, 225*

\[
\begin{align*}
\text{CuLi} & \quad \text{R} \\
& \quad \text{ZnBr}
\end{align*}
\]

1990, Knochel: Conjugated addition of a Zn-organyl to Cyclohexenone

\[
\begin{align*}
\text{O} & \quad \text{BrZn-} \\
& \quad \text{CO}_2\text{Et}
\end{align*}
\]

Knochel showed that in principal Zn-organyls can imitate every reaction that Cu-organyls do!

**Asymmetric addition of a Zn-Organyl to an aldehyde:**

\[
\begin{align*}
R & \quad \text{Zn} \quad R \\
\text{sp} & \quad \text{but} \quad \text{sp}^3
\end{align*}
\]

not very reactive

Oxygen heteroatom attached to the Zn changes hybridization and makes it more reactive.


*Soai, Chem. Rev. 1993, 93, 2117*
**Synthesis of (R)-Muscone**

**Enantioselective Addition to Aldehydes**

Oguri, *TL* 1984, 25, 2823

\[
\text{PhCHO} + \text{Et}_2\text{Zn} \rightarrow \text{PhOH}
\]


Noyori, *JACS*, 1995, 117, 4832

Noyori determines the mechanism of the reaction and improves the enantiomeric excess (ee) in his study:

**DAIB Ligand**

1% of catalyst loading is sufficient

99% ee

- Works well especially for ArCHO
- Hundreds of Aminoalcohol and Aminothiol Ligands have been synthesized that also yield products with ee in the high 90’s.

The DAIB Ligand shows a positive non-linear effect:

<table>
<thead>
<tr>
<th>Entry</th>
<th>ee (Ligand) (%)</th>
<th>ee (Product) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>91</td>
</tr>
</tbody>
</table>

Usually the ee of the product is less or equal than the ee of the catalyst!

How can these results be explained?

\[
R-Zn^{sp} + \text{Me}_2\text{N} \rightarrow \text{R-Zn}^{sp^3}
\]

Therefore a dimer is formed so that the empty orbital can be filled by interaction with the dimer partner. (Can be compared with AlCl$_3$ or BH$_3$, which also form dimers to get their electrons).
Synthesis of (R)-Muscone

For a chiral catalyst like the complex formed with Noyori's DAIB catalyst several Dimer-combinations are possible if the racemic mixture is used (R + S Monomer)

Possible combinations:
- If the 2 (R) monomers form a dimer: (R,R)
- If the 2 (S) monomers form a dimer: (S,S)
- If the (S) and (R) monomer form a dimer: (S,R) or (R,S)

In this case the (R,S) dimer proofed to be the most stable and thus the least reactive (it is more or less catalytically inactive). If for example we have a ee of the Ligand = 75% which corresponds to a mixture of e.g. 75% (R) and 25% (S) [or vice versa]. Then 25% of the (R) enantiomer and 25% of the (S) enantiomer would form the "inactive" (R,S) complex. This means that 50% of pure (R) enantiomer remains and forms an active (R,R) complex. So adding 1mol% of a Ligand with an ee of 75% is as effective as 0.5mol% of a Ligand with 100% ee.

Conclusion:

a) A non-linear effect is usually observed if there is at least one aggregation occurring.

b) The non-linear effect is:
- Positive: If the R,S or the S,R dimer is the more stable one.
- Negative: If the R,R or the S,S dimer is more stable.

Preparation of Zn-Reagents according to Knochel:

**Synthesis by Oppolzer et. al: JACS 1993, 115, 1593**

**Introductory information 1:**

1) DIBAL-H
2) I₂
Synthesis of (R)-Muscone

Similar reaction asymmetrically:

\[
\begin{align*}
\text{(Cy)}_2BH & \quad \text{Et}_2Zn \\
\text{sp}^2 & \quad \text{sp}^3 \\
& \quad \text{Et} \\
\text{sp}^2 & \quad \text{sp}^3 \\
& \quad \text{Et} \\
\text{R} & \quad \text{H} \\
\text{OH} & \quad \text{R} \\
\text{ee} > 95% \\
1\text{mol}\% \text{DAIB}
\end{align*}
\]

\[
\text{Cy} = \text{Cyclohexyl}
\]

\[\text{sp}^2 \text{is more reactive than the sp}^3 \text{ moiety and therefore is transferred faster.}\]

**Introductory information 2:**


**Mechanism:**

The driving force is the deprotonation of the sp-Proton to form a the corresponding anion (remember sp-C-H has a pk_a of only 25, whereas sp^3 C-H Protons have a pk_a ~ 50).

Abrams introduced the use of the KAPA base: K Amine Propyl Amide

Proton source and base is incorporated in one molecule leading to an “intramolecular” protonation, deprotonation.

The one equivalent of KOTBu has been added to deprotonate the acetylene-derivative completely.
**Synthesis of Oppolzer:**

\[
\begin{align*}
\text{C}_3\text{H}_5\text{Br} & \quad \text{C}_12\text{H}_{25} \quad \text{C}_12\text{H}_{25} \\
& \quad 1. \text{ KAPA} \\
\end{align*}
\]

One would expect that in the last step the ketone is reduced to the corresponding alcohol. A footnote in the this paper faces this problem:

"The use of rigorously dried liquid ammonia was essential to prevent the reported concomitant reduction of the carbonyl group".

---


**Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations**

Synthesis of (R)-Muscone

Use of heterocuprates:

Derived from camphor:

Kim, Tetrahedron Asymmetry. 2002, 13, 801

Pfaltz Synlett 2006, 1031

Pfaltz (Basel) was thinking of taking a more rigid dienone and thus getting better enantioselectivites (99% ee).

Slide-in unit: Creation of Lithiumenolates:

Due to its hardness MeLi attacks the silicon atom and creates thus a Lithiumenolate.

One Pot 1,4 Addition, Cyclopropanation.

More resources available at www.chemistforchrist.de
Synthesis of (R)-Muscone

OTMS

1. Br₂
2. NaOAc, MeOH, 20°C

Cyclopropane can be seen as a double bond (Reminder: Walsh Orbitals give π Character rather than σ-Character)

Br₂

Br

Br

Br

Br

OAc

Me₃Si

OAc

Synthesis of Muscone by Wender: JACS, 1983, 105, 3348

Literature for the methodology used by Wenders: Tet. Lett. 1981, 22, 2471
Tet. Lett. 1987, 37, 3967
JACS 1983, 105, 3348

1st Background information:
Revue Cope and Oxy-Cope reactions: Org. React. 1975, 22, 1

Oxycope reaction:

As base usually KOTBu is used (O-Li bond is stronger, therefore O-K bond is higher in energy shifting the equilibrium to the enolate. Crown ether (18-crown-6) is added to complex the K⁺ and give a highly basic OtBu⁻ which is not stabilized by ion ion interactions. 6 electrons are shifting during in the TS, which is therefore aromatic. Another aromatic system might be the following:

Now imagine a 7 membered ring would be on the left side of the molecule and thus giving a 15 membered ring.
Synthesis of \((R)\)-Muscone

**Second background information:**

\[
\begin{align*}
\text{OH} & \quad \text{Cl} & \quad \text{H}_2\text{O}, \text{Cl}_2 \\
& \quad \text{R-MgX} & \quad \text{O-MgX} \\
\text{anti S}_{\text{N}2} & \quad \text{intra}\text{molecular} & \quad \text{O} \\
\end{align*}
\]

In the second example the O\text{MgX} and the Cl are syn to each other and therefore a S\text{N}2 like displacement would be impossible. Instead a hydride shift takes place and the Cl is kicked out by the H.

**Third background information:**

Reduction of propargylic alcohols: Corey, *JACS*, 1967, 89, 4245

\[
\begin{align*}
\text{OH} & \quad \text{R} \\
\text{1. LiAlH}_4 & \quad \text{2. H}_2\text{O} \\
\text{OH} & \quad \text{OH} \\
\text{1. LiAlH}_4 & \quad \text{2. I}_2 \\
\text{AlR}_3 & \quad \text{I}_2 \\
\end{align*}
\]

Hydroalumination occurs in an antifashion (H transferred and iodine are on opposite sides of the double bond). The mixture of the 2 Products occurs due to impurities in the LiAlH\textsubscript{4} like e.g. AlCl\textsubscript{3}.

\[
\text{LiAlH}_4 + \text{AlCl}_3 \rightarrow \text{AlH}_3 + \text{LiCl} + \text{AlHCl}_2
\]

Corey found out that a mixture of LiAlH\textsubscript{4} and NaOMe (which neutralizes AlCl\textsubscript{3}) leads to the formation of:

\[
\begin{align*}
\text{OH} & \quad \text{R} \\
\text{1. LiAlH}_4 & \quad \text{2. I}_2 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Whereas alanes as produced by the AlCl\textsubscript{3} impurity give:

\[
\begin{align*}
\text{OH} & \quad \text{R} \\
\text{1. DIBAL-H} & \quad \text{2. I}_2 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Note: The first 2 hydrides of LiAlH\textsubscript{4} are very actively released, the others react much more sluggishly.
Synthesis of (R)-Muscone

Synthesis of Wenders:

Synthesis of Muscone by Baker, JCS Chem. Comm. 1972, 802

- 2 steps
- Problem: Only 5% yield

Review: Nickel catalyzed oligomerisation

Org React. 1972, 19, 115
Angew. Chem. Int. Ed. 1966, 5, 151
Synthesis of \((R)\)-Muscone

\[
\begin{align*}
\text{Ni}(0), L_n & \rightarrow \pi\text{-Allyl Species} \\
\text{Ni}(0) \rightarrow \text{Ni}(II) \rightarrow \text{Ni}(II) \rightarrow \text{COD} \rightarrow \text{COD}
\end{align*}
\]

Depending on the Ligand:
- COD as a bathtub-shape Ligand for transition metals.
- Di and Trimerization of Butadiene leads to inexpensive 8 and 12 membered macrocycles.

\[
\text{Ni}(II) + \text{CO} \rightarrow \text{Ni} \rightarrow \text{red. Elimination}
\]

A nickel Allyl-p-complex attacking a propadiene (Allene):

Propadiene instead of butadiene!

Now one carbon is still missing, this can be introduced by a CO-insertion:
Muscone was not isolated simply detected (most possibly by GC-MS). Even though the yield is very low (5%) this might be nevertheless be interesting for industrial applications due to the starting material being extremely cheap!

**General approach to macrocycles:**

In order to bring the 2 ends together in an intra rather than an intermolecular fashion it is extremely important to work under high dilution conditions (~ 1g/l). High dilution methods are only applicable in the academic realm. Industry could never afford wasting volume of reaction vessels or the huge quantities of solvent needed.

**Synthesis of muscone by Nicolau: JOC, 1979, 44, 4011**
Synthesis of the starting material:

Methylololate (C_{18})
Unsaturated fatty acid

Synthesis of SM1 and SM2:

Synthesis of (R)-Muscone

Acts as a soft Lewis acid (OPh was used to tune the Lewis acidity just right)

Synthesis of the starting material:

Slide-in unit: The Wacker oxidation

Oxidation of vinyl groups to methylketones.

Instead of using Pd(II) in a stoichiometrically way a external oxidant (in this case air) is used to complete the catalytic cycle. Oxygen present in air oxidizes Cu(I) to Cu(II).

After the formation of the p-complex the best nucleophile present in the reaction mixture (H₂O) is attacking the alkene at the higher substituted end of the complex. Keto / Enol tautomerization leads to the desired product.
Synthesis of (R)-Muscone


Key reaction:

$$\text{ClO}_2 + \text{Me}_2\text{Si} \quad \xrightarrow{\text{AlCl}_3} \quad \text{ClO}_2$$

Obvious route:

Starting material was made out of citronellol, the stereogenic centre is here already present in the right configuration. Task for you: How can the starting material above be made from citronellol?


Problem:
The diketone starting material has lots of degrees of freedom and only 20-25% yield could be obtained for the dienone. Therefore it was tried to make the diketone more rigid and thus give the system less opportunity to move.
Synthesis of \((R)\)-Muscone

Interesting observation: Only the Z-double bond reacts:

Takahashi for calculations and experiments:  
*TL* 1992, 33, 7561  
*Chem. Lett.* 1997, 1291

Used computational methods to calculate on which points on the ring substituents have to be attached to make the ring less flexible.

Yields for Z-isomer: 37%  
E-isomer: 64%

The calculations revealed that a E-double bond at the site shown make the system much more rigid and hence reduce the degrees of freedom which usually causes a problem in the synthesis of macrocycles.

Synthesis by Nicolaou et al: *JACS*, 1998, 120, 5132

- Use of metathesis reaction
Synthesis of (R)-Muscone

The **Grubbs I** catalyst doesn’t work for gem-disubstituted olefins as the case in citronellal, therefore the double bond had to be cleaved and converted to a methylene-unit (which easily undergoes a metathesis reaction).

In case of a protection of the OH group with TMS better yields were observed than without.

The **Grubbs II** catalyst is able to carry the metathesis reaction out even with sterically hindered double bonds.

Even though this is a highly efficient route it has no industrial application due to the large amounts of solvent needed for high dilution reactions.

**Industrial Synthesis of Muscone**

**Synthesis using a C-3 and a C-12 building block**

---

More resources available at www.chemistforchrist.de
12-membered macrocycles are inexpensive and therefore good starting materials for an industrial synthesis.

\[
\begin{array}{c}
\text{12} \\
\bigcirc \\
\text{5}
\end{array}
\]

to break the bond that fuses the 2 rings together is not an easy task.

**Synthesis by Trost**  *JACS* 1980, 102, 5680

Before Trost was working on Pd (Allylic Substitution reactions etc.) he was doing a lot of works on sulfur chemistry.

A Reversible Ring-opening reaction that is controlled by thermodynamics.

**Synthon**


Allylsilanes can be used under basic or acidic conditions.

**Basic conditions:**

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{E} \\
\text{F}^- & \quad \text{OH} \\
\text{Me}_3\text{Si} & \quad \text{R}
\end{align*}
\]

The F⁻ ion is attacking the Silicon due to Si-F bonds being extremely strong.

**Acidic conditions:**

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{R} \\
\text{OTMS} & \quad \text{R}
\end{align*}
\]

The activated Aldehyde is attacked by the Allylsilane to create an intermediate where the β-Carbenium Iod is stabilized through Hyperconjugation of the Silicon.

Sulfoxide  Sulfinate  Sulfonate

Sulphur is a better nucleophile than oxygen, so in sulfinates the sulfur atom will attack the electrophile.
Synthesis of (R)-Muscone

The same is true in corresponding Phosphor analogues:

Phosphinite

**Synthesis by TROST**

1. Base
2. Br₂
3. PhSO₂Na

Alternatively:

1. Base
2. Ph−S−S−Ph

Na/Hg cleaves the C-SO₂Ph bond.
Synthesis of (R)-Muscone


[Chemical reactions and structures diagram]

If it wouldn’t be an ester, a driving force to cleave the C(1)-C(2) bond would be missing rather the C(2)-C(3) bond would be cleaved.

Even though the muscone is produced in a racemic way, the other enantiomer doesn’t smell very different but only much less intense.
**Eschenmoser Fragmentation (late 1960’s)**

The starting material is an epoxide of an α,β-unsaturated ketone. Ketone is reacted with tosylhydrazine to give an alkyne.

![Chemical reaction diagram]

**Application in the Synthesis of Muscone:**
Büchi, *Tet. Lett.* 1976, 3585

![Synthesis of (R)-Muscone]

**Mechanism for the second step:**

More resources available at
[www.chemistforchrist.de](http://www.chemistforchrist.de)
This is a pretty general reaction sequence:

This is a pretty general reaction sequence:

A very nice synthesis of (R)-muscone using enantioselective intramolecular Aldol Addition/Dehydration has been published recently.