Département de Chimie, Section Chimie Organique
Université de Fribourg (Suisse)

Synthesis and Application of an Electronically Chiral Mimic of CpFe

THESE

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A ma mère

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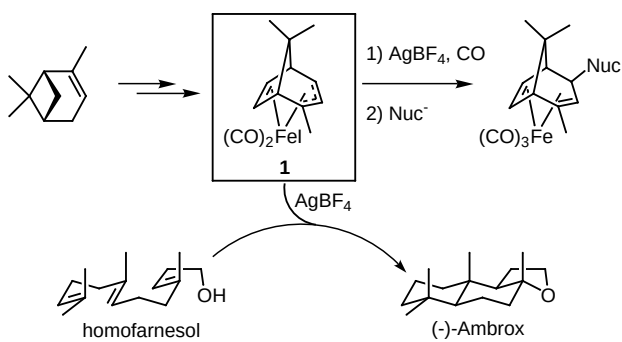
Résumé

Le domaine des composés organométalliques optiquement actifs est plus que jamais un champ d'activité important. Dans ce domaine, le complexe (-)-(1S)-dicarbonyliode[η^5-(2,8,8-triméthylbicyclo[3.2.1]oct-3,6-diène)2-yle] fer (**1**), appelé $2\text{-Me-BOD-Fe(CO)}_2\text{I}$, se profile comme une nouvelle étape dans le développement de complexes cyclopentadiènyles chiraux apparentés.

L'étude de la réactivité du complexe **1** a démontré que le système η^5 discontinu ainsi que sa chiralité inhérente le différencient des complexes apparentés comme FpI (η^5-$(\text{C}_5\text{H}_5)\text{Fe(CO)}_2$I). Plus stable que FpI, le seul moyen de l'activer de manière utile est l'utilisation de sels d'argent, par exemple AgBF_4, qui génèrent un complexe cationique insaturé, capable de compléter sa sphère de coordina-



tion soit en acceptant un ligand fortement électrodonneur (par ex. CO) soit en complexant une double liaison. Dans le premier cas, le complexe tricarbonylé cationique ainsi obtenu est stable et peut subir une attaque régiosélective d'un nucléophile formant ainsi un complexe dièniques, qui, après décomplexation, fournit d'intéressantes molécules organiques. Dans le deuxième cas, la faible

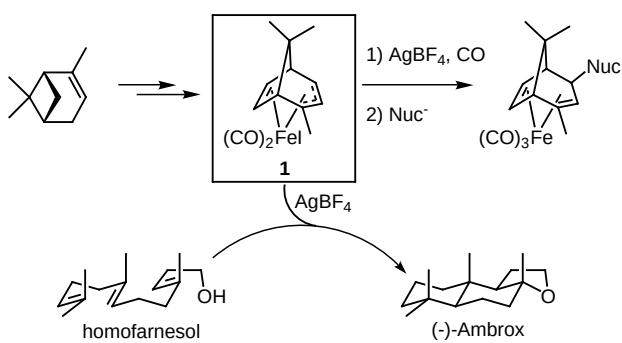
acidité de Lewis de $2\text{-Me-BOD-Fe(CO)}_2^+$ initie une cyclisation tandem cascade si la double liaison appartient à un polyène. Nous nous sommes particulièrement intéressés à la cyclisation de l'homofarnesol en Ambrox®, un important parfum. Malgré une faible induction asymétrique et un rendement plutôt modeste (42%), la diastéréosélèctivité s'avère très bonne ($dr \cong 80\%$). Une analyse du processus est présentée et des hypothèses concernant le mécanisme sont émises.

Afin d'optimiser et de varier les applications décrites précédemment, plusieurs dérivés de $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ ont été synthétisés en substituant le groupe méthyle stéréogénique avec des groupes électrodonneurs et des groupes électroattracteurs. De plus, comme le rendement de la synthèse de $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ chute dramatiquement lors de l'augmentation de l'échelle de sa synthèse, le contrôle de tous les paramètres concevables ainsi qu'une investigation IR en temps réel nous ont aidés à améliorer et à mieux comprendre sa synthèse.

Summary

The field of new optically active and reactive organometallic species is of tremendous interest. Within this area, (-)-(1S)-dicarbonyliodide[η^5-(2,8,8-trimethylbicyclo[3.2.1]oct-3,6-diene)2-yl] iron (**1**), called $2\text{-Me-BOD-Fe(CO)}_2\text{I}$, emerges as a new stage in the development of chiral cyclopentadienyl-like complexes.

Studying the reactivity of **1** has shown that both its non-contiguous η^5-system and its inherent chirality differentiate it from related complexes like FpI (η^5-$(\text{C}_5\text{H}_5)\text{Fe(CO)}_2$I). Of higher stability than FpI, the only means to activate it in a controlled manner is the use of silver salts, like AgBF_4, which generates an unsaturated cationic complex able then to complete its coordination sphere either with a strong electron donating ligand (e.g. CO), or by complexing a double bond. In the first case, the resulting stable tricarbonyl cationic complex



can undergo a regiospecific attack of a nucleophile forming thereby a diene complex which, after decomplexation, yields interesting organic molecules. In the second case, the weak Lewis acidity of $2\text{-Me-BOD-Fe(CO)}_2^+$ can initiate a tandem cascade cyclization if the double bond belongs to a polyene. We have focused our attention on the cyclization of homofarnesol into Ambrox®, a fragrance of importance. Although the asymmetric induction is very weak and the yield modest (42%), the diastereoselectivity is very good ($dr \cong 80\%$). An analysis of the process is presented and hypotheses about the mechanism are drawn.

In order to optimize, and to vary the applications described above, a series of derivatives of $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ have been synthesized by substituting the stereogenic methyl group with electron donating as well as with electon withdrawing groups. Moreoever, as the yield of $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ synthesis has dramatically decreased during the scale-up of its synthesis, control of all conceivable parameters and a real-time IR investigation helped us to improve its synthesis and to better understand its mechanism.

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Bn	benzyl
B.p.	boiling point
BOD	bicyclo[3.2.1]octadienyl
Bz	benzoyl
CI	chemical ionization
Cp	cyclopentadienyl
Fp	η^5-$(\mathrm{C_5H_5})\mathrm{Fe}(\mathrm{CO})_2$
DAST	(diethylamino)sulfur trifluoride
DMF	N,N-dimethylformamide
DMFDMA	N,N-dimethylformamide dimethyl acetal
ee	enantiomeric excess
EI	electronic ionization
eq.	equivalent
FAB	fast atom bombardement
GC	gas capillary chromatography
GC-MS	gas capillary chromatography - mass spectroscopy
HAS	hydroxylamine-O-sulfonic acid
IBDA	iodobenzene diacetate
IR	infra red
LTA	lead tetraacetate
M	molar
MHz	mega herz

M.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
TASF	tris(dimethylamino)sulfonium diflurotrimethylsilicate
TBAF	tetrabutylammonium fluoride
THF	tetrahdrofuran
TLC	thin layer chromatography
UV	ultra violet
VIS	visible

Part I

Theoretical Part

Chapter 1

Introduction

This work belongs to organometallic chemistry, a fascinating domain because it lies at the intersection of organic and inorganic chemistry: many functional groups can change their reactivity once complexed with transition metals. Organometallic chemistry exploits this intervening change of reactivity on the level of the organic molecule in order to transform the ligand even with reactions difficult with the free ligand. Once the transformations are completed, the ligand can be released.

The huge variety of transition metals and their combinations allow this domain to be theoretically boundless. But, unlike the ones, that are highly toxic (i.e. Os, Hg, ...) and expensive (i.e. Rh, Pd, ...), iron is not limited to catalytical applications. Indeed, iron is not only an environementally friendly metal, but also a cheap source: it is abundant (4.5% of the lithosphere), omnipresent in nature and above all it plays a vital role in animal and vegetal life (think about haemoglobin, ferredoxins, cytochromes, photosynthesis, ...). However, although stoechiometric applications with iron are conceivable and practicable, catalytic reactions continue to draw considerable attention, even if iron remains nowadays a sparsely documented catalyst compared to other elements of the first period and is negligible compared to the highly used catalysts of the second and third transition metal row of the periodic table. Thus there is room for improvement, especially concerning stereoselective processes.

Organometallic compounds containing chiral ligands have recently been regarded with intense interest as potential mediators of enantioselective transfor-

mations. Their development has been closely connected to the discovery of new optically active and reactive organometallic complexes, especially those containing chiral cyclopentadienyl ligands. Nevertheless, their development seems to be rather limited since it involves so far only substitution of the flat cyclopentadienyl. Only three exceptions were described in the literature: the η^5-pyrrolyl system of Van Vranken [1], the tropine derived ligand of Bergman [2] and the carborane ligand of Stone [3].

Recently, Jacques Raemy [4], studying the reactivity of tricarbonyl iron complexes towards organolithiated compounds, has isolated a new complex **1**, whose structure shown in figure 1.1, is strongly reminiscent of the widely used FpI (Fp= cyclopentadienyl(dicarbonyl) iron moiety) because it possesses two carbonyls, one iodine, and a fragmented cyclopentadienyl unit. Furthermore, **1**, called $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ (where BOD stands for the 6,6-dimethyl**B**icyclo[3.2.1]**O**cta**D**ienyl system), is chiral, and this lets us expect a very promising future for this complex.

The aim of this work was also to study the synthesis and the reactivity of complex **1** and of some of its derivatives, in addition to the search for applications. All the concepts used for this work will be presented in the next chapters. The subjects studied within this Ph.D. thesis will be described in details in the "results and discussion" part. A subject like the *Synthesis and Applications of electronically chiral mimics of CpFe* can't be processed exhaustively with only one Ph. D. thesis, which remains after all an exploratory work, and will lead to further investigations. For that reason the second part will conclude with the presentation of several outlooks issued from this work.

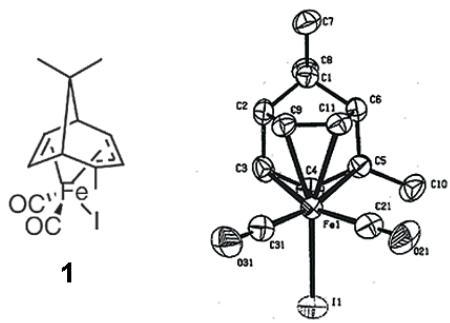


Figure 1.1: Structure and X-ray of 2-Me-BOD-Fe$(CO)_2$I

Chapter 2

Iron carbonyls in synthesis

The chemistry of transition metal carbonyls dates to the discovery of nickel tetracarbonyl by Monde in 1891[5]. Carbon monoxide coordinates to virtually all transition metals, and a prodigious number of complexes are known; among them cyclopentadienyl iron carbonyls have found numerous applications and continue to arouse the interest of many chemists.

2.1 Iron: an omnipresent element

2.1.1 Abundance and importance

Iron constitutes 4.5% of the lithosphere and is there the most abundant metal after aluminium (figure 2.1 on page 9 [6]). It is also a vital constituent of vegetal and animal life: it is an essential element for almost all organisms (exception: bacteria of lactic acid [7]), and microorganisms (more than 200 different bacteria, yeasts and mushrooms are known nowadays to incorporate iron). For example, the iron-sulfur clusters are essential to the photosynthesis, the cell breathing and the nitrogen fixation, and they also catalyze redox and non redox process (i.e. in hydrogenases) and act as O_2 detectors. Moreover, the [4Fe-4S] center is involved in endonuclease III, an ADN-repairing enzyme. In the human body iron is the most important transition metal (figure 2.1 on page 9 [7]), and is present in several heme and non-heme protein that play an important role in breathing (haemoglobin) and in the electron transport chain (cytochromes, ferredoxins). Thus, its lack procures several diseases, from which the well-known anaemia.

As a consequence of its abundance and its omnipresence in nature, iron is not only an environmentally friendly metal (its degradation gives the non-toxic rust and a lot of organisms metabolize it), but also a cheap source compared to other metals (i.e. Pd, Os, Rh , ...); so that stoechiometric applications are conceivable and practicable. Although catalytic reactions continue to draw a considerable attention, iron remains a sparsely documented catalyst compared to other elements of the first period and is negligible compared to the highly used catalysts of the second row of the periodic table. Thus, there is room for improvement, especially concerning the iron carbonyls, an important group in organometallic chemistry. This chapter will focus on their origin, their properties and their applications.

2.1.2 From ores to carbonyls

Iron is not found as a free metal in nature, because the pure silvery and lustrous metal is very reactive chemically, and it rapidly corrodes, especially in moist air or at elevated temperatures to give hydrated iron oxide ($Fe_2O_3 \cdot H_2O$) [8]. This does not protect the iron core to further reaction since the oxidized iron flakes off. This process is called rusting and is familiar to any car owner. On heating with oxygen in the absence of H_2O, the iron gives the oxides Fe_2O_3 and Fe_3O_4 (equations 1 and 2). Iron is therefore found mostly as haematite (iron oxide, Fe_2O_3), and in other minerals such as magnetite (iron oxide, Fe_3O_4), which is seen as black sands on beaches. Nearly all iron produced commercially is used in the steel industry and is made using a blast furnace, in which Fe_2O_3 is reduced with carbon as coke (equation 3). Nowadays it is believed that the actual reducing agent is carbon monoxide [8].

Small amounts of pure iron can be made through the purification of crude iron with carbon monoxide. The intermediate in this process is iron pentacarbonyl, $Fe(CO)_5$, a musty smelling, yellow volatile oily complex[1] which is easily flushed from the reaction vessel leaving the impurities behind. The carbonyl decomposes on heating to about 250°C to form pure iron powder (equation 4). Other routes to small samples of pure iron include the reduction of Fe_2O_3 with hydrogen.

[1] Pentacarbonyliron is toxic, but its relative high vapor pressure allows it to be handled and it can be easily decomposed in the presence of hydrochloric acid or nitric acid.

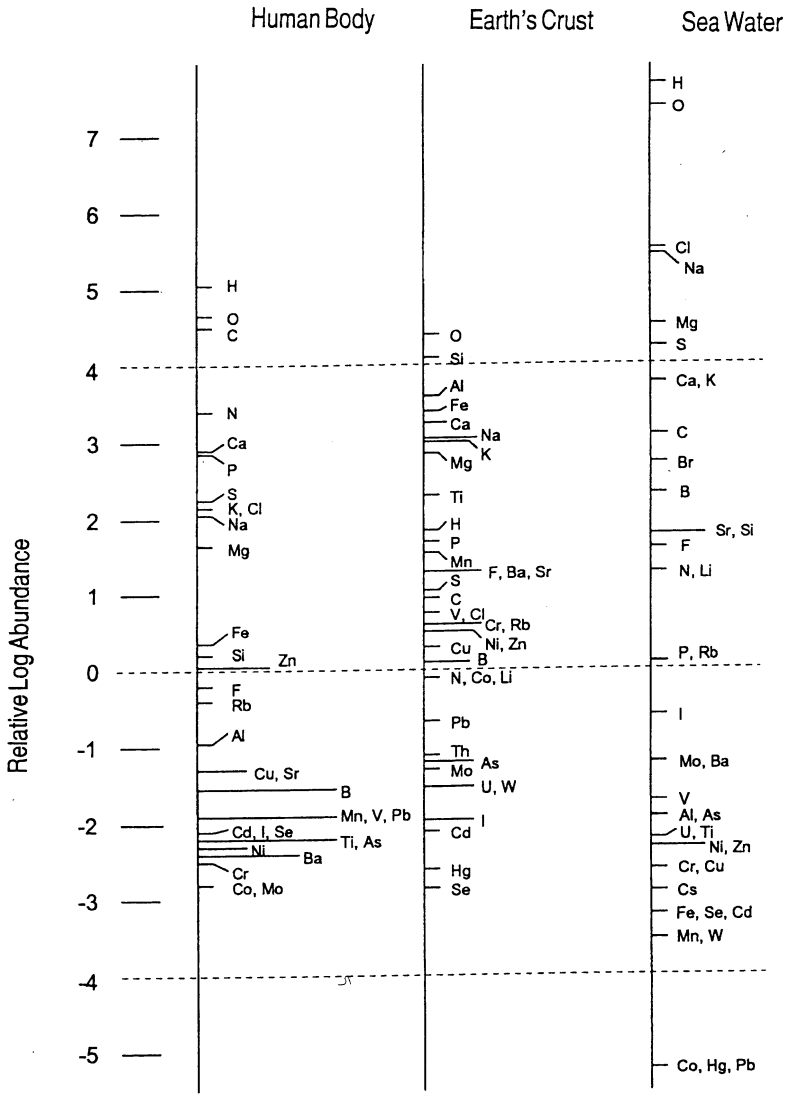


Figure 2.1: Abundance of iron

$$4\,Fe + 3\,O_2 \longrightarrow 2\,Fe_2O_3 \quad (1)$$

$$3\,Fe + 2\,O_2 \longrightarrow Fe_3O_4 \quad (2)$$

$$2\,Fe_2O_3 + 3\,C \longrightarrow 4\,Fe + 3\,CO_2 \quad (3)$$

$$Fe + CO \longrightarrow Fe(CO)_5 \xrightarrow{250°C} Fe + 5\,CO \quad (4)$$

2.2 Complexation methods [9, 10]

The iron carbonyl complexes can be obtained from one of the three stable commercially available iron carbonyl sources: pentacarbonyliron, nonacarbonyldiiron and dodecacarbonyltriiron. $Fe_2(CO)_9$ [11] and $Fe_3(CO)_{12}$ [12, 13] are obtained from $Fe(CO)_5$, discovered independently by Monde [5] and Berthelod [14]. The active species complexing double bonds is usually the unsaturated $Fe(CO)_4$, obtained photochemically [15], thermically [9], sonochemically [16] or chemically [17] from one of the three carbonyl sources. A general overview is given in figure 2.2.

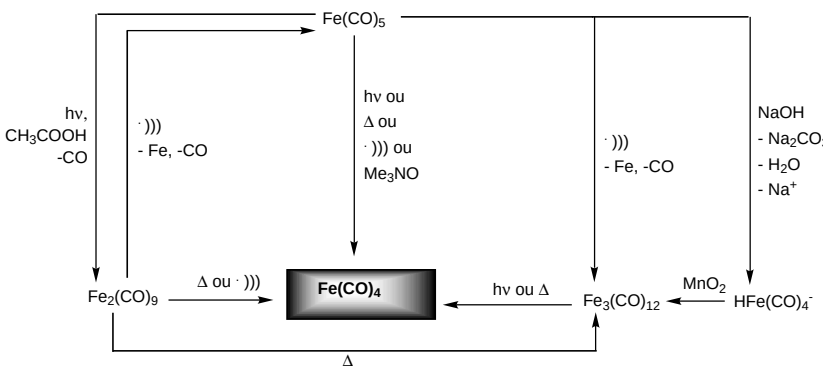


Figure 2.2: Possible complexation methods

Table 2.1 on the next page shows that the energy required to remove one carbonyl group from an $Fe(CO)_x$ fragment varies considerably with the value of x [18]. The first dissociation requires the most amount of energy, while the dissociation of one CO from $Fe(CO)_4$ does not require much energy. Thus, the decomposition of iron pentacarbonyl would lead essentially to iron tricarbonyl species (figure 2.3 on the facing page). Photolysis of iron pentacarbonyl leads to CO dissociation with a quantum yield of 0.8 and the formation of $^3Fe(CO)_4$ [15, 19]. Overall substitution of two carbonyls can be explained by

Table 2.1: Dissociation of CO

reaction	E_a [kcal/mol]
$Fe(CO)_5 \rightarrow Fe(CO)_4 + CO$	$55.3(\pm 12)$
$Fe(CO)_4 \rightarrow Fe(CO)_3 + CO$	$5(\pm 9)$
$Fe(CO)_3 \rightarrow Fe(CO)_2 + CO$	$32(\pm 7)$
$Fe(CO)_2 \rightarrow Fe(CO) + CO$	$23(\pm 7)$
$Fe(CO) \rightarrow Fe + CO$	$23(\pm 7)$

a labile triplet intermediate, $^3Fe(CO)_4L$, that competitively loses one more CO and intersystem-crosses to the ground-state singlet. The relative rate of these processes depends on the structure of L and on the ratio of $^3Fe(CO)_4L$ and $^3Fe(CO)_3L$.

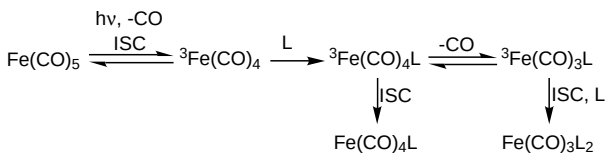


Figure 2.3: Photolysis of $Fe(CO)_5$

Another method for obtaining iron carbonyl complexes consists of transferring the $Fe(CO)_3$ entity from a labile complex to an appropriate ligand [20]. Among these transfer reagents are the well-known benzylideneacetone complex (BDA) [21], the widely applicable Grevels complex [22] and the azadiencomplexes of Knölker [20] (see figure 2.4 on the next page). Chiral versions of this methodology were also developed in the last few years [20, 23, 24] .

2.3 The cyclopentadienyl unit in iron carbonyl complexes

2.3.1 Introduction and focal orientation

There are several types of iron complexes. In some of them, the organic ligand is either σ- or π-bounded to the metal center. We distinguish between η^1, η^2,

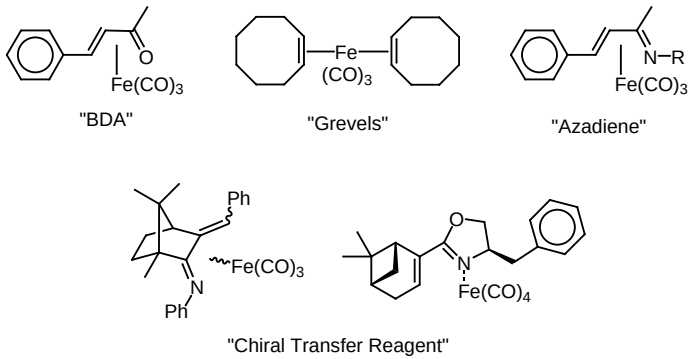


Figure 2.4: Transfer reagents

η^3, η^4, η^5 and η^6 complexes, each of them having their own characteristics. An exhaustive review of all the types of iron complexes and their applications largely exceeds the framework of this thesis. A lot of reviews and books on this subject have been written [9, 25].

A restriction to η^5 complexes seems appropriate since the main part of this thesis deals with $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ (**1**) (figure 1.1 on page 5), which in a larger sense belongs to this group. Although ferrocene is probably the most widely known representative of this class, it will not be introduced, because its sandwich structure differs too much from **1**.

2.3.2 Precursors of $\mathrm{CpFeL_2}$

The cyclopentadienyl ligand (abbreviated Cp) has played a major role in the development of organometallic chemistry and continues to be the archetype of a cyclic polyene. The precursors for the complex containing the Cp unit are either the red crystalline dimer $\mathrm{[Cp(CO)_2Fe]_2}$ $(\mathrm{Fp_2})$, which is prepared by reaction of cyclopentadiene with iron pentacarbonyl (see figure 2.5 on the next page) [26], or the orange crystalline ferrocene. Treatment of ferrocene with $\mathrm{AlCl_3}$ in presence of aromatic compounds or under CO atmosphere affords arene complexes [27] or respectively $\mathrm{CpFe(CO)_3}^+$ cation [28] that can be further transformed into $\mathrm{CpFeLL'L''}$ species [29–31]. But the most interesting chemistry is provided by $\mathrm{Fp_2}$ that is converted into $\mathrm{[Cp(CO)_2Fe]Na}$ by reduction with sodium/mercury amalgam [32], and used in situ as a precursor for most of the

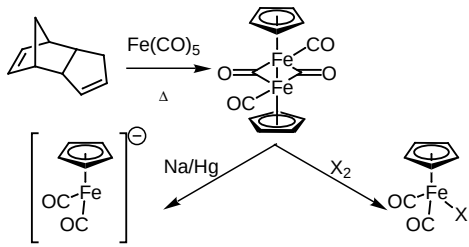


Figure 2.5: Basic transformations of $\mathrm{Fp_2}$

other iron complexes (figure 2.5). This dimer can also be transformed with halogens into the corresponding FpX complex, a very similar species to $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ (**1**).

2.3.3 FpI

A species belonging to the $\mathrm{CpFeLL'}$ family deserves detailed attention because it resembles the main complex of this thesis ($\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$) and has found numerous applications in organic synthesis. This species includes iron complexes bearing the cyclopentadienyl(dicarbonyl)iron moiety (Fp).

Reactivity

Because of their great stability, 18 electron compounds maintain their ligand bound to the metal center under rather harsh conditions and it is possible to carry out a variety of transformations on the Cp ligands and on the other ligands. Moreover, the application of η^5-cyclopentadienyl ligands as a support for introducing chirality is particularly attractive due to the large array of possible structural modifications of the ligand which are synthetically approachable, and due to the impressive bond strengths with which this ligand is attached to transition metals (up to 118 kcal/mol). This coordination is so strong that there is almost no chance of ligand association resulting in racemization [33]. Pentamethylcyclopentadienyl ($\mathrm{Cp^*}$) confers greater stability than the unsubstituted cyclopentadiene ligand on iron compounds.

As a consequence of strong electron-withdrawal by the electropositive metal center, the carbonyls can be subjected to nucleophilic attack. Moreover if a

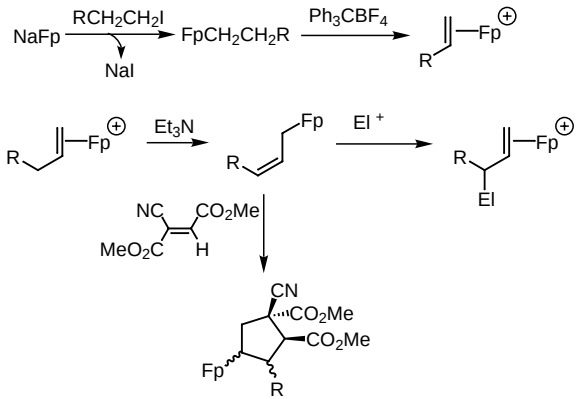


Figure 2.6: Applications of NaFp

coordination site is vacant, electrodonating molecules or a double bond are easily complexed, and the alkene centers of cationic olefin-$\mathrm{Fe(CO)_2Cp}$ complexes are rendered highly susceptible toward nucleophilic attack.

Finally, planar-chiral cyclopentadienyl-metal complexes are advantageous as catalytic and stoichiometric mediators for asymmetric organic reactions because the electron donnor/acceptor properties and steric bulk of the cyclopentadienyl ligands are easily altered.

Applications [34]

In the presence of allylic halides, the highly nucleophilic sodium dicarbonyl (cyclopentadienyl) ferrate gives σ-alkyl-Fp complexes in good yield. Such complexes can be further deprotonated to give cationic η^2-alkene-Fp complexes. The allyl-Fp complexes react with various electrophiles [35], and with electron deficient alkenes resulting in a tandem electrophile/nucleophile addition sequence to give products corresponding to an overall [3+2] cycloaddition [36, 37] (figure 2.6).

The dimer can also be oxidatively cleaved by bromine or iodine to give the corresponding $\mathrm{CpFe(CO)_2Br/I}$. Removal of the halogen with a suitable Lewis acid (i.e. $\mathrm{AlCl_3}$) [38] or a silver salt [39] in presence of an unsaturated bond forms cationic dicarbonyl(cyclopentadienyl)alkene, alkyne or allene iron complexes,

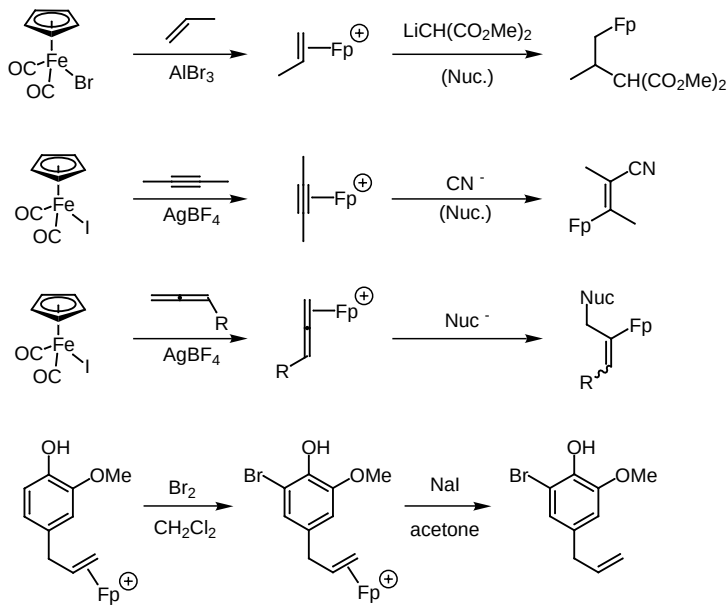


Figure 2.7: Applications of FpX

which were extensively examined in carbon-carbon bond formation, due to the observed activation of the unsaturated ligand towards nucleophilic addition or polymerization. The cationic Fp can also be used as a protecting group of alkenes, alkynes or allenes (see figure 2.7).

Additionally the reaction of $[\mathrm{CpFe(CO)_2Cl}]$ or $[\mathrm{CpFe(CO)_2Br}]$ with a Lewis acid (e.g. $\mathrm{AlCl_3}$) in the presence of aromatic compounds affords arene-FeCp complexes, a huge field in organometallic chemistry. An extensive review published by Astruc [40] in 1983 covers this field.

Whereas the cyclopentadienyliron dicarbonyl species (Fp) is one of the most widely studied organometallic families, pentamethylcyclopentadienyl (η^5-$\mathrm{C_5Me_5}$ $= \mathrm{Cp^*}$) homologues are less common. This ligand has proved to be useful for the organometallic chemistry of iron as well as many other transition metals. Iron sandwich compounds are known with the $\mathrm{Cp^*}$ ligand: decamethylferrocene was reported by Bercaw [41] together with a very useful synthesis of pentamethylcyclopentadiene and $[\mathrm{Cp^*Fe(CO)_2]_2}$ (Fp'$_2$) was reported by King [42]. Catheline

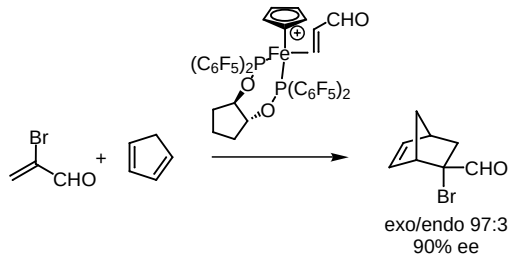


Figure 2.8: Diels Alder reaction catalyzed by a chiral CpFe

and Astruc reported the very important synthesis of $\mathrm{Fp'Br}$ [43], as well as other coordinatively unsaturated piano-stool $\mathrm{Fp'}$ complexes [29] (i.e. $\mathrm{Fp'(CO)^+}$).

Chirality [44]

The chirality in cyclopentadienyl metal complexes can have several different origins. An organo- metallic complex may be chiral due to the coordination of chiral or prochiral ligands to a nonstereogenic metal; this is the ligand-derived chirality. Alternatively, the chirality may arise from an asymmetric arrangement of achiral ligands around a stereogenic metal center (metal-centered chirality) or from a combination of both.

One of the most popular example for the metal-centered chirality is the iron chiral auxiliary $[(\eta^5\text{-}\mathrm{C_5H_5})\mathrm{Fe(CO)(PPh_3)}]$ that has been extensively developed over the past few years for the asymmetric synthesis of organic molecules generally via carbon-carbon bond formation. This iron chiral auxiliary exerts powerful stereochemical control in a wide variety of reactions of attached acyl ligands including alkylations [45], aldol reactions, tandem Michael additions and alkylations [45], Diels-Alder reactions [46] and others. Optical activity is relayed in this case and is lost upon work-up.

Although transition metal complexes attached to the most common auxiliary, chiral chelating diphosphines, have been used successfully in several cases as seen in figure 2.8 [47], their stereodifferentiating ability can suffer due to their lability as complexing agents. For an efficient transfer of asymmetry to a substrate the chiral ligand must be bound to the metal during the stereodifferentiating step. The relative weak bonding ability of many such ligands is a potential

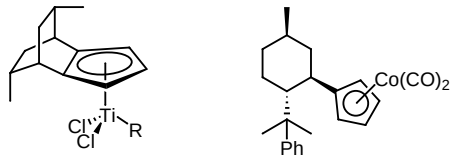


Figure 2.9: Homotopic like Cp

drawback that limits their applications and invites displacement of chirality to a more stable system, i.e. the η^5-cyclopentadienyl unit because of the superior tenacity with which it attaches itself to transition metals, involving bond strengths as high as 118 kcal mol^{-1}. Chiral cyclopentadienyl ligands are becoming recognized as potent chiral auxiliaries for asymmetric organometallic reactions. Despite their promise, relatively few chiral cyclopentadienyl ligands have been prepared when compared to the many examples of other chiral ligands such as phosphines, amines and alcohols. It is useful to recognize three types of cyclopentadienyl ligand-derived chirality in cyclopentadienyl complexes, which depend on how the two faces of the ligand are related to one another (table 2.2). Two examples of homotopic cyclopentadienyls are shown in figure 2.9: the

Table 2.2: Topicity of $\mathrm{CpMLL'L''}$

topicity	Chirality on	
	center	face
homotopic	√	
enantiotopic		√
diastereotopic	√	√

C_2-symmetrical ligand in the Ti complex is based on the bicyclo[2.2.2]octane framework [48, 49]. The cobalt complex is used in Vollardt's cyclization [50]. In either case, chirality rests outside the Cp ligand. Other cyclopentadienyls can be enantiotopic like the ruthenium complex shown in the figure 2.10 on the following page. This complex includes an additional bridged ligand with the Cp ring [51]. There is a planar chirality. Finally some diastereotopic cyclopentadienyls are shown in figure 2.11 on the next page. The zirconium complexe includes a BINAP derivative to bridge the two Cp's derivatives [52]. This complex is used for catalytic polymerization or hydrogenation of olefins. In the case of the iron complex [33], the chirality resides in the planar chirality and a chiral

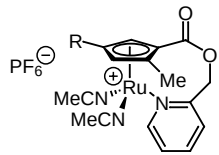
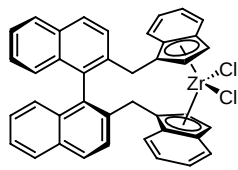


Figure 2.10: Enantiotopic like Cp



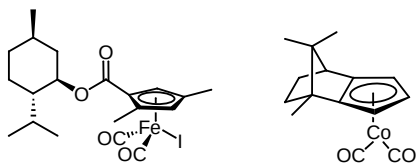


Figure 2.11: Diastereotopic like Cp

substituent derived from menthol. The last diastereotopic example is given by a fused Cp with a camphor molecule also used in Vollhardt's cyclization but with less success than the previous cobalt complex [50].

2.3.4 New classes of ligands derived from Cp

Concentrating our attention on the cyclopentadienyl derived chirality, we can conclude that the development of such complexes involves so far only substitution of the flat cyclopentadienyl. Except the development of metal complexes based on the corresponding η^5-pyrrolyl which remains a sparsely documented class [1], and a complex reported recently by Bergman [2] where the heteroatom from the tropine derived ligand is used to complex the metal center (figure 2.12 on the facing page), the actual strategies seem to be rather limited.

A new type of complex is illustrated by $2\text{-}\mathrm{Me}\text{-}\mathrm{BOD}\text{-}\mathrm{Fe}(\mathrm{CO})_2\mathrm{I}$ (**1**), the complex at the origin of this work. In this organometallic molecule, the organic ligand

exhibits an inherent chirality. In other words, the chirality originates from the ligand itself and not from its substitution. For a Cp like ligand this means that the η^5-skeletton of the Cp should be broken in an $\eta^2\eta^3$-system. Moreover, this model eliminates the question of face topicity because only one face can be complexed. This reinforces the idea of inherent chirality, and substitution of the allylic system desymmetrizes this part of the molecule and polarizes the allylic system. The $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ (**1**) does not only fulfil the mentioned criterions, but it also originates from a cheap representative of the chiral pool by a few step transformation.

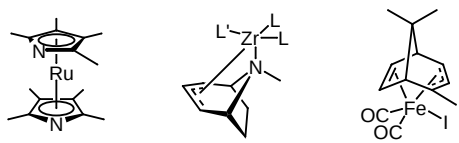


Figure 2.12: New classes of Cp

Before concluding, Stone [3] described recently a new type of iron complex based on a related Cp skeleton. In fact the transition metal ion is ligated both by carbonyl groups and a $[\eta^5\text{-}7\text{-}\mathrm{CB_{10}H_{11}}]^{3-}$ icosahedral cage fragment like the one depicted by the figure 2.13. The reactivity of $[\mathrm{Fe(CO)_3}(\eta^5\text{-}7\text{-}\mathrm{CB_{10}H_{11}})]^-$ is very different from the $[\mathrm{Fe(CO)_3}(\eta^5\text{-}\mathrm{C_5H_5})]^+$ because the carborane ligand has a non-spectator role and reacts readily [3, 53].

2.4 Conclusion

Iron carbonyl complexes bearing the cyclopentadienyl unit find a rapidly growing number of applications in organic synthesis, because the metal exerts a

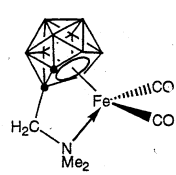


Figure 2.13: A new type of complex

predictable regio- and stereospecific influence on the location of the reaction. In case of enantioselective reactions involving complexes containing a $\mathrm{CpFeLL'}$ unit, the chirality resides either on iron (L $\neq$ L') or on the auxiliary ligands L and/or L'. Iron complexes with modified chiral Cp units are known but have found no applications in synthesis so far. A further evolution to the complexes described in the last section of this chapter, is provided by the $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ complex (**1**), because the chirality is inherent to the η^5-system and this will probably influence the outcome of reactions. Such iron complexes in which the organic ligand does not contain a contiguous π-system are much less investigated. However, its structure and its reactivity is a sign of large applications potential . Indeed, by virtue of its highly electrophilic nature, the iron center can complex a double bond and this iron-olefin π complex allows additional functionality to be introduced directly onto the double bond by a nucleophilic addition process. Moreover, if the double bond belongs to a polyolefinic chain terminated by a nucleophile, a tandem cyclization would be induced. For example, the $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2}^+$ complex should promote the tandem cyclization of homofarnesol into Ambrox®, a commercially important product in the perfume industry.

Chapter 3

Tandem reactions

As one of the fundamental objectives of organic synthesis is the construction of complex molecules from simpler ones, the importance of synthetic efficiency becomes immediately apparent[54]. Thus the creation of many bonds, rings and stereocenters in a single transformation is a necessary (though not sufficient) condition for high synthetic efficiency. Tandem reactions fulfil this prerequisite with the advantage of diminishing the reaction waste as well as the amount of solvent. These advantages reduce the pollution of our environment, which is a major issue of today. The ultimate, perfect situation would be a single-step synthesis...[54]

The concept of tandem reactions as a strategy for the rapid construction of complex structure is well-known and has been reviewed [54–57]. Within the universe of tandem reactions (for example tandem Knoevenagel-Hetero-Diels-Alder [58], Claisen-Cope rearrangement [59] cycloaddition/N-acylium ion cyclization [60], cyclopropanation-Cope rearrangement [61], ...), a tandem sequential process was used in the design of 2-Me-BOD-$\mathrm{Fe(CO)_2I}$ (**1**) and was chosen as first test case for a hopefully catalytic application of a tandem cascade cyclization of a suitable polyene into (-)-Ambrox®.

3.1 Definition [54,55]

A tandem reaction is composed from several reactions that occur one after the other without isolation of the intermediates. Cascade (previously also called

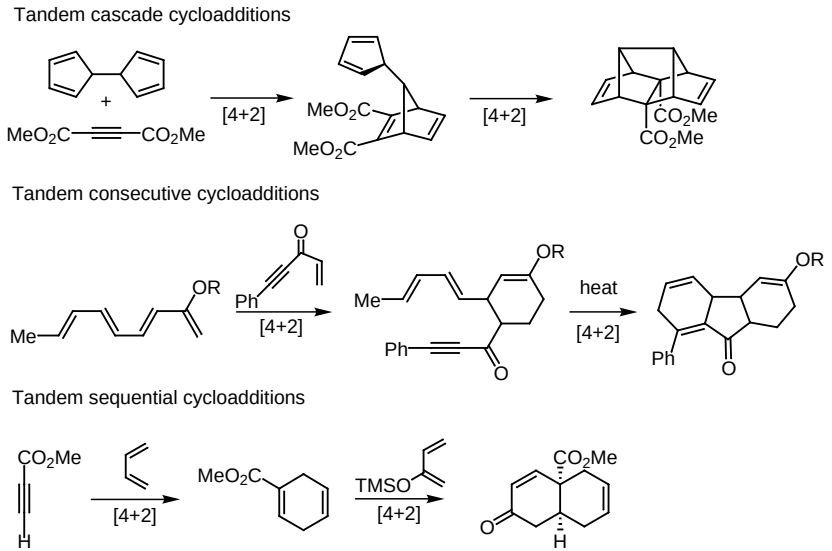


Figure 3.1: Types of tandem reactions

domino), consecutive, and sequential specify how the two or more reactions follow each other (Figure 3.1 shows typical examples). In a *tandem cascade* process, the reactions are intrinsically coupled, i.e. each subsequent stage can occur by virtue of the structural change brought about by the previous step under the same reaction conditions. In a *tandem consecutive* reaction, the first step is necessary but not sufficient for the tandem process, i.e. external reagent, mediator, catalyst or changes of reaction conditions are required to facilitate propagation. Finally in a *tandem sequential* process the second stage requires the addition of one of the reaction partners or another reagent. Note that an iterative process is the repetition of the same reaction, that can be performed as a domino, consecutive, sequential or as one single reaction.

3.2 Tandem cascade cyclization

A tandem cascade cyclization of an acyclic starting material is a very interesting alternative to the laborious step by step convergent ring synthesis. In such a field the initiation and the termination of the cascade cyclization is the crucial

challenge, as well as the controlled formation of several new chiral centers.

Such cascade cyclization can be initiated with promotors or catalysts. Cationic biomimetic cascades, that follows the biogenetic isoprene rule, belong to such reactions [62–64]. Recently these reactions were scheduled in new ways with internal oxygen nucleophiles like carbonyl, hydroxy or β-ketoester groups. As can be seen in figure 3.2 trans,trans-farnesylacetone furnishes, under Nishizawa conditions, a cyclic enolether that can be further transformed to sclareoloxide [65, 66]; a precursor of a smell like Ambra compounds.

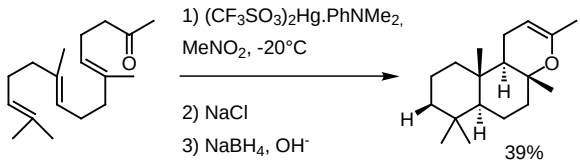


Figure 3.2: Cyclization of trans, trans-farnesylacetone

Most of the time, tandem cyclizations are initiated by several other electrophiles like protons, bromonium ion, Lewis-acid [67] and benzenselenenyl triflate [68]. Since the eighties, radical cascade cyclizations have gained a growing interest in natural products syntheses [56].

For a long time, the reactions catalyzed by transition metals did not play a paramount role in the synthesis of complex organic structures, but this has profoundly changed. A lot of cascade cyclization catalyzed by Pd, Rh and Co have been reported in the literature [55, 56]. Recently Yamamoto published the synthesis of (-)-Ambrox® via a tandem cascade cyclization of homofarnesol catalyzed by tin chloride (figure 4.22 on page 43) [64].

Chapter 4

Ambrox®

The tricyclic ether (3aR,5aR,9aS,9bS)-3a,6,6,6,9a-tetramethyldodecahydro-naphtho[2,1-b] furan, commonly called Ambrox®, a registered trademark by Firmenich, is the commercially most important ambergris chemical. The history of this material is a fascinating chapter of natural product and synthetic chemistry with a commercial background. Today, (-)-Ambrox® costs around 1000 US dollars per kg, and the world consumption of it and of almost identical products commercialized under a different name (e.g. Ambroxan®(Henkel)) is over 30 tons per year. Although present in traces in natural ambergris, it was first synthesized from sclareol by oxidative degradation.

4.1 Ambergris: origin and characteristics [69]

Since ancient times, ambergris has been one of the most highly valued parfumery material, because apart from its own fragrance, it is an exceptional fixator. The name is derived from the French, ambre gris, gray amber, distinguishing itself from brown amber, the fossilized resin. It is a metabolic product of the sperm whale (*Physeter macrocephalus* L., figure 4.1 on the following page [70]) which accumulates as concretions in the gut. It is usually associated with the beaks of the whale's principal food, the common cuttlefish, *Sepia officinalis*. It consists of 80% ambrein, a cholesterol derivative which may be either an indigestible component of the squid or a secretion of the whale's gut in response to the constant irritation caused by the sharp beaks of the squid. It is thought that the production of ambergris is pathological in nature but there

is limited evidence for this assumption. In the gut of the whale the ambergris is a black, semiviscous and foul-smelling liquid. On exposure to sunlight and air it quickly oxidizes and hardens to a pleasantly aromatic, marbled, grayish, waxy pellucid substance in which the squid beaks are still embedded. It possesses a subtle odor reminiscent of seaweed, wood and moss but with a peculiar sweet, yet dry undertone of unequalled tenacity.

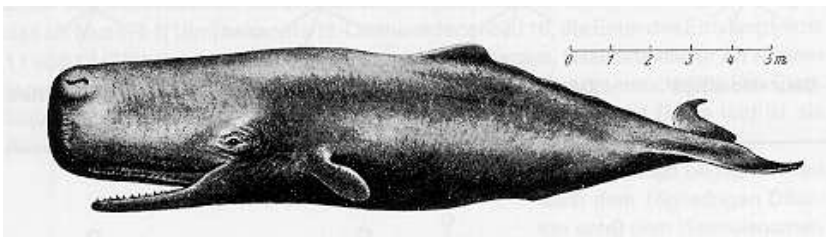


Figure 4.1: The sperm whale

Ambergris which is released into the sea takes the form of lumps which are rarely more than 20 cm in diameter. The largest piece ever found weighed 400 kg (figure 4.2 on the next page [69]) and was taken from the intestine of a whale which had been killed in 1954 by the whaling vessel Southern Harvest.

4.2 Ambergris: historical background [69]

From ancient times it has been used in the West as a fixator for rare perfumes since it has the effect of making other fragrances last much longer than they would otherwise. It is said that a single drop of tincture of ambergris applied to a paper and placed in a book will remain fragrant after 40 years and that once handled, the fingers will smell of it even after several days and several washings. Before 1000 BC the Chinese referred to ambergris as lung sien hiang, "dragon's spittle perfume", because it was thought that it originated from the drooling of dragons sleeping on rocks at the edge of the sea. In the Orient it is still known by this name and is used as an aphrodisiac and as a spice for food and wine. The Japanese have also known ambergris from ancient times and called it kunsurano fuu, "whale droppings", and was used to fix floral fragrances in

Figure 4.2: The largest mass of ambergris ever recovered

perfumes. Ambergris was known to the Arabs as 'anbar and was originally called amber in the West. It was used by the Arabs as medicine for the heart and brain. The Arabs believed that raw ambergris emanated from springs near the sea. In the Thousand and One Nights, Sinbad is shipwrecked on a desert island and discovers a spring of stinking crude ambergris which flows like wax into the sea where it is swallowed by giant fishes and vomited up again as fragrant lumps to be cast up on the shore. The Greeks also believed that ambergris came from springs in or near the sea. They believed that it enhances the effects of alcohol when smelled before drinking wine or when it is added to wine.

In the West, true amber (yellow amber or Prussian amber, the "elektron" of the Greeks) and ambergris were thought to have the same or similar origins, probably because both were fragrant, rare, costly, somewhat similar in appearance and found cast up on seashores. To the earliest Western chroniclers, ambergris was variously thought to come from the same bituminous sea founts as amber, from the sperm of fishes or whales, from the droppings of strange sea birds (probably because of confusion over the included beaks of squid) or from the large hives of bees living near the sea. Marco Polo was the first Western chronicler who correctly attributed ambergris to sperm whales which he saw hunted on the island of Socotra in the Indian Ocean but which he also thought vomited it up after having eaten it in the depths of the sea. In 1783 the botanist Joseph Banks presented a paper (*Western confusion over ambergris and its origins*) by Dr.

Franz Xavier Schwediawer at the Royal Society. It correctly identified ambergris as a production of the often morbidly distended gut of sick sperm whales and associated its production with the beaks of the whale's principal foods, squid and cuttlefish. In 1820 two French chemists, Joseph-Bienaim Caventou and Pierre-Joseph Pelletier [71] first isolated, characterized and named ambrein, the major constituent of ambergris. Since then a great deal has been published on the chemistry of compounds with an ambergris-like scent, especially the more fragrant oxidative derivatives of ambrein such as Ambrox®.

4.3 Ambergris: a chemical insight

The ambergris, first collected on certain shores, contributed to the exaggerated hunting of the blue whale (*Physeter macrocephalus* L.). This hunting is nowadays forbidden, so that it proved to be necessary to find other access to the odorous products constituting the fragrance of the ambergris.

The ambergris materials used in perfumery nowadays are essentially entirely of synthetic or semi-synthetic origin. Compounds from various plants of the *Podocarpaceae* (pandanus family), *Salvia sclarea* (clary sage), oak moss and various fungi can be converted to ambergris-like odorants. Ambergris-like odorants can also be synthesized from chemical feedstocks with great difficulty because of the complex stereochemistry.

Before tackling the subject it is useful and interesting to recall that the ambergris owes its properties to the oxidation of its principal component ambrein, a colourless triterpene studied in 1820 by Pelletier and Caventou [71]. Ohloff could obtain the same type of degradation products performing an in vitro photooxygenation of ambrein [72]. As shown in figure 4.3 on the facing page, they are mono-, bi- and tricyclic derivatives. The oxidation with potassium chromate or permanganate of ambrein affords different products, depending on the experimental conditions, which are similar or derived either from the monocyclic part of the γ-dihydroionone, either from the bicyclic part of sclareolide (**2**) or ambrenolide (**3**). The reduction of sclareolide (**2**) provides Ambrox® (**4**), which is present in traces in ambergris and is almost certainly a degradation product of ambrein.

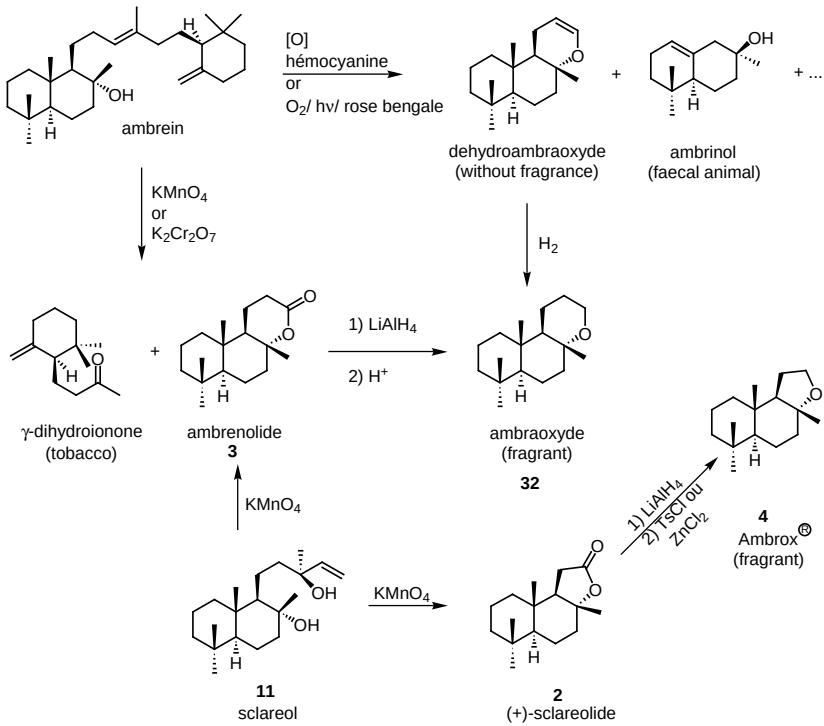


Figure 4.3: Derivatives of (-)-ambrein

4.4 Racemic Ambrox®: a chemical insight [73]

The increasing demand for Ambrox® on the one hand, and the fact that racemic Ambrox® is olfactorily very similar to (-)-**4** on the other hand, prompted different laboratories to design new syntheses of (±)-**4**. The synthesis of racemic Ambrox®, also called Cetalox® (a Firmenich trademark), is generally obtained from acyclic building blocks as well as from dihydro-β-ionone (**12**).

- **Dihydro-β-ionone (12)** is converted to the β-keto ester **13**. A tin mediated cyclization of **13** affords the bicyclic β-keto ester **14** which is further transformed to the racemic diol **15** [74] obtained with a Grignard reaction (figure 4.4 on the next page). Further dehydration affords the racemic Ambrox® **4** with an overall yield of 15% from **14** [75]. The originality of this approach consists in the transformation of **15** to (±)-**4** avoiding

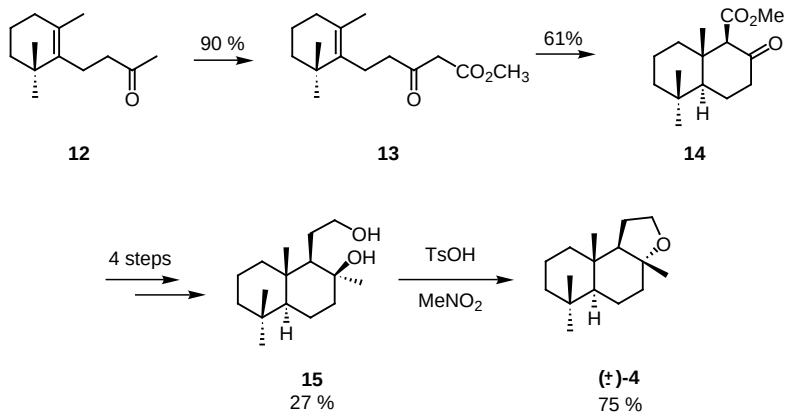


Figure 4.4: Synthesis of (±)-Ambrox® from dihydro-β-ionone

the formation of the thermodynamically more favoured iso-Ambrox (**5**). Thus a kinetical control of the reaction had to be found, since **4** is kinetically more favoured than **5**, because the steric hindrance from the angular methyl group disfavours the transition state [75]. Büchi found that performing the cyclization of the diol **15** in nitromethane in the presence of a catalytic amount of p-toluensulfonic acid suppresses to a large measure the formation of iso-Ambrox and produces (±)-Ambrox® in 75% yield [75]. The β-keto ester **13** can be obtained from geranyl acetone [76] or from cyclogeranyl bromide [74] in 10 or 31% yield, respectively. Snowden published in 1991 an alternative route starting from the β-keto ester **13** via the bicyclic enone **16** shown in figure 4.6 on page 32 [77].

- **Farnesylacetone (17).** As shown in figure 4.7 on page 32 the cyclization of **17** with mercury (II)triflate-*N,N*-dimethylaniline complex followed by demercuration affords sclareol oxide (**18**) in 23% yield [78], which is converted to (±)-Ambrox® (**4**) in 4 steps (78% yield) [79, 80]. Note that sclareol oxide can also be obtained from natural sclareol (**11**) in 63% yield (see figure 4.3 on the preceding page).

- **Homofarnesoic acid (19).** Its acid-catalyzed cyclization leads to racemic **20** in 18% yield [81–83] (figure 4.8 on page 33), which can be further transformed into racemic Ambrox® (**4**) according to the common procedure.

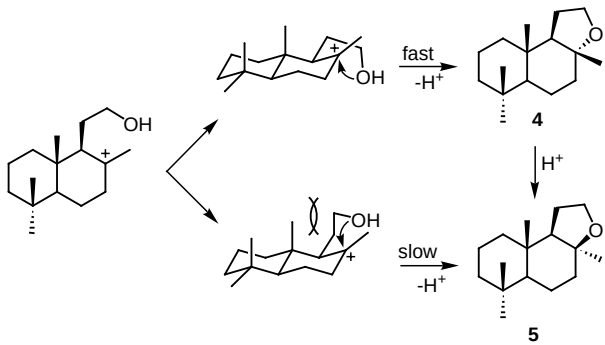


Figure 4.5: (±)-iso-Ambrox: origin

- **Homofarnesol (21).** Based on the successful cyclization of the lower homologue (*E,E*)-farnesol to drimenol [84], this low-temperature cyclization with fluorosulfonic acid was then used for the one step synthesis of (±)-(**4**) from (*E,E*)-homofarnesol (**21**) in 73% yield [85]. In a detailed study, all four stereoisomers were separately treated with fluorosulfonic acid and the product mixtures analyzed [86]. The most important result was, that under these conditions the isomerization of (*E,E*)-**21** (*Z,E*)-**21** is fast enough to compete with the cyclization. Thus pure (*E,E*)-**21** furnishes a mixture of 40% racemic Ambrox® and 35% 9-epi-Ambrox (**6**). The feasibility of the process depends on the accessibility of the all-trans homofarnesol (**21**), or the corresponding monocyclo homofarnesol, which can be cyclized to Ambrox®.

4.5 (-)-Ambrox®: a chemical insight [73]

(-)-Ambrox® (**4**) has been isolated from the absolute of *Nicotiana tabacum* [87,88]. It occurs also naturally in trace amounts in ambergris and in the essential oil of *Salvia sclarea* L., *Cistus labdaniferus* L., and *Cupressus sempervivens* L. Several syntheses of (-)-**4** have been developed since its first preparation by Hinder and Stoll in 1950 [89,90], where many are based on naturally occuring sesqui- or di-terpenes as starting material. Nowadays, (-)sclareol (**11**) is the main starting material used in industry. The lack of abundance and the relatively high price

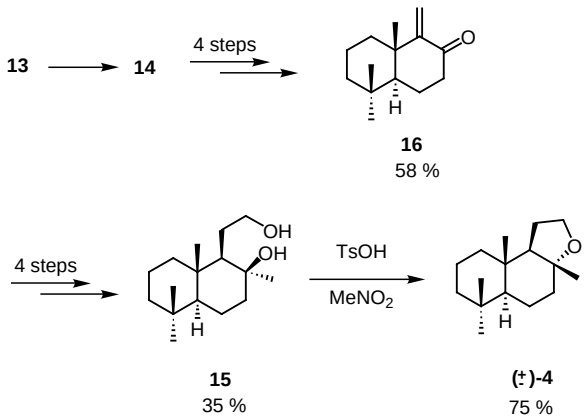


Figure 4.6: Synthesis of (±)-Ambrox® from the β-keto ester **13**

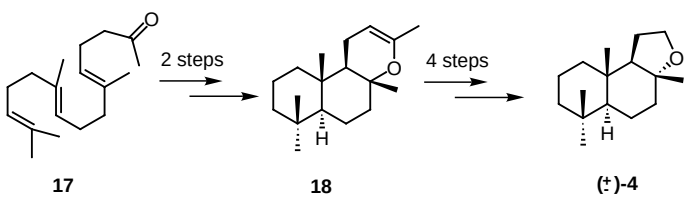


Figure 4.7: Synthesis of (±)-Ambrox® from farnesyl acetone

of (-)-Ambrox® has encouraged an ongoing search for new syntheses, whose various strategies can be classified according to the composition of the skeleton of the starting products.

4.5.1 Ambrox® from a tricyclic building block

- **l-Abietic acid (24)** is an easily available diterpenoid from pine resin. Recently, Koyama et al. [91] have reported the conversion of **24** into (-)-Ambrox® (**4**) in 15 steps with an overall yield of 7% (figure 4.10 on page 34). The prime challenge in the use of abietic acid **24** is that a major skeletal alteration is required to afford a five membered ring C. The first difficulty is the regioselective oxidation of the conjugated dou-

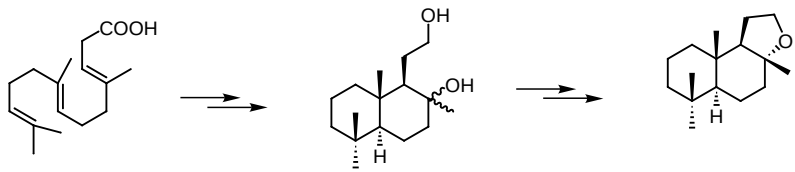


Figure 4.8: Synthesis of (±)-Ambrox® from homofarnesoic acid

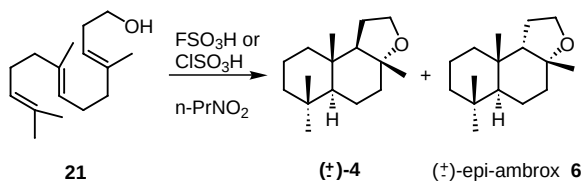


Figure 4.9: Synthesis of (±)-Ambrox® from homofarnesol

ble bond avoiding isomerization or easy aromatization of ring C. Indeed, **24** is known to be very sensitive to auto-oxidation. Koyama used a catalytic amount of osmic acid to oxidize regioselectively the double bond of ring C. Further esterification of the acid function and oxidative cleavage of the C-ring with $\mathrm{Pb(OAc)_4}$ furnishes after 5 other steps intermediate **25**. The second difficulty is the cyclization of the tetrahydrofuran ring with a controlled configuration at C-8, the only stereocenter not provided by abietic acid. Oxidation of **25** with $\mathrm{OsO_4}$, mesylation, epoxidation, reduction and cyclization with mesitylenesulfonylchloride in pyridine affords **26** with a correct configuration of the C-8 center. The alcohol is then transformed to a methyl group with the Ireland-Liu method [92, 93].

4.5.2 Ambrox® from bicyclic building blocks

- **Sclareol (11)**, a constituent of clary sage oil (*Salvia sclarea* L.), presents attractive structural features, especially the configuration of the 8-hydroxyl group which is the same as in Ambrox® (**4**). Since the first preparation of **4** from (-)-sclareol (**11**) [89, 90] with chromic acid (figure 4.11 on page 35), several improvements of the oxidation, reduction and cyclization steps

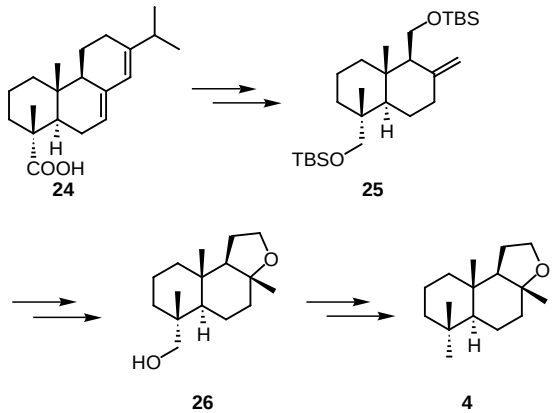


Figure 4.10: Synthesis of (-)-Ambrox® from abietic acid

were published [79, 80, 94–98].

This hemisynthesis is one of the most efficient and is used for the industrial production of Ambrox®. Three distinct stages are involved:

- an oxidative degradation of sclareol (**11**) side chain resulting in sclareolide (**2**) and sometimes in isosclareolide (**27**).
- a reduction of this compound to ambradiol (**20**).
- a cyclodehydration of **20** to give Ambrox® (**4**).

The critical step involves the oxidative degradation of the side chain of sclareol[1] (**11**). Several alternatives to chromium acid were published. CrO_3 was successfully replaced by a ruthenium oxide catalyzed procedure (figure 4.11 on the facing page) [88, 99]. Another alternative is to dehyrate chemio- and regioselectively the alcohol at C-13 in order to break oxidatively the double bond 12-13. This strategy involves an acylation of (-)-**11** followed by the elimination of an acetate using a palladium catalyst (figure 4.12 on page 36)[99]. This step affords an inseparable mixture of abienol (**29**), isoabienol (**30**) and neoabienol (**31**), which are further oxidized to sclareolide (**2**) and ambrenolide (**3**). These products

[1] commercial sclareol (**11**) generally contains small amounts of episclareol (**28**)

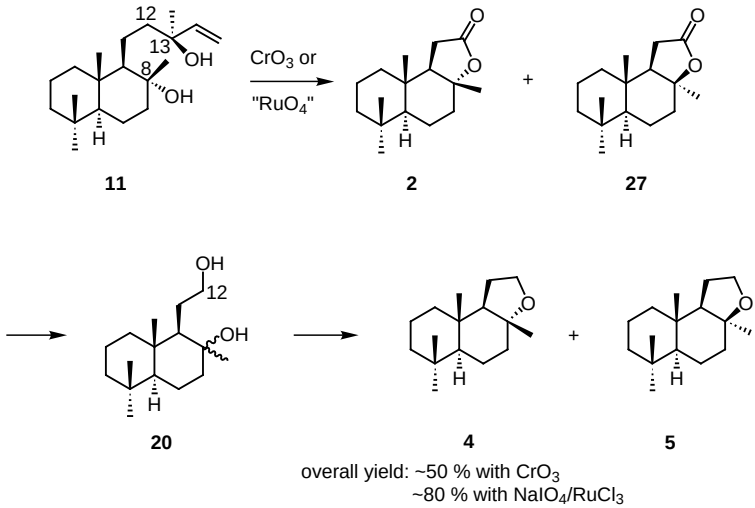


Figure 4.11: Synthesis of (-)-Ambrox® from sclareol

are transformed into (-)-Ambrox® (**4**) (overall yield from sclareol: 43%) and ambraoxide (**32**) (figure 4.3 on page 29) in 2 steps.

While the second step is easily achieved, the main drawback of the latter one is that acidic conditions are used to perform the cyclization and special care must be taken, since Ambrox® (**4**) isomerizes readily under acidic conditions to the more thermodynamically stable, but olfactively much weaker iso-Ambrox (**5**). Moreover the configuration at C-8 needs to be preserved during the intramolecular nucleophile substitution of the tertiary alcohol at C-8 on the C-12 that bears the primary alcohol. Thus the elimination of the 8-hydroxyl group must be prevented. This is carried out with $\mathrm{ZnCl_2}$ or by the transformation of the primary alcohol into a better leaving group like mesylate, tosylate or methoxy methyl ether. Several other strategies to circumvent this problem were published. For example, the system $\mathrm{OsO_4}$-$\mathrm{NaIO_4}$ oxidizes also sclareol (**11**) to afford the product **33** in high yield (figure 4.13 on the next page) [100]. This product is transformed into **4** through a Baeyer-Villiger oxidation and a reduction. The above transformation **11** to **33** has been improved when using $\mathrm{O_3}$-$\mathrm{NaIO_4}$ [101] instead of the toxic and expensive $\mathrm{OsO_4}$. Another

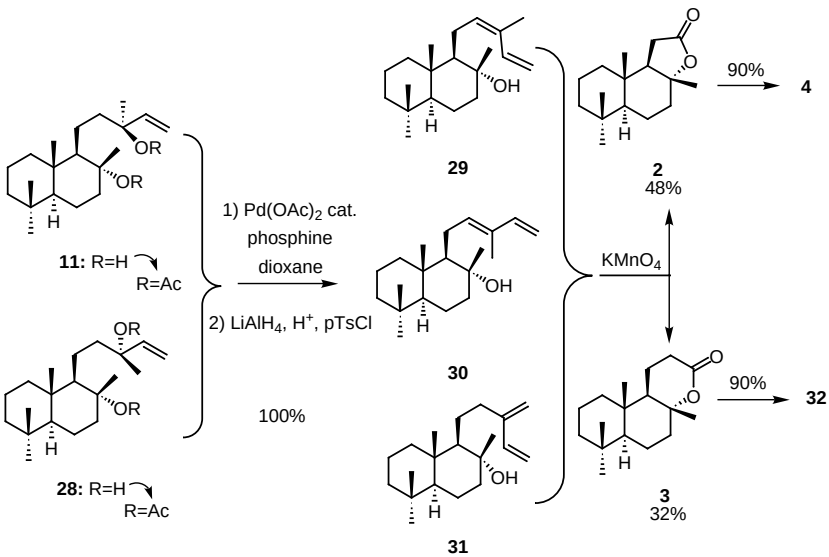


Figure 4.12: Palladium catalyzed synthesis of (-)-Ambrox®

environmentally friendly oxidation of (-)-sclareol (**11**) uses a microbiological pathway using *Hyphozyma roseoniger* or *Cryptococcus* [102, 103]. These procedures have the advantage of avoiding the cyclization step of diol **20**.

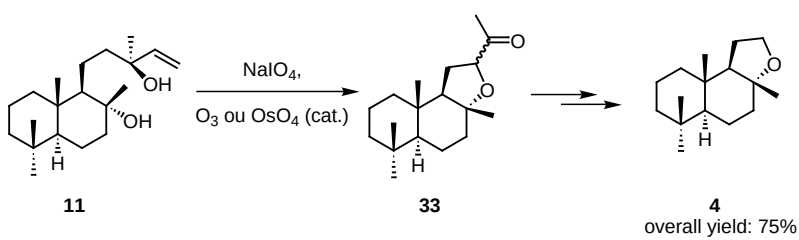


Figure 4.13: Synthesis of (-)-Ambrox® from sclareol

Two other ingenious approaches on the same idea were reported. The first one, recently published by Jang and Song [104, 105], used a thionolactone as the key compound. This compound, obtained from sclareolide (**2**) in a one step procedure (Lawesson's reagent, 30% yield), is desulfurized with Ph_2SiH_2 in presence of catalytic amount of Ph_3SnH to afford

the cyclic ether **4** in a 60% yield. The second approach, published by Näf is based on a degradation process of sclareol (**11**), presumably via a β-cleavage of an oxygen-centered radical (figure 4.14) [96]

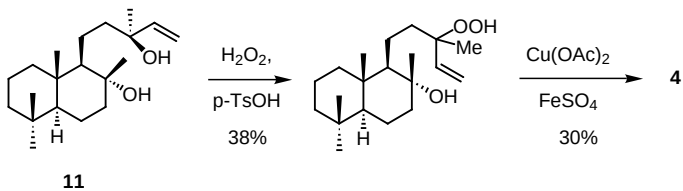


Figure 4.14: Radical synthesis of (-)-Ambrox®

In conclusion, the oxidative degradation of the side chain of sclareol (**11**) by RuO_4 generated in situ followed by the reduction of sclareolide (**2**) and the cyclization of diol **20** yields 80% of Ambrox® in three steps. This is the most efficient and shortest synthesis up to now [99].

- **(-)-cis-Abienol (29)** (figure 4.12 on the preceding page), isolated from Canadian balsam (48%), is transformed into Ambrox® (**4**) after ozonolysis and subsequent treatment with lithium aluminium hydride and tosyl chloride in pyridine (overall yield: 84%) [106].

- **Communic acids** are found in many species of the *Cupresaceae* family. For example, the methyl *trans*-communate (**34**) is directly crystallized from diazomethane treated acid fractions of hexane extracts of *Juniperus sabina* L. wood. This fact, along with the *trans*-decalin junction, converts the communic acid in good chiral synthon for the synthesis of **4**. The methyl ester of the cis- and trans-communic acids (**34**) has been ozonized, reduced and then cyclized under Buechi-conditions to afford **35** (figure 4.15 on the following page), the kinetic product and the only isomer synthesized at room temperature. The major difference from the previous approaches is the absence of a hydroxyl at C-8, and the 12-hydroxyl group is the nucleophile. In three further steps, necessary for the transformation of the ester into a methyl group, (-)-Ambrox® (**4**) was successfully synthesized [107].

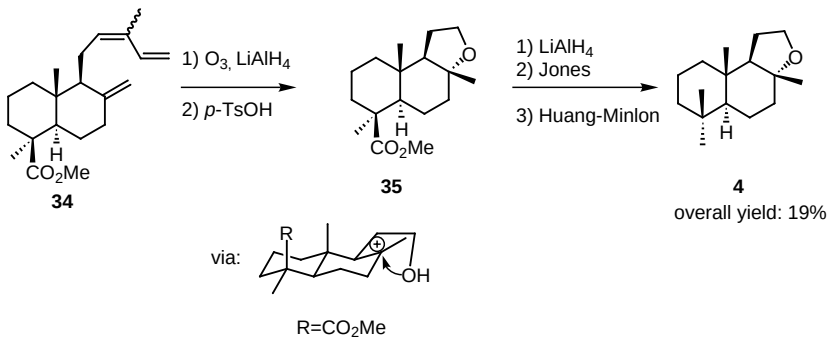


Figure 4.15: Synthesis of (-)-Ambrox® from communic acids

- **Labdane derivatives.** The n-hexane extract of *Cistus Ladaniferus* L. (Rock-rose) contains mainly labdanolic acid (**36**) and labdanediol (**37**). They are converted into (-)-Ambrox® (**4**) with an overall yield of 15% [108] and 60% [109], respectively. The degradation of **36** is not an easy task, since the carboxyl is the only accessible functional group in the side chain. The main drawbacks of this method is the isolation of the labdanolic acid (**36**) and the use of IBDA and iodine in the decarboxylation procedure. When a cheaper procedure can be found for this reaction, **36** will be a good alternative for the industrial preparation of (-)-Ambrox® (**4**). The

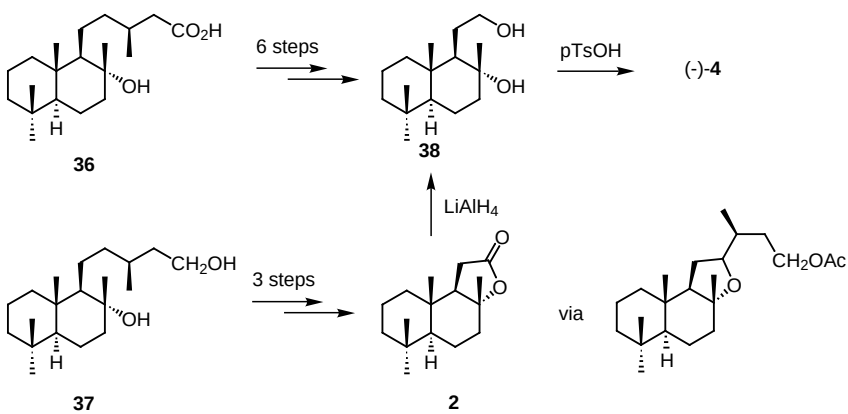


Figure 4.16: Synthesis of (-)-Ambrox® from labdanolic acid and labdandiol

case of labdandiol (**37**) is less problematic, since the 15-hydroxyl group is acylated and further treament with LTA/I_2 (71%) followed by an oxidation with Na_2CrO_4 to affords sclareolide (**2**) in excellent yield (97%), a considerable improvement on the yield of **2** using CrO_3. Note that the side chain is removed after the formation of ring C.

- **Drimenol and Wieland-Miescher ketone**. Drimenol (**39**) has been transformed into (-)-Ambrox® (**4**) in 10 steps with an overall yield of 28% (figure 4.17 on the next page) [110]. It is isolated from the bark of *Drimys winteri* Forst[2], and can also be synthesized from albicanol (**40**) [111], a natural product isolated by steam distillation of the liverwort *Diplophyllum albicans* or from methanol extract of intact specimens of *Cadlina luteomarginata*. Here, one carbon must be added to the side chain in order to obtain the furan ring C and the chirality at C-8 must be created (pure enantiomeric product is obtained after a chromatographic separation of diastereomeric intermediates over SiO_2). The albicanol (**40**) is also obtained in a few steps from the Wieland-Miescher ketone (**41**) [112], a starting material easily obtained from 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone [113–115].

4.5.3 Ambrox® from monocyclic starting building blocks

- **Thujone (42)**, a waste material of the Canadian forest industry, can be converted in 15 steps to (-)-Ambrox® (**4**) with an overall yield of 30% (figure 4.18 on page 41) [116]. This approach is a subtle game of chiral induction. Indeed, the chiral center C-8 is missing in **42**. It will be induced at the end of the synthesis by the methyl on the chiral center C-10, whose chirality is introduced during the first step, a Robinson annulation between ethyl vinyl ketone and thujone (**42**) that leads to the tricyclic enone **43**. Moreover the single chiral center of the starting material is lost during the formation of β-cyperone **44**, which is further transformed to diol **46** via the enone **45** [117, 118]. Finally, the trans-decalin skeleton is obtained ingeniously by a selective kinetic dehydration of the diol **46**, that is further transformed to **4** via the enone **47**.

[2] 6% of the mass of the bark

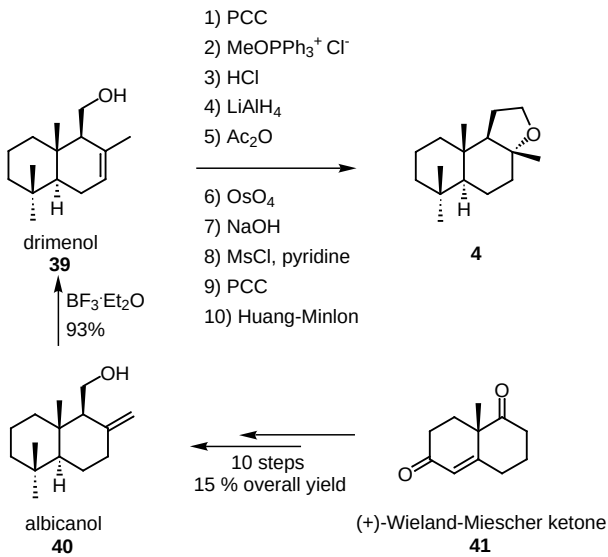


Figure 4.17: Synthesis of (-)-Ambrox® from drimenol, albicanol and Wieland-Miescher ketone

- **(S)-(+)-Carvone (48).** Conjugate addition of allyl magnesium chloride, followed by annulation of the corresponding silyl enol ether with methyl vinyl ketone affords the decalone **49** which is further transformed to (-)-Ambrox® (**4**) in 10 steps with an overall yield of 10% (figure 4.19 on page 42). A second route to (-)-**4** was developed starting from the hydroxy ketone **50**, which was obtained from S-(+)-carvone (**48**) in two steps. The hydroxy ketone **50** is then converted to **4** in 11 steps with an overall yield of 30%, starting from **48** [119, 120]. Both of these pathways are very similar to the one of thujone (**42**).

4.5.4 Ambrox® from acyclic building blocks

These approaches have almost always the same task. The rings A, B and C must be constructed; generally, the trans-decalin system is obtained in one step and the furan ring C is built in a separate manner. The major task is to obtain this trans-decalin system and the correct chirality at C-8. Here the chirality is induced from thermodynamically or kinetically effects, from resolution or from

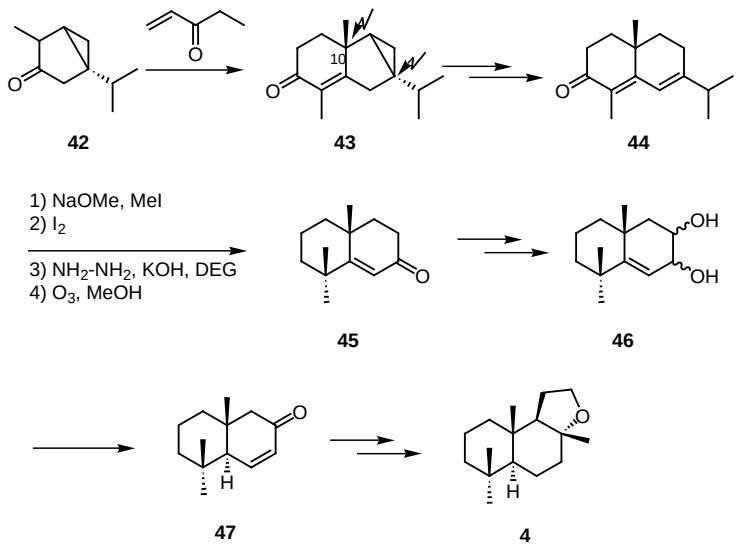


Figure 4.18: Synthesis of (-)-Ambrox® from thujone

an external source, like a chiral auxiliary or catalyst.

- **Geranylacetone (51).** A methoxycarbonylation of **51** with NaH and $\mathrm{CO(OMe)_2}$ and further cyclization with $\mathrm{SnCl_4}$ furnishes the trans-decaline skeleton **14** (figure 4.20 on page 43) [121, 122]. Optical resolution of the corresponding alcohol of the racemic intermediate **14** via its naphthylcarbamate derivative gives the pure **52**. To invert the stereocenter C-8, the alcohol is transformed into an inseparable mixture of epoxides **53** and **54**, that are further opened to diol **20** and cyclized under acidic conditions to (-)-Ambrox® (**4**) (major product, 2.2% overall yield through 15 steps) and iso-Ambrox (**5**).

- **Farnesylacetate (55)**. The racemic substrates (±)-**56** and its monoacetate are prepared by cyclization of farnesyl acetate (**55**) with chlorosulfonic acid (figure 4.21 on page 43). Here the chirality is provided by enzymatic resolution of the racemic **56** with lipase PS-30 (*Pseudomonas sp.* Amano)[123]. The resolved intermediate (+)(1R)-drimandiol (**57**) is further transfomed to (-)-**4** with an overall yield of 35%. Another variation of this approach was published by Akita et al. [124]

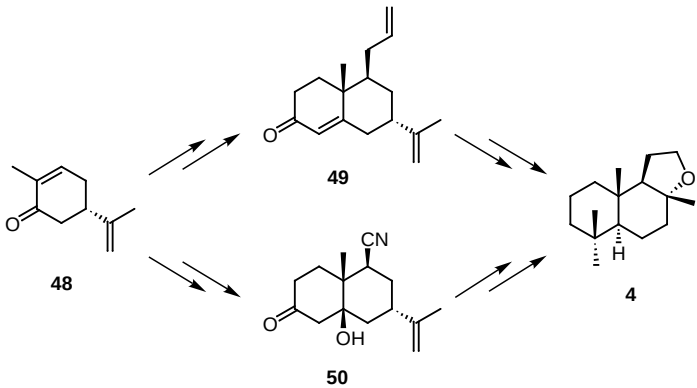


Figure 4.19: Synthesis of (-)-Ambrox® from carvone

- **Homofarnesol (21).** The biomimetic, acid-catalyzed cyclization of the polyene alcohol **21** (see subsection 4.4 on page 31) represents a breakthrough in the synthesis of racemic Ambrox®, since all the three rings A, B and C of (**4**) with a trans-decalin junction between rings A and B, are built in one step. Nevertheless, since no chiral source is present in the starting material, a chiral auxiliary or a chiral catalyst must be used to get the desired enantiomer of Ambrox® (**4**). Although a large number of studies have been carried out dealing with the biomimetic olefin cyclization into carbocycles, effective chiral induction is still a remaining problem in this field, though few procedures have been reported [125–127]. Recently, Yamamoto et al. published an enantioselective version of this cyclization with $SnCl_4$ and a chiral ligand derived from binaphthol (figure 4.22 on the next page) [64]. However, he used stoichiometric quantities of chiral ligand and Ambrox® is obtained with low yield and low enantiomeric excess.

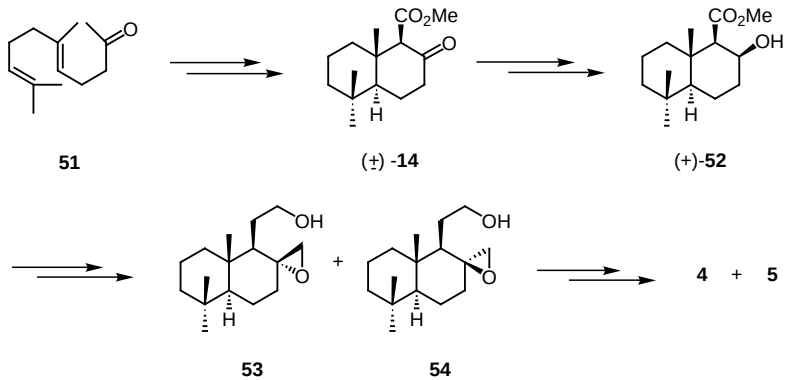


Figure 4.20: Synthesis of (-)-Ambrox® from geranyl acetone

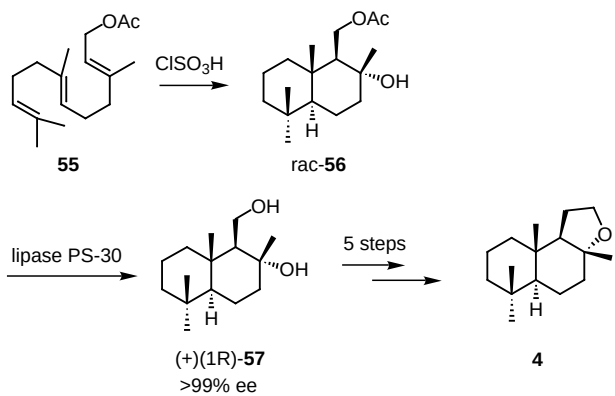


Figure 4.21: Synthesis of (-)-Ambrox® from farnesyl acetate

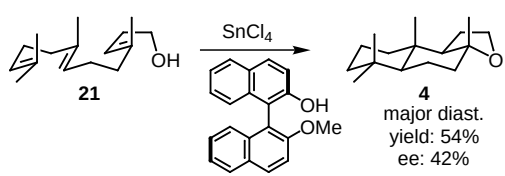


Figure 4.22: Biomimetic cyclization of homofarnesol to (-)-Ambrox®

Chapter 5

Homofarnesol

The (3*E*,7*E*)-4,8,12-trimethyl-3,7,11-tridecatrien-1-ol (**21**), usually called homofarnesol, has all the required elements to cyclize into Ambrox® (**4**), it was thus chosen as substrate for our investigation.

Several more or less efficient syntheses are described in the literature. The major challenge of this synthesis is the configuration of the double bonds, because only the all-trans homofarnesol is interesting as a starting material, but only few articles describe such a selective approach.

From a biochemical point of view, the most beautiful approach would consist of forming polyisoprenoic chains starting from an isoprene unit and to finish by homologation. These ways were studied, but their results are discouraging, because of the poor selectivity of the isoprene connections [70, 128, 129]. Identical results were obtained by the transformation of geranylpyrophosphate with 4-methyl-4-pentenylpyrophosphate in presence of farnesylpyrophosphate synthetase into the *E*/*Z*-homofarnesol [130, 131].

Homofarnesol (**21**) can be prepared from *E,E*-farnesol (**58**) in an analogous procedure to that described by Leopold for the synthesis of homogeraniol from geraniol [132]. *E,E*-Farnesol (**58**) is first converted to farnesal (**59**) via a Swern Oxidation. Treatment of farnesal with methylenetriphenylphosphorane affords the tetraene **60**. Further hydroboration followed by an oxidative workup gives homofarnesol (**21**) (figure 5.1 on the following page)[133].

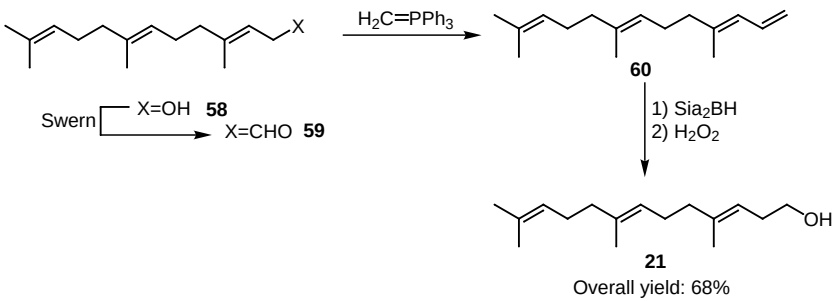


Figure 5.1: Homologation of homofarnesol

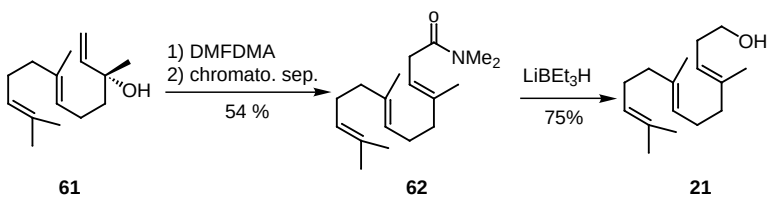
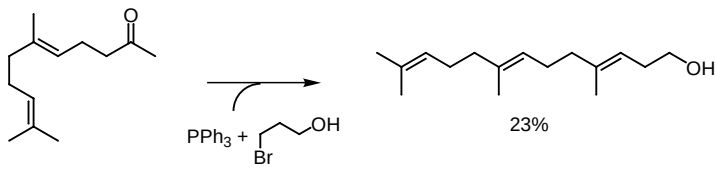


Figure 5.2: Barrero's approach

Barrero[134] reported recently the synthesis of *E,E*-homofarnesol (**21**) from (+)-(*E*)-nerolidol (**61**) (figure 5.2), a commercially available product. The key step of this synthesis is the known Eschenmoser [2,3]-sigmatropic rearrangement of the allylic alcohol to the homologous amide promoted by heating the corresponding alcohol with N,N-dimethylformamide dimethyl acetal [135]. After a chromatographic separation of the *E/Z* mixture of the β,γ-unsaturated amides **62**, a hydride reduction gives the desired alcohol **21**.

As shown in figure 5.3 on the facing page, the commercially available geranylacetone (**51**) is transformed into **21** using a Wittig reaction. After a chromatographic separation of the resulting *E/Z* stereoisomeric mixture, pure *E,E*-homofarnesol (**21**) is obtained in a modest yield (21-23%) [86].

Numerous syntheses of the commercially available isoprenoides used in the previous description (i.e. geraniol, geranylacetone, geranylbromide [130]) are described, but their general review would greatly exceed the framework of this thesis. Moreover their syntheses are generally not very efficient: several steps



51 **21**

Figure 5.3: Snowden's approach

are needed and *E/Z* mixtures are obtained with medium to poor yields. Starting from a simpler substrate Julia et al. published in 1960 a simple iterative approach leading to the all-trans homofarnesol (**21**) (figure 5.4 on the next page) [136]. Performing a Grignard reaction on methyl cyclopropane ketone followed by an acidic treatment, the bromide **63** can be obtained, which, after conversion to a Grignard reagent, is reacted again with the methyl cyclopropylketone. Repeating the procedure, all-trans homofarnesol (**21**) can be obtained. This method allows the formation of polyisoprenoic chains. At each stage, a primary or tertiary alcohol can be obtained, like homogeraniol, homofarnesol, ... by saponification of the acetate issued from the bromide. Farnesylacetone (**17**) can also be obtained from the farnesylbromide via the farnesylacetonitrile. They also describe the synthesis of linalool and nerolidol (**61**).

Based on the same idea, another procedure was published by Kociensky in 1989 (figure 5.5 on the following page) [137]. This reaction is easily done on a substantial scale and gives good yields. This procedure can be applied in an iterative sense to the synthesis of homogeraniol, homofarnesol and homogeranylgeraniol. Each turn of the cycle requires the alkylation of 5-lithio-2,3-dihydrofuran with a homoallylic iodide followed by a $\mathrm{Ni}(0)$-catalyzed coupling with methylmagnesium bromide. The resultant homoallylic alcohol can then be converted to the corresponding iodide and the cycle is repeated.

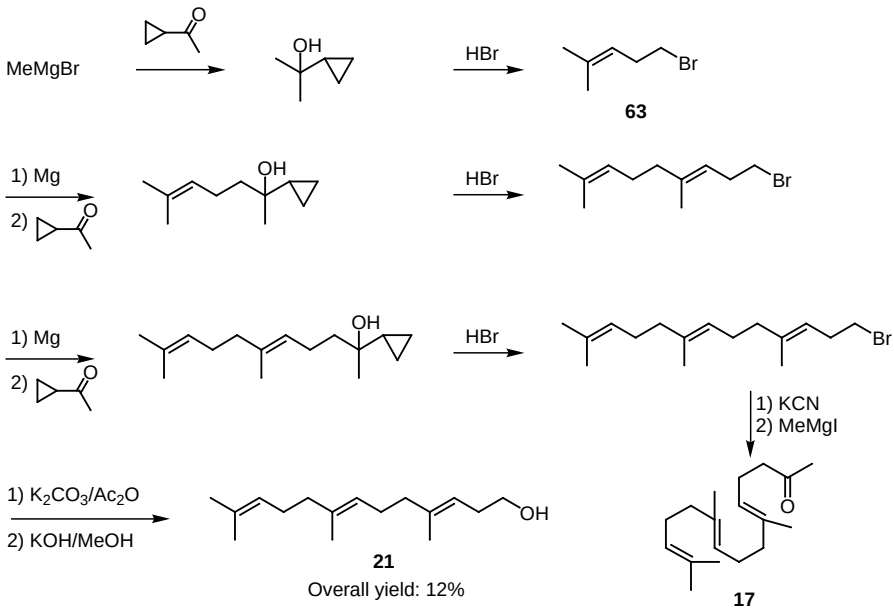


Figure 5.4: Julia's approach

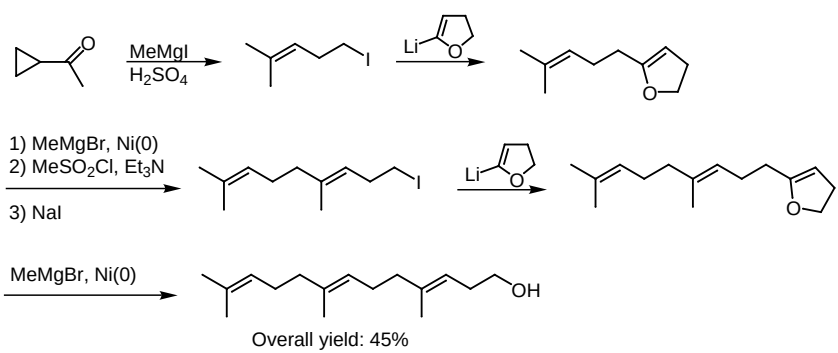


Figure 5.5: Kocienski's approach

Part II

Results and discussion

Chapter 6

2-Me-BOD-$Fe(CO)_2I$: synthesis and reactivity

6.1 Synthesis and large scale optimization

The synthesis of complex **1** is easily achieved in a three step procedure from optically active (-)-β-pinene, a monoterpenoid isolated on large scale from turpentine oil. Identical results are obtained with (-)-α-pinene, because iron isomerizes the exo double bond of (-)β-pinene into (-)-α-pinene [138, 139].

Optically active iodo complexes **65** are readily accessible from apopinene ($\mathrm{R} = \mathrm{H}$), pinene ($\mathrm{R} = \mathrm{CH_3}$), and nopol derivatives ($\mathrm{R} = \mathrm{CH_2CH_2OR'}$) via a two step synthesis. Ring opening complexation of **63** with $\mathrm{Fe(CO)_5}$ produces complexes **64** [140, 141], which react further with iodine to afford iodo complexes **65** in 70% yield independent of substituent R. The last step is usually done in a phosphate buffer aqueous solution (pH 7) [142], but it can also be performed neat in a mortar with a 66% yield based on recovered starting material. This step could probably be optimized by performing this reaction over a longer period of time. Bicyclic ketones **66** and **67**, resulting from oxidative decomplexation and carbon monoxide insertion into the chelated σ-alkyl, π-allyl metal complex [138], are also isolated in 6% yield.

Lithiation of **65** with $^t\mathrm{BuLi}$ at low temperature affords carbene complex **68** (spectroscopically detected [4], not isolated) which yields quantitatively either

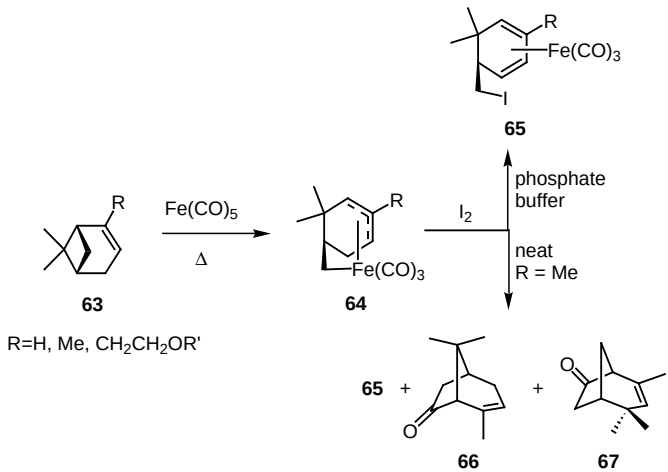


Figure 6.1: Synthesis of iodo complex **65**

one of the three different products (**1**, **69** or **70**) depending on the reaction conditions [4]. Quenching carbene complex **68** with a weak proton source (e.g. acetophenone) furnishes σ-alkyl, π-allyl complexes **70** and **71**, whereas reaction with strong aprotic electrophiles (e.g. m-(trifluoromethyl)benzoyl chloride) blocks the carbenoid structure of **68** by acylation. Warming of the latter product in presence of CO or phosphines results in an intramolecular carbene addition to the diene yielding **69**, while in presence of an olefine (e.g. isoprene), it produces complex **1** containing a novel chiral ligand.

The yield of this one pot synthesis critically depends on the reaction scale and on the nature of the substrate: for $\mathrm{R} = \mathrm{CH_3}$ the reaction is nearly quantitative, when run in a one millimolar scale or below, but a two to twentyfold increase of the reaction scale reduces the yield to 5% at best, whereas complexes **65** obtained from nopol derivatives yield only 15% so far. In order to gain information about the origin of this scale-up problem, all conceivable parameters in the procedure to form complex **1** were studied.

First of all, the reagents and the solvent used in this reaction showed an influence but did not cause the observed decrease of yield. Indeed, replacement of isoprene with 2-butyne does not change the result and the addition of isoprene before $^t\mathrm{BuLi}$ does not help, since it reacts with the iodo complex by ligand

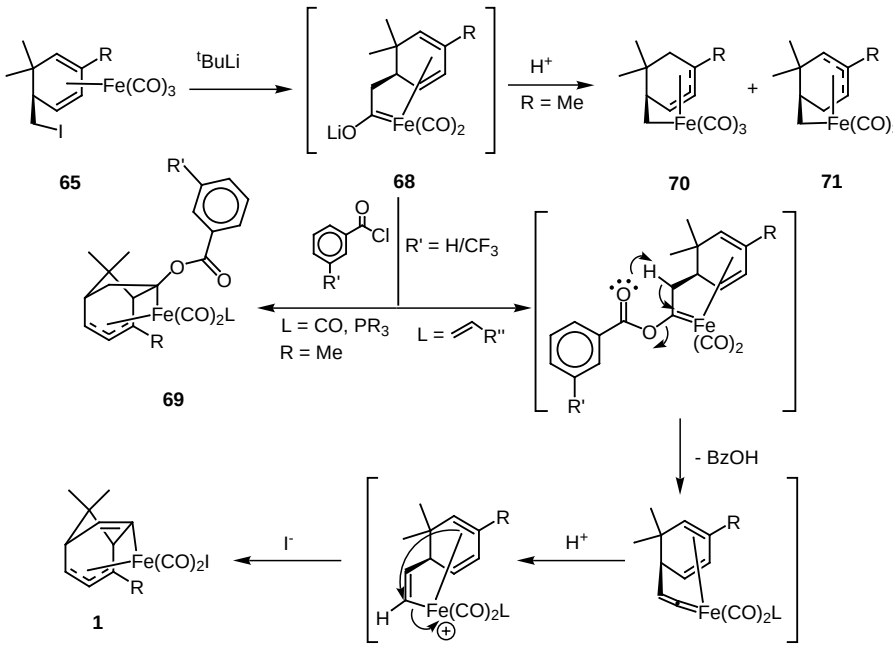


Figure 6.2: Intramolecular carbonyl alkylation

exchange and affords an isoprene complex. Using benzoyl chloride instead of m-(trifluoromethyl)benzoyl chloride decreases the yield, since this latter acid chloride is a better leaving group and favours the formation of **1**. However, we have found that two equivalents of m-(trifluromethyl)benzoyl chloride, as used by Raemy, are not only unnecessary but they also complicate the work-up, since one equivalent of the corresponding carboxylic acid is formed and yields an inseparable mixture with the desired complex **1**: separation by crystallization as well as chromatography fails. The only way to separate them is to treat the mixture with triethylamine and to extract **1** with an organic solvent. But this additional step decreases the yield. Furthermore, the quality of the $^{t}\mathrm{BuLi}$ seems to slightly influence the outcome of the reaction: a low molarity favours the secondary complex **69** at the expense of **1**. It is also not necessary to wash the organic phase with saturated KI aqueous solution, water being sufficient. Finally, replacement of diethylether by tetrahydrofuran is not judicious, since THF is not inert and reacts with $^{t}\mathrm{BuLi}$ and further with

m-(trifluromethyl)benzoyl chloride to afford the products depicted in figure 6.3. Thus, for small scale (1 mmol of **65**), 2.1 eq. of $^t\mathrm{BuLi}$[1], 10 eq. of isoprene, 1.1 eq. of m-(trifluoromethyl)benzoyl chloride and 1 eq. of triethylammonium iodide[2] are used without any yield loss compared with the procedure described by Raemy [4]. In addition, this recipe affords a better yield (55%) in a medium scale synthesis (5 mmol, table 6.1 on page 57).

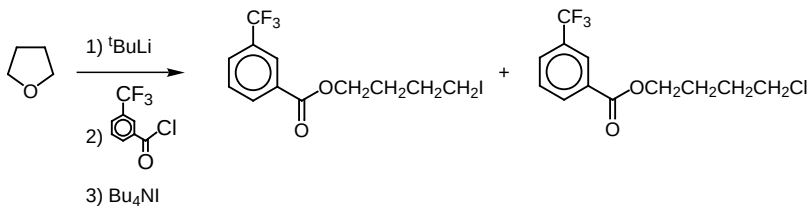


Figure 6.3: Side reaction of THF

Consequently, the reaction conditions should explain the difference between small and "large" scale results. As seen in table 6.1 on page 57, the temperature seems to be the most important factor. The experiments 6, 7 and 8 show that for a small scale synthesis with rigorously identical conditions (same quality of products, reactions done in parallel), the results are strongly correlated with the temperature at which the products are mixed together. Indeed, a too low temperature favours the formation of the secondary complex (entry 6), and a rapid addition of the reagents (entry 8), implying a local rise in temperature, provides more or less the same results. However, the fundamental difference between entries 7 and 8, is the duration of addition of $^t\mathrm{BuLi}$ and the waiting period at -90°C. Nevertheless, the warming up phase to room temperature seems also to play a role as well. Indeed, a slow warming up with a pause at about -40/-45°C favours the formation of complex **1** (entries 1, 2, 3 and 5).

In situ monitoring by using a React-IR spectrometer did not clarify the above mentioned problem, since it was impossible to synthesize complex **1** during the monitoring to date, complex **69** was always formed instead. The failure of $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ (**1**) formation also emphasizes the crucial role of temperature. Indeed, the flask used for the React-IR investigation was larger and

[1] to render the Schlenk equilibrium irreversible by the formation of isobutylene.
[2] without iodide the yield is much lower and ammonium iodide does not improve the yield.

this obliged us to use more solvent (figure 6.5 on the following page). Moreover, due to continuous warming by the IR-probe, lowering the temperature of the reaction medium to more than -90°C was difficult to realize, since the addition of $^{t}\mathrm{BuLi}$ easily increases the temperature by about 15 to 20°C. In addition, we have noticed that the yellow color of the reaction mixture normally turned red after $^{t}\mathrm{BuLi}$ addition. If this red color is not observed, complex **1** is formed in a smaller amount or even not formed. In the runs using the React-IR, the mixture never turned red at low temperature.

Investigating the formation of **69** using the React-IR technique, shows that three intermediates are formed during the reaction (figures 6.5, 6.6, 6.7 and table 6.2 on page 58). The first intermediate (ν_{CO} at 1945 and 1876 cm^{-1}) is stable up to -50/-40°C, even in presence of m-(trifluoromethyl)benzoyl chloride and isoprene. Then the second intermediate (ν_{CO} at 1964, 1910 and 1860 cm^{-1}) is transformed into the third one (ν_{CO} at 2018, 1980 and 1907 cm^{-1}) at about -10°C and over 0°C, complex **69** (ν_{CO} at 2054, 1992 and 1976 cm^{-1}) is then obtained. The react-IR investigation also reveals that $^{t}\mathrm{BuLi}$ reacts readily with the iodo complex **65**: the reaction is over in less than 20 seconds (the time required for recording one IR spectrum). This observation is in complete agreement with the low temperature NMR investigation [4] that pointed out the fairly rapid formation of the carbene intermediate **68**. But it is possible that the observed intermediate is not identical in both cases. Moreover, Raemy observed the formation of two intermediates during the $^{t}\mathrm{BuLi}$ addition [4] and this could be in fact the origin of the formation of either **1** or **69**. However, these products are very similar according to their ^{13}C-NMR, and Raemy suggested that one could be **68** and he ruled out for the other the structure **72** issued from a deprotonation of the α-position of the carbene, since the addition of a third eq. of $^{t}\mathrm{BuLi}$ reacts with another carbonyl to generate the intermediate

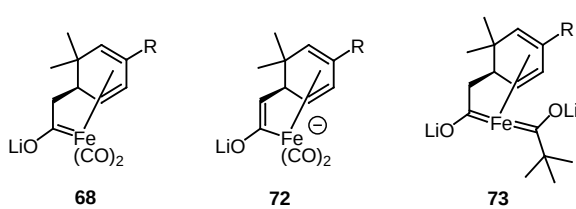


Figure 6.4: Hypothetical intermediates

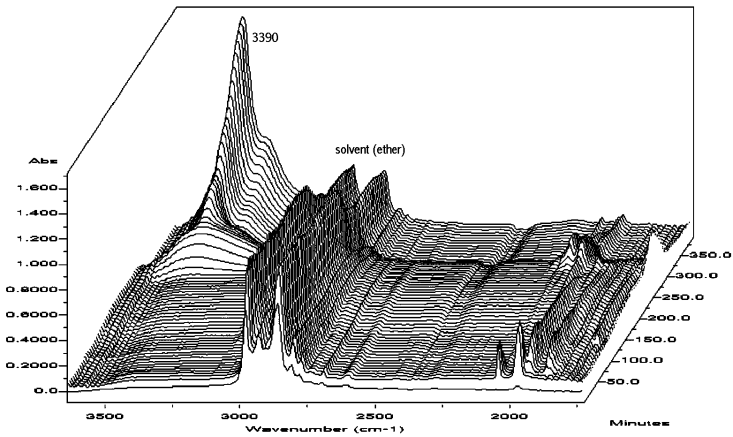


Figure 6.5: React-IR monitoring: global view

73. Thus he proposed that the second observed intermediate is a coordination isomer of **68**, but this would abolish the possibility of a discrimination between **1** and **69** at this early stage. In addition, accepting that a different complex is at the origin of the second set of ^{13}C-NMR signals, hardly explains why identical products (**70** and **71**, see figure 6.2 on page 53) are obtained in the presence of a proton source.

In conclusion, on one hand several results point out that the differentiating step occurs already at the beginning of the process. On the other hand, it is difficult to explain why in the absence of isoprene, only **69** is formed, and why the warming up temperature and the type of acid chloride also influence the outcome. Nevertheless, even though a lot of elements coroborate the mechanism depicted in figure 6.2 on page 53, the results obtained so far point out that the reaction mechanism is much more complex than anticipated. Further research is still needed to clarify this last point in order to allow the optimization of the yield of complex **1**.

Table 6.1: optimisation

reactions	entries							
conditions	1	2	3	4	5	6	7	8
scale	16.9 mmol	4.97 mmol	4.97 mmol	4.56 mmol	5.87 mmol	1 mmol	1 mmol	1 mmol
solvent	ether	ether	ether	ether	ether	ether	ether	ether
	2.1 eq.	2.1 eq.	2.1 eq.	2.1 eq.	2.1 eq.	2.1 eq.	2.1 eq.	2.1 eq.
^{t}BuLi	P	SP	SP	SP	P	P	P	P
	at -90°C	at -95/-85°C	at -95°C	at -95°C	at -95°C	at -100°C	at -90°C	at -90°C
duration	10 min	90 min	120 min	70 min	27 min	10 min	10 min	2 min
pause	-	1h at -60°C	80 min at -95°C	30 min at -95°C	20 min at -95°C	20 min at -100°C	32 min at -90°C	-
	10 eq.	10 eq.	10 eq.	10 eq.	10 eq.	10 eq.	10 eq.	10 eq.
isoprene	P	SP	P	P	P	P	P	P
	at -90°C	at -90°C	at -95°C	at -95°C	at -95°C	at -100°C	at -90°C	at -90°C
duration	5 min	10 min	10 min	15 min	3 min	5 min	5 min	2 min
	2 eq.	2 eq.	2 eq.	1 eq.	1 eq.	2 eq.	2 eq.	2 eq.
mBzCl	P	SP	P	P	P	P	P	P
	at -90°C	at -90°C	at -95°C	at -95°C	at -95°C	at -100°C	at -90°C	at -90°C
duration	5 min	10 min	15 min	10 min	9 min	5 min	2 min	2 min
pause	-	-	80 min at -70/65°C	-	-	-	-	-
warming up	without CB	without CB	with water bath at 25°C	with CB	with CB	with CB	with CB	with CB
duration	1h	1h45	few minutes	2h30	5h40	7h50	5h25	5h25
pause	-	45 min at -45°C	-	-	1h at -45°C	2h25 at -45°C	-	-
yield of 1	5%	15%	4%	41%	55%	13%	40%	25 %
yield of 69	50%	50%	48%	28%	6%	47%	34%	28%

mBzCl = m-(trifluoromethyl)benzoyl chloride
CB = cooling bath
P = in portions
SP = by syringe pump.

Table 6.2: Reaction events

Time [min]	Temperature [$^\circ C$]	Events
0	−85	addition of **65**
17	−85	addition of ^{t}BuLi (start)
35	−85	addition of ^{t}BuLi (end)
		warming up
71	−55	
		cooling down
76	−78	addition of isoprene (start)
81	−78	addition of isoprene (end)
85	−80	addition of m-(trifluoromethyl)benzoyl chloride (start)
89	−75	addition of m-(trifluoromethyl)benzoyl chloride (end)
		warming up
93	−70	
115	−49	
135	−45	
146	−46	
163	−40	
223	−15	
244	−11	
293	−3	
357	5	
395	10	stop - work up

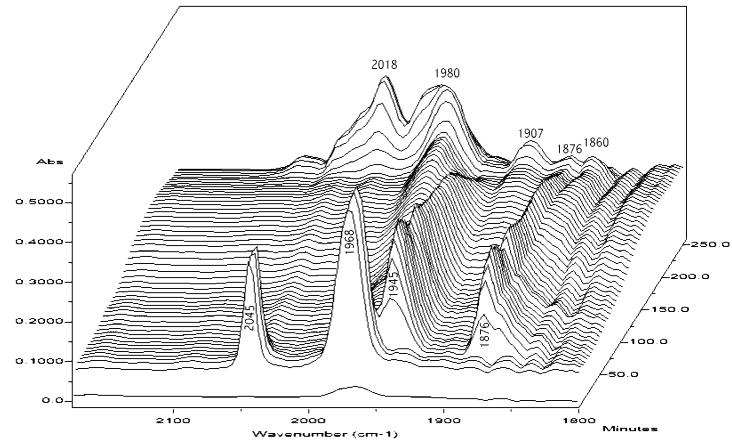


Figure 6.6: React-IR monitoring: start of the reaction

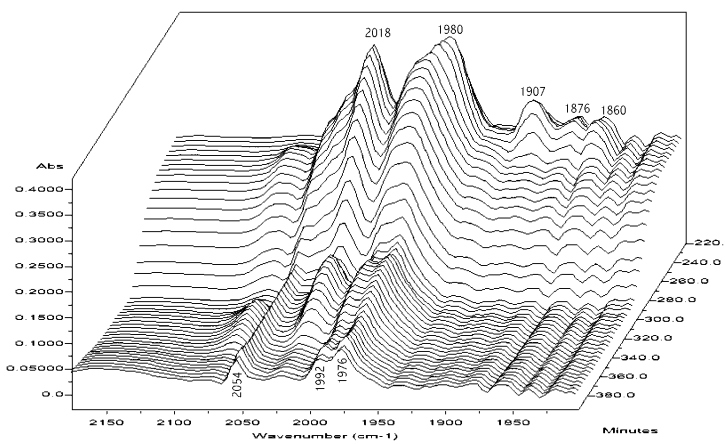


Figure 6.7: React-IR monitoring: end of the reaction

6.2 Properties and reactivity

The burgundy crystalline complex **1** is fairly stable (it can be stored in air for one day and under argon for months without major degradation) and is slightly soluble in pentane or hexane, but is really soluble in ether or any more polar solvent.

A CD spectra of **1** (figure 6.8) reveals a negative Cotton effects which supports the previous available data about the chirality of this complex [4]. The UV/VIS absorption (see figure 6.9 on the next page) shows four absorption bands (520 nm, ε= 260 lmol^{-1}cm^{-1}; 334 nm, ε=1430 lmol^{-1}cm^{-1}; 262 nm, ε=5810 lmol^{-1}cm^{-1}; 230 nm, ε=18120 lmol^{-1}cm^{-1}; in pentane) where photochemistry is possible, especially at the level of cleavage of iodide and carbonyl ligands.

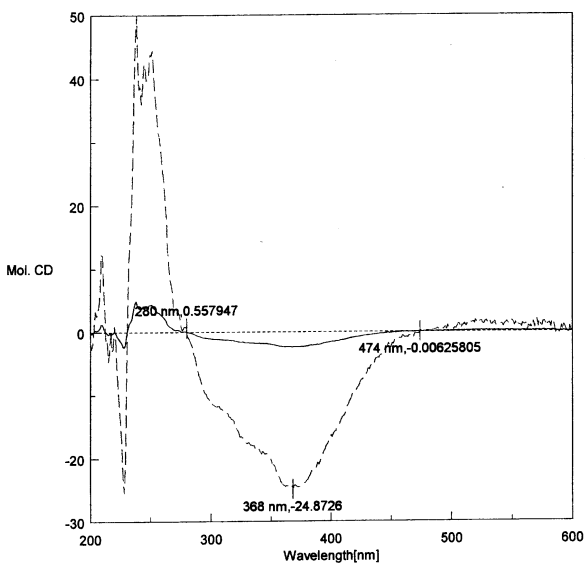


Figure 6.8: CD spectrum of 2-Me-BOD-Fe(CO)$_2$I

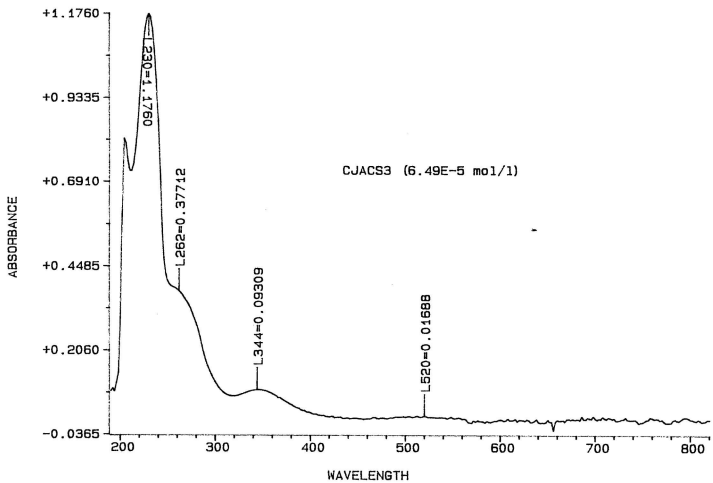


Figure 6.9: UV/VIS spectrum of 2-Me-BOD-$Fe(CO)_2I$

6.2.1 Photochemical reactivity

Sunlight irradiation of complex **1** at room temperature in acetonitrile decomposes the complex into a messy mixture, whereas its photolysis with visible light and down to 300 nm in a solution of pentane/dioxane (1:1) during one day lets the complex intact[3]. However, after three days a white precipitate which blackens in the absence of a solvent is observed. The same obervation is done when **1** is irradiated in pentane, but the reaction is faster (20 hours), probably because the dioxane stabilizes an intermediate species. But, in this case, detection of $Fe_3(CO)_{12}$ indicates that an unstable species is formed. During the irradiation of **1** in neat glacial acetic acid or 5% acid in ether, the same phenomenon is observed: the complex disappears and numereous products are formed that remain unidentified since the transformations were performed on a too small scale. In addition, the products are volatile and some of them are even unstable. The most scheming observation is the white precipitate which turns black in the absence of a solvent. This solid dissolves in chloroform, methanol and acetonitrile, thus indicating a polar products. Moreover, a Lassaigne test reveals the presence of iodine and an ESI spectrum shows several peaks higher

[3]Identical results were obtained with irradiation with Hg lamp and quartz glasswares.

than 1000. Its nature remains unknown, but we can only speculate about an oligomer containing iron and iodine.

In conclusion, irradiation of **1** removes probably one or two carbonyls leaving an unstable species, that could be stabilized theoretically by complexing isoprene or triphenylphsophine. However, irradiation in presence of isoprene produced the already known white precipitate, while triphenylphosphine decomposes the complex **1** but this time without producing this white precipitate. It is possible that not only carbonyls but also iodine[4] are removed photochemically. In this case, aromatic compounds could replace the leaving ligands to form arene complexes. But neither the irradiation of **1** in presence of anisol nor the reaction with a mixture of $AlCl_3$ and anisol did produce the expected arene complex (figure 6.10), but once again the white precipitate was formed.

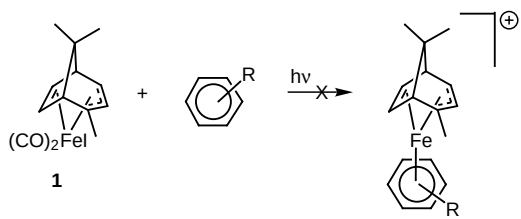


Figure 6.10: Arene complex synthesis

6.2.2 Non-photochemical process

Obviously, 2-Me-BOD-Fe(CO)$_2$I (**1**) is fairly stable as long as its coordination sphere is not disturbed, but as soon as a free coordination site is generated, it becomes rather unstable. As photochemistry does not provide useful results, other methods were tried to remove or activate either the iodine or the carbonyls.

Iodide abstraction from FpX complexes is known to proceed with a suitable Lewis acid like $AlCl_3$ or $AlBr_3$ [9], as well as with $AgBF_4$ [37, 144]. The reaction generates the active intermediate Fp^+ in solution, which complexes donor ligands like olefins, acetylenes, THF, ... But with 2-Me-BOD-Fe(CO)$_2$I (**1**), only silver salts were able to remove the iodide forming thereby a complex with

[4] Irradiation of FpI is known to remove iodide in presence of maleimide [143].

THF or isoprene, that was impossible to isolate, even by replacing the tetrafluoroborate or the haloaluminate counterion with PF_6^-, that generally gives more stable salt.

If treatment of **1** with $AgBF_4$ forms an unstable compound that is able to lose its carbonyls, the complexation of an arene will be possible and this would provide an access to intramolecular arene complexes like the one presented in figure 6.11. Such an arene complex could be activated by light [?] leading to an unsaturated Lewis acid that could perfom catalytical reactions since once the reaction on the complexed product is finished, it can return to the arene complex. The preparation of such arene complexes was first achieved via the treatment of an aromatic compounds with $CpFe(CO)_2Cl$ in the presence of aluminum chloride [40], but this broadly used approach failed with complex **1**, whatever conditions were (-80 to 168°C) and whatever aromatic compound was used (benzene, anisol, mesytilene, ethyl 4-methylphenyl ether). Nevertheless, we can strictly not exclude that the desired arene complex is formed since a NMR spectrum showed traces which could correspond to the desired product, but either the reaction is not efficient, or the resulting arene complex is very unstable. At low temperature (-80 to 20°C), no reaction occurs and at higher temperature (>60°C), rust is isolated.

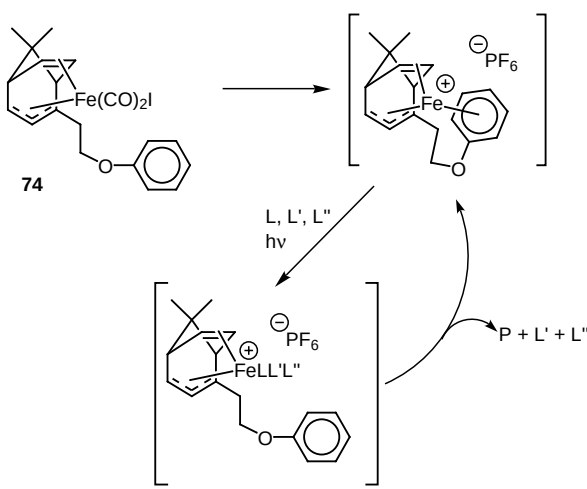


Figure 6.11: Possible application of arene complex

Finally, treatment of 2-Me-BOD-Fe(CO)$_2$I (**1**) with $AgBF_4$ under CO atmosphere affords the cationic tricarbonyl complex **75**. This electrophilic complex reacts regiospecifically with an hydride to give complex **76** (figure 6.12). This opens the way to stoechiometric application, since decomplexation of **76** could lead to interesting products.

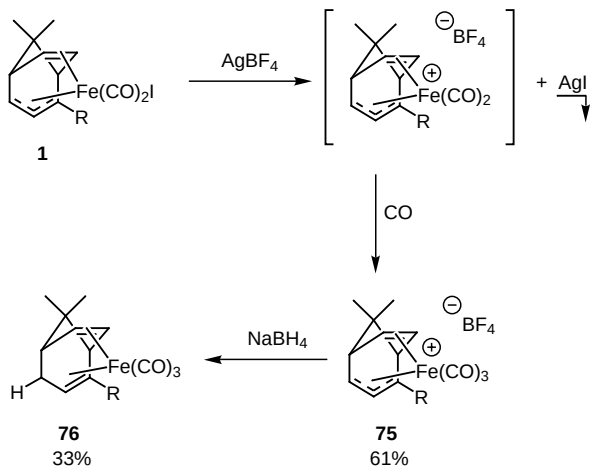


Figure 6.12: Iodide abstraction

In conclusion, 2-Me-BOD-Fe(CO)$_2$I (**1**) has a different reactivity than FpI: it is less reactive and it reacts in presence of light to give unidentified species so far. However, $AgBF_4$ provides the best method to remove the iodine atome leaving an unsaturated cationic species, even at room or lower temperature. Moreover, this unsaturated Lewis acid is chiral and could be used for the promotion of tandem cascade cyclization of polyenes.

Chapter 7

Tandem cascade cationic cyclization of homofarnesol

The complex $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ **1** can be activated in situ by iodide abstraction with silver tetrafluoroborate in dichloromethane forming thereby a weak Lewis acid (see subsection 6.2.2 on page 62). This new complex, contrary to the $\text{CpFe(CO)}_2\text{X}$ family, does not only efficiently complex electron rich double bonds but also leads to efficient cascade cyclizations, e.g. producing (-)-Ambrox® (**4**) from homofarnesol, a fragrance of importance (see chapter 4 on page 25). The role of the Lewis acid is twofold: it activates the substrate and it creates an environment that accommodates the substrate in a specific arrangement.

In fact the all-trans homofarnesol (**21**) emerges as the substrate of choice: it can easily be synthesized even on a large scale and it has all the required skeletal characteristics to be cyclized into Ambrox® (**4**): it has the same chemical formula ($\text{C}_{16}\text{H}_{28}\text{O}$), a suitable number and position of methyl groups and double bonds and the intramolecular participation of the nucleophilic hydroxyl group to terminate the cyclization by forming the heterocycle C.

Cyclization of homofarnesol (**21**) or silyl protected homofarnesol **22** or **23** can theoretically lead to a large number of isomers, depending on which double bond the catalyst is complexed to, on the sequence of the cyclization and on the conformation of the polyene. But, these possibilities are limited with the

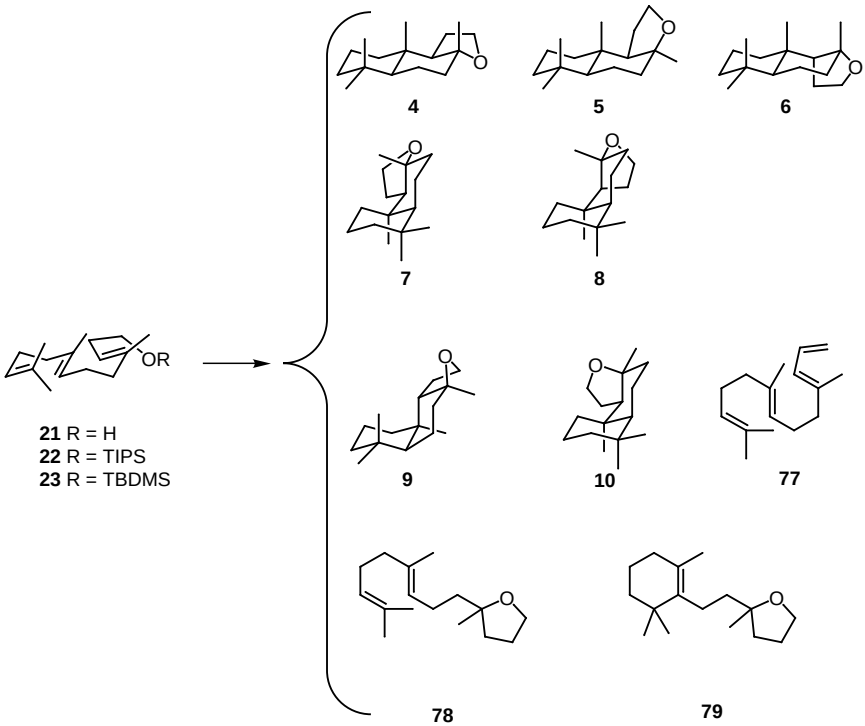


Figure 7.1: Cyclization overview

use of an all-trans starting material. A lot of cyclized products were obtained, but only those drawn in figure 7.1 were identified.

7.1 Unique behaviour of the 2-Me-BOD-Fe(CO)$_2$ complex

The figure 7.2 on the facing page shows several iron containing promotors that we have chosen for the cyclization of homofarnesol (**21**) and its derivative **22**. Removing one or more ligands of these complexes generates one or more free

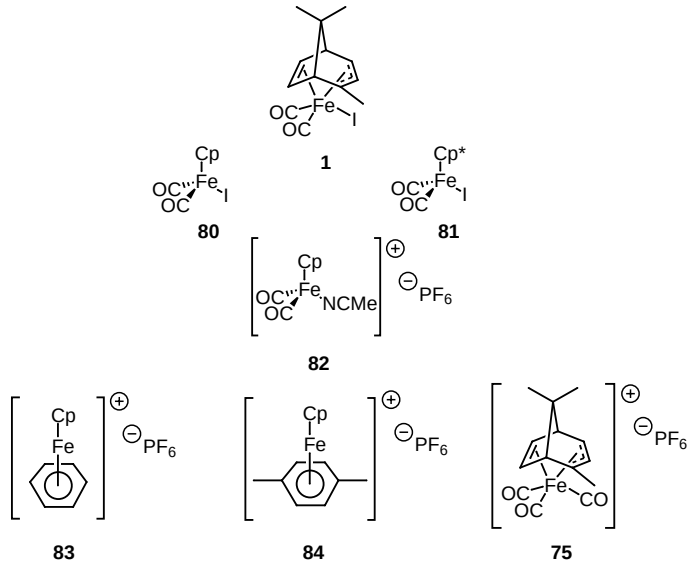


Figure 7.2: Precursors of coordinatively unsaturated complexes

coordination sites available for a π-complexation of a double bond. This step is the prerequisite for the tandem cascade cyclization.

The active species derived from the $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ complex **1** shows the best results for the cyclization of either protected or unprotected homofarnesol (entries 1 and 2, table 7.1 on the next page). The parent complexes **80** and **81** favor the deprotection of the starting material (entries 3 and 4), while complexes **75** and **82** were not suitable for this reaction, due to their stability even under photochemical or thermal activation (entries 6 and 10) [145]. However, these two Lewis acids are able to deprotect effectively the starting material. Arene complex **83** is known to lose its benzenic moiety when irradiated (entry 7). But no reaction occured in our hands and the complex was almost entirely recovered (96%). When the more labile complex **84** is irradiated in acetonitrile, substitution of p-xylene by three acetonitriles occurs (entry 8) [30]. Stable at low temperature, this latter complex exchanges two of its nitrile with a two-electrondonor at higher temperature. However, the decomposition of this complex turned out to be the only reaction. If a good complexing diene is present in solution, irradiation of **84** should give a Lewis acid with only

Table 7.1: Potential iron promotors

Entry	Promotor	R	Duration	Temperature	Products obtained [%]		
			[*d*]	[°*C*]	conversion	**21**	**4-10**
1[a]	**1**	*H*	6	*rt*	72	–	42
2[b]	**1**	*TIPS*	6	*rt*	70	28	26
3[b]	**80**	*TIPS*	19	*rt*	95	90	4
4[a]	**81**	*H*	18	*rt*	43	–	14
5[a]	**81**	*TIPS*	18	*rt*	52	73	1
6[c]	**82**	*TIPS*	0.75	84	62	61	0
7[d,e]	**83**	*TIPS*	10	*rt*	0	0	0
8[e,f]	**84**	*TIPS*	1	−40	5	0	0
9[e,g]	**84**	*TIPS*	0.08	−10	40	62	2
10[e,h]	**75**	*TIPS*	14	*rt*	42	78	< 1
11[i]	no catalyst	*TIPS*	19	*rt*	0	0	0

All reactions were performed with 0.5 mmol of substrate in 10 ml of solvent. [a]solvent: CH_2Cl_2, 0.5 eq. of complex filtrated over ALOX and 0.55 eq. of $AgBF_4$; [b]solvent: CH_2Cl_2, 0.7 eq. of complex filtrated over ALOX, 0.77 eq. of $AgBF_4$; [c]solvent: dichloroethane, 0.5 eq. of complex; [d]solvent: benzene, 1 eq. of complex; [e]irradiation; [f]solvent: CH_3CN, 1 eq. of complex; [g]solvent: CH_2Cl_2, 0.3 eq. of complex, 2 eq. of 1,5-cyclooctadiene; [h]solvent: CH_2Cl_2, 0.5 eq. of complex; [i]1 eq. of $AgBF_4$ in CH_2Cl_2.

one unsaturated coordination site, the two others would be occupied with the diene. This approach revealed to be more relevant but the results remained disappointing (entry 9).

Looking in more detail at the product distribution in the case of 2-Me-BOD-Fe(CO)$_2$I (**1**) and Fp'I (**81**), their behaviour is rather different (entries 2 and 3, table 7.2). The former favours the formation of Ambrox® (**4**), while the latter cyclizes **21** preferentially into epi-Ambrox **6**. Moreover, the achiral Fp'I complex (**81**) can not induce optical activity during the process.

Table 7.2: Diastereoselectivity of **1** versus **81**

Entry	Promotor	R	Product distribution [%]						
			4	**5**	**6**	**7**	**8**	**9**	**10**
1[a]	**1**	*TIPS*	65	2	26	7	0	0	0
2[b]	**1**	*H*	51	3	0	6	0.5	39.5	0
3[c]	**81**	*H*	30	5	51	12	0	0	1

All reactions were performed with 0.5 mmol of substrate in 10 ml of CH_2Cl_2 *at room temperature.* [a] 0.7 eq. of complex and 0.77 eq. of $AgBF_4$, duration: 6 days; [b] 0.5 eq. of complex, 0.55 eq. of $AgBF_4$, duration: 6 days; [c] 0.5 eq. of complex and 0.54 eq. of $AgBF_4$, duration: 19 days.

In conclusion, the behaviour of 2-Me-BOD-Fe(CO)$_2$I (**1**) is unique: other iron containing Lewis acid like **75**, **82**, **83** or **84** failed to promote the cyclization due to electronic effects as well as enhanced instability of such Lewis acids in favour of a tremendous deprotection effect, whereas the structurally related complexes **80** and **81** act in a less efficient and less selective way. Moreover entry 11 indicates clearly that $AgBF_4$ alone is not able to perform the cyclization and that a promotor is needed. Several control experiments were conducted to assess the effect of the solvent, the temperature and the protective group on this cyclization.

7.2 2-Me-BOD-Fe(CO)$_2$: catalyst or promotor ?

Cylization of **21** or **22** with 2-Me-BOD-Fe(CO)$_2$I affords Ambrox® and its diastereomers, as well as other cyclized products, from which **77**, **78** and **79** have been identified. Considering all these products, the activity of the complex **1** is rather stoechiometric than catalytic, because the yield of cyclization with

0.5 eq. of complex **1** has never exceeded 50% except for two cases (about 70%) with **21**. It seems that the unprotected alcohol is more favourable to a catalytic process, but we can not exclude that the unidentified cyclized products arise from decomposition products of **1**. Thus, $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ (**1**) should be considered as a promotor rather than a catalyst.

Moreover, if we consider the mechanism of this cyclization, it is obvious that the resulting σ-iron-carbon bond must be broken to regenerate the catalyst. To do that, a proton source is necessary. In case of **21**, the proton could be

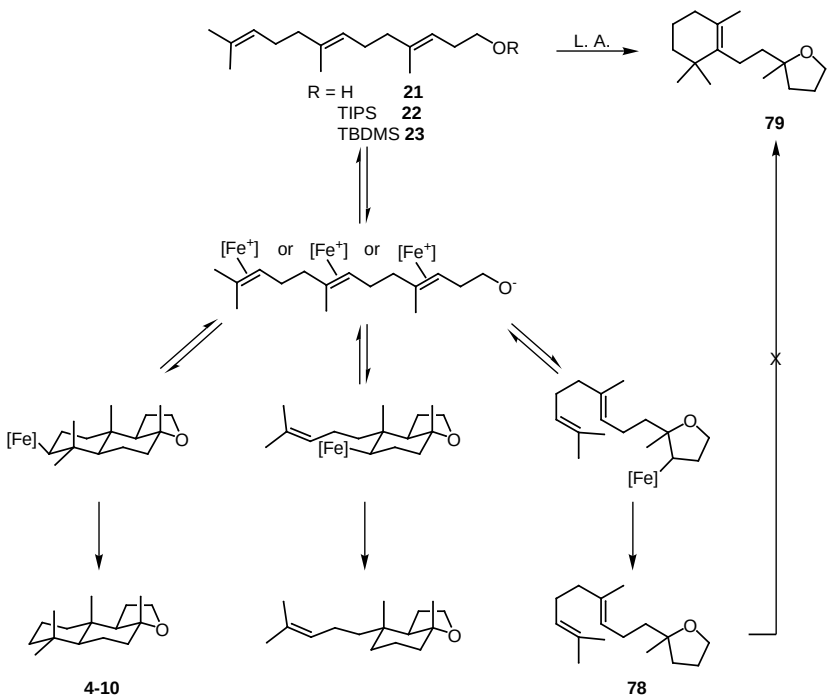


Figure 7.3: Mechanistic hypothesis

furnished by the substrate itself, while in case of the protected alcohol **22** this proton source is not available: this is the reason why we have tried fruitlessly to use some additives.

In conclusion, the real cyclization mechanism remains unclear and needs to

be investigated in order to optimize and to perform a truly catalytical cycle. Moreover the reaction needs to be speeded up so that it can be done at lower temperature in a reasonable amount of time. The reaction slowness can be explained by a series of equilibria except of the last step. Formation of so many products would seem to prove that several active species are involved. The formation of a tetrahydrofuran derivative **79** can be catalyzed by another Lewis acid, since it was only observed when **22** was cyclized. No further evolution of the reaction would be possible until a proton cleaves the σ-iron-carbon bond.

7.3 Reaction conditions and cyclization efficiency

7.3.1 Solvent and temperature: influence

Table 7.3 shows that the solvent has a major impact on the efficiency of the cyclization. In apolar solvents, like supercritical CO_2 (entry 1) or alkanes, the abstraction of the iodide from the complex is not efficient due to the lack of solubility of $AgBF_4$, whereas polar solvents tend to decompose the promotor. Nitropropane oxidized probably the complex **1** producing more than 32 products lacking any major one (entry 6). Acetone proves to be an excellent solvent to

Table 7.3: Solvent and temperature effects

Entry	Solvent	Temperature	Duration	Products obtained [%]				
		[°C]	[days]	conversion	**21**	**4-10**	236[a]	218[b]
1	$SCCO_2$	*rt*	19	30	57	6	6	0
2	CH_2Cl_2	*rt*	14	100	54	10.5	27	1
3	CH_2Cl_2	40	6	94	< 1	10	0	0
4	acetone	*rt*	6	92	62	3	10	22
5	acetone	56	7	99	83	0	2	1
6	CH_3NO_2	80	16	100	more than 32 products			
7	CH_3CN	*rt*	7	74	3	< 1	12	12

All reactions were performed with 0.5 mmol of ***22*** *in 10 ml of* CH_2Cl_2 *in presence of 0.5 eq. of* ***1*** *and 0.55 eq. of* $AgBF_4$. [a] *Cyclized products of mass 236.* [b] *Dehydrated products of mass 218 like* ***77***.

deprotect and to dehydrate the starting material (entry 4 and 5). This trend is increased when heated at reflux. Thus, the dehydration power is in the following order:

$$\text{acetone} > CH_3CN > CH_2Cl_2 > CO_2$$

For these reasons, dichloromethane turned out to be the best choice. It is sufficiently polar to slightly solubilize $AgBF_4$, allowing then the abstraction of iodide, and preventing decomposition to occur. Heating speads up the reaction accomplishment (entries 2 and 3) without altering the enantiomeric excess, the yield and the diastereoselectivity.

7.3.2 Additives influence

Using acetone (entries 4 and 5 in table 7.3 on the preceding page) has revealed that, especially when heated at reflux, additives like ketones could influence the reactivity of **1**. This could be explained by their acidity. Moreover, in order to get a catalytical cycle, the removal of the protective group and the regeneration of the catalyst is required. In a first approach, addition of a proton to the resulting intermediate σ-iron complex was believed to solve this problem. Indeed, as seen in table 7.4, the more acidic the proton source, the more deprotection will occur but without increasing the yield of the cyclization. Moreover with tert-butanol and SiO_2 the promotor is inhibited.

Table 7.4: Effects of the additives

Entry	Additives (1 eq.)	pK_a	Products obtained [%]		
			Conversion	**21**	**4-10**
1	no additive		100	54	14
2	2-butanone	20.5	100	47	16
3	acetone, 2 eq.	19	93	44	15
4	acetophenone	17.7	85	59	7
5	2-indanone	12.21	80	65	12
6	silica gel		0	0	0
7	tert-butanol	17	12	0	0

All reactions were performed with 0.5 mmol of ***22*** *in 10 ml of* CH_2Cl_2 *in presence of 0.5 eq. of* ***1*** *and 0.55 eq. of* $AgBF_4$.

7.3.3 Role of protecting groups

At the beginning of our investigation, the cyclization of homofarnesol (**21**) afforded more than 75% of elimination products (products of mass 218). This

problem was solved by protecting the alcohol with the TIPS group, whereas the TBDMS group revealed to be not stable enough towards hydrolysis (table 7.5). However, protection with TIPS decreases the yield of Ambrox® formation. Recently we have discovered that impurities issued from the decomposition of 2-Me-BOD-$Fe(CO)_2I$ (**1**) were responsible of the observed dehydration. These impurities are removed by filtration over ALOX. The difference of reactivity be-

Table 7.5: Effects of the protectives groups

Entry	R	Duration	Products obtained [%]			
		[*d*]	Conversion	**21**	**4-10**	Mass 218
1	-	9	91	–	22	75
2	TBDMS	17	23	52	0	traces
3	TIPS	14	100	54	14	0

All reactions were performed with 0.5 mmol of substrate in 10 ml of CH_2Cl_2 *in presence of 0.5 eq. of* **1** *and 0.55 eq. of* $AgBF_4$.

tween **21** and **22** shown in table 7.5 could be explained by the nucleophilicity of the oxygen, that is diminished in presence of the electoattractive silicium atom. Thus, the nucleophilic termination of the cyclization is less efficient. Moreover, steric factors can also not be excluded. But three experiments were designed to investigate the necessity or not of a protecting group as well as its influence on the cyclization. The results given in table 7.6 clearly show that the protecting group is first removed to give an alcohol or an alcoholate which will be further cyclized. This also explained the reason why the reaction is slower with TIPS protected homofarnesol.

Table 7.6: Influence of the TIPS group

Entry	Starting materials	Products [%]			
		4-10	**21**	**22**	Other cyclized products
1	**21**	42	28	–	21
2	**22**	6	51	35	1
3[a]	$^1/_2$ **21** + $^1/_2$ **22**	26	56	3	14
4[b]	$^1/_2$ **21** + $^1/_2$ **22**	24	39	17	11

The reaction is performed in CH_2Cl_2 *(10 ml) at room temperature during 6 days. 0.2 eq. of* **1** *filtrated over ALOX and 0.23 eq. of* $AgBF_4$ *are used for 0.42 mmol of substrate.* [a] *experimental value.* [b] *theoretical value.*

In conclusion, the dehydrated product **77** can be avoided by an appropriate protection of the alcohol **21** (TIPS) or better, by filtration of the promotor precursor over ALOX before use. Moreover, the cyclization is the most efficient with unprotected homofarnesol.

7.4 Stereochemistry

7.4.1 General considerations

During its cyclization, homofarnesol (**21**), which has no chiral center, is converted into a tricyclic ether in which four new asymmetric carbons have been generated. An absolute control of these stereocenters represents the state of the art of cationic olefin polycyclization. During the course of cyclization, a number of different stereochemical relationships can be generated. The absolute stereochemistry is controlled by the optically active $2\text{-Me-BOD-Fe(CO)}_2{}^+$ moiety involved at the initiating process: the prochirality of the last double bond exerts a π-facial discrimination during the complexation.

In an olefinic cyclization, the nucleophilic double bond can be endocyclic or exocyclic to the ring that is about to be formed (Baldwin's rule [146]). Unless there is a bias in the other direction, polycyclization of 1,5-dienes leads predominantly to six-membered rings via the endocyclic process [147]. Moreover, it is amply demonstrated that a polycyclization of all-trans olefines generally produces the anti-relationship between adjacent rings, and the diastereomers distribution of an acid-mediated cyclization may be rationalized by the Stork-Eschenmoser hypothesis [62, 147] which postulates that cyclization occurs via chairlike conformations of the nascent cyclohexane rings and that addition to each double bond takes place in an antiparallel fashion. It explains in an elegant way how the all-trans polyolefine is transformed into the trans-anti-trans stereochemistry of polycyclic terpenes or terpenoids. Whether this cyclization occurs via a sequential closure of discrete cationic intermediates or by a synchronous pathway still has to be completely resolved [86]. In contrast to the fusion of six-membered rings, in which the most commonly trans stereochemistry is the thermodynamic favoured one, the trans B/C ring junction is less stable than the cis. This is consistent with the selectivity expected on ring closure of a discrete carbonium ion intermediate. It can be readily understood on the basis of a non-concerted cyclization due to steric constraints or weakly nucleophilic termination.

Although this postulate generally holds true in biomimetic cyclizations, there are a number of instances in which it breaks down. Severe deviations of the previous rules are observed in our case.

7.4.2 Diastereoselectivity

Table 7.7 shows clearly that Ambrox® (**4**) is always the favoured diastereomer, while **5**, **8** and **10** are produced only in traces. The *E-Z* geometry of olefinic bonds is translated into the stereochemical relationships between substituents along the back-bone in the product, thereby implying a certain degree of concertedness, at least in the early stage of the cyclization. Thus it seems that an all chairlike conformation for the transition state prevails, and that cyclizations proceeds without major intervention of deprotonation-reprotonation (without alkene-cation equilibria) [148]. Finally, the stereochemistry of termination (ring C) results from a selective anti-addition to the terminal double bond.

Table 7.7: Diastereomeric distribution

Entry	R	Additives	**4-10**	Product distribution [%]						
			[%]	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1[a]	*TIPS*	-	10	50.5	2	41	6.5	0	0	0
2[b]	*TIPS*	-	10.5	45	3	11	7	0.5	34	0.5
3[c]	*TIPS*	-	26	65	2	26	7	0	0	0
4[d]	*OH*	-	42	51	3	0	6	0.5	39.5	0
5[e]	*OH*	-	4	85	0	0	7	0	8	0
6[f]	*TIPS*	2-butanone	18	44	7	0	6.5	0.5	41	1
7[g]	*TIPS*	acetone	23	42	5	47	5	0.5	0	0.5
8[h]	*TIPS*	2-indanone	6	41	2.5	30	25.5	0	1	0

All reactions were performed with 0.5 mmol of substrate in 10 ml of CH_2Cl_2 *at room temperature (except for entry 1).* [a] 0.5 eq. of **1** and 0.55 eq. of $AgBF_4$, temperature: 40°C, duration: 6 days; [b] 0.7 eq. of **1**, 0.77 eq. of $AgBF_4$, duration: 14 days; [c] 0.74 eq. of filtrated **1**, 0.84 eq. of $AgBF_4$, duration: 6 days; [d] 0.5 eq. of filtrated (over Alox) **1**, 0.55 eq. of $AgBF_4$, duration: 6 days; [e] 0.25 eq. of filtrated (over Alox) **1** and 0.25 eq. of $AgBF_4$, duration: 9 days; [f] 0.4 eq. of **1** and 0.5 eq. of $AgBF_4$, duration: 19 days, 1 eq. of 2-butanone; [g] 0.5 eq. of **1** and 0.6 eq. of $AgBF_4$, duration: 19 days, 2 eq. of acetone; [h] 0.4 eq. of **1** and 0.5 eq. of $AgBF_4$, duration: 18 days, 1 eq. of 2-indanone.

Iso-Ambrox (**5**) can be formed by acid catalyzed epimerization [86] of (-)-Ambrox® or through the cyclization process itself. But in this case, **4** is kinetically more

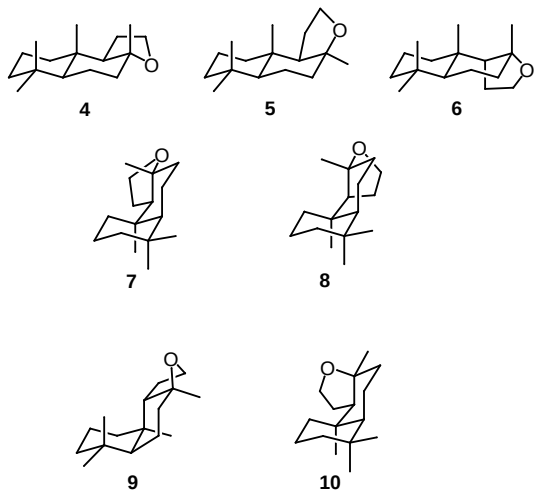


Figure 7.4: Ambrox® and its diastereomers

favoured than **5**, because the steric hindrance from the angular methyl group disfavours the transition state [75, 118] (figure 4.5 on page 31). Diastereomers **8** and **10** are strongly disfavoured since their formation requires isomerization of (*E,E*)-homofarnesol in (*Z,Z*)-homofarnesol.

Depending on the reactions conditions, either **6** or **9** is the second diastereomer favoured. Unfortunately, the results given in table 7.7 on the page before and summarized schematically in figure 7.5 on the facing page are extremely difficult to explain, and a mechanistic rationalization is actually impossible to formulate. Nevertheless, the experimental results we have collected so far has helped us to draw a few conclusions:

- **Stoechiometric process:** entry 5 points out that $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ complex (**1**) acts as a promotor and not really as a catalyst, since reducing the amount of **1** considerably reduces the efficiency of cyclization. This confirms our previous observation (section 7.2 on page 69).

- **Stepwise mechanism:** formation of the diastereomer **9** tends to discredit a non-synchronous cyclization involving prior ring closure to a cyclohexenyl cation whose conformational inversion is slower than subsequent cy-

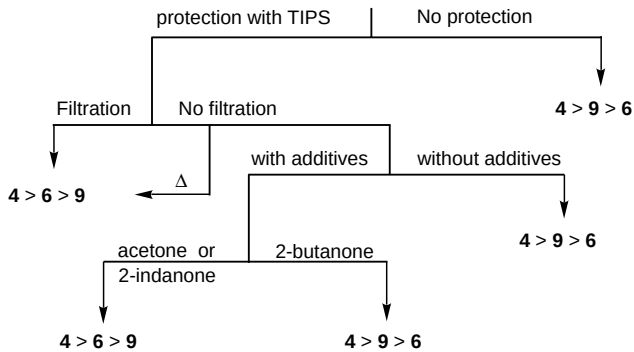


Figure 7.5: Schematic representation of results

clization [86]. Thus the cyclization of homofarnesol (**21**) or **22** promoted by **1** seems to take place stepwise via cationic intermediates with flexible conformation, in which internal anti additions are controlled by a strong kinetic preference for equatorial C-C and C-O bond formation, a hypothesis supported by the work of Nishizawa [149] and Dewar [150].

- **A new pathway:** as the diastereomeric distributions are different from those of a Brønsted acid [86, 134] or $\mathrm{SnCl_4}$, whose strategy is based on a combined system of Lewis acid and a chiral Brønsted acid [64, 151], a different pathway is certain, since entries 4, 5 and 6 definitely discredit an identical pathway. Unlike the published cyclizations of (*E,E*)-homofarnesol under acidic conditions, that favour the formation of **4** and **6** or **7** in the Yamamoto case (entry 5), our promotor prevents the formation of **6** and favours the formation of **4** and **9**. In the Yamamoto case (entry 5), the proposed transition state (figure 7.6 on the following page) shows a complicated interaction between the tin center, the hydroxyl group, chlorides and the substrate.

- **First step:** table 7.6 on page 73 reveals that the first step of the cyclization of **22** is the deprotection of the silylether.

- **Olefinic isomerization:** carbenium ion conformational preferences clearly play a role in cyclization stereospecificity. Unlike the cis/trans decalin that can be explained by a β, α-attack of the carbocation by the nucleophile, respectively, the origin of the C(3)=C(4) isomerization is unclear. Snowden has stated that this isomerization due to a protonation-deprotonation

Table 7.8: Products distribution

entry	substrate	methods	Product distribution [%]						
			4	**5**	**6**	**7**	**8**	**9**	**10**
1	(*Z,Z*)-**21**	FSO_3H	0	0	5	6	57	0	6
2	(*E,Z*)-**21**	FSO_3H	5	0	4	46	0	16	0
3	(*Z,E*)-**21**	FSO_3H	0	0	69	0	7	0	0
4	(*E,E*)-**21**	FSO_3H	40	0	35	2	0	1	0
5	(*E,E*)-**21**	$SnCl_4$[1]	56	0	9	26	0	9	0
6	(*E,E*)-**21**	**1**	51	3	0	6	0.5	39.5	0

Data provided by: Snowden et al., J. Org. Chem. 1992, 57, 955 and Yamamoto et al., J. Am. Chem. Soc., 1999, 121, 4906. [1]*: together with a modified chiral BINAP*

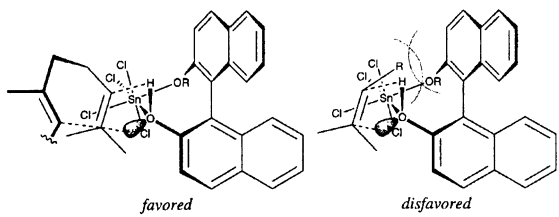


Figure 7.6: Proposed transition-state for the Yamamoto system

is accelerated by neighbouring group participation of the protonated hydroxyl group [86]. Nevertheless as we do not work with a Brønsted acid, we must single out the participation of a Lewis acid.

- **Role of prochiral olefin:** the prochirality of the C(11)=C(12) double bond determines the face of complexation (subsection 7.4.3 on page 80). This step is followed by an exo (regarding the metal center) nucleophilic attack of the next double bond. Thus, the optically active moiety determines which diastereotopic face of the complexed olefine is attacked by the nucleophile, as well as probably the stereochemical outcome of the other cyclizations, since iron forms a σ-bond in the equatorial position of the produced cyclohexenyl cation. This carbocation is further attacked by the next double bond from α or from β side producing the trans or the cis decalin, respectively. However, the formation of the ring C is unequivocal after the formation of the second cycle. Indeed the trans C(3)=C(4) gives **7** or **9** while the cis double bond gives either **6**, **8** or

10. The isomerization of this double bond can occur before or after the complexation.

- **Role of the TIPS group:** the cyclization with the protected alcohol is slower than without protecting groups (Table 7.6 on page 73 demonstrates that the deprotection occurs predominantly and preceds the other steps). Moreover, the presence of the TIPS group seems to favour the C(3)=C(4) double bond isomerization. This could be explained by some decomposition products of **1** that produces other Lewis acidic species responsible for the observed isomerization. Thus, the results of entry 2 can be explained by the action of an unknown Lewis acid due to the longer period of the reaction. However, the mechanism of this isomerization remains obscure. Filtration of the promotor **1** over ALOX before use removes such Lewis acids and this corroborates with the formation of **6** in a smaller amount in this case (entry 3).

- **Role of the additives:** addition of 2-Butanone (entry 8) modifies the outcome of the cyclization, by preventing the formation of **6**. Thus, cyclization of **22** in the presence of 2-butanone leads to similar results as the cyclization of **21**. Nevertheless entry 7 is somewhat surprising because acetone is not much more acidic than 2-butanone and they should exhibit identical reactivity. In this respect, we consider that, either (less likely) the difference of pKa of acetone and 2-butanone is sufficient to explain the different behaviour, or these ketones interact in different ways with the TIPS group and 2-butanone would facilitate the removal of the TIPS group, e.g. by transsylilation, leaving an unprotected substrate. Note that when **22** was cyclized, triisopropylsilanol was always isolated.

In conclusion, it is impossible to give at present a satisfactory hypothesis about the mechanism, since there are not many experiments and the influence of the protective groups and of the ketones remains unclear. The most difficult task lies in the preferred formation of either **6** or **9** depending on certain reaction conditions. Compared to the Brønsted acid mediated cyclization, the complexation of homofarnesol obviously modifies the relative energies of transition states.

7.4.3 Enantiomeric excess

Analytical separation of enantiomers was a difficult task, because the samples were invariably diastereoisomeric mixtures. Moreover only samples **4** and **6** are available as optically pure stereoisomers, so an absolute determination for the other enantiomers was not possible. Thus, the enantiomeric excesses of Ambrox® (**4**) and epi-Ambrox (**6**) were determined by chiral gas chromatography with three different methods:

- **Method I:** injection on the chiral column 6-TBDMS-2,3-DiEt β-cyclodextrine, 25m x 0.32m, film 0.25μm with isotherme at 125°C.
- **Method II**[1]**:** injection on the chiral column Hp-5890/1, 25m x 0.3mm, film 0.25μm with isotherme at 140°C with a flux of helium of 0.66ml/minute.
- **Method III**[2]**:** injection on the chiral column CP CHIRASIL-DEX (Chrompack), 25m. x 0.25mm, film 0.25μm with isotherme at 160°C with a flux of helium of 1 ml/minute.

As the results given by the three methods I, II and III are not identical and sometimes even rather different, a careful analysis is thus necessary and an unequivocal conclusion is impossible to formulate. As the enantiomeric excess of **6** was only measured with method III, our discussion will be restricted to Ambrox® (**4**). While method I gives about 30% ee, II gives 22% and III -4% (table 7.9 on page 83). The last result is surprising because the absolute value is much lower than with the other methods and the (+)-enantiomere is favoured instead of the (-) one. This prompt us to examine carefully the chromatograms:

- **Method I:** we have observed, that the ee of **4** decreased with the intensity of the signal at 70.62 min. Moreover the signal of (-)-**4** at 72.45 min is broadened, probably due to an overlap of (-)-Ambrox (**4**) with the enantiomeric partner of the molecule at 70.62 min. This clearly shows that the enantiomeric excess obtained is overestimated (figure 7.7 on the next page).
- **Method II:** the chromatogram of the racemic mixture of diastereomers shows obviously that the signal which comes out at 27.46 min has no

[1]These analyses were kindly performed by M. C. Vial (Firmenich SA).
[2]These analyses were kindly performed by M. A. Saxer (University of Bern).

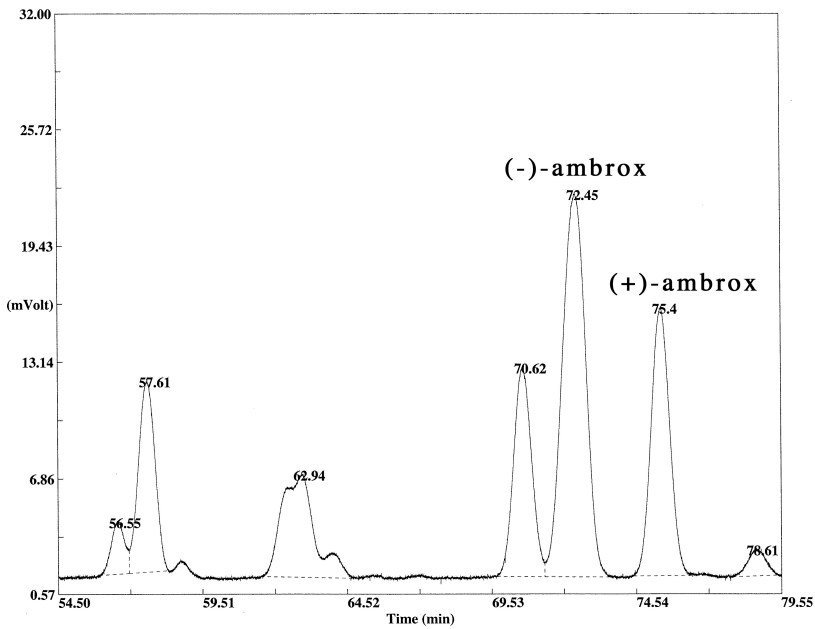


Figure 7.7: Chiral GC, method I

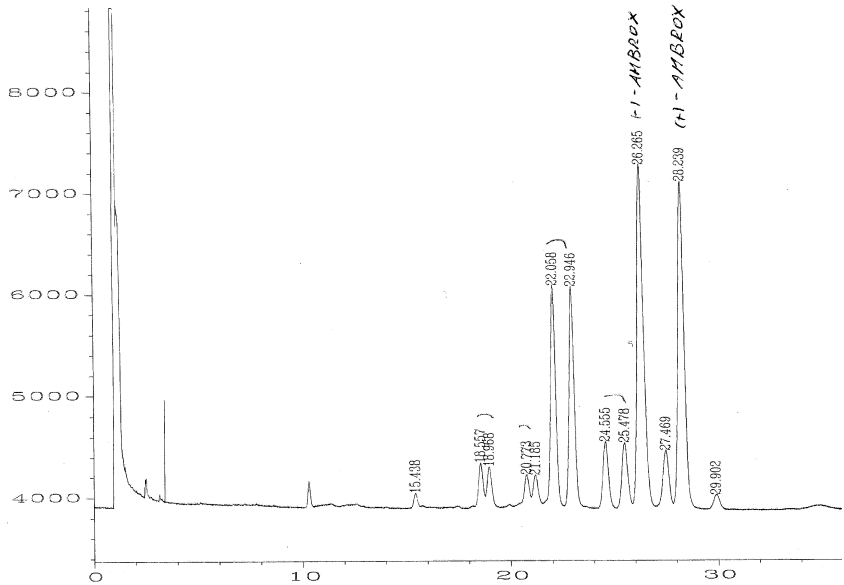


Figure 7.8: Chiral GC, method II

partner. Another possibility is that the single signal is the one at 24.55 min and the partner of 27.46 min would be the signal at 25.47 min. In fact the widened signal of (-)-Ambrox **4** at 26.26 min probably points out that it is superimposed on the enantiomer of 27.46 min or 24.55 min (figure 7.8).

- **Method III:** the enantiomer **7** has no partner and if we consider the same resolution for this diastereomer than for the others it is reasonable to conclude that its partner is under the enantiomer (+)-**4** (figure 7.9 on the next page).

These results do not seem to be reliable, but taking into account the previous observations, we can correct the results by substracting the signal which is superimposed on either (-)-**4** or (+)-**4** (method I and II, respectively III). Of course, we have supposed that the superimposed signal is issued from a racemic pair of enantiomer, that is probably not the case if the reaction shows enantioselectivity. Moreover we can not exclude that other impurities and other Ambrox® isomers are superimposed. According to these hypothesis, the re-

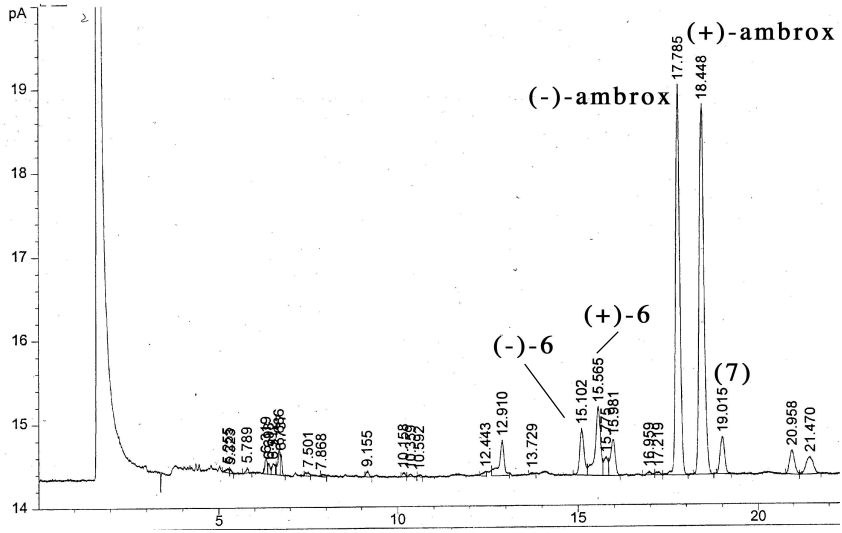


Figure 7.9: Chiral GC, method III

Table 7.9: Enantioselectivity of the cyclization

Entry	Additif	Duration [days]	ee [%] Method I	II	III
1[1]	-	6	30 (1)	18 (-5)	-5 (1.8)
2[2]	-	6	40 (0.3)	-	-4 (1.5)
3	-	6	-	22 (-6)	-
4	-	6	-	27 (-3)	-4 (1)
5	acetone	19	36 (1.6)	-	-3 (2.7)
6	acetophenone	19	30 (0.6)	-	-
7	2-indanone	19	44 (2.3)	-	-4 (1.6)
8	2-butanone	20	28 (0.8)	-	-4 (1)

The numbers between brackets give the corrected value. Cyclization conditions: 0.5 mmol of the TIPS protected homofarnesol is mixed in dichloromethane (10 ml) at room temperature in presence of 0.5 eq. of 2-Me-BOD-Fe$(CO)_2$I *complex with 0.55 eq. of* $AgBF_4$. [1] *0.75 eq. of* 2-Me-BOD-Fe$(CO)_2$I *and 0.8 eq. of* $AgBF_4$ *are used.* [2] *the reaction is performed at 40° C.*

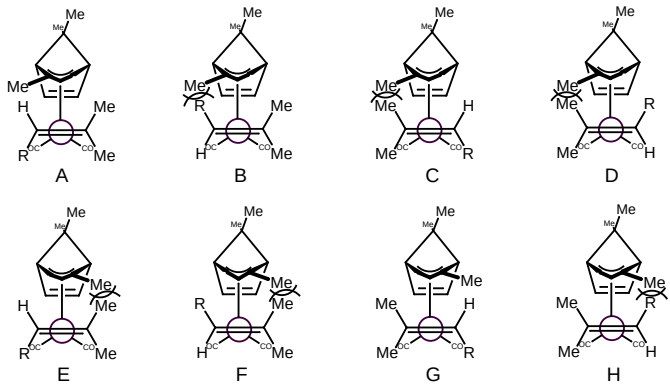


Figure 7.10: Complexation of the prochiral alkene in homofarnesol

sults of method I and III are in rough agreement and the enantiomeric excess of Ambrox®, is estimated to be 2-3%, but the results of method II diverge from the others (table 7.9 on the preceding page). As the difference between the (+) and the (-) isomer is small, a little error in the substraction can give erroneous results.

In this reaction the enantioselectivity may arise by complexation of the terminal alkene of homofarnesol. As this alkene possesses enantiotopic faces, the cationic complex $2\text{-Me-BOD-Fe(CO)}_2{}^+$ performs a prochiral recognition. Iodide abstraction of the $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ complex generates a vacant site and the olefin coordinates to give complexes depicted in figure 7.10. Two structural features are crucial to the selectivity: the stereogenic methyl group of the catalyst and the alkyl rest R of the alkene. These factors discriminate approach A (favorable) from approach B (unfavorable). Approaches C and D are believed to be disfavored for steric reasons. The same considerations with the enantiomeric catalyst show that approach G is favoured. In fact approach A reflects the appropriate complexation for cyclizing homofarnesol into (-)-Ambrox and G for (+)-Ambrox. Thus the results provided by method II are definitely to be discarded. However, considering the corrected results of method I and III, (-)-Ambrox is slightly favoured by the $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ complex. This weak chiral induction can result from:

- the stereogenic methyl substituent that is perhaps not large enough to discriminate the complexation B in favour of A. Thus replacement of this

stereogenic methyl with a bigger substituent should increase the enantioselectivity. Another solution would consist in having a substituent that interacts with the oxygen atom of homofarnesol in order to better control the oxygen attack over the generated carbocation, as the formation of the five-membered cycle is the least selective. This would also fold the molecule in the right way for the cyclization. However, such an approach should be paralleled by a computational investigation. Moreover, the functional group complexing the oxygen atom should not decrease its nucleophilic character.

- the rotation of the olefin about the iron-olefin axis. We do not believe that such rotation occurs in the present study, since the rotational barrier in Fp complexes is sufficient to avoid such a rotation [152], but if it is the case, this problem could be overcome by substitution of one of the carbonyl with a larger ligand like a phosphine or a tin [153], or by increasing the bond strength between the olefin and the iron by a decrease of the electronic density of the metal center. An electron withdrawing substituent instead of the 2-methyl could solve this problem.

- the rotation of the BOD system about the iron-BOD centroid. Indeed, the NMR shows a dynamic behaviour of this complex. In fact, the rotamers presented in figure 7.10 on the facing page represent the prefered orientation of the ligands in the solid state, because they are based on the x-ray structure in which, the iodide, replaced by the olefin is anti to the double bond of the BOD system. To prevent this rotation, the BOD system should have a substituent able to substitute one or both carbonyls, thus behaving like an anchor.

- the reaction conditions: lower temperatures will perhaps increase the enantioselectivity, but this implies that the reaction efficiency is increased because at low temperature, the reaction is extremely slow.

Generally, the enantiomer **6** exhibits more or less the same enantiomeric excess as **4**. This is logical since the chiral source is the same. However, the results show uncertainty, because they vary a lot due to the proximity of another signal in the GC.

7.5 Conclusion

The metal-mediated asymmetric cyclization of simple unfunctionalized trienols, where the hydroxyl is far distant from the complexed double bond, still represents a particular challenge because of the lack of pendant group favoring stereocontrol by conformational rigidity via auxiliary interactions. In case of the $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ complex (**1**), the cyclization of homofarnesol **21** affords Ambrox® (**4**) with good diastereoselectivity, modest yield and very low enantioselectivity, even if the promotor synthesized from optically active (-)-β-pinene (92% ee) is non-racemic. This low asymmetric induction could result from the small size of the 2-methyl group or from the reaction conditions themselves. Our study reveals also that the protection of homofarnesol (**21**) with the TIPS group is not necessary and provides worse results that are extremely difficult to rationalize. Finally, if it turned out in further studies that the (+)-enantiomer is favoured, then this tendency should be reversed by using the enantiomer of **1**.

Chapter 8

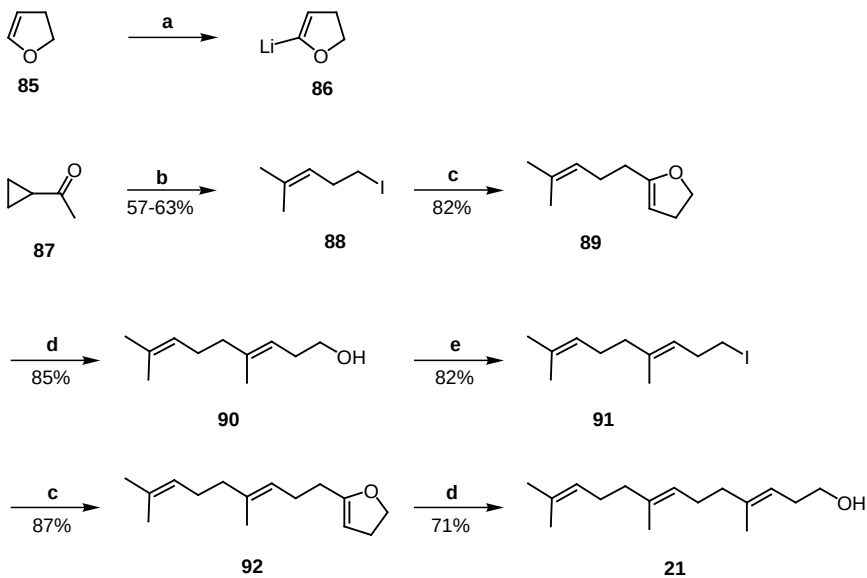
Homofarnesol

As outlined in the previous chapter, the (*E,E*)-homofarnesol (**21**) is the key substrate towards Ambrox® (**4**). A simple and efficient synthesis was published by Kociensky [137]: it affords in an easy and recursive manner the all-trans homofarnesol (**21**). Moreover, the yield is quite acceptable: overall six steps yield 21%. Although every step proves to be highly effective, yielding crude reaction mixtures that contained only few and easily removable impurities, this procedure was improved by some changes.

8.1 Synthetic improvements

The homofarnesol , as well as its derivatives, can be easily synthetized according to a published protocol [137], where the authors present an iterative procedure to extend the alkyl chains by isoprenyl units in a three step reaction shown in the figure 8.1 on the next page. A nucleophilic attack of the lithiated 2,3-dihydrofuran onto an alkyliodide adds a four-carbon unit to the latter that possesses a double bond. Stereoselective ring opening by a transfer of a methyl from a low valent nickel species leads to an extended molecule bearing an alcohol group in ω-position (Wenkert reaction [154, 155]). This can be converted to the corresponding iodide and the cycle can be repeated as previously. The starting material **88** is synthesized according to a published protocol [156].

For the reaction of type **c**, a large excess of 2,3-dihydrofuran (**85**) is used instead of a large excess of $^t\mathrm{BuLi}$, because it is obvious that the latter is not



a: $^{t}\mathrm{BuLi}$, THF, -30 °C; **b:** 1. MeMgI, $\mathrm{Et_2O}$; 2. $\mathrm{H_2SO_4}$; **c: 86**, THF, -50 °C ... 25 °C; **d:** 1. $\mathrm{MeMgX(X{=}Br,\ I)}$, $\mathrm{[Ni(PPh_3)Cl_2]}$, MePh, ↑↓; **e:** 1. MsCl, $\mathrm{NEt_3}$, $\mathrm{Me_2N(CH_2)_3NH_2}$, $\mathrm{CH_2Cl_2}$, 0 °C, 2. NaI, $\mathrm{Me_2CO}$, ↑↓.

Figure 8.1: Synthesis of homofarnesol

desirable, as free $^{t}\mathrm{BuLi}$ can give rise to undesired side products, resulting from addition or elimination reactions on the iodide **88** and **91**, respectively. The following alkylation **d** proved to be rather a slow reaction (after 30 min, only half of the iodide had reacted). Reaction time was therefore expanded from 18 to 36 hours. In disagreement to the protocol, it is not possible to distil the 5-alkyl-2,3-dihydrofuran **89** at 90 °C and water pump vacuum without severe alteration. Using a turbo molecular pump decreases the boiling point to *ca.* 40°C. In the next step the homogeraniol (**90**) was purified only by distillation. The 5-alkyl-2,3-dihydrofuran **92** is not volatile enough to be distilled at ambiant temperature with the turbo molecular pump. Also chromatography on silica gel is considered to be harmful because of its acidity. Therefore a 10% impurity, not giving any problems in the following reaction step was not removed. Finally, the crude homofarnesol (**21**) contained $\mathrm{PPh_3}$ from the decomposition of the catalyst and another non-polar impurity. Whereas the phosphine could easily removed by complexation to silver nitrate, the other impurity is removed by chromatography. Adsorption onto a $\mathrm{SiO_2}$ plug, and elution of the impurity with pentane followed by the mobilisation of **21** with $\mathrm{CH_2Cl_2}$ proved to be highly effective and less consuming in silica gel and solvent than the original procedure.

The advantage of this procedure is to produce an all-trans molecule, because the key step of the reaction is the highly stereoselective nickel catalysed coupling of a Grignard reagent with 5-alkyl-2,3-dihydrofurans (see figure 8.2 on the following page). The chloride is substituted by a methyl in the $\mathrm{Ni}(0)$ species, to afford $[\mathrm{Ni(PPh_3)_2Me_2}]$ followed by a reductive elimination of ethane, yielding the catalyst back. The dihydrofuran ring is opened by an oxydative addition onto the nickel center of the catalyst. By reductive elimination of the methyl and the opened ring fragment, the catalyst is regenerated affording the homoallylic alcohol after protonation.

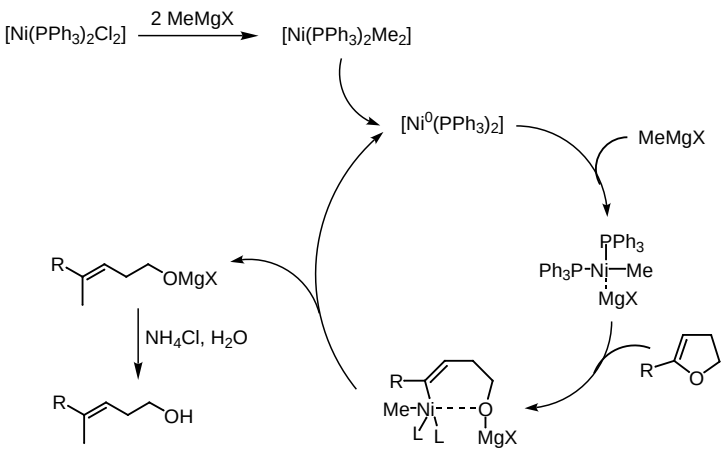


Figure 8.2: Stereoselectivity in the synthesis of homofarnesol

Chapter 9

Synthesis of analogues to the 2-Me-BOD-$Fe(CO)_2I$ complex

9.1 Introduction

The reactivity of a molecule can change more or less drastically with small electronic or structural variations. Such modifications can provide different stoechiometric applications and, in the case of a catalyst, they can fine tune its properties. Moreover, the synthesis of several derivatives improves the knowledge about the reactivity of the family of these compounds. Thus several derivatives of the $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ complex (**1**) were planed.

We have restricted our approach on derivatives easily obtained from commercially available products having a pinenic skeleton.

As outlined in figure 9.1 on the next page, eight positions of the organic ligand of the $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ complex are available for modifications, but practically only a substitution at the positions 1, 2, 3, 4, and 6 is conceivable and many examples are given in literature:

- the position 7 can not be modified since it stems from the insertion of one of the carbonyls in the last step of the synthesis.

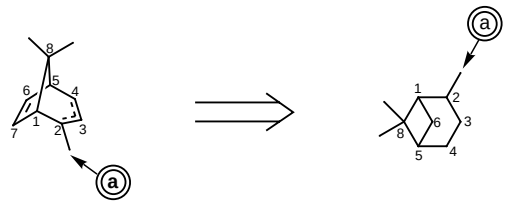


Figure 9.1: Possible substitutions
(the random numbering shows the correlation between the two structures)

- the substitution of the gem-dimethyl groups (position 8) will have no influence in the final complex, because they are at the opposite side of the metal center.

- no substitution of the positions 5 is known nowadays.

In this preliminary study, we have limited our investigations to the substitution at ⓐ, because this position directly influences the chirality and the electronic properties of **1**. Moreover, several commercially available products (i.e. myrtenol, myrtenal, nopol) are already substituted in this position, and modifications of their substituent at carbon atom 2 should provide a simpler access to several derivatives than any other position. Thus our approach is based on the 2-substitution of apopinene (R = H) with either electron donating or electron withdrawing groups (figure 9.2).

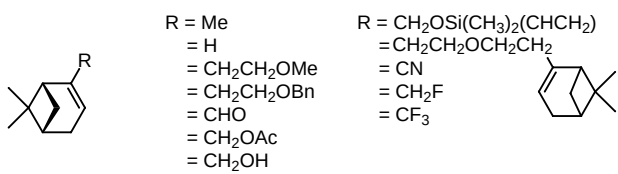


Figure 9.2: Chosen substitution pattern

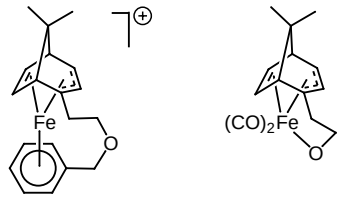


Figure 9.3: Arene versus scorpion complexes

9.2 Substitution with electron donating groups

9.2.1 R = CH_2CH_2OR'

Having a longer aliphatic chain than α-pinene and a hydroxyl group at its end, that can be interconverted into other functional groups, nopol ($\mathrm{R} = \mathrm{CH_2CH_2OH}$) (**93**) is a very promising candidate for a ligand. These properties could be useful to build intramolecular arenic complexes or scorpion's complexes as depicted in figures 9.3 and 6.11 on page 63. As the ring opening complexation of this alcohol risks to suffer of water elimination producing the corresponding nopadiene complex (**96**), the alcohol function was protected with an ether.

The nopyl methyl ether (**94**) is obtained according to a procedure published by Schlosser [157]. Deprotonation of the alcohol with sodium hydroxyde in presence of a phase transfer catalyst followed by a treatment with dimethylsulfat affords the desired ether **94** in 79% yield (figure 9.4 on the following page). Its complexation affords 21% of the desired complex **95** as well as the nopadiene complex (**96**) and other unidentified complexes. Elimination of methanol explains the formation of **96**. Thus the protection of **93** with a methyl is not stable enough, hence protection with a more nucleophilic moiety like benzyl was prefered.

Figure 9.5 on the next page shows that a Williamson synthesis with nopol (**93**) and benzylbromide in presence of sodium hydride affords nopyl benzyl ether (**97**) (96%) [158]. Ring opening complexation of nopyl benzyl ether **97** in presence of $\mathrm{Fe(CO)_5}$ in dioxane/heptane at reflux yields 42% of the desired complex **98** without traces of **96**, which confirms our prior hypothesis. About 30% of the starting material **97** are also recovered. The complex **98** reacts further with iodine to give the iodo complex **99** in a 70% yield. Lithiation with $^t\mathrm{BuLi}$ fol-

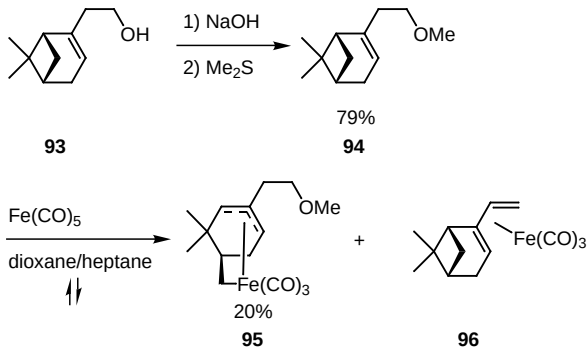


Figure 9.4: Nopyl methyl ether

lowed by addition of isoprene and m-(trifluoromethyl)benzoyl chloride affords 15% of **100**.

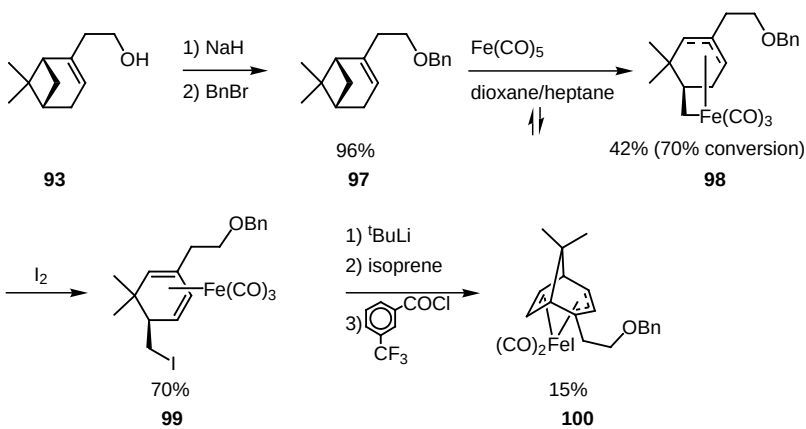


Figure 9.5: Nopyl benzyl ether

Complexation of a molecule that contains two complexation sites like the bis[2-(6,6-dimethyl bicyclo[3.1.1]hept-2-en-2-yl)ethyl]ether (**103**), does not only introduce an important steric effect but the second iron moiety exerts also a steric shielding effect on the first one complexed unit. Thus the dinopylether (**103**) was synthesized (figure 9.6 on the facing page). Tosylation of nopol **93** with triethylamine and p-toluenesulfonyl chloride is very effective (yield 96%). The

tosylate **101** reacts with nopol (**93**) in presence of KOH to afford nopadiene (**102**) in a 33% yield and nopol (**93**). Similar results were obtained by using NaH. Nethertheless, no traces of **102** have been detected when $^{n}\mathrm{BuLi}$ was used. Nopadiene (**102**) is obtained because the alcoholate reacts not only as a nucleophile but also as a base which deprotonates the tosylated nopol **101** [159] to give nopol (**93**) and nopadiene (**102**). Several attempts to improve the yield has failed. Under the ring opening complexation conditions, the dimer **103** deteriorates slowly and no complexes were isolated. Performing the complexation at a lower temperature (85 °C) in dimethoxyethane, the monocomplexed product **104** was isolated in low yield (28%) as well as other complexes, whose structure remains unidentified to date. The second site remains strangely uncomplexed. Does the first complexation prevent the second ?

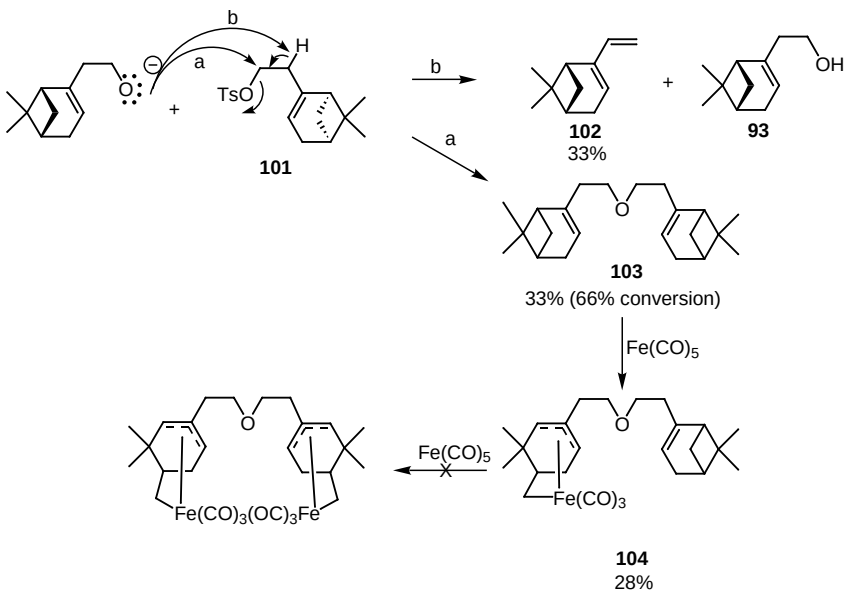
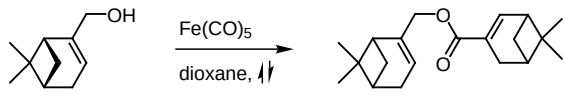


Figure 9.6: Dinopylether

We notice that the solvent plays an important role in the ring opening complexation. Dioxane proves to be the solvent of choice, because the lone pairs of its oxygens stabilize weakly iron intermediate species [141]. Replacement of dioxane with toluene gives worse result and the reaction does not occur with



105 **106**

Figure 9.7: Complexation of myrtenol

aliphatic solvents. Stephan Lauper [142] noticed that water was formed during the process. That's why he used a Dean & Stark apparatus with heptane as cosolvent. But we discovered that similar yields can be obtained without such precautions. The observed water is probably not formed during the reaction but comes likely from the glassware or from one of the products. Moreover, the replacement of dioxane with another cyclic ether like eucalyptol gives the same yield as dioxane even if the lone pair of the oxygen in eucalyptol are electronically richer and less reachable. Another ether, dimethoxyethane, allows also such reactions.

9.2.2 R = CH_2OR'

Complexation of myrtenol (**105**) ($\mathrm{R}= \mathrm{CH_2OH}$) affords, instead of the expected complex, an ester which structure is depicted in the figure 9.7. This ester **106** could issue from a Cannizaro reaction of the myrtenal (**108**), present as impurity in the bottle. However, a GC-MS investigation of the starting material does reveal neither traces of myrtenal (**108**) nor traces of the ester **106**. We can then conclude that the ester **106** is issued from a new reaction that would be interesting to study in a separate project.

Consequently, we envisaged to protect myrtenol (**105**) before complexation. When the latter is protected with a TMS group and treated afterwards with iron pentacarbonyl, cis and trans exocyclic double bond **109** and **110** are isolated in a 63% yield together with traces of myrtenal (**108**) and complex **111** (figure 9.8 on the facing page). These results suggest first that the protected oxygen is electronically too rich and the isomerization of the double bond occurs rapidly avoiding any complexation. Secondly, the presence of an aldehyde in spite of the high purity of the starting material confirms our previous hypothesis about the origin of the ester **106**, so the alcohol would be first deprotected, then oxidized and finally would undergo a Cannizaro reaction. But in this case, the

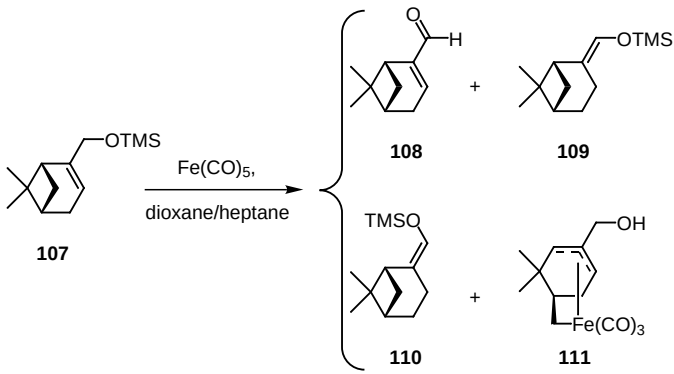


Figure 9.8: Isomerization of the double bond

last step did not occur, because either the reaction time was not long enough or the reaction conditions were not suitable. Oxidation of alcohols to aldehydes with iron pentacarbonyl is not known, but several examples with Fe^{II} and Fe^{III} species were reported [160, 161]. Unfortunately, the oxidizing agent remains unknown in our case.

Myrtenol (**105**) was also protected as an acetate ester that offers the advantage of being interchanged in other functional groups after complexation. Moreover, the removal of the acetate with a Lewis acid (i.e. $\mathrm{BF_3{\cdot}OEt_2}$) should provide a trimethyl methane (TMM) cationic complex, which could further react with a nucleophile. This kind of nucleophilic substitution of acetate assisted by the iron moiety was already described by Uemura for dienic acetates of iron tricarbonyl [162–164]. Thus, this approach could open the window on a library of derivatives of the $\mathrm{2\text{-}Me\text{-}BOD\text{-}Fe(CO)_2I}$ complex. Acylation of myrtenol (**105**) with acetic anhydride catalyzed by trimethylsilyl trifluoromethansulfonate gave the desired acetate **112** in a high yield (94%) [165]. Complexation of **112** in presence of iron pentacarbonyle in dioxane at reflux affords the desired complex **113** in low yield (10%) as well as 5 other products of mass 270. It seems that the elimination of acetate is favoured. The figure 9.9 on the next page outlines an hypothetical pathway to the observed products. As two allylic positions can be coupled since the starting material was optically impure, several diastereomers of **114**, **115** and **116** were produced.

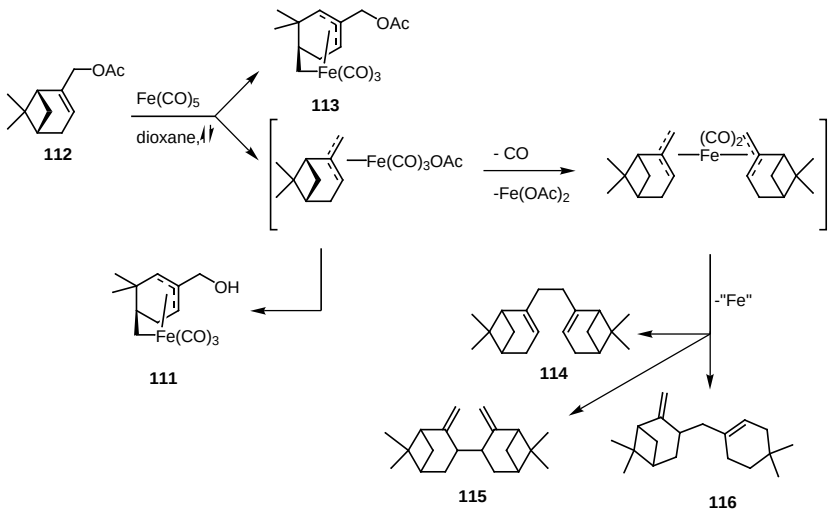


Figure 9.9: The acetate approach

As can be seen in figure 9.10 on the facing page, treatement of the acetate complex **113** with a nucleophile (PhLi) in presence of trifluoroborate etherate gave three products but not the desired one. Two possible pathways can explain the formation of the alcohol **111**: either the enolate is produced in presence of phenyllithium and $\mathrm{BF_3}$ (pathway **A**), or the $\mathrm{BF_3}$ cleaves the acetate producing the cationic trimethylmethane complex (pathway **B**). Hydrolysis of the resulting intermediate affords in both cases the alcohol **111**, which turned out to be an important intermediate towards the synthesis of fluorinated derivatives (see the section 9.3.2 on page 101). As the alcohol **111** is formed almost quantitatively (92%), and as the use of a fluoride (from TASF or DAST) as nucleophile instead of the phenyl give only small amounts of the starting complex **113** without any traces of **111**, the pathway **B** seems to be very unlikely. Finally, acetophenone (**117**) (30%) and 1,1-diphenyl-1-ethanol (**118**) (60%) were isolated[1] when using phenyllithium. The expected fluorinated complex was not observed with TASF or DAST.

A last protection of myrtenol (**105**) was tried with the dimethylvinylsilane. Nor-

[1]yields regarding the PhLi.

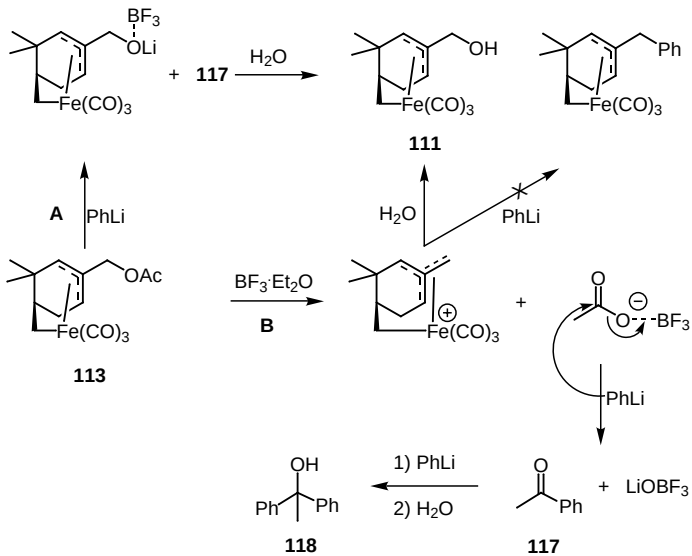


Figure 9.10: Nucleophile addition on **113**

mally a protective group should not interfere in the process of complexation. Fortunately the dimethylvinylsilane group could facilitate the complexation of **119**. Tetramethyldivinyldisiloxane was shown to transfer a $\mathrm{Fe(CO)_3}$ moiety to dienes when irradiated in the presence of $\mathrm{Fe(CO)_5}$ [166]. The oxygen next to the silicon atom as well as the two double bonds are necessary for this transfer; consequently the protection of the myrtenol with dimethylvinylsilane affords a substrate similar to the tetramethyldivinyldisiloxane. The so introduced dimethylvinylsiloxane can be used as an internal transfer moiety as well as a protective group for the alcohol. Unfortunately neither the photochemical nor thermal complexation attempts afforded the desired complex (figure 9.11 on the following page).

9.2.3 R = CHO

Myrtenal (**108**) is a commercially available product of high optical purity. Treatment of **108** with iron pentacarbonyl in a mixture of dioxane and heptane (5:1) at reflux affords almost exclusively decomposition products. Traces of a complex have been isolated, which ressembles to the desired one, but the aldehyde function was transformed into another group, whose final structure remained

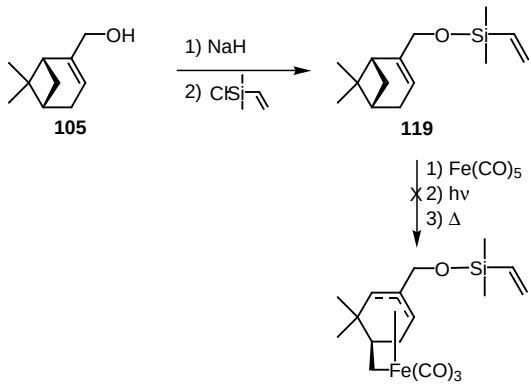


Figure 9.11: The dimethylvinylsiloxane approach

unclear. Enals are known to form complexes like the one shown in figure 9.12. Iron tetracarbonyl complexes like **120** are known to be formed at low temperature [167]. At higher temperature they either decomposed or loose one of their carbonyls to open a strained ring like a cyclopropane [167] or complex the adjacent carbonyl group [168]. In our case, the high temperature of the reaction probably favours the decomposition against the ring opening complexation of myrtenal (**108**).

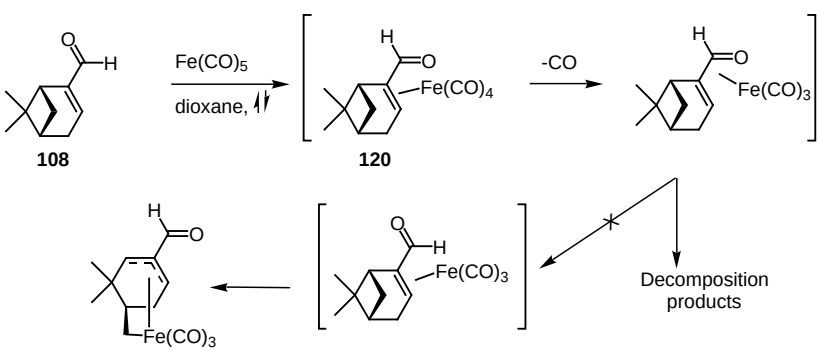


Figure 9.12: Complexation of myrtenal

9.3 Substitution with electron-withdrawing groups

Two electron-withdrawing groups were considered: the nitrile and fluorous groups (CF_3, CHF_2, CH_2F).

9.3.1 R = CN

The hydroxylamine-O-sulfonic acid (HAS) proved to be an excellent and efficient reagent for the conversion of the aldehyde of myrtenal (**108**) into nitrile **121** in high yield [23, 169].

The reaction of **121** in the presence of $Fe(CO)_5$ in dioxane and heptane at reflux leads to unstable complexes. The nitrile **121** was therefore irradiated in the presence of iron pentacarbonyl in dry diethylether, but the starting material and $Fe_3(CO)_{12}$ were recovered. When the nitrile **121** was heated at reflux in presence of $Fe_2(CO)_9$ in benzene, a new complex was visible on TLC but no complex could be isolated. The same result was obtained when using the Grevels reagent [22, 170]. Using the BDA complex [21] instead, no formation of a complex was observed.

In conclusion the ring opening complexation can not be carried out with the nitrile **121**. A possible explanation could be the formation of unstable intermediates unable to open the strained cyclobutane ring, because once the iron tetracarbonyl moiety has complexed the olefinic double bond or the nitrile, it is blocked on this position and does no longer lose one of its carbonyls. Another possibility is that tetracarbonyl iron species lose one of their carbonyls to form other unstable complexes, that also decompose. Indeed it is known that nitriles are complexed by iron pentacarbonyl [171, 172] and that the resulting complex $(RCN)_2Fe(CO)_3$ undergoes partial or complete decomposition after standing for 3-6 weeks ($R = Ph$). In our case the decomposition is much faster than for benzonitrile.

9.3.2 R = $CH_{n-x}F_x$

The introduction of a fluorinen substituent into a molecule often leads to a significant change in its physical and chemical properties. First, fluorine and hydrogen are comparable in size (the Van der Waal's radii of F and H are 1.35 and 1.1 $\AA$ respectively). Despite a molecule and its fluoro analogues would be

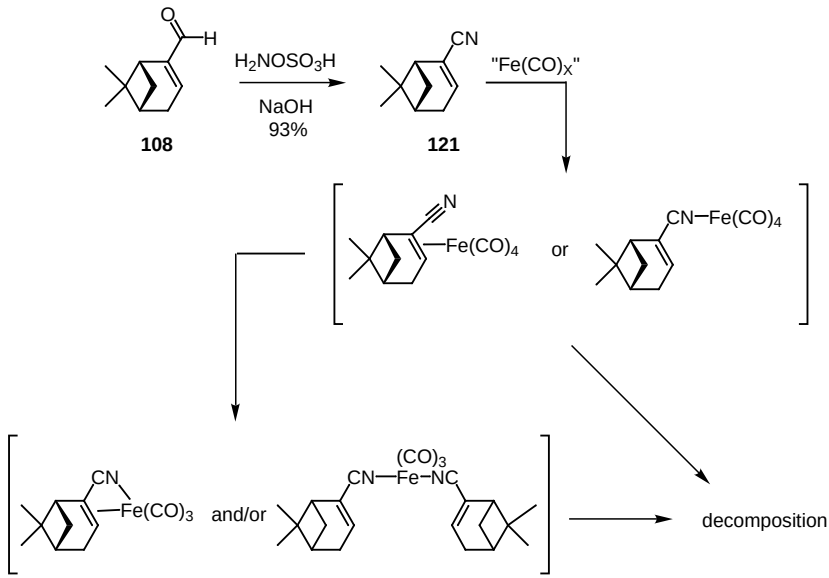


Figure 9.13: Complexation of the nitrile derived from the myrtenal

sterically almost indistinguishable to a guest molecule, their chemical behaviour could be very different from one another. Second, the high C-F bond energy (about 116 kcal/mol) leads to enhanced thermal stability [173].Finally, due to its high electronegativity, fluorine containing molecules often show different electronic properties.

Consequently, the substitution of one or more hydrogens of the 2-methyl group in α-pinene by fluorine will influence the electronic properties of the double bond and of the 2-($\mathrm{CH}_{n-x}\mathrm{F}_x$)-BOD-$\mathrm{Fe(CO)_2I}$ complex.

Mono- and bisfluorinated products can be obtained with the (diethylamino)sulfur trifluoride (DAST) from alcohols or aldehydes, respectively [174, 175]. One advantage of this reagent is that dehydration products and carbonium ion rearrangements occurs to a lesser extent than with other reagents like $\mathrm{SF_4}$, $\mathrm{SeF_4}$·pyridine and $(\mathrm{C_2H_5})_2\mathrm{NCF_2CHClF}$. It is also useful for fluorination of aldehydes, ketones and alcohols that are sensitive to acid. Thus, this method applied at low temperature on the complex **111** yielded two products (figure 9.14). The minor one (23%) seems to be the desired complex **122**, that forms an inseparable

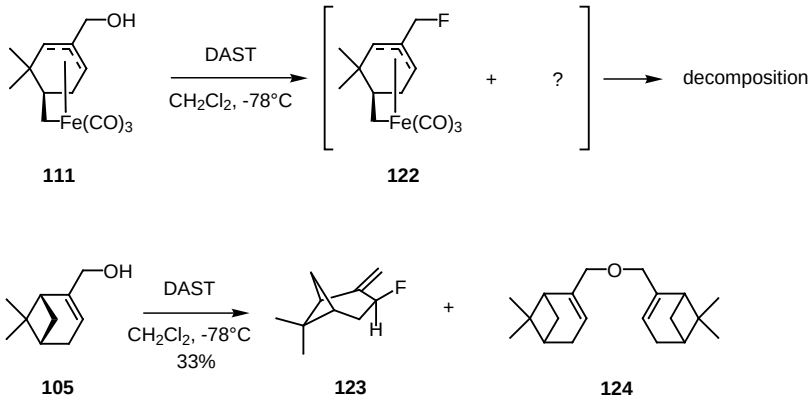


Figure 9.14: Monofluorinated complex

mixture with the second and whose instability prevents any further steps. It turned out that the sample contained traces of HF, either as an impurity or formed during the decomposition of one of the products, which is responsible of the observed decomposition. Repeating the synthesis in presence of K_2CO_3 in a less polar solvent did not improve the reaction. On the same basis, the reaction of myrtenol (**105**) in presence of DAST and further complexation of the resulting monofluorinated substrate should afford the desired product **122**. But even this alternative did not provide better results, since the reaction between **105** and DAST produces mainly the allylic substituted product **123** (33%) and a product that could be the dimeric ether **124** (figure 9.14) [174]. The NOE experiment given in figure 9.15 on the next page reveals the spatial proximity between the proton on C(3) and one of the gem-dimethyl group. This clearly shows that the fluorine is on the opposite side with respect to the gem-dimethyl group. As complex **111** is obtained from the acetate **112**, two last experiments were performed without success. They consisted in reacting the complex **113** with either DAST or with the anhydrous, highly anionic and soluble TASF [176]. In conclusion, the best precursor of **122** remains the complex **111**.

The DAST reagent is also known to convert an aldehyde into a CH_2F group. But with myrtenal the reaction is very slow, even when increasing the temperature to 45 °C and the desired product was impossible to be isolated even though it was observed by GC-MS, because of the sensitivity of myrtenal towards acidic conditions. Only the starting material and polymers have been isolated.

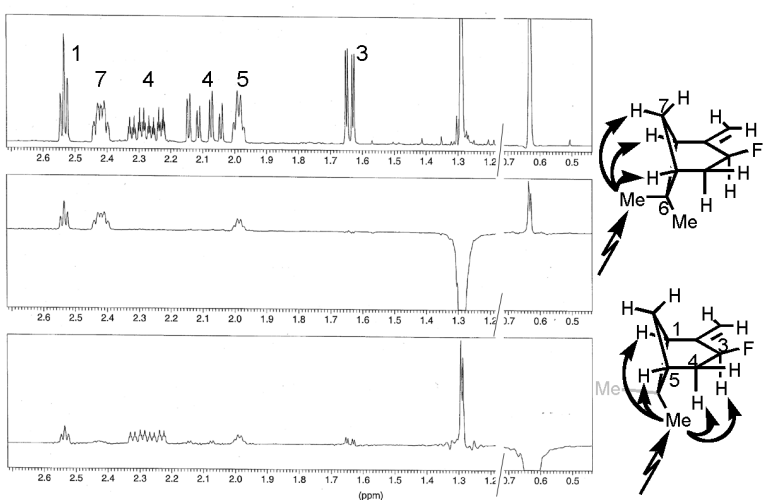


Figure 9.15: NOE experiment

Although the literature abounds with examples of introducing perfluoroalkyl groups into carbonyl compounds, the procedures are seldom applicable to trifluoromethylation. Recently, electrochemical trifluoromethylation of carbonyl compounds was reported. However, yields were poor with ketone and aldehydes [177]. Also the use of (trialkylsilyl) (trifluoromethyl)diazenes as nucleophilic trifluoromethylating reagent was reported [178]. Prakash used trifluormethyltrimethylsilane in a very efficient manner [173, 179]. Reaction of this reagent is based on the hard-soft reactivity principle, with the silicon acting as the hard acid and the electronegative substituent as the soft base. If we consider the reaction of nopinone with trifluorotrimethylsilyl, the propensity of silicon to form strong bonds with the hard base oxygen can be a thermodynamically favorable process to drive the reaction. As silicon is known to from strong bonds with oxygen and fluorine, fluoride ion is used as the catalyst. The resulting trimethylsilyl ether is then hydrolyzed by aqueous acid (HCl) to give the trifluromethylated carbinol in excellent overall yield. But this was not the case with nopinone (**125**).

The synthesis of the 6,6-dimethyl-2-(trifluoromethyl)bicyclo [3.1.1]heptan-2-ene (**129**) therefore starts from (-)-β-pinene. Ozonolysis of β-pinene followed by

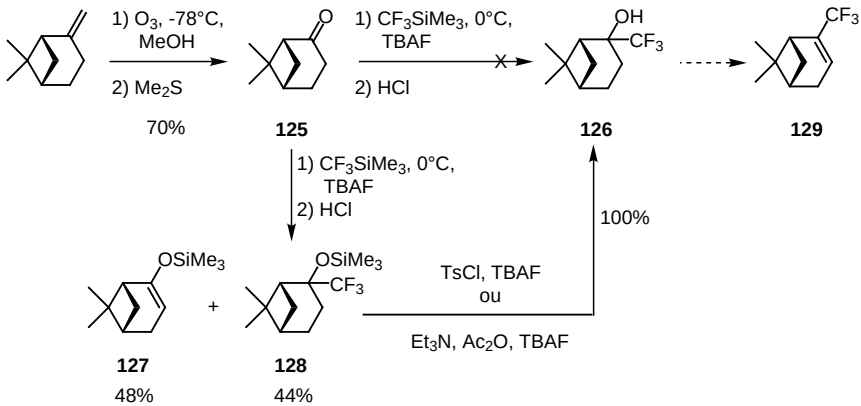


Figure 9.16: α,α,α-Trifluoro-α-pinene

a reductive work-up yields 70% of nopinone **125** [180]. Its trifluoromethylation with trifluoromethyltrimethylsilyl catalyzed by TBAF affords 26% of the intermediate product **126** and 48% of **125** even if a GC-MS investigation shows a complete consumption of **125** [173].

A possible mechanism is outlined in the figure 9.17. Treatment of nopinone (**125**) with trifluoromethyltrimethylsilyl in presence of TBAF leads to a competition beetwen an acid-base reaction due to the highly basic nature of the CF_3^- anion and an electrophile-nucleophile reaction. After purification over silica gel, nopinone (**125**) is recovered, because the 6,6-dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]hept-2-yl trimethylsilyl ether (**127**) is sensitive even to weakly acidic conditions.

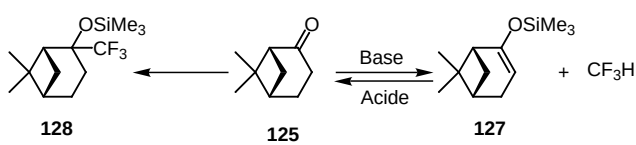


Figure 9.17: Alternative pathways during the trifluoromethylation

In order to understand and to optimize the synthetic procedure, we have investigated this reaction in more details. The table 9.1 on the next page suggests

that the secondary product **127** is favoured at higher temperatures (0°C and rt). The polarity of the solvent plays a crucial role, because in polar solvents like THF (entry 1) the secondary product **127** is much more favoured than in pentane (entry 11) or the reaction does not occur like in dichloromethane. The pentane proves to be the most efficient solvent, but its efficiency depends on the temperature. At -80°C no reaction occurs (entry 5) because some products became insoluble. At -50°C the reaction occurs with the best ratio between the desired product and the secondary product, but the reaction is slow (entries 7 and 8). It is slightly accelerated by increasing the temperature to -30°C (entry 9). But the best conditions consist in mixing all the component at -80°C and to let the temperature go up to room temperature: 64% of product **128** were isolated (entry 10).

Table 9.1: Trifluoromethylation of nopinon

entry	solvent	temp. [°C]	Time	conv. [%]	% **128**[a]	% **127**[a]
1	THF	0	120'	93	44	48
2	$CHCl_2$	rt	5d	0		
3	toluene	0	102'	0		
4	toluene	rt	5d	79	60	40
5	pentane	-80	70'	0		
6	pentane	-20[c]	130'	100	75/52[b]	25
7	pentane	-50	90'	37	75	25
8	pentane	-50	550'	68	75	25
9	pentane	-30[d]	100'	94	74/54[b]	26
10	pentane	-80	180'	100	75/64[b]	25
11	pentane	0	45'	100	63/55[b]	37

[a] *GC yield;* [b] *Isolated yield;* [c] *Additions occur at -80°C;* [d] *Additions occur at -50°C*

The product **128** needs to be converted to the 2-trifluoromethyl nopinene **129** in order to be complexed. As suggested in different papers, the best procedure to hydrolyze the trimethylsilyl group is to use HCl [173]. But the product **128** is not hydrolyzed in presence of HCl 1M and more acidic conditions would rearrange the acid sensitive pinenic skeleton. Thus, in order to make the trimethylsilyloxy a better leaving group, its tosylation was tried. However, tosylation with $TsCl$ in presence of TBAF affords quantitatively the carbinol **126**. As we need a double bond, pyrolysis of the corresponding acetate is known to produce alcene.

But the synthesis of acetate failed leading to the alcohol **126** in a quantitative yield. These failures are probably due to the presence of water in TBAF. In

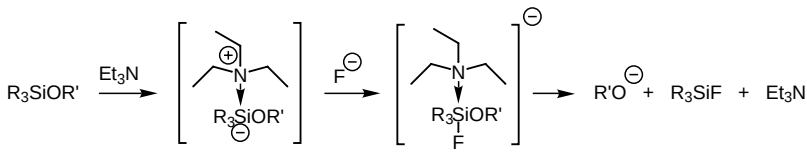


Figure 9.18: Nucleophile assisted S_N

fact it is impossible to obtain dry TBAF. This hypothesis was supported by an additional experiment. Reaction with a "dry" TBAF (0.1-0.3 mol of water) leads to 50% of the alcohol and 40% of the starting material. Finally, the best procedure is to treat **128** with TBAF and triethylamine in acetic anhydride. The alcohol **126** is obtained in a quantitative yield using this way, while it fails without triethylamine, which is a nucleophile that assists the nucleophilic substitution as can be seen on figure 9.18 [181].

The dehydration of the alcohol **126** failed with $POCl_3$ in pyridine [182] whereas the Martin's dehydrating reagent [183–185] gives satisfactory results even under mild conditions (figure 9.19 on the next page). If the reaction is done in chloroform, the desired product **129** is obtained in low yield (16%) with the rearranged alcohol **130** (34%). This result is not the expected one, but this procedure provides a new synthetic way to obtain a trifluoromethylated campher derivative **130**. The yield of **129** is low because the trifluoromethyl group makes the product very volatile and its isolation extremely complicated. The rearranged product **130** is issued from an E_1: the carbocation **131** rearranges into a secondary carbocation, that leads to the alcohol **130** after hydrolysis. It is interesting to see in this case a rearrangement from a tertiary to a secondary carbonium ion. This contradicts the common stability sequence. However, the driving forces are first the breaking of a strained system (the cyclobutane moiety), and secondly the stabilization of the cationic charge on a electron richer secondary center. Indeed, the cation in **131** is located in a very poor tertiary electron center. To avoid this side reaction, less acidic and less polar solvents were tried. Pentane proves to be better than dichloromethane and much better than THF. GC-MS measurement shows a complete reaction after one night at room temperature. Despite all our efforts (bulb to bulb or carefull Fisher distillation), it was impossible to separate the product from pentane, because its boiling point is only a

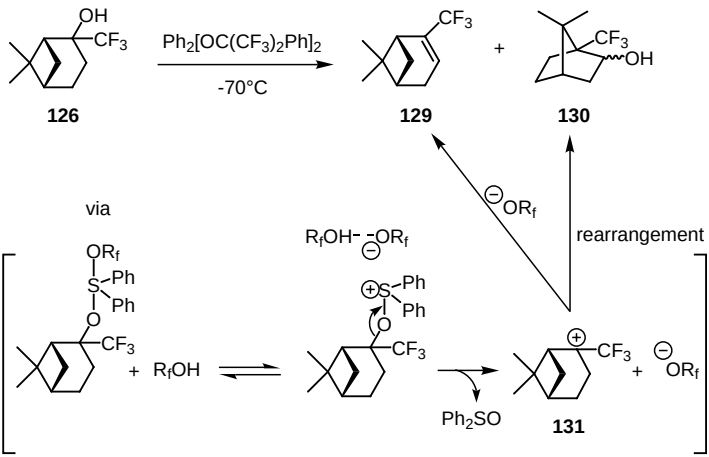


Figure 9.19: Dehydration

few degrees Celsius above the one of pentane. Only Fisher distillation allowed us to remove some pentane. The best results are estimated to be about 30%, but the yield is certainly higher because a lot of product was lost during work-up.

The figure 9.20 shows that the complexation of **129** in pentane with the tetramethyldivinyldisiloxane [166] and iron pentacarbonyl leads to several complexes which structures remain unknown as well as to the complex **132**. Nevertheless, no ring opening complexation takes place. The same results were obtained when heating or irradiating the $\mathrm{Fe(CO)_4}$ complex **132**.

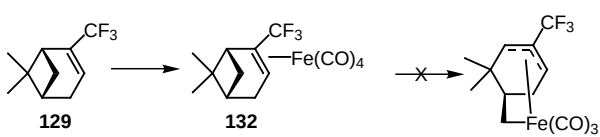


Figure 9.20: Complexation of the trifluromethylnorpinane

In conclusion, the synthesis of 6,6-dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]heptan-2-ene **129** was performed successfully but its high volatility prevents any complexation.

9.4 Conclusion

The substitution at the carbon 2 of apopinene proved to be more complicated than assumed at the beginning of this project. However, the substitution with electron-donating groups gave much more promising results than with electron-withdrawing groups, even if the monofluorinated complex was successfully synthesized although not isolated. Some unexpected results during the complexation of myrtenol **105** open new applications, even if its mechanism remains not understood. Indeed, the complexation of myrtenal **108** under the same conditions than for myrtenol **105** never produced the ester **106**. This exludes a Cannizaro reaction to be at the origin of the formation of the ester **106** and consequently a completely new reaction is to be considered.

Chapter 10

Conclusion

The various investigations performed during this thesis illustrate that both the synthesis of 2-Me-BOD-$Fe(CO)_2I$ (**1**) and its derivatives, and the control of its reactivity are still not completely mastered. Nevertheless, solutions were outlined and the modest results obtained through this exploratory work will allow to better target complex **1** and its derivatives in the future. Nonetheless, some important remarks should be outlined.

First, the yield decrease in the synthesis of **1** during the scale-up points out that the temperature plays a central role on the outcome of this reaction. Thus further investigation will be necessary to increase the yield from 55% (the best results to date) to a hopefully quantitative yield. The real-time IR analysis is probably the best technique to achieve this target as well as to better understand the reaction mechanism. However, this approach suffers from a technical drawback: efficient cooling of the big diameter of the IR-probe needs to be solved as well as a solution for a small scale preparation under these conditions has to be found. To circumvent this problem, the first critical step, consisting in the addition of ^tBuLi to iodo complex **65**, should be performed in a mixing chamber and the resulting red mixture[1] injected directly in the flask for the IR investigation. Of course, such a technique prevents the observation of the first step, but the resulting intermediate can be analyzed as well as the rest of the reaction.

[1] The use of a mixing chamber has been successfully applied in the synthesis of **1**.

Secondly, the synthesis of derivatives of **1** by substituting the stereogenic methyl group proved to be a more difficult task than anticipated. Even though, it is feasible in case of electron donating substituents, while substitution with electron withdrawing group still fails except for the monofluorinated methyl derivative **122**; its conversion to **133** is of interest since it will allow to study the electronic influence on the reactivity. Another entry to get this monofluorinated product, based on analoguous transformations [186], is depicted in figure 10.1. However, the ring opening complexation of such species remains unexplored.

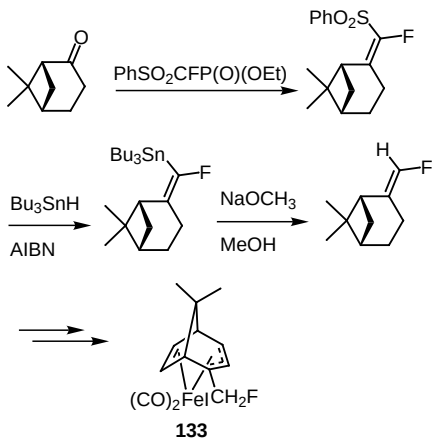


Figure 10.1: Alternative pathway to monofluorinated complex

Finally, $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ (**1**) has proven to be at the same time stable and very reactive. To date, a silver salt like AgBF_4 is the only way to activate this latter without decomposing it into a useless mixture of products. In presence of CO, the cationic tricarbonyl complex **75** is formed, and can react further with a nucleophile. Decomplexation of the resulting species, should afford organic molecules that remain valid starting point for future exploration (figure 10.2 on the facing page). In the presence of homofarnesol, a cyclization is induced to give Ambrox® with a very good diastereoselectivity, but unfortunately with a very low enantiomeric excess, although promotor **1** is optically active. If this low asymmetric induction arises from steric induction, that is still insufficient with the stereogenic methyl group, its substitution with a bulkier substituent should solve this problem. Nevertheless, for a truly catalytical cycle a suitable proton source or another additive must be found.

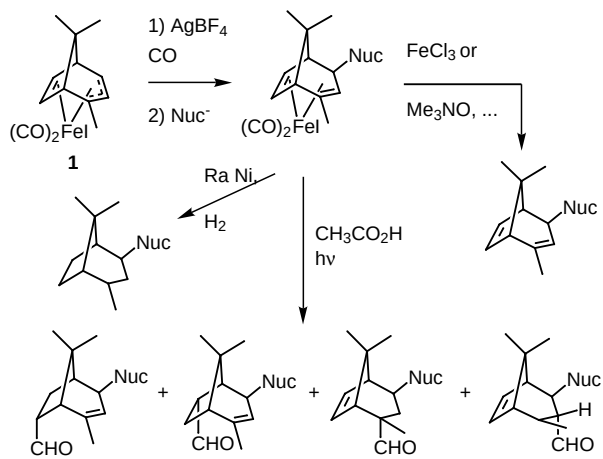


Figure 10.2: Potential synthetic scope of **1**

Part III

experimental part

General Considerations

Most of the products are provided by Fluka and Acros. Some are provided by Aldrich, Merck and Strem. TLC are done on aluminium plates covered with silica gel 60 F_{254}, and on plastic sheets covered with aluminium oxide 60 F_{254}, both from Merck. Most of the products were revealed with $KMnO_4$ or with a solution of universal developer[2] Iron complexes were revealed by spraying on the TLC plate diluted nitric acid followed by an aqueous solution of $K_4[Fe(CN)_6]\cdot 3(H_2O)$ or a solution of sodium thiocycanate. Column chromatography was done with silica gel 60 (0.04 - 0.063 (230 - 400 mesh ASTM) or 0.063 - 0.2 (70 - 230 mesh ASTM)) from Merck. The solvents (pentane, dioxane, ether, benzene, THF) were distilled and dried over Na. Dichloromethane and chloroform were distilled and dried over phosphorus pentoxide. Iradiation was performed either with a Philips HPK 125W mercury lamp or with a 500W halogen lamp.

^1H and ^{13}C-NMR: Brucker Avance DRX 500 (500 and 125.7 MHz), Bruker AM 360 (360 and 90.6 MHz) and Varian Gemini 200 (200 and 50.4 MHz). MS carried out on a Hewlett Packard HP 5988A Quadrupol Mass Spectrometer and on a Vacuum Generators Micromass VG 70/70E, and on a FTMS 4.7T BioAPEX of Brucker. IR: FTIR Uicam Mattson 5000 spectrometer. UV/VIS: Perkin-Elmer Lambda 40 diode array spectrophotometer. Optical rotation: Perkin-Elmer 241 MC polarimeter. CD: Omnilab Jasco J-715. GC: Carlo Erba HGRC-Mega 2. GC-MS: ThermoQuest TraceGC 2000/Voyager.

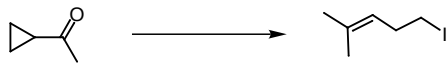
[2] $Ce(SO_4)_2$ (0.5 g) + H_2O (50 ml) + $H_3[P(Mo_3O_{10})_4]_{aq}$ (1.25 g) + H_2SO_4 97% (3 ml).

Chapter 11

Synthesis of organic substrates

11.1 Homofarnesol synthesis

11.1.1 1-Iodo-4-methylpent-3-ene

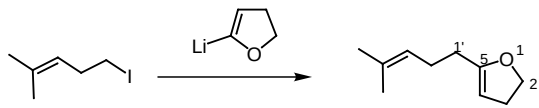


87 88

To activated (glacial acetic acid) and carefully dried Mg turnings (5.59 g, 230 mmol) in dry ether (100 ml) under nitrogen atmosphere, methyl iodide (32.6 g, 230 mmol) in dry ether (50 ml) was added dropwise in the way that mixture is gently refluxing. After the addition was complete, the solution was heated to reflux for another hour. The solution was cooled down in an ice bath and acetyl cyclopropane (18.86 g, 224 mmol) in dry ether (30ml) was added dropwise. After 30 min, the white suspension that has formed was poured in portions into diluted H_2SO_4 (100 ml, 8M) at 0°C. The heterogenic mixture was stirred for 30 min, and extracted with ether (7 x 40 ml). The organic phases were washed with $NaHSO_3$ and $NaHCO_3$ solutions and dried ($MgSO_4$). After evaporation of the solvent, a distillation gave 29.5 g of product (63%). Clear colourless liquid[1] with fruity odour. B.p. 71°C/14 mmHg. (Optima 5-MS, 40°C, 2'; 20°C/min; 150°C, 10'): rt = 5.13, >98%. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.11 (tm, J = 7.1, 1H, H-C(3)), 3.12 (t, J = 7.3, 2H, H-C(1)), 2.58 (q, J = 7.3, 2H, H-C(2)), 1.71 (s, 3H, Me), 1.63 (s, 3H, Me).

[1] to circumvent the rapid decomposition of the product, storage over a silver foil in the dark at low temperature (< 5°C) is required.

11.1.2 5-(4-Methylpent-3-enyl)-2,3-dihydrofuran

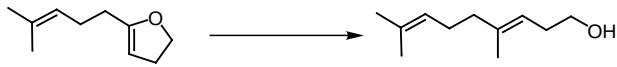


88 **89**

To a solution of 2,3-dihydrofuran (17.5 g, 250 mmol) in dry THF (50 ml) at -30°C under argon atmosphere, $^{t}\mathrm{BuLi}$ (100 ml, *ca.* 150 mmol) was added dropwise. The mixture was stirred at 0°C for 30 min[2], and a solution of 1-iodo-4-methylpent-3-ene[3] (22.5 g, 107 mmol) in dry THF (50 ml) was added at -50°C. The solution was allowed to warm up to room temperature over night. After 36h, it is quenched by 200 ml of saturated aqueous solution of $\mathrm{NH_4Cl}$ containing 10% concentrated $\mathrm{NH_3}$. After extraction with ether (5 x 40 ml), the organic phases were washed with aqueous $\mathrm{NaHCO_3}$, and dried ($\mathrm{MgSO_4}$). After evaporation of the solvent, volatile impurities were removed by continued stirring at 0.75 mmHg before a *trap to trap* distillation gave 13.3 g of product (81%). Clear colourless liquid. B.p. ca. 35°C, $8{*}10^{-6}$ mmHg. GC (Optima 5-MS, 40°C, 2'; 20°C/min; 150°C, 10'): rt = 9.10, >99.5%. ^{1}H-NMR (200 MHz, $\mathrm{CDCl_3}$): 5.13 (m, 1H, H-C(3')), 4.58 (tt, J = 2.3, 1.1, 1H, H-C(4)), 4.3 (t, J = 9.2, 2H, H-C(2)), 2.59 (tq, J = 9.3, 2, 2H, H-C(3)), 2.25-2.05 (m, 4H, H-C(1'), H-C(2')), 1.69 (d, J = 1, 3H, Me), 1.61 (s, 3H, Me).

[2] a white suspension has formed.
[3] dried over MS 4Å.

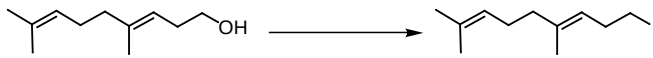
11.1.3 Homogeraniol



89 90

(3E)-4,8-Dimethyl-3,7-nonadien-1-ol 90: To a solution of $[Ni(PPh_3)Cl_2]$ (2.81 g, 4.3 mmol) in dry toluene (300 ml), $MeMgBr$ in ether (83 ml, ca. 250 mmol) was added dropwise under argon atmosphere. The mixture turned dark red, and after 20 min a solution of 5-(4-methylpent-3-enyl)-2,3-dihydrofuran (13.1g, 93.4 mmol) in dry toluene (50 ml) was added. The mixture turned olive-green and was heated to 45°C for 30 min and then to reflux for 40 min. The chilled mixture was poured into 200 ml concentrated aqueous NH_4Cl solution, and stirred for 20 min. After extraction with ether (4 x 30 ml), the organic phases were washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and filtered through a plug of silica gel. After evaporation of the solvent, a distillation gave 13.4 g of product (85%). Clear colourless oil. B.p. ca. 80°, 8*10^{-6} mmHg. GC (Optima 5-MS, 80°C, 2'; 20°C/min; 150°C, 10'): rt = 19.45, >99%. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.08 (m, 2H, H-C(3), H-C(7)), 3.61 ($br.t$, 2H, H-C(1)), 2.28 (q, J = 6.5, 2H, H-C(2)), 2.14-2.01 (m, 4H, H-C(5), H-C(6)), 1.68 (s, 3H, Me), 1.64 (s, 3H, Me), 1.60 (s, 3H, Me).

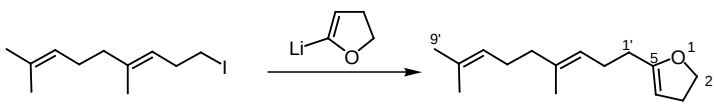
11.1.4 (3E)1-Iodo-4,8-dimethyl-4,8-nonadien



90 **91**

To a solution of homogeraniol (14.2 g, 84.4 mmol) and triethylamine (18.9 g, 187 mmol) in dry dichloromethane (80 ml) under nitrogen atmosphere, a solution of mesityl chloride (10.9 g, 95 mmol) in dry dichloromethane (20 ml) was added dropwise at 0°C. A white precipitate appeared and after 30 min, 3-dimethylamino-propyl-1-amine (3.4 g, 43 mmol) was added. The mixture was stirred for an additional 10 min and poured into ice water (200 ml). After extraction with ether (4 x 50 ml), the organic phases were washed with brine solution that contains 5% acetic acid and with aqueous $\mathrm{NaHCO_3}$. After drying ($\mathrm{MgSO_4}$) and evaporating the solvent, dry acetone (500 ml) and anhydrous NaI (86.2 g, 575 mmol) were added and the mixture was heated at reflux under nitrogen atmospere for 2 h. The resulting mixture was concentrated to dryness and the remaining solid was extracted with pentane and water. The organic phases were washed with aqueous $\mathrm{NaHCO_3}$, dried ($\mathrm{MgSO_4}$), and the solvent was evaporated. The residue was filtered through silica gel (200 g) using pentane as eluent. Evaporation of the solvent gave 19.3 of product (82%). Clear colourless liquid. ^{1}H-NMR (200 MHz, $\mathrm{CDCl_3}$): 5.09 (tm, $J =$ 7, 2H, H-C(3), H-C(7)), 3.11 (t, $J = 7.5$, 2H, H-C(1)), 2.58 (q, $J = 7.5$, 2H, H-C(2)), 2.07 (m, 2H, H-C(5) or H-C(6)), 1.99 (m, 2H, H-C(5) or H-C(6)), 1.69 (d, $J = 1.1$, 3H, Me), 1.61 (s, 6H, Me).

11.1.5 5-[(3E)-4,8-Dimethyl-3,7-nonadienyl]-2,3-dihydrofuran

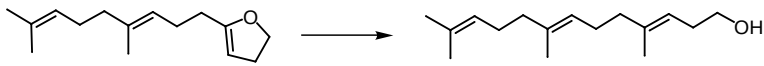


91 **92**

To a solution of 2,3-dihydrofuran (12.6 g, 180 mmol) in dry THF (40 ml) at -30°C under argon atmosphere, $^{t}\mathrm{BuLi}$ (70 ml, *ca.* 115 mmol) was added dropwise. The mixture was stirred at 0°C for an additional 30 min[4], and a solution of (3*E*)-1-iodo-4,8-dimethyl-4,8-nonadien[5] (19.1 g, 68.7 mmol) in dry THF (40 ml) was added at -50°C. The solution was allowed to warm up to room temperature over night. After 36h, it was quenched by 150 ml of saturated aqueous solution of $\mathrm{NH_4Cl}$ containing 10% concentrated $\mathrm{NH_3}$. After extraction with ether (6 x 30 ml), the organic phases were washed with aqueous $\mathrm{NaHCO_3}$, dried ($\mathrm{MgSO_4}$), and the solvent was evaporated. The crude product was filtered through $\mathrm{Al_2O_3}$ (80 g, activity II-III) using pentane as eluent. Evaporation of the solvent gave 13.35 g (87%) of product that contained ca. 10% of the olefin resulting from HI elimination of the starting material, according to NMR. Clear colourless oil ^{1}H-NMR (360 MHz, $\mathrm{CDCl_3}$): 5.13 (m, 1H, H-C(3') or H-C(7')), 5.08 (m, 1H, H-C(3') or H-C(7')), 4.58 (tt, J = 3.5, 1.2, 1H, H-C(2)), 4.3 (t, J = 9.2, 2H, H-C(2)), 2.6 (tq, J = 9.1, 2, 2H, H-C(1')), 2.2, 2.11, 2.05, 1.98 (m, 8H, H-C(3), H-C(2'), H-C(5'), H-C(6')), 1.68 (d, J = 1, 3H, Me), 1.60 (s, 6H, Me).

[4] a white suspension has formed.
[5] dried over MS 4Å.

11.1.6 Homofarnesol



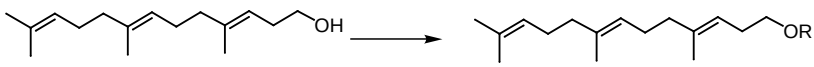
92 21

(3E,7E)-4,8,12-Trimethyl-3,7,11-tridecatrien-1-ol 21: To a solution of $[Ni(PPh_3)Cl_2]$ (1.57 g, 2.4 mmol) in dry toluene (200 ml), $MeMgI$ in ether (70 ml)[6] was added dropwise. The mixture turned dark red, and after 20 min a solution of 5-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2,3-dihydrofuran[7] (13.2 g, 60 mmol) in dry toluene (30 ml) was added and heated to 45°C for 30 min and then to reflux for 40 min. The chilled mixture was poured into 150 ml saturated aqueous NH_4Cl solution, and stirred for 20 min. After extraction with ether (4 x 30 ml), the organic phases were washed with aqueous $NaHCO_3$ and the solvent was evaporated. The crude reaction mixture was dissolved in ether (50 ml) and stirred with a solution of $AgNO_3$ (1 g) in water (50 ml) for 1 h in order to remove traces of PPh_3. The etheral phase was separated and dried ($MgSO_4$). After evaporation of the solvent, the resulting yellow oil was adsorbed onto silica gel (40-62 μm, 60 g for 4 g of crude product). Less polar impurities were eluted with pentane, before the product was washed off with dichloromethane. Evaporation of the solvent gave homofarnesol (10.1g, 71%). Clear, light yellow oil. GC (Optima 5-MS, 70°C, 10'; 10°C/min; 250°C, 10'): rt = 23.07, >99%. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.13 (tq, J = 7.3, 1.3, 1H, H-C(3)), 5.09 (tm, J = 7, 2H, H-C(7), H-C(11)), 3.62 (t, J = 6.5, 2H, H-C(1)), 2.29 (q, J = 6.5, 2H, H-C(2)), 2.13-2.02 (m, 6H, H-C(6), H-C(10) and H-C(5) or H-C(9)), 1.97 (t, J = 8.3, 2H, H-C(5) or H-C(9), 1.68 (d, J = 1.1, 3H, H-C(14)) 1.65 (m, 3H, Me), 1.6 (s, 6H, Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 138.9, 138.3, 131.3 (C(4), C(8), C(12)), 123.3, 124, 119.9 (CH, C(3), C(7), C(11)), 62.45 (CH_2, C(1)), 39.8, 39.7, 26.7, 26.5 (CH_2, C(5), C(6), C(9), C(10)), 31.5 (CH_2, C(2)), 25.5, 17.7, 16.2, 16 (CH_3, Me). EI-MS: 236 (M^+, 1), 136 (11), 123 (17), 121 (14), 107 (22), 95 (13), 93 (17), 81 (27), 79 (12), 69 (100), 67 (31), 55 (27).

[6] prepared from Mg turnings (4.38 g, 180 mmol) and MeI (24.13 g, 170 mmol).
[7] which was not further purified.

11.2 Cyclization of homofarnesol

11.2.1 Protection of homofarnesol



21

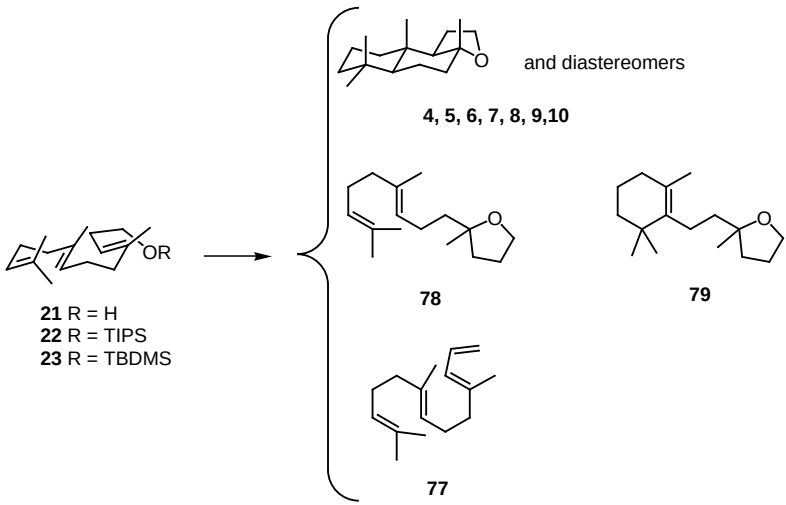
R = TIPS **22**
= TBDMS **23**

Triisopropyl-(3E,7E)-4,8,12-trimethyl-3,7,11-tridecatrienyl ether 22: To a solution of homofarnesol (2 g, 8.47 mmol) and triisopropysilyl chloride (1.64 g, 8.47 mmol) in dry DMF (6 ml), imidazol (1.44 g, 21.2 mmol) was added. After a night at room temperature, pentane (80 ml) was added and the mixture washed with water (3 X 30 ml). The organic phases were dried ($MgSO_4$), filtrated and evaporation of the solvent yielded quantitatively pure **22** (3.04 g). GC (Optima 5-MS, 70°C, 10 min; 10°C/min; 250°C, 10 min): rt = 29.16, >99%. TLC (SiO_2, pentane/ether 50:1): $R_f = 0.84$. TLC (SiO_2, pentane): $R_f = 0.2$. ^{1}H-NMR (360 MHz, $CDCl_3$) 5.17-5.08 (m, 3H, H-C(3), H-C(7), H-C(11)), 3.65 (t, $J = 7.04$, 2H, H-C(1)), 2.32-2.2 (m, 2H, H-C(2)), 2.11-1.95 (m, 8H, H-C(5), H-C(6), H-C(9), H-C(10)), 1.68 (s, 3H, Me), 1.62 (s, 3H, Me), 1.59 (s, 6H, Me), 1.08 (d, $J = 5$, 3H, H-C(^{i}Pr)) 1.06 (d, $J = 5$, 18H, Me (^{i}Pr)). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 136.9, 134.9, 131.2 (C, C(4), C(8), C(12)), 124.4, 124.2, 120.4 (CH, C(3), C(7), C(11)), 63.3 (CH_2, C(1)), 39.8, 39.7 (CH_2, C(5), C(9)), 32 (CH_2, C(2)), 26.7, 26.6 (CH_2, C(6), C(10)), 25.7 (CH_3, 3 Me), 18 (CH_3, 6 Me), 17.7 (CH_3, Me), 12 (CH, C(^{i}Pr)). EI-MS: 392 (M^+, 5), 349 (11), 308 (5), 217 (14), 191 (13), 169 (20), 131 (13), 127 (9), 81 (23), 70 (100).

tert-Butyl(dimethyl)silyl-(3E,7E)-4,8,12-trimethyl-3,7,11-tridecatrienyl ether 23: To a solution of homofarnesol (0.6 g, 2.54 mmol) and tert-butyl(dimethyl)silyl chloride (0.46 g, 3.05 mmol) in dry DMF (1 ml), imidazol (0.43 g, 6.3 mmol) was added. After a night at 30°C, an aqueous solution of conc. NH_4Cl was poured onto the reaction mixture and extracted with ether. The organic phases were dried ($MgSO_4$) and the solvent evaporated. A filtration over a plug of silica gel with pentane/ether (20:1) gave the pure product (884 mg, 98%). TLC (SiO_2, pentane/ether 20:1): $R_f = 0.67$. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.17-5.08 (m, 3H, H-C(3), H-C(7), H-C(11)), 3.59 (t, $J = 7.22$, 2H, H-C(1)), 2.24 (dq, $J = 7.22$, 0.47, 2H, H-C(2)), 2.12-1.96 (m, 8H, H-C(5),

H-C(6), H-C(9), H-C(10)), 1.69 (d, $J = 1.1$, 3H, Me), 1.63 (d, $J = 0.63$, 3H, Me), 1.61 (s, 6H, Me), 0.91 (s, 9H, H-C(^{t}Bu-Si)), 0.08 (s, 6H, H-C(Me-Si)). ^{13}C-NMR (125.7 MHz, $\mathrm{CDCl_3}$): 137 (C(4)), 134.9 (C(8)), 131.1 (C(12)), 124.4 (CH, C(7)), 124.2 (CH, C(11)), 120.3 (CH, C(3)), 63.1 (CH_2, C(1)), 39.8 (CH_2, C(5)), 39.7 (CH_2, C(9)), 31.9 (CH_2, C(2)), 26.8 (CH_2, C(6)), 26.6 (CH_2, C(10)), 26 (CH_3, Me_3-C-Si) 25.7 (CH_3, Me), 18.35 (C, $(Me)_3$-C-Si), 17.65 (CH_3, Me), 16.1 (CH_3, Me), 16 (CH_3, Me), -5.25 (CH_3, Me-Si)

11.2.2 Cyclization of homofarnesol



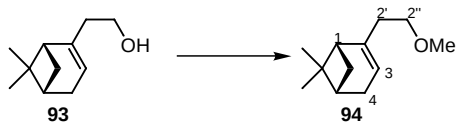
All the described trials presented throughout this thesis are based on the following experimental procedure: to a solution of homofarnesol or protected homofarnesol (0.5 mmol), $AgBF_4$ (0.44 eq.) in dichloromethane (5 ml) in a shlenk under argon atmosphere in the dark, a solution of $2\text{-Me-BOD-Fe(CO)}_2\text{I}$ **1** (0.4 eq.) in dichloromethane (5 ml) was added through a column of neutral ALOX and stirred at room temperature for 6 days. The reaction mixture was filtered through a plug of celite and the solvent evaporated. After chromatographic purification (SiO_2, pentane/ether 20:1), samples containing Ambrox® and its diastereomers, as well as other cyclized products were obtained. These compounds were not isolated, and their identification was effected by comparison of their ^{1}H-NMR, ^{13}C-NMR with the published one [64, 86, 187], and above all by comparison of their GC/GC-MS chromatogram with authentic samples. GC Method I (injection on the chiral column 6-TBDMS-2,3-DiEt β-cyclodextrine, 25m x 0.32m, film 0.25μm with isotherme at 125°C): rt((-)-**4**) = 72.45, rt((+)-**4**) = 75.4. GC Method II (injection on the chiral column Hp-5890/1, 25m x 0.3mm, film 0.25μm with isotherme at 140°C with a flux of helium of 0.66ml/minute)[8]: rt((-)-**4**) = 17.89, rt((+)-**4**) = 18.51 , rt((+)-**5** = 15.08, rt((-)-**6** = 15.14,

[8]The analysis were kindly performed by C. Vial (Firmenich SA, Geneva).

rt((+)-**6** = 15.64, rt((+/-)-**7** = 18.58 and 19.05. GC Method III (injection on the chiral column CP CHIRASIL-DEX (Chrompack), 25m x 0.25mm, film 0.25μm with isotherme at 160°C with a flux of helium of 1 ml/minute)[9]: rt((-)-**4**) = 26.26, rt((+)-**4**) = 28.24. GC (injection on the column HP-1, 25m x 0.25mm, film 0.1μm, 50°C, 1 min; 50°C/min; 280°/min, 2 min.) rt ((±)-**4**) = 4.31, rt ((±)-**5**) = 4.2, rt ((±)-**6**) = 4.25, rt ((±)-**7**) = 4.34, rt ((±)-**8**) = 4.27, rt ((±)-**9**) = 4.26, rt ((±)-**10**) = 4.22. GC (injection on Optima 5-MS, 30m x 0.25mm, film 0.25μm, 70°C, 10 min; 10°C/min; 250°/min, 10 min.) rt ((±)-**4**) = 22.78, rt ((±)-**9**) = 22.5, rt ((±)-**5, 6, 7, 8, 10**) = 22.06, 22.13, 22.26, 22.39, 22.9.

[9]The analysss was kindly performed by A. Saxer (University of Bern).

11.3 Nopyl methyl ether



93 **94**

2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl methyl ether 94 [157]: a solution of (1R)-2-(6,6)-dimethyl-2-bicyclo[3.1.1]hepten2-yl)ethanol (nopol, 13 g, 78.2 mmol) in hexane (10 ml) was poured in a solution of sodium hydroxide (7.68 g, 192 mmol) and benzyltriethylammonium chloride (0.3 g, 1.3 mmol) in water (10 ml). Dimethylsulfate (8.55 ml, 89 mmol) was added dropwise, over a period of 90 min, to the vigorously stirred two-phase mixture. After additional 5 h, a 25% aqueous solution of ammonia (3 ml) was then added and the stirring continued for another 30 min. Finally the organic layer was separated and the aqueous phase extracted with hexane (5 x 30 ml). The solution was dried ($MgSO_4$), the solvent evaporated and distillation of the crude material under reduced pressure gave the nopyl metyl ether **94** (8.9 g, 63%) and nopol 1 (2.61 g, 20%). Colourless liquid. B.p. 62-65°C/1 mmHg. TLC (SiO_2, pentane/ether 1:3): R_f=0.62. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.28 (m, 1H, H-C(3)), 3.39 (tm, J = 7.1, 2H), 3.32 (s, 3H, OMe), 2.42-2.2 (m, 4H), 2.18-2 (m, 3H), 1.28 (s, 3H, Me), 1.15 (d, J = 8.2, 1H), 0.82 (s, 3H, Me).

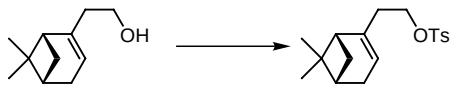
11.4 Nopyl benzyl ether

93 97

2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl benzyl ether 97: a dry 500 ml three-necked flask with a condenser and an addition funnel was charged with nopol (16.66 g, 100 mmol) and dry THF (200 ml). NaH 60% (5.8 g, 145 mmol) in mineral oil was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. Benzyl bromide (20.86 g, 122 mmol) was dropped and the mixture was refluxed for 24 h. After cooling to room temperature, the mixture was poured into water (250 ml) and extracted with ether (4 x 60 ml). The organic phases were washed with water (100 ml), followed by saturated aqueous $NaCl$ (100 ml), and then dried ($MgSO_4$). After evaporation of the solvent a distillation of the crude mixture gave **97** (24.73 g, 96%). Colourless liquid. B.p. 120°C/0.8 mmHg. TLC (SiO_2, pentane): R_f=0.05. TLC (SiO_2, pentane/ether 4:1): R_f=0.7. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.32 (s, 2H, aromatic), 7.30 (s, 3H, aromatic), 5.26 (m, 1H, H-C(3)), 4.47 (s, 2H, $PhCH_2O$), 3.48 (t, J = 7.02, 2H, H-C(2")), 2.37-2.25 (m, 3H), 2.21 (dm, J = 12.2, 2H), 2.1-2 (m, 2H), 1.26 (s, 3H, Me), 1.16 (d, J = 8.55, 1H), 0.8 (s, 3H, Me). ^{13}C-NMR(50.4 MHz, $CDCl_3$): 145.1 (C(2)), 138.5 (C(1")), 128.3 (CH aromatic), 127.6 (CH aromatic), 117.8 (CH, C(3)), 72.8 (CH_2O), 68.8 (CH_2O), 45.8 (CH), 40.7 (CH), 38 (C(6)), 37.1 (CH_2), 31.6 (CH_2), 31.3 (CH_2), 26.3 (CH_3), 21.1 (CH_3).

11.5 Dinopyl ether

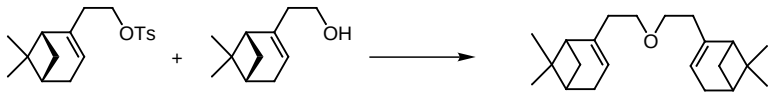
11.5.1 Tosylation of nopol [188, 189]



93 **101**

2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl toluene-p-sulfonate 101: a freshly distilled (60°C, 20 mmHg) solution of nopol (4.49 g, 27 mmol) in triethyl amine (7 ml) was added p-toluensulfonyl chloride (5.91 g, 31 mmol). The reaction mixture was stirred at room temperature for 2 hours. After addition of HCl 50% (20 ml), the solution was extracted with ether (4 x 20 ml) and dried ($\mathrm{K_2CO_3}$). After evaporation of the solvent, pure product was obtained (8.3 g, 96%). Transparent crystals. TLC ($\mathrm{SiO_2}$, pentane/ether 4:1): R_f = 0.23. TLC ($\mathrm{SiO_2}$, pentane): R_f = 0.0. ^{1}H-NMR (360 MHz, $\mathrm{CDCl_3}$): 7.8 (d, J = 8, 2H, OTs), 7.57 (d, J = 8, 2H, OTs), 5.23 ($br.$ s, 1H, H-C(3)), 4.02 (td, J = 7, 2.75, 2H, H-C(2^2)), 2.45 (s, 3H, OTs), 2.3 (m, 3H), 2.18 (dm, J = 11.3, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.24 (s, 3H, Me), 1.08 (d, J = 8.54, 1H), 0.77 (s, 3H, Me). ^{13}C-NMR(50.4 MHz, $\mathrm{CDCl_3}$): 144.6 (C(2)), 142.6 (C, OTs), 133.26 (CH, OTs), 129.7 (CH, OTs), 127.8 (CH, OTs), 119.6 (CH, C(3)), 68.5 (CH_2, C(2^2)), 45.5 (CH, C(1)), 40.5 (CH, C(5)), 37.9 (C(6)), 36 (CH, C(2^1)), 31.4 (CH_2, C(4) ou C(7)), 31.2 (CH_2, C(7) ou C(4)), 26.1 (CH_3, Me), 21.5 (CH_3, OTs), 21 (CH_3, Me).

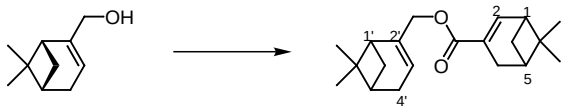
11.5.2 Dinopyl ether



101 **93** **103**

bis[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl]ether 103: In a dry three-necked flask equiped with a septum, an argon inlett and an addition funnel, $^{n}\mathrm{BuLi}$ (12.5 ml, 12.5 mmol) was added dropwise via a serynge under argon at -16°C to a solution of nopol (1.49 g, 9.94 mmol) in dry THF (35 ml). The mixture was allowed to warm up to room temperature then to 67°C, which turned the yellow colour to transparent. $^{n}\mathrm{BuLi}$ (1.25 ml, 1.25 mmol) was added and the yellow mixture was stirred at reflux for 3 hours. A solution of tosylated nopol **101** (3.4 g, 10.61 mmol) in dry THF (10 ml) was added dropwise. The mixture was stirred at reflux for 65 hours. The red mixture was poured on water (100 ml), extracted with ether (5 x 30 ml) and dried ($\mathrm{MgSO_4}$). The solvent was evaporated and a flash chromatography ($\mathrm{SiO_2}$, pentane/ether (4:1)) afforded two fractions. A flash chromatography ($\mathrm{SiO_2}$, pentane)of the first one (TLC ($\mathrm{SiO_2}$, pentane/ether (4:1): R_f = 0.58-0.76) afforded the product **103** (683 mg, 22%) and the tosylated nopol **101** (1.17 g, 34%). Transparent liquid. B.p. 45-48°C/8*10^{-6} mmHg. TLC ($\mathrm{SiO_2}$, pentane): R_f = 0.15. ^{1}H-NMR (500 MHz, $\mathrm{CDCl_3}$): 5.26-5.24 (m, 2H, H-C(3)), 3.44-3.36 (m, 4H, H-C(2^2)), 2.35 (dt, J = 8.5, 5.73, 2H, H-C(7)), 2.28-2.14 (m, 8H, H-C(2^1, 4)), 2.09-2.05 (m, 2H, H-C(1)), 2.03 (dt, J = 5.68, 1.51, 2H, H-C(5)), 1.26 (s, 3H, Me), 1.13 (d, J = 8.5, 1H, H-C(7)), 0.82 (s, 3H, Me). ^{13}C-NMR(125.7 MHz, $\mathrm{CDCl_3}$): 145.2 (C(2)), 117.7 (CH, C(3)), 69.21 (CH_2, C(2^2)), 45.9 (CH, C(1)), 40.8 (CH, C(5)), 38 (C(6)), 37.2 (CH_2, C(2^1)), 31.6 (CH_2, C(7)), 31.3 (CH2, C(4)), 26.3 (CH_3, Me), 21.15 (CH_3, Me). CI-MS: 315 (M^+, 54), 299 (8), 271 (4), 179 (40), 149 (100), 121 (7),95 (8).

11.6 Ester 106

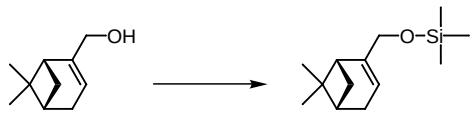


105 **106**

(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl-6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-carboxylate 106: in a dry flask under argon, myrtenol (2 g, 13.15 mmol) in dioxane[10] (15 ml) and iron pentacarbonyl (2.7 ml, 20 mmol) were refluxed[11] for 5 days. After cooling down to room temperature, the mixture was filtrated over ALOX[12] and the solvent and the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. A flash chromatography (SiO_2, pentane and pentane/dichloromethane 4:1) gave the ester **106** (350 mg, 20%). Transparent liquid. TLC (SiO_2, pentane): $R_f = 0.05$. TLC (SiO_2, pentane/dichloromethane 1:1): $R_f = 0.73$. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.85 (m, 2H, H-C(2'^{1})), 2.88 (t, $J = 8.6$, 1H, H-C(2)), 2.29 ($quintet$, $J = 7.6$, 1H, H-C(2')), 2.18-2.1 (m, 3H, H-C(1, 4, 7')), 2.1-2 (m, 2H, H-C(4, 7)), 1.9-1.82 (m, 3H, H-C(5, 5', 4')), 1.81-1.78 (m, 2H, H-C(1', 3)), 1.77-1.75 (m, 1H, H-C(4')), 1.74-1.69 (m, 2H, H-C(3)), 1.62 (dt, $J = 14.6, 8.6$, 1H, H-C(3')), 1.53 (d, $J = 8.78$, 1H, H-C(7')), 1.35 (d, $J = 10.25$, 1H, H-C(7)), 1.31-1.25 (m, 1H, H-C(3')), 1.22 (s, 3H, Me), 1.21 (s, 3H, Me), 0.87 (s, 3H, Me), 0.85 (s, 3H, Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$)[13]: 176.8 (C, ester), 67.9 (CH_2, C(2'^{1})), 43.7 (CH, C(1)), 42.4 (CH, C(1')), 41.4 (CH, C(2)), 40.8 (CH, C(5) or C(5')) 40.1 (CH, C(5) or C(5')), 39.2 (C(6) or C(6')), 39.1 (C(6) or C(6')), 34.2 (CH, C(2')), 26.6 (CH_3, Me), 26.4 (CH_3, Me), 24.2 (CH_2, C(7')), 24 (CH_2, C(3)) 23.9 (CH_2, C(4')), 23.4 (CH_2, C(7)), 20.2 (CH_3, Me), 20.1 (CH_3, Me), 18.2 (CH_2, C(3')), 16.8 (CH_2, C(4)). EI-MS: 304 (M^+, 1.5), 222 (5), 168 (32), 137 (37), 136 (48), 123 (44), 121 (58), 107 (24), 95 (93), 93 (75), 82 (85), 81 (100), 69 (84), 27 (88), 55 (25), 41 (43).

[10] filtrated over ALOX
[11] bath at 120°C
[12] caution: pyrophoric iron may be present in the medium
[13] the quaternary carbons are not given

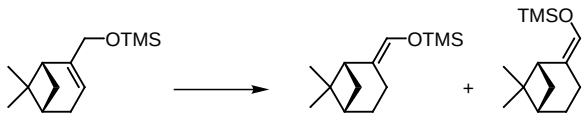
11.7 Pinenyl trimethylsilyl ether



105 107

(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl trimethylsilyl ether 107: myrtenol (10 g, 6.58 mmol) in dry dichloromethane was added dropwise at 0°C to a solution of NaH 60% (2.9 g, 7.24 mmol) in dry dichloromethane (25 ml) under nitrogen atmosphere. To dissolve the pasty foam, dry dichloromethane (20 ml) was added. The mixture was stirred at room temperature for 40 min, and TMSCl (9.15 ml, 2.24 mmol) was added dropwise at 0°C. The mixture was stirred for 20 hours, washed with water and extracted with dichloromethane (6 x 20 ml). After evaporation of the solvent and filtration over ALOX with dichloromethane, product **107** (14.3 g, 97%) was isolated in its pure form. Colourless liquid. TLC ($\mathrm{SiO_2}$, pentane): R_f=0.21 ^{1}H-NMR (360 MHz,$\mathrm{CDCl_3}$): 5.3(m, 1H, H-C(3)), 3.82 (s, 2H, H-C(2^1)), 2.25 (dd, J = 19.7, 5.9, 1H), 2.23-2.14 (m, 1H), 2.14-2.04 (m, 1H), 2.01-1.94 (m, 1H), 1.89 (tm, J = 5, 1H), 1.07 (d, J = 8.17, 1H, H-C(7)), 0.8 (s, 3H, Me), 0.71 (s, 3H, Me), 0.05 (s, 9H, Me-Si). ^{13}C-NMR (90.6 MHz, $\mathrm{CDCl_3}$): 147.6 (C(2)), 116.6 (CH, C(3)), 65.5 (CH_2, C(2^1)), 43.4 (CH, C(5)), 41.4 (CH, C(1)), 38.4 (C(6)), 31.8 (CH_2, C(7) or C(4)), 31.4 (CH_2, C(4) or C(7)), 26.6 (CH_3, Me), 21.3 (CH_3, Me), 0 (CH_3, Me-Si).

11.8 Isomerization of the pinenyl trimethylsilyl ether



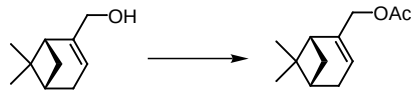
107 **109** **110**

(6,6-Dimethylbicyclo[3.1.1]hept-2-ylidene)methyl trimethylsilyl ether 109 and 110: in a dry three-necked flask fitted a condenser with a bubbler and a Dean & Stark trap filled with molecular sieves and dry heptane, a solution of pinenyl trimethylsilyl ether **107** (section 11.7 on the page before, 10 g, 44.64 mmol) and iron pentacarbonyl (9 ml, 67.6 mmol) in dry dioxane (25 ml) and dry heptane (5 ml) was heated at reflux[14] in the dark for 40 hours under an argon stream. After cooling down to room temperature, the mixture was filtrated over ALOX[15] and the solvent and the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. A flash chromatography (SiO_2, pentane then dichloromethane) gave the cis/trans products **109/110** (5.1 g, 63%), the complex **111** (273 mg, 2%) and the starting material (137 mg, 1.5%). Yellow oil. TLC (SiO_2, pentane): R_f = 0.4. ^{1}H-NMR (360 MHz,$CDCl_3$): **Major isomer**: 5.94 (m, 1H, H-C(2^1)), 1.3 (d, J = 9.97, 1H, H-C(7)), 1.13 (s, 3H, Me), 0.61 (s, 3H, Me). **Minor isomer**: 5.74 (m, 1H, H-C(2^1)), 1.2 (d, J = 9.54, 1H, H-C(7)), 1.07 (s, 3H, Me), 0.58 (s, 3H, Me). **Common peaks**: 2.4-2.1 (m, 3H$_{major}$ + 3H$_{minor}$), 1.95-1.6 (m, 4H$_{major}$ + 4H$_{minor}$).

[14] bath at 130°C.

[15] caution: pyrophoric iron may be present in the medium.

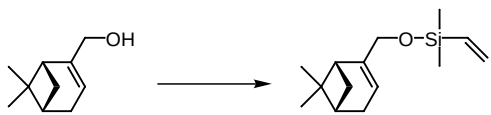
11.9 Myrtenyl acetate



105 112

(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl acetate 112: to a solution of myrtenol (10 g, 65.8 mmol) in acetic anhydride (13.4 g, 131.6 mmol), TMSOTf (0.46 ml, 2.6 mmol) in acetonitrile (20 ml) was added under an argon stream. The mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. After addition of methanol (3 ml), the solution was neutralized with $\mathrm{NaHCO_3}$, then $\mathrm{K_2CO_3}$. The organic layer was washed with water, dried ($\mathrm{MgSO_4}$), filtrated. Evaporation of the solvent yielded pure **112** (11.75 g, 92%). Colourless liquid. ^{1}H-NMR (360 MHz,$\mathrm{CDCl_3}$): 5.56 (s, 1H), 4.47 (d, J = 12.5, 1H), 4.41 (d, J = 12.5, 1H), 2.43-2.37 (m, 1H), 2.28 (dm, J = 13.2, 2H), 2.23 (s, 3H, Me acetate), 2.11 (dm, J = 5.47, 2H), 1.29 (s, 3H, Me), 1.18 (d, J = 8.64, 1H), 0.82 (s, 3H, Me).

11.10 Pinenyl dimethyl(vinyl)silyl ether

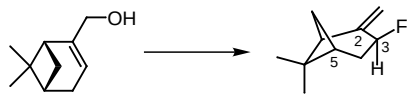


105 **119**

(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyldimethyl(vinyl)silyl ether 119: to a solution of NaH 60%[16] (0.8 g, 20 mmol) in dry THF (25 ml), myrtenol (2 g, 13.15 mmol) in dry THF (15 ml) was added dropwise at 0°C. The mixture was stirred at room temperature for 60 min and chloro-dimethyl-vinylsilane (1.95 ml, 14.46 mmol) in dry THF (5 ml) was added dropwise. The mixture was stirred at reflux over night. The solvent was evaporated and a flash chromatography ($\mathrm{SiO_2}$, pentane) of the crude mixture gave **119** (170 mg, 5.5% for a conversion of 28%)[17]. TLC ($\mathrm{SiO_2}$, pentane): R_f = 0.17. ^{1}H-NMR (500 MHz, $\mathrm{CDCl_3}$): 6.13 (dd, J = 20.26, 14.91, 1H, H-C$_{vinyl}$(1)), 6 (dd, J = 14.91, 4.03, 1H, H-C$_{vinyl}$(2)), 5.75 (dd, J = 20.26, 4.03, 1H, H-C$_{vinyl}$(2)), 5.42 (m, 1H, H-C(3)), 3.97 (m, 2H, H-C(2^1)), 2.37 (dt, J = 8.51, 3.18, 1H, H-C(7)), 2.33-2.27 (m, 1H, H-C(4)), 2.24-2.19 (m, 1H, H-C(4)), 2.08 (m, 1H, H-C(5)), 2 (dt, J = 5.62, 1.37, 1H, H-C(1)), 1.18 (d, J = 8.51, 1H, H-C(7)), 1.27 (s, 3H, Me), 0.82 (s, 3H, Me), 0.02 (s, 6H, Me-Si). ^{13}C-NMR (125.7 MHz, $\mathrm{CDCl_3}$): 147.1 (C(2)), 137.5 (CH, vinyl), 133.1 (CH_2, vinyl), 116.3 (CH, C(3)), 65.3 (CH_2, C(2^1)), 43 (CH, C(5)), 41 (CH, C(1)), 31.4 (CH_2, C(7)), 31 (CH_2, C(4)), 26.2 (CH_3, Me), 21 (CH_3, Me), -2.1 (CH_3, Me-Si).

[16] in parafine.
[17] the NaH used was apparently too old.

11.11 Fluorination of myrtenol

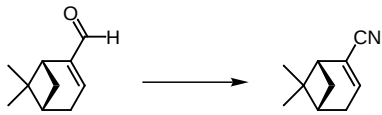


105 **123**

3-fluoro-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane 123 [174]: in a dry two-necked flask, a solution of DAST (1.7 ml, 13.2 mmol) in dry dichloromethane (6 ml) was cooled to -78°C under a nitrogen atmosphere. A solution of myrtenol (2 g, 13.15 mmol) in dichloromethane (3 ml) were added dropwise via s syringe[18]. The solution was allowed to warm up to room temperature, then it was extracted with dichloromethane, washed with a saturated aqueous solution of K_2CO_3 and water, filtrated, dried ($MgSO_4$). Evaporation of the solvent yielded a residue, that was purified by flash chromatography (SiO_2, pentane and dichloromethane) to give **123** (0.67 g, 33%). Transparent liquid. TLC (SiO_2, pentane): $R_f = 0.32$. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.07 (dd, $J =$ 6.9, 52, 1H, H-C(3)), 5.06 (dd, $J = 6.41$, 84, 2H, H-C(2')), 2.53 (t, $J = 5.5$, 1H, H-C(1)), 2.42 (m, 1H, H-C(7)), 2.28 ($dddt$, $J = 30.5$, 15.5, 6.9, 2, 1H, H-C(4)), 2.09 (ddd, $J = 35$, 15.5, 4.39, 1H, H-C(4)), 1.98 (m, 1H, H-C(5)), 1.64 (dd, $J = 10.15$, 3.4, 1H, H-C(7)), 1.29 (s, 3H, Me), 0.63 (s, 3H, Me). ^{13}C-NMR (50.4 MHz, $CDCl_3$): 149.6 (d, $J = 11.19$, C(2)), 115.4 (d, $J =$ 9.37, CH_2, C(2')), 88.16 (d, $J = 168.35$, CH, C(3)), 50 (CH, C(1)), 40.6 (C(6)), 39.1 (CH, C(5)), 33.1 (d, $J = 22.42$, CH_2, C(4)), 27.6 (CH_2, C(7)), 25.8 (CH_3, Me), 21.9 (CH_3, Me). EI-MS: 136 (26), 119 (28), 107 (38), 105 (22), 93 (100), 91 (99), 79 (72), 92 (32), 77 (38), 69 (21). CI-MS: 134 (84), 133 (25), 121 (29), 107 (41), 93 (100), 91 (24), 79 (54), 81 (21).

[18] Myrtenol is not soluble at this temperature.

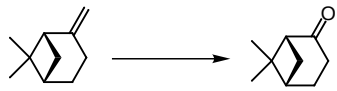
11.12 2-Nitrile-apopinene



108 **121**

6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carbonitrile 121 [23]: to a solution of myrtenal (5 g, 33.33 mmol) in water (25 ml) was added dropwise a solution of HAS (3.8 g, 33.33 mmol) and water (18 ml). The mixture was stirred at room temperature for 1 h, then at 45°C for 20 min. The clear yellow solution became turbid and white. The reaction mixture was allowed to cool at room temperature and NaOH 2N was added until the pH reached 12. The mixture was allowed to stand at room temperature for 2 hours. Ether (45 ml) was added and the solution was washed with water until neutral pH. The solution was extracted and the organic phase dried ($\mathrm{MgSO_4}$). Evaporation of the solvent gave the 2-nitrile-apopinene **121** (4.5 g, 93%) with a purity $> 95\%$. This product can be purified by distillation or by flash chromatography (pentane/ether 15:1). Colourless liquid. B.p. 105°C/15 mmHg. CCM ($\mathrm{SiO_2}$, pentane/ether 15:1): R_f(**108**) = 0.38, R_f(**121**) = 0.3. ^{1}H-NMR (200 MHz, $\mathrm{CDCl_3}$): 6.58 (m, 1H, H-C(3)), 2.45 (m, 5H), 2.18 (m, 1H), 1.33 (s, 3H, Me), 1.25 (d, J = 8.5, 1H, H-C(7)), 0.85 (s, 3H, Me). ^{13}C-NMR(50.4 MHz, $\mathrm{CDCl_3}$): 141.9 (CH, C(3)), 120.9 (C, C(2)), 118.3 (C, CN), 44.52 (CH), 39.8 (CH), 38.1 (C, C(6)), 32.57 (CH_2), 31.2 (CH_2), 25.6 (CH_3, Me), 20.9 (CH_3, Me). EI-MS: 148 (35, M^+), 132 (25), 117 (19), 105 (100), 104 (99), 91 (22), 77 (31), 65 (15), 53 (16) 43 (50), 41 (55), 39 (81).

11.13 Nopinone



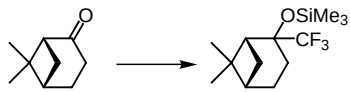
125

6,6-dimethylbicyclo[3.1.1]heptan-2-one 125 [180]: in a three-necked flask, a solution of β-pinene (63 ml, 397 mmol) in methanol (120 ml) and dichloromethane (120 ml) was exhaustively ozonized at -78°C. The flask was flushed with nitrogen and treated with excess dimethyl sulfide[19] (150 ml) at -78°C. The mixture was allowed to warm up to room temperature and then stirred for additional 36 h. The volatile products were removed by distillation under reduced pressure (80°C, 40 mmHg). The resulting yellow oil was treated with ether (50 ml) and then with a 5% aqueous ferrous sulfate solution and stirred for 15 min. The organic layer was removed, and the aqueous layer was extracted with ether (3 x 40 ml). The combined organic layers were treated with a saturated sodium bicarbonate solution and stirred for 1h. The organic layer was removed, dried ($\mathrm{MgSO_4}$). Evaporation of the solvent and distillation of the crude material gave nopinone (37.6 g, 69%). Colourless liquid. B.p. 80-82°C/20 mmHg. GC (γ-cyclodextrine, 50°C, 20'; 10°C /min.; 150°C , 10'): 95 % ee. GC (Optima 1701, 80°C, 5'; 15°C /min.; 250°C , 5') rt = 8.44. GC (Optima 5-MS, 80°C, 5'; 15°C /min.; 250°C , 5') rt = 8.64. ^{1}H-NMR (360 MHz, $\mathrm{CDCl_3}$): 2.65-2.49 (m, 3H), 2.34 (ddd, J = 19, 9.08, 2.04, 1H), 2.28-2.21 (m, 1H), 2.1-1.9 (m, 2H), 1.59 (d, J = 19, 9.99, 1H), 1.31 (s, 3H, Me), 0.88 (s, 3H, Me). ^{13}C-NMR(90.6 MHz, $\mathrm{CDCl_3}$): 215 (CO), 57.8 (CH, C(1)), 41.1 (C(6)), 40.3 (CH, C(5)), 32.7 (CH_2, C(3)), 25.8 (CH_3, Me), 25.3 (CH_2, C(7)), 22.1 (CH_3, Me), 21.3 (CH_2, C(4)). EI-MS: 139 (19, M^+), 109 (22), 96 (23), 95 (47), 83 (100), 81 (61), 79 (22), 69 (23), 67 (53), 55 (53).

[19] The sulfur contaminated equipment and solvent were treated with bleach.

11.14 Trifluoromethylation of nopinone

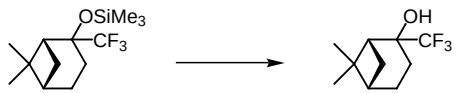
11.14.1 6,6-Dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]hept-2-yl trimethylsilyl ether



125 **128**

In a two-necked flask, a solution of nopinone (section 11.13 on the preceding page, 3.85 g, 27.9 mmol), calcium carbonate (150 mg, 2.34 mmol) and $CF_3Si(CH_3)_3$ (4.74 g, 33.9 mmol) in dry pentane (50 ml) was cooled to -80°C under argon atmosphere [173]. After addition of TBAF (70 mg, 0.21 mmol), the mixture was allowed to warm up to room temperature and then stirred for an additional 12 h. After evaporation of the solvent, a flash chromatography (SiO_2, pentane) gave the product **128** (4.94 g, 64%). White crystalline product. TLC (SiO_2, pentane): $R_f = 0.62$ GC (Optima 1701, 80°C, 5'; 20°C /min.; 250°C , 5') rt = 7.91. GC (Optima 5-MS, 80°C, 5'; 15°C /min.; 250°C , 5') rt = 6.68. ^{1}H-NMR (360 MHz, $CDCl_3$): 2.26-2.18 (m, 3H), 2.07-1.99 (m, 1H), 1.89 (m, 1H), 1.85-1.73 (m, 2H), 1.44 (dm, $J = 8.5$, 1H), 1.26 (s, 3H, Me), 1.07 (s, 3H, Me), 0.13 (s, 9H, Me_3Si). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 126.7 (q, $J =$ 287.5, CF_3), 80.37 (q, $J = 25$, C(2)), 46.8 (CH), 39.9 (CH), 38.8 (C(6)), 27.4 (Me), 25.7 (CH_2), 25.5 (CH_2), 23.8 (Me), 23.22 (CH_2), 1.9 (Me_3-Si). EI-MS: 280(3, M^+), 225 (18), 211 (19), 191 (32), 190 (59), 175 (16), 147 (30), 127 (30), 121 (36), 113 (32), 107 (21), 96 (27), 83 (100), 69 (47).

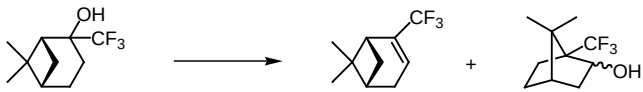
11.14.2 6,6-Dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]heptan-2-ol



128 **126**

The product **128** (1.08 g, 3.85 mmol) was stirred with TBAF (1.32 g, 4.19 mmol) and triethylamine (3 ml) at room temperature for 1 h. The solution was washed with water and HCl 1N up to a pH of 6. After extraction with ether, the organic layer was dried ($MgSO_4$, then K_2CO_3). Evaporation of the solvent yielded pure **126** (800 mg, 100%). White crystralline product. M.p. 58.7-61°C. TLC (SiO_2, pentane/ethyl acetate 9:1): $R_f = 0.26$. GC (Optima 5-MS, 50°C, 5'; 15°C /min.; 250°C , 5') rt = 7.44. ^{1}H-NMR (360 MHz, $CDCl_3$): 2.33-2.15 (m, 3H), 2.12-2.01(m, 1H), 1.98 (s, OH), 1.99-1.92 (m, 1H), 1.91-1.81 (m, 1H), 1.73 (dm, $J = 9.53$, 1H), 1.47 (dd, $J = 10.89$, 1.37, 1H), 1.28 (s, 3H, Me), 1.11 (s, 3H, Me). ^{13}C-NMR (50.4 MHz, $CDCl_3$): 126.7 (q, $J = 286.7$, CF_3), 78.1 (q, $J = 26.7$, C(2)), 46.3 (CH), 40 (CH), 39.1 (C(6)), 27.4 (Me), 25.8 (CH_2), 23.9 (CH_2), 23.5 (Me), 22.9 (CH_2). EI-MS: 208 (2, M^+), 190 (8), 153 (20), 139 (10), 127 (13), 83 (76), 79 (28), 69 (44), 55(100), 41 (76). CI-MS: 208 (1.6, M^+), 191 (100), 169 (5.35), 149 (34), 141 (11), 133 (12), 57 (8).

11.14.3 6,6-Dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]hept-2-ene



126 **129** **130**

6,6-dimethyl-2-(trifluoromethyl)bicyclo[3.1.1]hept-2-ene 129: [185] in a dry two-necked flask[20], a solution of **126** (320 mg, 1.54 mmol) in pentane (3 ml) was added to a solution of $Ph_2S[OC(CF_3)_2Ph]_2$ (1.31 g, 1.94 mmol) in dry pentane (10 ml) at -90°C under argon. The mixture was stirred for 2 h at -90°C and allowed to warm to room temperature. After filtration (SiO_2, pentane) of the crude mixture, a Fisher distillation (bath: 38°C , b.p. 32°C) removed the $(CF_3)_2PhCOH$ and the major amount of pentane. The product **129** was obtained (85 mg, 29%) with pentane (545 mg), and **130**, which stay at the top of the column, used for the filtration, was washed off with dichloromethane.

Product 129 GC (Optima 5-MS, 50°C, 5'; 15°C /min.; 250°C , 5') rt = 5.79. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.17 (m, 1H, H-C(3)), 2.5 (dt, J = 9.04, 5.66, 2H, H-C(7)), 2.41-2.38 (m, 1H, H-C(1)), 2.38 (qq, J = 18.8, 3.23, 2H, H-C(4)), 2.16-2.12 (m, 1H, H-C(5)), 1.51 (s, 3H, Me), 0.84 (s, 3H, Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 137.88 (C(2), q, J = 31.3), 126.3 (CH, q, J = 6.5, C(3)), 123.1 (CF_3, q, J = 270), 40.72 (CH, C(1)), 40.46 (CH, C(5)), 32.1 (C(6)), 31.28 (CH_2, C(7)), 30.93 (CH_2, C(4)), 25.74 (CH_3, Me), 20.8 (CH_3, Me). EI-MS: 190 (16, M^+), 175 (71), 161 (71), 155 (22), 141 (40), 127 (100), 121 (58), 115 (32), 93 (27), 91 (29), 79 (35), 77 (41).

Product 130 TLC (SiO_2, pentane): $R_f < 0.1$. GC (Optima 5-MS, 50°C, 5'; 15°C /min.; 250°C , 5') rt = 8.71. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.88 (dd, J = 4.07, 1.39, 1H, H-C(2)), 3.62 (m, 1H, OH), 2.01-1.95 (m, 1H, H-C(6)) 1.85 (m, 1H, H-C(4)), 1.82-1.77 (m, 2H, H-C(5, 3)), 1.57-1.48 (m, 2H, H-C(5, 6)), 1.46 (dd, J = 9.9, 1.7, 1H, H-C(3)), 1.05 (s, 3H, Me), 0.91 (s, 3H, Me. ^{13}C-NMR (125.7 MHz, $CDCl_3$): 122.7 (CF_3, q, J = 286.6), 78.3 (CH, C(2)), 56.5 (C(1), q, J = 25.57), 47.6 (CH, C(4)), 39.6 (C(7)), 35 (CH_2, C(3)), 30.4 (Me), 24.9 (CH_2, C(5)), 19.8 (Me), 18.5 (CH_2, C(6)). EI-MS: 208

[20] Martin's reagent is extremely hygroscopic and should be handled in a dry box under argon.

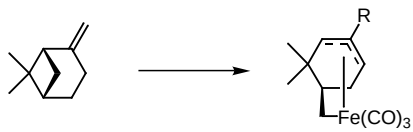
(6, M^+), 190 (47), 177 (22), 175 (22), 121 (33), 105 (31), 83 28), 72 (31), 69 (61), 57 (50), 55 (100), 43 (82).

Chapter 12

Syntheses and transformations of complexes

12.1 Synthesis of 2-Me-BOD-Fe(CO)$_2$I

12.1.1 Complexation of (-)-β-pinene [4]

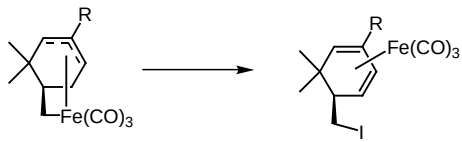


(R=Me) **64**

[η^4-Methylen-(2,2,4-trimethyl)-4-cyclohexene-1,3-diyl)]tricarbonyliron 64: in a dry three-necked flask[1] equiped with a condenser with a bubbler and with a Dean & Stark trap filled with molecular sieves and dry heptane, a solution of (-)-β-pinene (36 g, 264 mmol) and iron pentacarbonyl (20 ml, 160 mmol) in dry dioxane (100 ml) and dry heptane (20 ml) was heated at reflux[2] for 3 days in the dark under argon atmosphere. After cooling down at room temperature, the mixture was filtrated over ALOX[3] and the solvent with the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. After a flash chromatography (SiO_2, pentane), 46 g (63%) of product were isolated. Yellow oil. TLC (SiO_2, pentane): R_f = 0.8. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.1 (*dddd*, J = 4.3, 2.1, 1.8, 1.2, 1H, H-C(5')), 4.04 (*dd*, j = 2.1, 1.8, 1H, H-C(3')), 2.05 (*ddt*, J = 14.3, 2.9, 1.8, 1H, H$_{exo}$-C(6')), 1.89 (*br. s*, 3H, H-C(4')), 1.59 (*ddd*, J = 9.7, 2.9, H$_{pro-S}$-C(1)), 1.52 (*dddt*, J = 3.6, 2.9, 2.4, 1H, H-C(1')), 1.28 (*ddd*, J = 14.3, 4.3, 3.6, 1H, H$_{endo}$-C(6')), 1.09 (*dd*, J = 9.7, 2.4, 1H, H$_{pro-R}$-C(1)), 0.94 (*s*, 6H, Me). ^{1}3C-NMR (125.7 MHz, $CDCl_3$): 216.9 (CO), 215.5 (CO), 207.2 (CO), 103.4 (C(4')) 87.2 (CH, C(5')), 76.8 (CH, C(3')), 49.1 (CH, C(1')), 40.3 (C(2')), 33.8 (CH$_2$, C(1)), 33.7 (CH$_2$, C(6')), 28.1 (CH$_2$, C(2'^{1})), 28.1 (CH$_3$, C(4'^{1})), 26.8 (CH$_3$, C(2'^{1})).

[1] better results are obtained if the flask was already used for this synthesis.
[2] bath at 130°C.
[3] caution: pyrophoric iron may be present in the medium.

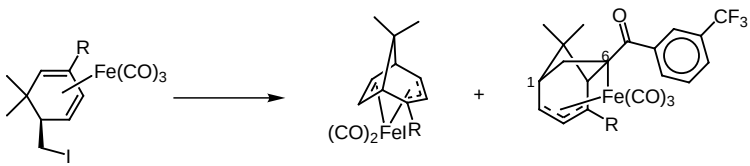
12.1.2 Iodation of the seco-pinene complex



64 (R=Me) **65**

[η^4-5-Iodomethyl-2,6,6-trimethylcyclohexa-1,3-diene]tricarbonyl iron 65: in a 50 ml flask the seco-pinene complex (7.7 g, 28 mmol) in a phosphate buffer solution (50 ml, pH=7) was vigorously stirred (mechanical stirring). Iodine (28 x 500 mg every 3 minutes, 55 mmol) was added [4]. After 45 min a saturated aqueous solution of sodium thiosulfate (220 ml) was added. The solution was extracted with ether (6 x 40 ml), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, pentane), the solvent evaporated and the complex **65** (8 g, 70%) was recristallized in pentane (*ca.* 10 ml) Yellow oil. TLC (SiO_2, pentane): R_f = 0.4. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.29 (d, J = 6.4, 1H, H-C(3)), 3.35 (dd, J = 9.6, 5, 1H, H-C(5^1)), 3.09 (d, J = 10.2, 1H, H-C(5^1)), 3.06 (dd, J = 6.4, 1.8, 1H, H-C(4), 2.76 (s, 1H, H-C(1)), 2.08 (s, 3H, H-C(2^1)), 1.91 ($dddd$, J = 9.23, 5.65, 1.9, 1.1, 1H, H-C(5)), 1.06 (s, 3H, H-C(6^1)), 1.02 (s, 3H, H-C(6^1)). ^{1}3C-NMR (125.7 MHz, $CDCl_3$): 212 (CO), 102 (C(2)), 85.1 (CH, C(3)), 80.1 (CH, C(1)), 62 (CH, C(4)), 50.1 (CH, C(5)), 42.4 (C(6)), 35.9 (CH_3, C(6^1)), 24.6 (CH_3, C(6^1)), 22 (CH_3, C(2^1)), 9.4 (CH_2, C(5^1)).

12.1.3 Synthesis of 2-Me-BOD-Fe(CO)$_2$I



65 (R=Me) **1** **69**

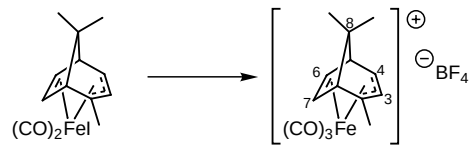
Iodo[η^5-(2,8,8-Trimethylbicyclo[3.2.1]oct-3,6-diene)2-yl]dicarbonyl iron 1: in a dry 25 ml two-necked flask, the complex **65** (369 mg, 1 mmol), tetrabutylammonium iodid (402 mg, 1 mmol) and ether (10 ml) were cooled to -90°C under an nitrogen atmosphere. $^t\mathrm{BuLi}$ (1.3 ml, 2.2 mmol) was added thoroughly over a 25 min period. After 10 min. a solution of freshly distilled isoprene (1 ml, 10 mmol) in dry ether (5 ml) and then a solution of m-(trifluoromethyl)benzoyl chloride (0.162 ml, 1.1 mmol) were added, each over a 5 min period. The reaction mixture was allowed to warm up to -45°C and was stirred at this temperature for 45 min. After warming up to 10°C, the mixture was washed with water (10 ml) under an argon atmosphere and the organic phase was transfered under inert atmosphere in a schlenk. After evaporation of the solvent, a flash chromatography ($\mathrm{SiO_2}$, pentane/ether 4:1) afforded **1** (360 mg, 94%) A recristallization of the complex in ether by diffusion of pentane is possible.

Complex 1 Burgundy solid. M.p. 141°C. TLC ($\mathrm{SiO_2}$, pentane/ether 9:1): R_f = 0.2. ^{1}H-NMR (500 MHz, $\mathrm{CD_2Cl_2}$, 243K): 4.64 (d, J = 6.6, 1H, H-C(7)), 3.85 (t, J = 6.6, 1H, H-C(6)), 2.79 (t, J = 4, 1H, H-C(4)), 2.75 (t, J = 4, 1H, H-C(3)), 2.28 (d, J = 4.5, 1H, H-C(1)), 2.3-2.25 (m, 1H, H-C(5)), 2.12 (s, 3H, H-C(2^1)), 0.73 (s, 3H, H-C(8)), 0.72 (s, 3H, H-C(8)). ^{13}C-NMR (125.7 MHz, $\mathrm{CD_2Cl_2}$, 243K): 215.8 (CO), 214.8 (CO), 101.8 (CH, C(7)), 56.7 (C(2)), 48.3 (CH, C(1)), 45.6 (C(8)), 41.8 (CH, C(5)), 40 (CH, C(4)), 38.1 (CH, C(3)), 31.9 (CH, C(6)), 22.9 ($\mathrm{CH_3}$, C(2^1)), 22 ($\mathrm{CH_3}$, Me) 15.9 ($\mathrm{CH_3}$, Me). IR (NaCl): 3070 (w), 2987 (w), 2960 (m), 2938 (m), 2904 (w), 2868 (w), 2013 (s, ν[CO]), 1966 (s, ν[CO]), 1440 (m), 1363 (m), 1028 (m), 637 (m), 560 (s), 527 (s).

Complex 69 Orange oil. ^{1}H-NMR (360MHz, $\mathrm{CDCl_3}$): 8.54 (s, 1H, C$_{aromatic}$), 8.15 (d, J = 3.6, 1H, C$_{aromatic}$), 7.28 (d, J = 3.6, 1H, C$_{aromatic}$), 6.81 (t, J

$= 3.6$, 1H, $C_{aromatic}$), 4.37 (t, $J = 6.4$, 1H, C(2)), 4.19 (d, $J = 6.4$, 1H, C(3)), 2.98 (dd, $J = 11.2, 1.8$, 1H, H-C(7)), 2.24-2.19 (m, 2H, H-C(5), H-C(7)), 1.45 (s, 3H, H-C(4^1)), 1.39-1.35 (m, 1H, H-C(1)), 0.73 (s, 3H, H-C(8^1)), 0.53 (s, 3H, H-C(8^1)).

12.2 [2-Me-BOD-Fe(CO)$_3$]BF$_4$

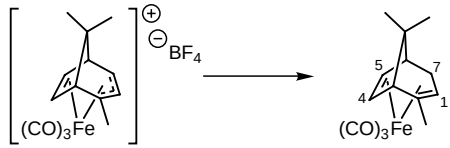


1 **75**

[η^5(2,8,8-Trimethylbicyclo[3.2.1]octa-3,6-dien)2-yl]tricarbonyl iron(I) tetrafluoroborate 75: To $AgBF_4$ (60 mg, 0.3 mmol) in the dark under a CO atmosphere[4] a solution of 2-Me-BOD-Fe(CO)$_2$I **1** (100 mg, 0.26 mmol) in dry dichloromethane (10 ml) was added. After 13 hours the reaction mixture was filtrated through a plug of celite with dichloromethane as eluent and the solvent was evaporated. The crude mixture was filtered through a plug of silica gel with acetone as eluent and addition of ether precipitate the complex which gave **75** (55 mg, 61%) after filtration. Yellow solid. ^{1}H-NMR (360 MHz, acetone-d6) 5 (m, 1H, H-C(7)), 4.2 ($br.s$, 2H, H-C(3), H-C(4)), 4.1 (mt, J = , 1H, H-C(6)), 2.5 (m, 2H, H-C(1), H-C(5)), 2.05 (s, 3H, H-C(2^1)), 1.05 (s, 3H, H-C(8^1)), 0.95 (s, 3H, H-C(8^1)). ^{13}C-NMR (90.4 MHz, acetone-d6): 206.8 (CO), 206.1 (CO), 91.55 (CH, C(7)), 72.4 (C, C(2)), 59.25 (CH, C(4)), 57.14 (CH, C(3)), 49.6 (C, C(8)), 49.4 (CH, C(1)), 42.5 (CH, C(5)), 40.7 (CH, C(6)), 25.5 (CH$_3$, H-C(2^1)), 21.7 (CH$_3$, H-C(8^1)), 16 (CH$_3$, H-C(8^1)). ^{1}H-NMR (500 MHz, CD_2Cl_2): 5 (m, 1H, H-C(7)), 4.22 (m, 2H, H-C(3), H-C(4)), 4.13 (m, 1H, H-C(6)), 2.7 (m, 2H, H-C(1), H-C(5)), 2.18 (s, 3H, H-C(2^1)), 0.98 (s, 3H, H-C(8^1)), 0.93 (s, 3H, H-C(8^1)). ^{13}C-NMR (125.7 MHz, CD_2Cl_2): 204 (CO), 90.6 (CH, C(7)), 71.8 (C(2)), 58.7 (CH, C(4)), 56.2 (CH, C(3)), 49.2 (C(8)), 49 (CH, C(1)), 41.8 (CH, C(5)), 25.8 (CH$_3$, C(2^1)), 21.4 (CH$_3$, C(8^1)), 15.7 (CH$_3$, C(8^1)). FAB-MS (matrix NBA): 286.9 (M$^+$, 5), 258.9 (-CO), 230.9 (-CO), 203 (-CO).

[4]The CO atmosphere can be generated by the addition of a solution of $FeCl_3$ (2.4 g) in water (10 ml) on $Fe(CO)_5$ (1 ml), but better results were obtained by using a CO bottle.

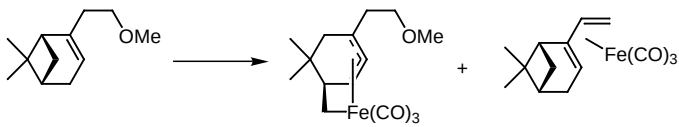
12.3 Reaction of [2-Me-BOD-Fe(CO)$_3$]BF$_4$



75 **76**

[(2,8,8)-Trimethylbicyclo[3.2.1]-2,6-octadiene)]tricarbonyl iron 76: in a schlenk under an argon atmosphere, a solution of **75** (96 mg, 0.26 mmol) in dry THF (3ml) and methanol (7 ml) was added dropwise to a solution of $\mathrm{NaBH_4}$ (20 mg, 0.52 mmol) in dry THF (6 ml) at room temperature. After 30 min, water (10 ml) was added and extracted with ether (3 x 10 ml). The organic phases were washed with brine and dried ($\mathrm{MgSO_4}$) and the solvent removed. A column chromatography ($\mathrm{SiO_2}$, pentane/ether 4:1) gave **76** (25 mg, 33%), that decomposes at reduced pressure. TLC ($\mathrm{SiO_2}$, pentane/ether 4:1): R_f = 0.66. ^{1}H-NMR (500 MHz, $\mathrm{C_6D_6}$) 3.14 (dt, J = 4.98, 1.92, 1H, H-C(4)), 3.03 (ddt, J = 10.9, 4.85, 3.75, 1H, H-C(5)), 2.42 (md, J = 2.01, 1H, H-C(1)), 2.14-2.04 (ddd, J = 14.59, 4.85, 2.47, 1H, H-C(7)), 1.87 (mdd, J = 14.59, 1.8, 1H, H-C(7)), 1.79 (md, J = 5.12, 1H, H-C(3)), 1.43 (s, 3H, H-C(2^1)), 1.12-0.9 (m, 1H, H-C(6)), 0.76 (s, 3H, Me), 0.34 (s, 3H, Me) ^{13}C-NMR(125.7 MHz, $\mathrm{C_6D_6}$): 216.4 (CO), 70.5 (C(2)), 70.3 (CH, C(1)), 68.9 (CH, C(5)), 49.8 (CH, C(3)), 49.5 (C(8)), 43.4 (CH, C(6)), 41 ($\mathrm{CH_2}$, C(7)), 32.1 (CH, C(4)), 29 ($\mathrm{CH_3}$, H-C(2^1)), 24.6 ($\mathrm{CH_3}$, Me), 16.03 ($\mathrm{CH_3}$, Me). EI: 288 ($\mathrm{M^+}$, 9), 260 (57), 232 (20), 204 (55), 188 (70), 162 (66), 105 (11), 84 (18), 56 (100).

12.4 Complexation of nopyl methyl ether



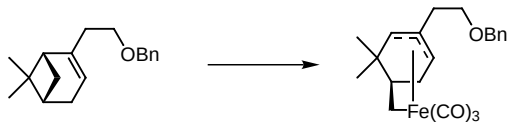
94 **95** **96**

[η^4-methylen-(2,2-dimethyl-4-(ethyl methyl ether)-4-cyclohexene-1,3-diyl)]tricarbonyl iron 95: in a dry three-necked flask[5] equiped with a condenser with a bubbler and with a Dean & Stark trap filled with molecular sieves and dry heptane, a solution of nopyl methyl ether (section 11.3 on page 130, 2 g., 11 mmol) and iron pentacarbonyl (3 ml, mmol) in dry dioxane (15 ml) and dry heptane (5 ml) was heated at reflux[6] for 7 days in the dark under argon atmosphere. After cooling down at room temperature, the mixture was filtrated over ALOX[7] and the solvent with the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. After a flash chromatography (SiO_2, pentane/ether 15:1), four complexes were isolated. Removal of the starting material **94** from the fraction containing the product **95** by a distillation under reduced pressure (70 °C, 1 mmHg) afforded 270 mg of an unseparable mixture of two complexes and nopadiene[8] **96**, and 710 mg (21%) of pure **95**. Yellow oil. B.p. 80-82°C/1 mmHg. TLC (SiO_2, pentane/ether 15:1): R_f=0.37. ^{1}H-NMR (360 MHz, $C_6D_6Cl_3$): 4.48-4.4 (m, 1H), 4.1-4 (m, 1H), 3.62-3.49 (m, 2H, H-C(4'')), 3.38 (s, 3H, OCH_3), 2.16 (t, J=6.4Hz, 1H), 2.1-1.98 (m, 2H), 1.66-1.59 (m, 1H), 1.54-1.5 (m, 1H), 1.35-1.24 (m, 1H), 1.14 (dd, J=9.8, 2.45Hz, 1H), 0.98 (s, 3H, Me), 0.94 (s, 3H, Me).

[5] better results are obtained if the flask was already used for this synthesis.
[6] bath at 130°C.
[7] caution: pyrophoric iron may be present in the medium.
[8] the ^{1}H-NMR and ^{13}C-NMR were in accordance with the published one [190]

12.5 Synthesis of the complex 100

12.5.1 Complexation of nopyl benzyl ether



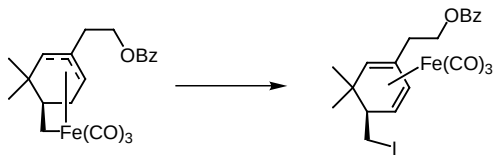
97 **98**

[η^4-methylen-(2,2-dimethyl-4-(ethyl benzyl ether)-4-cyclohexene-1,3-diyl)]tricarbonyl iron 98: in a dry three-necked flask[9] equiped with a condenser with a bubbler and with a Dean & Stark trap filled with molecular sieves and dry heptane, a solution of nopyl benzyl ether **97** (section 11.4 on page 131, 14.5 g, 56.7 mmol) and iron pentacarbonyl (20 ml, 160 mmol) in dry dioxane (150 ml) and dry heptane (35 ml) was heated at reflux[10] for 15 days in the dark under argon atmosphere. After cooling down at room temperature, the mixture was filtrated over ALOX[11] and the solvent with the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. After a flash chromatography (SiO_2, toluene), 11.13 g (50%) of product **98** were isolated. Yellow oil. TLC (SiO_2, toluene): $R_f = 0.7$. ^{1}H-NMR (500 MHz, C_6D_6): 7.35 (s, 4H, aromatic), 7.32-7.28 (m, 1H, H-C(4)), 4.54 (dd, J = 25.3, 11.8, 2H, H-C(2^2)), 4.48 (m, 1H, H-C(3')), 4.06 (t, J = 1.92, 2H, H-C(5')), 3.72-3.6 (m, 2H, H-C(1^1)), 2.27-2.2 (m, 1H, H-C(2^1)), 2.09 (t, J = 5.58, 1H, H-C(2^1)), 2.07-2.01 (m, 1H, H-C(6')), 1.62 (dt, J = 9.79, 2.83, 1H, H-C(1)), 1.51 (s, 1H, H-C(1')), 1.3 (dt, J = 14.27, 3.93, 1H, H-C(6')), 1.12 (dd, J = 9.79, 2.37, 1H, H-C(1)), 0.96 (s, 3H, Me), 0.9 (s, 3H, Me). ^{13}C-NMR (125.7 MHz, C_6D_6): 216 (CO), 215.4 (CO), 207.2 (CO), 138.1 (C(1)), 128.3 (C aromatic), 127.6 (C aromatic), 104 (C(4')) 87.3 (CH, C(5')), 77.8 (CH, C(3')), 73 (CH_2, C(2^2)), 72.3 (CH_2, C(1^1)), 49.1 (CH, C(1')), 42.6 (CH_2, C(4^1)), 40 (C(2')), 33.9 (CH_2, C(1)), 33.8 (CH_2, C(6')), 28.1 (CH_3), 26.8 (CH_3). EI-MS: 396 (M^+, 6), 368 (12), 340 (28), 312 (100), 282 (19), 221 (14), 191 (11), 91 (53), 56 (11). Anal. calc. for $C_{21}H_{24}O_4Fe$ (396.27): C 63.65, H 6.1; found C 63.9, H 6.28. $[\alpha]_D^{24}$ = -66.06 (c=1, chloroform). IR (NaCl): 3032 (w), 2953 (s), 2922 (s), 2850 (s), 2040 (s, ν[CO]), 1971 (s, ν[CO]), 1454 (m), 1361 (m), 1168

[9] better results are obtained if the flask was already used for this synthesis.
[10] bath at 130°C.
[11] caution: pyrophoric iron may be present in the medium.

(m), 1101 (m), 735 (m), 698 (m), 625 (s), 590 (s).

12.5.2 Iodation of the complex 98

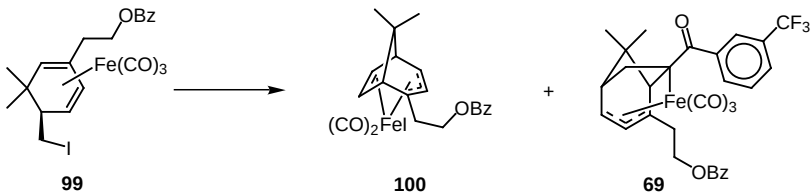


98 **99**

[η^4-methylen-5-iodomethyl(2-(ethyl benzyl ether)-6,6-dimethyl-cyclohexa-1,3-diene)] tricarbonyl iron 99: In a 50 ml flask the complex **98** (1.5 g, 3.79 mmol) in a phosphate buffer solution (15 ml, pH=7) was vigorously stirred (mechanical stirring). Iodine (4 x 470 mg every 3 minutes, 7.44 mmol) was added. After 45 min a saturated aqueous solution of sodium thiosulfate (30 ml) was added. The solution was extracted with ether (3 x 20 ml), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, pentane/ether 20:1) to give the complex **99**[12] (1.39 g, 70%). Yellow oil. TLC (SiO_2, pentane/ether 18:1): $R_f = 0.41$. TLC (SiO_2, pentane/ether 9:1): $R_f = 0.65$. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36 (m, 2H, aromatic), 7.35 (m, 2H, aromatic), 7.33-7.27 (m, 1H, H-C$_{aromatic}$(4), 5.39 (d, $J = 6.41$, 1H, H-C(3)), 4.57 (d, $J = 11.83$, 1H, H-C(1^1)), 4.53 (d, $J = 11.83$, 1H, H-C(1^1)), 3.72 (dt, $J = 9.24, 5.68$, 1H, H-C(2^2)), 3.64 (ddd, $J = 9.24, 5.24, 8.1$, 1H, H-C(2^2)), 3.33 (dd, $J = 9.65, 5.07$, 1H, H-C(5^1)), 3.12-3.05 (m, 2H, H-C(4), H-C(5^1)), 2.76 (d, $J = 1.73$, 1H, H-C(1), 2.57 (ddd, $J = 14.18, 7.96, 5.76$, 1H, H-C(2^1)), 2.38 (dt, $J = 14.18, 5.49$, 1H, H-C(2^1)), 1.9 (dd, $J = 4.98, 10.2$, 1H, H-C(5)), 1.07 (s, 3H, Me), 0.96 (s, 3H, Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 211 (CO), 137.9 (C(1), 128.4 (CH, aromatic), 127.7 (CH, aromatic), 85.8 (CH, C(3)), 80.1 (CH, C(1)), 73.1 (CH_2, C(1^1)), 70.2 (CH_2, C(2^2)), 62.4 (CH, C(4)), 50.1 (CH, C(5)), 36.8 (CH_2, C(2^1)), 35.9 (CH_3), 24.6 (CH_3), 9.2 (CH_2, C(5^1)). ESI-MS: 545 ([M+Na]$^+$). Anal. calc. for $C_21H_24O_4Fe$ (522.16): C 48.31, H 4.59; found C 48.56, H 4.59. $[\alpha]_D^{24} =$ -102.03 (c=1, chloroform). IR (NaCl): 3031 (w), 2956 (m), 2859 (m), 2041 (s, ν[CO]), 1962 (s, ν[CO]), 1454 (m), 1361 (m), 1197 (m), 1101 (m), 736(m), 697 (m).

[12] this complex decomposes under reduced pressure.

12.5.3 Synthesis of the complex 100



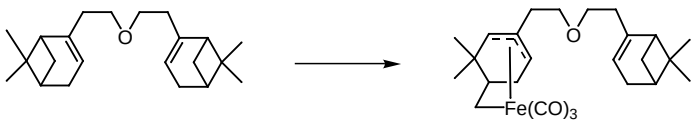
Iodo[η^5-(2-(ethyl benzyl ether)-8,8-dimethylbicyclo[3.2.1]oct-3,6-diene)-2-yl]dicarbonyl iron 100: In a dry 25 ml two-necked flask, the complex **99** (381 mg, 0.729 mmol), tetrabutylammonium iodid (269.5 mg, 0.729 mmol) and ether were cooled to -90°C under an argon atmosphere. $^t\mathrm{BuLi}$ (1.26 ml, 1.537 mmol) was added thoroughly over a 12 min period. After 10 min. freshly distilled isoprene (0.7 ml, 7 mmol) and then m-trifluoromethylbenzoyl chloride (0.129 ml, 0.87 mmol) were added. The reaction mixture was allowed to warm up to -45°C and was stirred at this temperature for 45 min. After warming up to 10°C, the mixture was washed with water (10 ml) under an argon atmosphere and the organic phase was transfered under inert atmosphere in a schlenk. After evaporation of the solvent, a flash chromatography ($\mathrm{SiO_2}$, pentane/ether 4:1) afforded the products **100** (40 mg, 15%) and **69** (81 mg, 19%).

Complex 100 Burgundy oil. TLC ($\mathrm{SiO_2}$, pentane/ether 4:1): R_f = 0.32. ^{1}H-NMR (500 MHz, $\mathrm{CDCl_3}$): 7.36-7.27 (m, 5H, aromatic), 4.79 (d, J = 6.41, 1H, H-C(7)), 4.5 (s, 2H, H-C(1^1)), 3.85-3.79 (m, 1H, H-C(6)), 3.76 (dt, J = 9.42, 5.67, 2H, H-C(2^2)), 2.75 (m, 3H, H-C(3), H-C(2^1)), 2.49 (d, J = 3.29, 1H, H-C(4)), 2.24 (tm, J = 4.81, 1H, H-C(5)), 1.05 (d, J = 4.67, 1H, H-C(1)), 0.7 (s, 6H, Me). ^{13}C-NMR (125.7 MHz, $\mathrm{CDCl_3}$): 214.2 (CO), 138 (C(1)), 128.4 (CH, aromatic), 127.7 (CH, aromatic), 126.6 (CH, C(7)), 73 (CH_2, C(1^1)), 72.9 (C, C(2)), 69.62 (CH_2, C(2^2)), 60.85 (CH, C(6)), 48.27 (CH, C()), 47.5 (CH, C(4)), 45.4 (C, C(8)), 42.5 (CH, C(5)), 36.2 (CH, C(3)), 29.7 (CH_2, C(2^1)), 22.4 (CH_3, Me), 19.6 (CH, C(1)), 16.4 (CH_3, Me). IR (NaCl): 3031 (w), 2956 (m), 2859 (m), 2041 (s, ν[CO]), 1962 (s, ν[CO]), 1454 (m), 1361 (m), 1197 (m), 1101 (m), 736(m), 697 (m).

Complex 69 Yellow oil. TLC ($\mathrm{SiO_2}$, pentane/ether 4:1): R_f = 0.7. ^{1}H-NMR (360 MHz, $\mathrm{CDCl_3}$): 8.28 (s, 1H, H-C(2") 8.2 (d, J = 7.9, 1H, H-C(4")), 7.79 (d, J = 7.94, 1H, H-C(6")), 7.56 (t, J = 7.94, 1H, H-C(5")), 7.38-7.3(m, 5H,

aromatic), 5.12 (d, J = 6.41, 1H, H-C(4)), 4.99 (dd, J = 6.41, 6.41, H-C(5)), 4.5 (s, 2H, H-C($1''^1$)), 3.72-3.6 (m, 2H, H-C(3^2)), 2.86 (dd, J = 11.29, 1.83, 1H), 2.63 (dt, J = 15.36, 6.41, 1H, H-C(2^1)), 2.5 (d, J =2.44, 1H), 2.37(dt, J = 15.36, 5.8, H-C(2^1)), 2.2 (dm, J = 11.29, 1H), 1.84 (dd, J = 6.1, 2.44, 1H), 1.08 (s, 3H, Me), 0.79 (s, 3H, Me).

12.6 Complexation of dinopyl ether

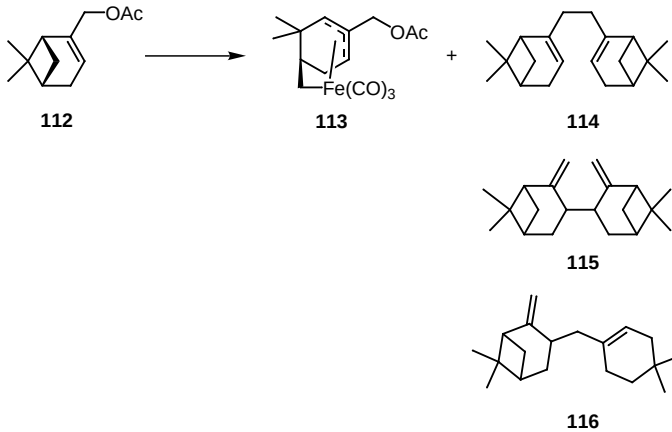


103 **104**

[η^4-methylen-(2,2-dimethyl-4-(ethyl nopyl ether)-4-cyclohexene-1,3-diyl)] tricarbonyl iron 104: In a dry three-necked flask[13] equiped with a condenser with a bubbler and with a Dean & Stark trap filled with molecular sieves and dry heptane, a solution of dinopyl ether (section 11.5.2 on page 133, 620 mg, 1.97 mmol) and iron pentacarbonyl (1 ml, 7.40 mmol) in 1,2-dimethoxyethane (15 ml) and dry heptane (5 ml) was heated at reflux[14] for 2 days in the dark under an argon atmosphere. After cooling down to room temperature, the mixture was filtrated over ALOX[15] and the solvent with the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. After a flash chromatography (SiO_2, pentane/ether 100:1), 256 mg of a mixture containing **104** and the starting material **103** were isolated. After removing **103** under reduced pressure (10^{-6} mmHg, 80°C), the monocomplex **104** was isolated. Yellow oil. TLC (SiO_2, pentane/ether 100:1): R_f = 0.3. ^{1}H-NMR (360 MHz, $CDCl_3$): 5.27 (m, 1H, H-C(3)), 4.45 (m, 1H, H-C(5')), 4.05 (s, 1H, H-C(3')), 3.66-3.5 (m, 2H, H-C(4'^{2})), 3.5-3.38 (m, 2H, H-C(2^2)), 2.4-2 (m, 11H, H-C(6', 4'^{1}, 4, 5, 7, 2)), 1.61 (dm, J = 12.2, 1H, H-C(1)), 1.52 (m, 1H, H-C(1')), 1.28 (s, 3H, Me), 1.15 (d, J = 12.2, 1H, H-C(1)), 1.17-1.1 (m, 1H, H-C(1*)), 0.95 (s, 3H, Me), 0.94 (s, 3H, Me), 0.84 (s, 3H, Me).

[13] better results are obtained if the flask was already used for this synthesis.
[14] bath at 100°C.
[15] cautious: presence of pyrophoric iron makes a fire risk.

12.7 Complexation of myrtenyl acetate



112 **113** **114**

115

116

[η^4-Methylen-(2,2-dimethyl)4-(methyl acetate)-4-cyclohexene-1,3-diyl)] tricarbonyl iron 113: in a dry two-necked flask[16] fitted with a condenser with a bubbler a solution of myrtenyl acetate (section 11.9 on page 137, 11.68 g, 60.2 mmol) and iron pentacarbonyl (12 ml, 90.3 mmol) in dry dioxane (40 ml) was heated at reflux[17] for 6 days in the dark under argon atmosphere. After cooling down at room temperature, the mixture was filtrated over ALOX[18] and the solvent and the rest of iron pentacarbonyl were distilled trap to trap under reduced pressure. After a flash chromatography ($\mathrm{SiO_2}$, pentane), the desired complex **113** (1.95 g, 10%), the starting material **112** (1.2 g, 10%) and 5 other dimeric products of mass 270 (1.34 g, 16%) were obtained.

Complex 113 Yellow oil. TLC ($\mathrm{SiO_2}$, pentane): R_f=0.43. ^{1}H-NMR (360 MHz,$\mathrm{C_6D_6Cl_3}$): 4.57-4.56 (m, 1H, H-C(5')), 4.38 (d, J = 11.43, 1H, H-C(4'^{1})), 4.28 (d, J = 11.43, 1H, H-C(4'^{1})), 4.18 (tm, J = 1.92, 1H, H-C(3')), 2.1 (s, 3H, Me acetate), 2.07 (dm, J = 14.63, 1H, H-C(6')), 1.74 (dt, J = 9.79, 2.92, 1H, H-C(1)), 1.56 (m, 1H, H-C(1')), 1.33 (dt, J = 14.63, 3.94, 1H, H-C(6')), 1.24 (dd, J = 9.79, 2.38, 1H, H-C(1)), 0.97 (s, 3H, Me), 0.94 (s, 3H, Me). ^{13}C-NMR (125.7 MHz,$\mathrm{CDCl_3}$): 216.1 (CO), 214.6 (CO), 206.6 (CO), 170.3 (C, acetate), 99.5 (C(4')), 86.9 (CH, C(3')), 76.7 (CH, C(5')),

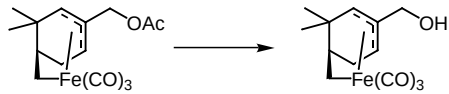
[16] better results would be probably obtained if the flask was already used for this synthesis.
[17] bath at 130°C.
[18] caution: pyrophoric iron may be present in the medium.

69.6 (CH_2, C(4'^{1})), 49.6 (CH, C(1')), 39.9 (C(2')), 35.1 (CH_2, C(1)), 33.5 (CH_2, C(6')), 27.8 (CH_3, Me), 26.1 (CH_3, Me), 20.9 (CH_3, Me acetate). EI-MS: 334 (4, M^+), 305 (17), 278 (62), 275 (98), 250 (100), 247 (99), 235 (23), 219 (45), 190 (38), 188 (31), 162 (16), 148 (30), 131 (22), 119 (68), 91 (73), 56 (44). IR (NaCl): 2936 (ls), 2342 (w), 2358 (w), 2046 (s, ν[CO]), 1977 (s, ν[CO]), 1745 (s), 1459 (m), 1366 (S), 1228 (s), 1169 (m), 1087 (m), 1024 (s), 739 (s).

Olefin 114 Colourless oil. TLC (SiO_2, pentane): R_f = 0.59. ^{13}C-NMR (125.7 MHz, $CDCl_3$): 149.2 (C), 116.5 (CH), 46.6 (CH), 41.8 (CH), 38.8 (C), 35.7 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 27.3 (CH_3, Me), 22 (CH_3, Me).).

Olefin 116 Colourless oil. TLC (SiO_2, pentane): $R_f = 0.59$. ^{13}C-NMR (125.7 MHz, $CDCl_3$): 158.3 (C), 149 (C), 118.8 (CH), 108.1 (CH_2), 53.4 (CH), 51.8 (CH_2), 46.7 (CH), 45.9 (CH), 42.1 (CH), 38.8 (C), 35.8 (C), 32.5 (CH_2), 32.4 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 27.3 (CH_3), 26.7 (CH_3), 22.5 (CH_3, Me), 21.9 (CH_3, Me).

12.8 Deprotection of 113

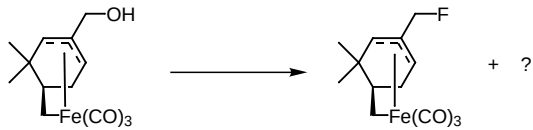


113 **111**

[η^4-Methylen-(2,2-dimethyl)4-(hydroxymethyl)-4-cyclohexene-1,3-diyl)] tricarbonyl iron 111: [162, 163] to a solution of **113** (section 12.7 on page 161, 0.2 g, 0.6 mmol) in dry dichloromethane (10 ml) in a dry two-necked flask, $BF_3{\cdot}Et_2O$ (0.24 ml, 0.7 mmol) was added dropwise under an argon atmosphere at -78°C. After 1h, phenyllithium (0.6 ml, 0.9 mmol) was added dropwise at -78°C and the mixture was stirred for 2 h, before it was quenched with a solution of $NaHCO_3$. After the mixture was warmed up to room temperature, the solution was extracted with dichloromethane (4 x 20 ml), washed with brine and dried ($MgSO_4$). After a column chromatographic purification (SiO_2, pentane/ether 4:1), 1,1-diphenyl-1-ethanol (105 mg, 60%), acetophenone (33 mg, 30%) and the complex of myrtenol **111** (161 mg, 92%) were isolated.

Complex 111 Yellow oil. TLC (SiO_2, pentane/ether 4:1): R_f=0.07. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.57-4.56 (m, 1H, H-C(5')), 4.14 (s, 1H, H-C(3')), 3.89 (md, J = 3.86, 2H, H-C(4'^{1})), 2.08 (dm, J = 14.3, 1H, H-C(6')), 1.74 (dt, J = 9.77, 2.9, 1H, H-C(1)), 1.58 (m, 1H, H-C(1')), 1.35 (dt, J = 14.3, 4.09, 1H, H-C(6')), 1.23-1.19 (m, 1H, H-C(1)), 0.98 (s, 6H, Me). EI-MS: 291 (2, M^+), 263 (32), 236 (66), 208 (100), 188 (52), 162 (57), 148 (93), 56 (95). IR (NaCl): 3604 (w), 3400 (lm), 2955 (s), 2853 (s), 2044 (s, ν[CO]), 1973 (s, ν[CO]), 1456 (m), 1383 (m), 1363 (m), 1265 (s), 1169 (s), 1018 (m), 1002 (m), 739 (s).

12.9 4'-fluoromethyl-seco-pinene complex



111 **122**

[η^4-(4'-Fluoromethyl-6',6'-dimethyl-4'-cyclohexen-1,3-diyl)methyl]tricarbonyl iron 122: in a dry two-necked flask, a solution of DAST (44 μl, 0.34 mmol) and dichloromethane were cooled to -78°C under argon atmosphere. A solution of **111** (100 mg, 0.34 mmol) (section 12.8 on the preceding page) in dichloromethane (0.3 ml) was added dropwise via a syringe. The solution was allowed to warm up to room temperature. After 30 minutes at a temperature of -50°C, a TLC showed the accomplishment of the reaction. After evaporation of the solvent, a chromatographic purification (SiO_2, pentane/ether 4:1) afforded a mixture of two yellow complexes (66 mg). The complex **122** accounts for 35%. CCM (SiO_2, pentane/ether 4:1): $R_f = 0.61$.

Complex 122 ^{1}H-NMR (500 MHz, $CDCl_3$): 4.07 (d, $J = 1.39$, 1H, H-C(4")), 3.97 (d, $J = 1.39$, 1H, H-C(4")), 4.06 (m, 1H, H-C(5')), 3.67 (t, $J = 1.92$, 1H, H-C(3')), 1.69 (m, 1H, H-C(6')), 1.67 (m, 1H, H-C(1)), 1.24 (m, 1H, H-C(1')), 1.16 (dd, $J = 9.7$, 2.3, 1H, H-C(1)), 0.94 (m, 1H, H-C(6')), 0.78 (s, 3H, Me), 0.73 (s, 3H, Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 216.5 (CO), 215(CO), 206.7 (CO) 99.34 (d, $J = 105$, C(4')), 86.8 (CH, C(3'), 87.7+86.4(d, $J = 650$, CH_2, C(4")), 77.3 (CH, C(5')), 49.9 (CH, C(1')), 39.7 (C(2')), 35.5 (CH_2, C(1)), 33.3 (CH_2, C(6')), 27.8 (CH_3, Me), 26.5 (CH_3, Me) .

Secondary complex ^{1}H-NMR (200 MHz,$CDCl_3$): 3.37 (dd, $J = 43.8$, 10.15, 1H), 1.82 (dm, $J = 14.5$, 1H), 1.74 (dt, $J = 9.78$, 2.93, 1H), 1.34 (m, 1H), 1.22 (d, $J = 9.78$, 2.28, 1H), 1.07 (m, 2H), 0.88 (s, 3H, Me), 0.86 (s, 3H, Me), 0.85 (d, $J = 2.93$, 1H). ^{13}C-NMR (50.4 MHz, $CDCl_3$): 217 (CO), 215.6 (CO), 207.4 (CO), 102 (C), 86.4 (CH), 76.7 (CH), 76.3 (CH_2), 50 (CH), 40 (C), 34.9 (CH_2), 33.5 (CH_2), 28 (CH_3), 26.8 (CH_3).

Part IV

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Part V

Curriculum Vitae

CURRICULUM VITAE

CHRISTOPHE ALLEMANN

Birthdate	1st February 1974
Nationality	Swiss
Origin	Ruettenen (SO)
Langages	French: mother tongue
	German: good knowledge
	English: very good knowledge

EDUCATION

2002	University of Fribourg (Switzerland), Section Chemistry, Ph. D. Thesis
1999	Ecole Polytechnique de France (Palaiseau, Paris), DEA
1997	University of Fribourg (Switzerland), Section Chemistry, diploma
1993	College du Sud, Bulle (Switzerland), Federal Maturity (University entrance)
1986-1989	Secondary School (Cycle d'Orientation de la Gruyere, Bulle, Switzerland)
1980-1986	Primary School at Broc (Switzerland)

EXPERIENCE

1998-2002	**Synthesis and Applications of an electronically chiral mimin of CpFe:** Ph. D. Thesis under the supervision of the Prof. Dr. T. Jenny, University of Fribourg (Switzerland)
1998-2000	**Group of Communication of the Natural Science Faculty University of Fribourg:** President
1997	**Brief Study on the Possibility to Perform Radical Reactions with Iron Tricarbonyl Complexes:** diploma work under the supervision of the Prof. Dr. T. Jenny, University of Fribourg (Switzerland)
1997	**Visualization and Applications of the Electronic Densities:** diploma work under the supervision of the Prof. Dr. C. A. Daul University of Fribourg (Switzerland)
1995 (4 months)	**Practical training in industry at Herbert's Puverlack, Landshut, Germany**
1995 (6 months)	**Professor of Chemistry at the College du Sud**

AWARD

2001	Best Poster Award sponsored by New Journal of Chemistry, a CNRS-Royal Society of Chemistry Journal, OMCOS 11, Taipei (Taiwan)