Synthesis of Highly Enantioenriched Compounds *via* Iron Mediated Allylic Substitutions

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This account is dedicated to Professor Elias J. Corey, who taught us chemistry as a science and art

Abstract: In this account we describe our efforts over more than a decade to develop a synthetically useful and practical methodology for the synthesis of highly enantioenriched compounds *via* iron promoted allylic substitutions. After first attempts based on a kinetic resolution of planar chiral tetracarbonyl(η^3-allyl)iron(1+) complexes and an auxiliary controlled diastereoselective formation of the iron complexes, the "chirality transfer" approach turned out to be an efficient solution. Starting from enantiopure easily accessible and cheap acceptor substituted allylic substrates, the corresponding (η^3-allyl)tetracarbonyl iron cation complexes are formed and trapped with a variety of carbon and heteroatom nucleophiles including silyl enol ethers, electronrich arenes and heteroarenes, functionalized organozinc compounds and amines. The iron mediated allylic substitutions proceed with virtually no loss of chirality information from central (C-O) over planar (C-Fe) back to central chirality (C-C or C-X) affording products of high enantiomeric purity with overall retention (double inversion). In addition, complete γ-regioselectivity and conservation of the double bond geometry is achieved. First applications in the synthesis of virtually enantiopure natural products are described.

1 Introduction

In recent years cationic metal π-complexes of odd and even numbered unsaturated polyenic ligands have received considerable attention as useful synthetic tools in organic synthesis. They can be regarded as stabilized carbocation equivalents coordinated to a transition metal. One advantage is their enhanced reactivity towards a multitude of soft carbon and hetero atom nucleophiles.[1,2] In addition, they are of increasing significance in enantiomerically pure form for the development of various new synthetic methods and as valuable building blocks for the convergent regio- and stereocontrolled construction of organic target molecules. In general, transition metal π-complexes of unsymmetrically substituted ligands in which the metal fragment distinguishes the two enantiotopic faces of the ligand are planar chiral.[3] Nucleophilic addition reactions are subject to complete stereocontrol by the metal-ligand moiety while regiochemical outcomes are mostly controlled by substitution patterns and/or the influence of substituents.

Among the various carbon-carbon and carbon-heteroatom bond forming reactions promoted or catalysed by transition metals, allylic substitution *via* electrophilic π-allyl complexes have been one of the most intensively investigated.[4-9] Current knowledge about the stereochemical course of the formation and reactivity of cationic tetracarbonyl(π-allyl)iron complexes is limited. Studies devoted to the synthetic potential of alkyl and aryl substituted tetracarbonyl(η^3-allyl)iron(1+) complexes have demonstrated that these species undergo regioselective nucleophilic attack by a multitude of soft carbon and heteroatom nucleophiles preferentially at the less substituted or at the *syn* substituted allyl termini affording addition products of (*Z*)-configuration.[10] Likewise, polar effects on the regioselectivity of nucleophilic addition reactions to tetracarbonyl(η^3-allyl)iron(1+) complexes caused by electron withdrawing functionalities (e.g. CO_2R, $CONR_2$) have been examined recently and independently to our work by *Green et al.*[11] and *Speckamp et al.*[12] to give allyl coupled addition products with complete γ-regioselectivity after oxidative removal of the stabilizing $Fe(CO)_4$-fragment.

Since the early eighties, our group has been engaged in the investigation of the influence of planar chirality of complexes of the forementioned type on the design of synthetic strategies and their use in the preparation of highly enantiomerically enriched organic target molecules.[13-22] In this course, we developed an efficient approach to acceptor-functionalized highly diastereo- and enantiomerically enriched planar chiral tetracarbonyl(η^3-allyl)iron(1+) complexes starting from easily accessible enantiopure precursors based on natural products. A general use of these iron complexes as synthetic equivalents of a^4-synthons for the homologous (1,5)-*Michael* addition[23] is of interest both as a form of umpolung[24] of classical d^4-chemistry and as a synthetic method of considerable potential. Now we have completed a series of preliminary studies towards mechanistic details and the stereochemical outcome of our iron mediated "chirality transfer" methodology. Furthermore, we have investigated the synthetic potential of this new process and have found some useful applications in natural product synthesis. In order to give an overview, we wish to summarize and to discuss our results obtained so far in this area of research.

2 Development of Basic Concepts

The following three basic concepts have been examined to reach our goals:

1) Nucleophilic addition of enantiopure d^2-nucleophiles to racemic planar chiral electrophilic tetracarbonyl(η^3-allyl)iron(1+) complexes ("kinetic resolution")

2) Preparation of diastereomerically enriched tetracarbonyl(η^3-allyl)iron(1+) complexes by means of an auxiliary controlled complexation of (*E*)-configurated enoates and subsequent addition of achiral nucleophiles

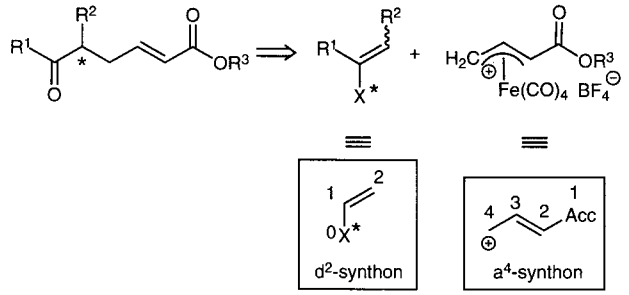
3) Diastereoselective complexation of enantiopure (*E*)-configurated acceptor substituted olefins, subsequent generation of enantiomerically

enriched acceptor substituted tetracarbonyl(η^3-allyl)iron(1+) complexes and addition of achiral nucleophiles ("chirality transfer")

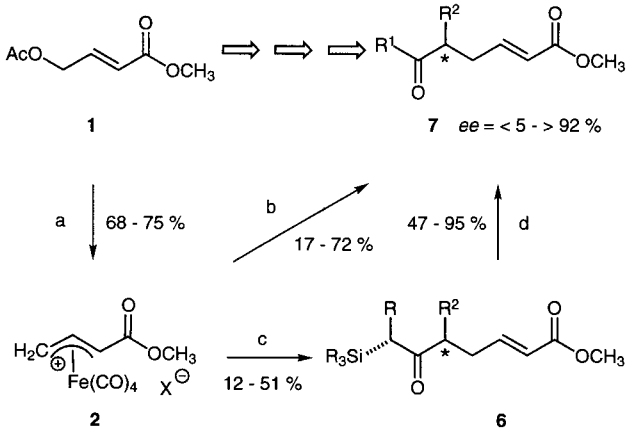
In the following discussion each of the concepts will be presented in greater detail taking account to its impact in understanding the stereochemical pathways of the complete reaction sequences as well as to its synthetic potential.

2.1 Kinetic Resolution / Chiral Nucleophile Approach

Scheme 1 displays the first concept in which the cationic (η^3-allyl)iron complex represents a planar chiral but racemic a^4-synthon and the nucleophile a chiral d^2-synthon offering an access to chiral 1,6-dicarbonyl compounds, which are proved to be versatile intermediates in the synthesis of more complex target molecules.



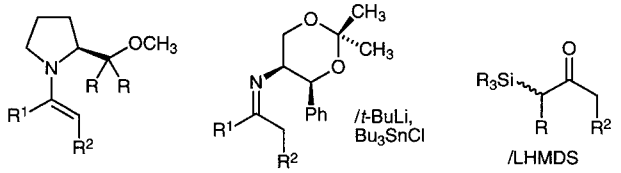
Scheme 1



1 **7** *ee* = < 5 - > 92 %

2 **6**

a) 1. $Fe_2(CO)_9$, CO, Et_2O; 2. HBF_4 or HPF_6, Et_2O; b) 1. **3**, THF, –78 °C, or **4**, *t*-BuLi, THF, –78 °C then Bu_3SnCl; 2. CAN/H_2O; c) 1. **5**, LHDMS, THF, –78 °C; 2. CAN/H_2O; d) HBF_4/THF (1 : 4)

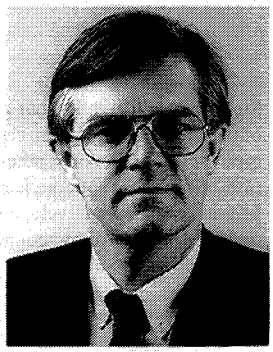


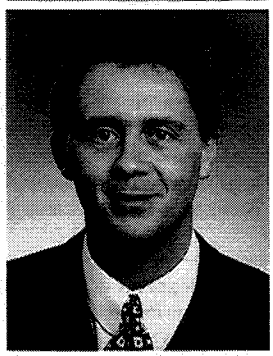
3 **4** **5**

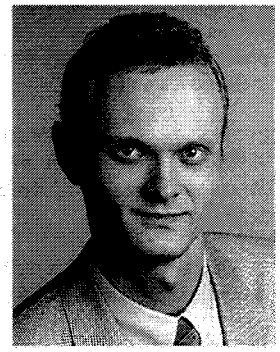
enamines metalated imines metalated α-silyl ketones

Scheme 2

Biographical Sketches







Dieter Enders was born in 1946 in Butzbach, Hessen. He studied Chemistry at the Justus Liebig Universität Gießen and received his Dr. rer. nat. in 1974 under the direction of Prof. D. Seebach. After postdoctoral studies at Harvard University with Prof. E. J. Corey he went back to Gießen and obtained his habilitation in 1979. In 1980 he moved to the Universität Bonn as an associate professor and in 1985 to his present position as Professor of Organic Chemistry and director at the Rheinisch-Westfälische Technische Hochschule Aachen. His current research interests are asymmetric synthesis, new synthetic methods using organometallics and the stereoselective synthesis of biologically active compounds.

Bernd Jandeleit, was born in 1965 in Stolberg, Germany. He received his diploma of chemistry and his Dr. rer. nat. from the Rheinisch-Westfälische Technische Hochschule Aachen under the supervision of Prof. Dr. D. Enders in 1995. In 1994 he was awarded the Springorum Award and 1996 the Borchers Award from the same university. He is currently a postdoctoral research associate with Prof. Dr. K. C. Nicolaou at the Scripps Research Institute, La Jolla, USA as a fellow of the German National Scholarship Foundation / BASF AG (1995-1997). His research interests are focused on metal-organic chemistry and total synthesis.

Stefan von Berg was born in 1969 in Jülich, Germany. He received his diploma of chemistry from the Rheinisch-Westfälische Technische Hochschule Aachen in 1995. Currently he is working on his Ph. D. thesis under the supervision of Prof. Dr. D. Enders.

The realisation of the concept is illustrated in scheme 2. The reaction of the ester **1** with diironnonacarbonyl [$Fe_2(CO)_9$] initially yields neutral methoxycarbonyl substituted tetracarbonyl(η^2-olefin)-iron(0) complexes, which are directly converted without isolation to the corresponding tetracarbonyl(η^3-allyl)iron(1+) salts **2** by treatment with excess anhydrous HBF_4 or anhydrous HPF_6 in diethylether, respectively.[25,26] The salts were obtained as pale yellow moderately moisture- and air stable powders in 68 - 78 % yield.

The complexes thus obtained were then used in nucleophilic addition reactions with chiral nucleophiles, such as enamines **3**, metalated imines **4** and metalated α-silyl ketones **5** (scheme 2).[27-29]

The first test series were carried out by the addition of the enantiopure (*S*)-proline derived enamines **3** to the complexes **2**. The enantiomeric excesses of the reaction products **7** are in line with the growing steric bulk of the substituents of the pyrrolidine ring in **3** increasing in the order R = H (*ee* = 34 %), R = Me (*ee* = 64 %), R = Et (*ee* = 72 %).

In addition, the reaction of various metalated *Schiff* bases was examined. The usual optimisation tests showed that best results were obtained when the imines were transformed to the α-lithio derivatives with *t*-BuLi and the reaction was carried out in THF at low temperature (–78 °C) (yield: 17 - 71 %, *ee* = 40 - 67 %).

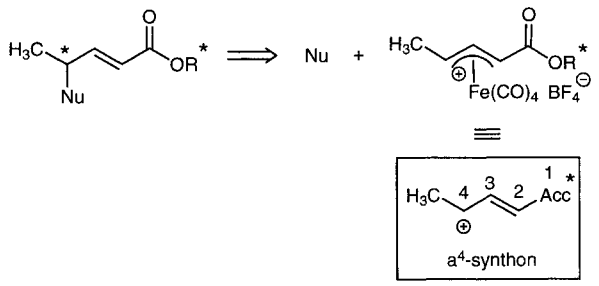
Furthermore, the reaction of lithiated acyclic α-silylated ketones furnished after workup diastereomeric mixtures (*de* = 49 - > 96 %) of α-silyl α'-allylated ketone derivatives, which could be desilylated furnishing the 6-oxoenoates **7** (yield: 35 - 95 %). Here, racemisation occured in some cases (*ee* = < 5 - 92 %) during the desilylation step.

In compilation, the resulting enantiomeric excesses obtained with the reaction of the metalated α-silyl ketones **5** are only slightly higher than those obtained by the alternative routes employing the enamines **3** or metalated imines **4**. The enantiomeric excesses of the 6-oxoenoates **7** thus obtained are generally in line with increase in steric bulk of the nucleophile, as for instance in the case of the enamines **3**. The results support the assumption that the planar chiral tetracarbonyl(η^3-allyl)iron(1+) complexes are effectively kinetically resolved by the predominant reaction of the enantiopure carbon nucleophiles **3**, **4** and **5** with one of the enantiomers of the racemic iron complexes **2**, as has been reported in the literature for similar systems.[30]

In summary, we have shown that the nucleophilic addition of various enantiopure d^2-carbon nucleophiles (chiral enamines **3** or metalated imines **4** and silylketone derivatives **5**) to racemic planar chiral electrophilic tetracarbonyl(η^3-allyl)iron(1+) complex **2** proceeds with complete γ-regioselectivity and with kinetic resolution of the iron complex. Subsequent oxidative demetalation opens an access to enantiomerically enriched (*ee* = < 5 - > 92 %) 1,6-dicarbonyl compounds **7** in moderate overall yields (14 - 53 %, 4 steps or 5 - 21 %, 5 steps) and with retention of the (*E*)-double bond geometry with respect to the starting material **1**.[20]

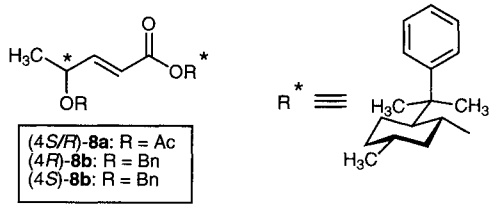
2.2 Auxiliary Controlled Complexation / Achiral Nucleophile Approach

The second concept, namely the synthesis of highly diastereomerically enriched tetracarbonyl(η^3-allyl)iron(1+) complexes *via* auxiliary controlled complexation is illustrated in scheme 3.



Scheme 3

To reach this goal, first we tried to find an approach to alkoxy carbonyl functionalized tetracarbonyl(η^3-allyl)iron(1+) complexes by complexation of the epimeric acetyl protected 8-phenylmenthylester (4*R*/*S*)-**8a**[31] as a model system employing the *Corey-Ensley* alcohol as chiral auxiliary.



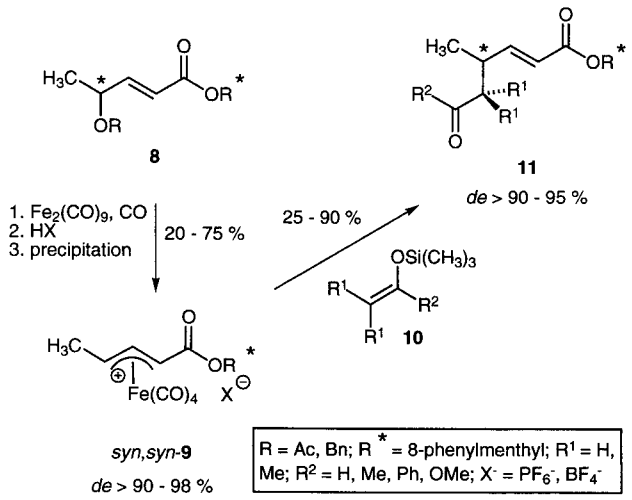
The (*E*)-enoate **8a** was transformed to the tetracarbonyl(η^3-allyl)-iron(1+) complexes by initial complexation with $Fe_2(CO)_9$ to the neutral tetracarbonyl(η^2-alkene)iron(0) species, followed by subsequent treatment with anhydrous HPF_6 or HBF_4 in diethyl ether yielding the cationic complex **9** with a moderate diastereomeric excess (80%, *de* ≈ 40 %). Repeated precipitation of **9** from a solution in nitromethane with cold ether afforded the complex in virtually diastereomerically pure form (20 %, *de* ≥ 98 %) as could easily be determined by ^{1}H-NMR spectroscopy. In addition, ^{1}H-NMR spectroscopic analysis showed that both the alkoxy carbonyl functionality and the methyl group of **9** are placed in a *syn* relationship with respect to the β-hydrogen atom of the allylic subunit. Unfortunately, the exact position of the $Fe(CO)_4$ fragment could not unambiguously be determined. Variations of the chiral auxiliary based on alternative chiral pool precursors [e.g. R* = (–)-menthol, (–)-borneol, (–)-*p*-anisidylmenthol][32] proved to be less diastereomerically discriminating during the complexation step (*de* ≈ 0 %). In addition, no synthetical attractive enrichment could be observed by precipitation.

In this context, the influence of the stereochemical uniformity of the carbon atom bearing the leaving group on the trajectory of the incoming $Fe(CO)_4$ moiety was examined next.

Starting from the diastereomerically pure epimeric benzyl-protected enoates (4*S*)-**8b** and (4*R*)-**8b**, which were readily obtained in acceptable yields from the corresponding protected enantiomeric lactaldehydes after conventional olefination procedures, the iron complexes (2*R*,3*R*,4*S*)-**9** and (2*S*,3*S*,4*R*)-**9** were obtained in highly diastereomerically enriched form (*de* > 90 %) and in acceptable to good yields [(2*R*,3*R*,4*S*)-**9**: (30 %); (2*S*,3*S*,4*R*)-**9** (53 %)] as single *syn*,*syn*-isomers as determined by ^{1}H-NMR spectroscopy. Furthermore, ^{1}H-NMR spectroscopy unambiguously demonstrated that the complex (2*S*,3*S*,4*R*)-**9** is, in contrast to (2*R*,3*R*,4*S*)-**9** not identical with the diastereomer **9** obtained from complexation of the epimeric acetates (4*R*/*S*)-**8a**. From these results it seems reasonable that the trajectory of complexation by the $Fe(CO)_4$-moiety is mainly determined by the configuration of the carbon atom bearing the leaving group, with less influence of the chiral auxiliary.

The electrophilic tetracarbonyl(η^3-allyl)iron(1+) complexes **9** thus obtained were subjected towards nucleophilic addition reactions by various achiral silyl enol ethers or silyl ketene acetals **10**, which in turn are readily accessible from their corresponding carbonyl precursors according to established procedures[33]. 6-Oxoenoates **11** of excellent diastereomeric purity (*de* > 90 % - ≥ 95 %) were obtained in fair to excellent yield (25 - 90 %) after oxidative removal of the $Fe(CO)_4$-moiety. The results showed that the reaction products of the iron complexes obtained from (*R*/*S*)-**8a** and (*R*)-**8b** with the silyl enol ether **10** are identical, whereas the reaction of iron complex obtained from (*S*)-**8b** with **10** generates a diastereomeric 6-oxoenoate differing in its absolute configuration at the carbon atom where the nucleophilic attack of the corresponding nucleophile **10** occurred (scheme 4).[21]

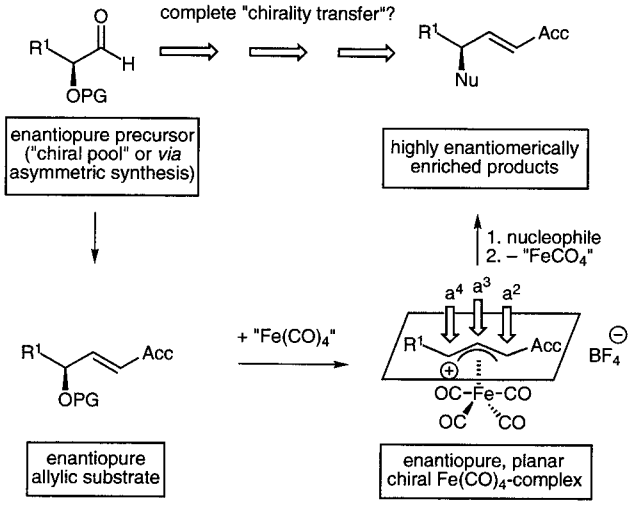
From the results obtained it is obvious that the facial selectivity of complexation of the double bonds in the starting enoates **8** by the $Fe(CO)_4$-moiety as well as the absolute configuration of the resulting nucleophilic addition products is predominantly controlled by the absolute configuration of the stereogenic center bearing the leaving group in **8**. Based on these results we examined the following third concept which is discribed in chapter 2.3.



Scheme 4

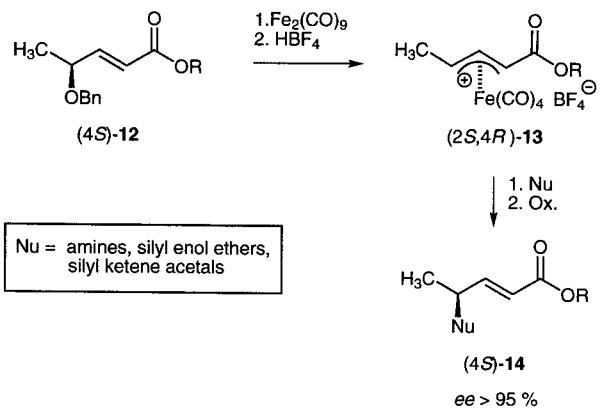
2.3 "Chirality Transfer" Approach

Starting from enantiopure protected α-hydroxy aldehydes, easily available from natural sources such as lactic acid or *via* asymmetric synthesis, are transformed into enantiopure, acceptor substituted allylic substrates, which in turn are converted into planar chiral iron-tetracarbonyl cation complexes. Reaction with carbon or heteroatom nucleophiles and removal of the iron moiety should then lead to the final allylic substitution products. The question was whether the whole procedure from central (C-O) over planar (C-Fe) back to central chirality (C-C or C-X) would be possible without any loss of chirality information.



Scheme 5

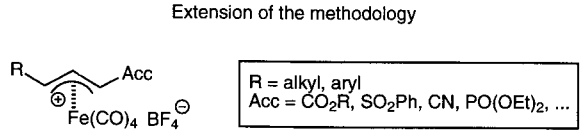
The transformation of the enantiopure easily accessible enoates (4*S*)- and (4*R*)-**12**[34] to the planar chiral tetracarbonyl(η^3-allyl)iron(1+) complexes (1*S*,2*S*,3*R*)-**13** and (1*R*,2*R*,3*S*)-**13**, following the reaction procedure described above yielded the electrophilic complexes as single *syn,syn*-configurated diastereomers (75 %, *de* ≥ 95 %) after repeated precipitation. Unfortunately it can not be excluded that a selective enrichment of the *syn,syn*-configurated isomers during the precipitation procedure has taken place. Furthermore, their enantiomeric purity could only be indirectly determined from the enantiomeric excesses of the addition products **14** obtained from nucleophilic addition reactions of various silyl enol ethers, silyl ketene acetals or amines (*ee* ≥ 95 %) (scheme 6).



Scheme 6

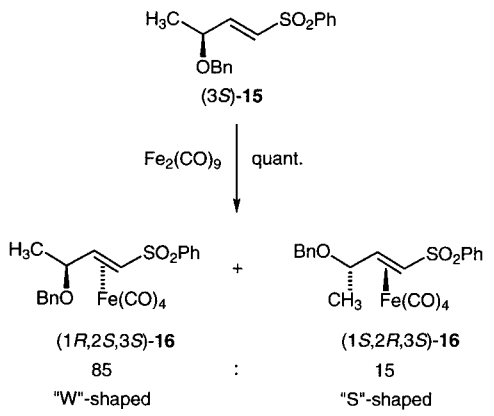
The absolute configuration of the stereogenic centers in the addition products **14** were unambiguously determined to be (*S*) by comparing the sign of optical rotation of derivatives of reaction products with those data given for authentic samples with known absolute configuration in the literature.

In general, variation of the substituents at the allylic termini of the iron complexes should extend the method to make it more flexible and valuable and hence more attractive for synthetic chemists. Considering the possibilities, one could vary the acceptor group and the substituent R simply by starting from different enantiopure precursors from cheap sources (scheme 7).



Scheme 7

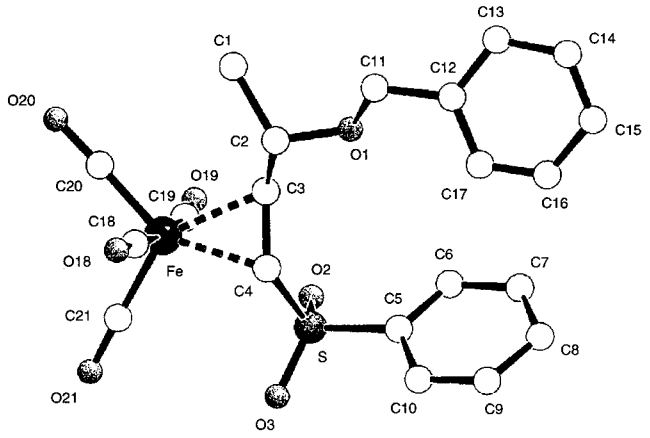
Based on the results obtained and in order to gain more insight into the overall stereochemical pathway of the formation and reactivity of allylic complexes of the type discussed, further investigations were emphasized on a phenylsulfonyl substituted model system. Due to their enhanced stability and easy accessibility reported so far in the literature,[35] we were inspired to try to isolate the initially formed neutral tetracarbonyl(η^2-alkene)iron(0) complexes and planned to examine their stereochemistry with respect to the stereochemistry of the resulting tetracarbonyl(η^3-allyl)iron(1+) complexes. Starting from (*S*)-ethyllactate the required enantiomerically pure sulfone (3*S*)-**15** is easily accessible.[36] Its reaction with nonacarbonyldiiron [$Fe_2(CO)_9$]



Scheme 8

initially yielded a mixture of the diastereomeric tetracarbonyl(η^2-alkene)iron(0) complexes (1*S*,2*R*,3*S*)-**16** and (1*R*,2*S*,3*S*)-**16** in a ratio of about 15 : 85 which was easily determined by ^{1}H-NMR spectroscopy (scheme 8).

The diastereomers (1*S*,2*R*,3*S*)-**16** and (1*R*,2*S*,3*S*)-**16** could be separated by fractional crystallisation and (1*R*,2*S*,3*S*)-**16** could be obtained in virtually diastereo- and enantiopure form (*de* > 99 %, *ee* > 99 %). The crystal structures of both enantiopure diastereomers could be solved.[37-39] Some structural aspects concerning the stereochemistry of the complexed ligand in (1*R*,2*S*,3*S*)-**16**, the major diastereomer, merit closer inspection (figure 1).

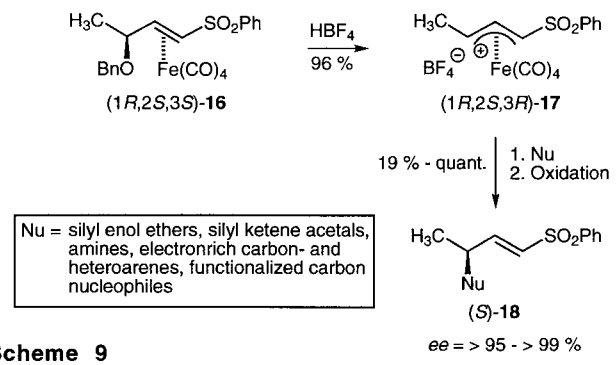


(1*R*,2*S*,3*S*)-**16**

Figure 1

The SO_2Ph unit is twisted away from the $Fe(CO)_4$ moiety and the terminal methyl group is, on the other hand, inclined slightly towards the Fe-atom resulting a "W"-shaped geometry of the ligand, which in turn determins a *syn,syn*-substitution pattern in the resulting cationic complex **17** (*vide supra*). As a consequence of the single configuration at the 3-position, one side of the double bond unit is selectively blocked by the $Fe(CO)_4$ moiety, which lies *trans* to the OBn leaving group. These stereochemical features are very important for the transformation of (1*R*,2*S*,3*S*)-**16** into the stereochemically well defined *syn,syn*-substituted cationic complex (1*R*,2*S*,3*R*)-**17**, which was obtained upon addition of excess anhydrous HBF_4 to an etheral solution of the neutral (η^2-olefin)iron complex (1*R*,2*S*,3*S*)-**16** in 96 % and in virtually isomeric pure form (*de*, *ee* > 98 %) as a pale yellow moderately moisture- and air stable powder.

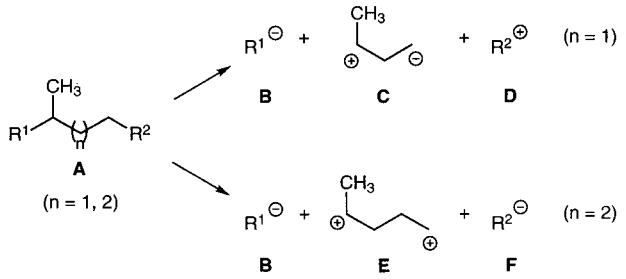
Since all starting materials are accessible in a multigram scale, even the complex (1*R*,2*S*,3*R*)-**17** can be synthesised in scales up to 10 g and can be stored for extended periods in a refrigerator. The complex (1*R*,2*S*,3*R*)-**17** thus obtained, was now used in reactions with a wide range of nucleophiles, including electronrich arenes and heteroarenes[16] and organozinc carbon nucleophiles bearing further functional groups (scheme 9).[22]



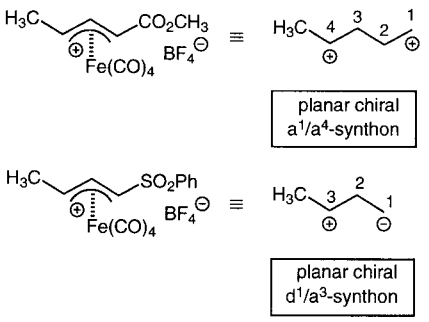
Scheme 9

We now had collected enough data to propose a reaction mechanism for the overall reaction sequence starting from the olefins (*S*)-**12** or (*S*)-**15**, respectively. Due to the shielding of the OBn-leaving group, complexation of the olefins (*S*)-**12** and (*S*)-**15** by an incoming $Fe(CO)_4$-moiety seems to be directed preferentially to the opposite face of the double bond with respect to the sterically demanding OBn-leaving group. Cleavage of the C-O-bond of the OPG leaving group proceeds with formation of a new Fe-C-bond. According to the relative *anti*-arrangement of the $Fe(CO)_4$-moiety and the OPG leaving group, the absolute configuration of the carbon atom C-3 which bore the OPG unit is inverted during this step. Based on the assumption of a uniform reaction mechanism for the complexes with all different types of soft nucleophiles employed and due to the overriding *anti*-directing effect of the $Fe(CO)_4$ fragment, the nucleophilic attack occurs from the opposite side with respect to the $Fe(CO)_4$ moiety as it has been described for similar nucleophilic addition reactions to several other transition metal complexed carbocations.[40] During the addition step a new carbon-carbon or carbon-hetero atom bond is formed with inversion of configuration at C-3 by cleavage of the C-Fe bond. The initially resulting neutral C-3 substituted tetracarbonyl(η^2-alkene)-iron(0) complexes have to possess the same relative and therefore absolute stereochemistry with respect to the $Fe(CO)_4$-moiety and the new substituents as described for the complex (1*R*,2*S*,3*S*)-**16**. Oxidative cleavage of the tetracarbonyliron fragment completes the reaction cycle without affecting the newly generated stereogenic centre. Thus, the reaction sequence proceeds with virtually complete "chirality transfer" from C-O over C-Fe to C-C or C-X and with overall retention (double inversion) of the stereochemistry of the stereogenic centre with respect to the starting materials (*S*)-**12** and (*S*)-**15**. In addition, the reaction proceeds with complete γ-regioselectivity and with conservation of the (*E*)-double bond geometry leading to highly functionalized molecules of well defined stereochemistry.

Due to their origin from enantiopure building blocks bearing methyl substituents (e.g. isoprenoids, alanine, lactic acid derivatives) many naturally occuring compounds possess methyl branched carbon atom skeletons containing structural fragments of the general type **A** which in turn can be retrosynthetically disconnected to the synthons **B**, **C** and **D** or **B**, **E** and **F** respectively (scheme 10).



Scheme 10



Scheme 11

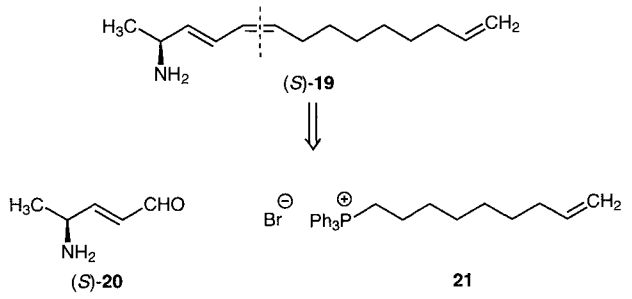
The synthetic equivalence of the methyl ester substituted iron complex with a chiral a^1/a^4-synthon as well as the synthetic equivalence of the phenylsulfonyl substituted iron complex with a d^1/a^3-synthon can be drawn back from their potential bifunctionality opening an approach to a flexible sequential functionalisation which in turn is of great synthetic value (scheme 11).

The following chapters demonstrate some of our efforts made so far in natural product synthesis taking advantage of our methodology.

3 Application in the Total Synthesis of Simple Natural Products

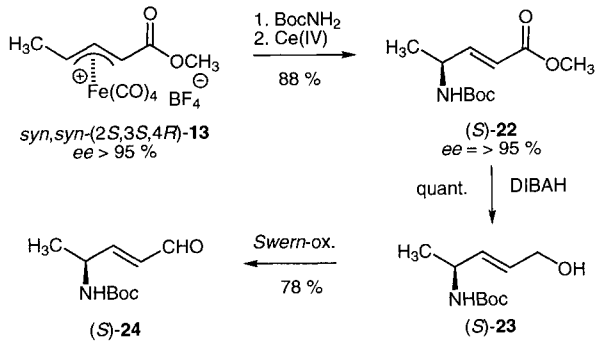
3.1 Synthesis of the C_{14}-Amine of the New Zealand Ascidian *Pseudodistoma Novaezelandiae*

The C_{14}-amine (2*S*,3*E*,5*Z*)-2-Amino-3,5,13-tetradecatrien [(*S*)-**19**] was first isolated and characterised in 1991 in connection with one of the large numbers of research programs directed towards the discovery of marine-derived drugs.[41] The compound was obtained as the major constituent of an extract of the New Zealand ascidian *Pseudodistoma novaezelandiae* and showed in biological assays cytotoxic activity against diverse cell lines (P 388 murine leukaemia and host mammalian cells). Furthermore, it was also active against the bacteria *Escherichia coli* and *Bacillus subtilis* and showed antifugal growth inhibiting activity against *Candida albicans*, *Cladosporium resinae* and *Trichophyton mentagrophytes*. As illustrated in scheme 12 the retrosynthetic analysis of the title compound (*S*)-**19** leads to two subunits, a γ-amino enal (*S*)-**20** and *Wittig* reagent **21**.



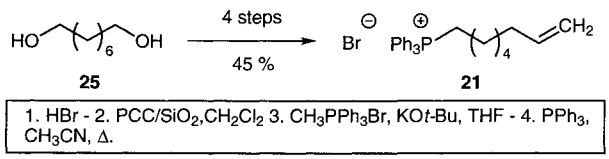
Scheme 12

Starting from the enantiopure complex *syn,syn*-(1*S*,2*S*,3*R*)-**13** the γ-amino enal (*S*)-**24** was prepared in three steps in an overall yield of 69 % (scheme 13). Key step in the reaction sequence is the nucleophilic addition of *t*-butyl carbamate to the cationic iron complex followed by oxidative cleavage of the tetracarbonyliron fragment yielding 88 % of the pure (*E*)-enoate (*S*)-**22** (*ee* ≥ 95 %). The reaction proceeded with complete γ-regioselectivity, conservation of the (*E*) double bond geometry and stereoselectively *trans* with respect to the tetracarbonyliron moiety. DIBAH-reduction and subsequent *Swern*-oxidation of the resulting allylic alcohol (*S*)-**23** afforded finally the protected γ-amino enal (*S*)-**24**.



Scheme 13

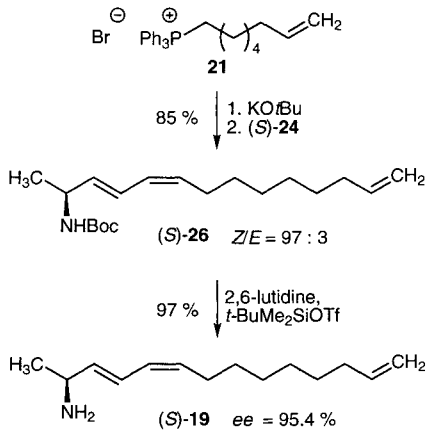
As illustrated in scheme 14, the synthesis of the *Wittig* salt **21** was readily accomplished in 4 steps and in an overall yield of 45 % starting from the commercially available octan-1,8-diol **25** according to standard literature procedures.



1. HBr - 2. PCC/SiO_2,CH_2Cl_2 3. CH_3PPh_3Br, KO*t*-Bu, THF - 4. PPh_3, CH_3CN, Δ.

Scheme 14

For the final construction of the carbon backbone of the target molecule the *Wittig* reagent **21** was transformed into the corresponding ylide by deprotonation with potassium *t*-butoxide. Its subsequent reaction with the γ-amino enal (*S*)-**24** furnished the protected amino triene (*S*)-**26** in 85 % yield with high (*Z*)-selectivity with respect to the geometry of the new generated carbon double bond [(*Z*)/(*E*) = 97:3] (scheme 15). Finally, after virtually quantitative cleavage of the carbamat protecting group from (*S*)-**26** the free amine (*S*)-**19** was obtained as a pale yellow viscous oil.



Scheme 15

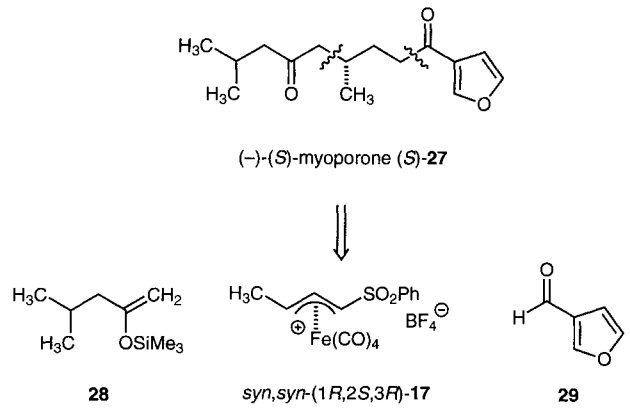
The enantiomeric purity (*ee* > 95 %) was determined by ^{13}C-NMR spectroscopy and GLC analysis of the corresponding *Mosher* amide of (*S*)-**19** and by comparison with the *Mosher* derivative of the racemic material obtained by an analogous route starting from the racemic complex *syn,syn*-(1*R*/*S*,2*R*/*S*,3*R*/*S*)-**13**. The absolute configuration of the stereogenic centre could be assigned as (*S*) based on our earlier investigations (*vide supra*). In conclusion, we have carried out, the first total synthesis of (2*S*,3*E*,5*Z*)-2-Amino-3,5,13-tetradecatrien [(*S*)-**19**] which in turn also confirmed its proposed structure. The compound was obtained in excellent overall yield starting from the iron complex *syn,syn*-(1*S*,2*S*,3*R*)-**13** (5 steps, 57 %) and in high enantiomeric purity (*ee* > 95 %).[15]

3.2 Synthesis of (–)-(*S*)-Myoporone

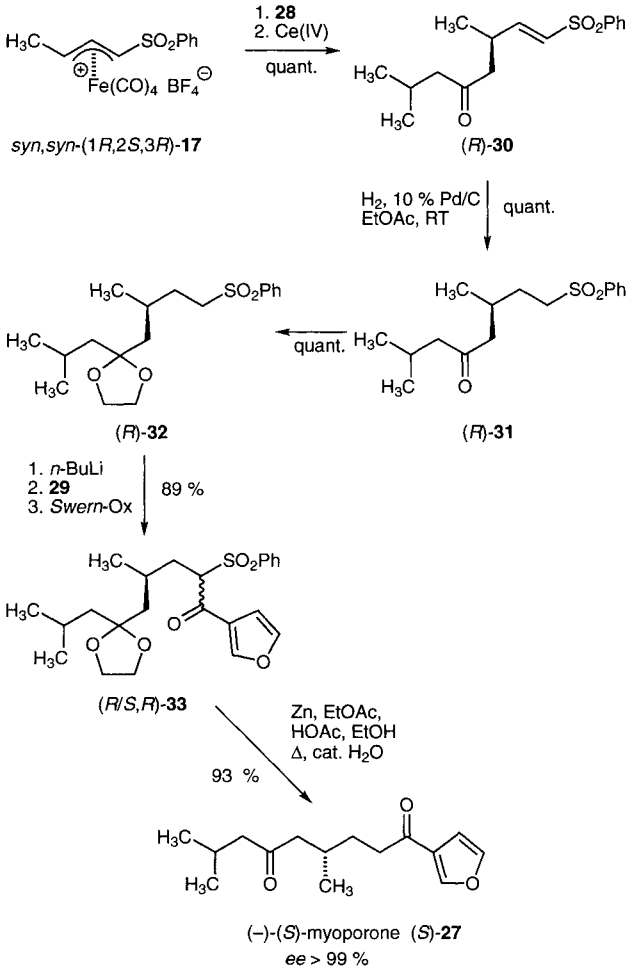
Myoporone, a hepatotoxic furanosesquiterpene diketone, was first reported in 1957 as the main furanoid constituent of the essential oil of the Japanese *Myoporum bontioides* A. Gray. Later its presence was also detected in various other *Myoporum* species, *Eremophila* species, *Eumorphia serica* and *Eumorphia prostata*. Interestingly, different species of *Myoporum* and *Eremophila* yielded myoporone samples of widely differing optical purity. The *Jackson* variety of the Australian shrub *Myoporum deserti* contains on the one extreme the (–)-(*S*)-myoporone as a secondary metabolite and *Myoporum montanum* on the other the (+)-(*R*)-enantiomer.[42,43] (–)-(*S*)-Myoporone was also

isolated in enantiopure form as a stress metabolite of sweet potatoes (*Ipomoea batatas*) during microbial infection ("black rotted disease") or under the challenge from mercuric chloride.[44] However, only a few total syntheses of myoporone have been reported so far in the literature starting either from enantiomerically enriched natural precursors or by asymmetric synthesis.[45]

As depicted in scheme 16, retrosynthetic analysis of the target molecule lead to three subunits, the silyl enol ether **28**, the cationic phenylsulfonyl substituted (η^3-allyl)tetracarbonyliron complex **17** and the aldehyde **29**.



Scheme 16



Scheme 17

As illustrated in scheme 17, the synthesis of the 6-oxosulfone (*R*)-**30** was accomplished by nucleophilic addition of the silyl enol ether **28**, easily obtained in 92 % yield as a single regioisomer from commercially available 4-methylpentan-2-one, to the enantiopure phenylsulfonyl substituted (η^3-allyl)tetracarbonyliron(1+) complex *syn,syn*-(1*R*,2*S*,3*R*)-**17** in dichloromethane after subsequent oxidative demetalation with aqueous ceric ammonium nitrate solution.

This key step proceeded as expected with complete regioselectivity and stereoselectively *anti* with respect to the metal carbonyl moiety. Thus, the reaction sequence resulted in an overall retention (double inversion) of configuration with respect to the starting material and the stereogenic centre at C-3 could be assigned the (*R*)-configuration as can be concluded from the sign of optical rotation of the final product (*S*)-**27** (*vide infra*). The enantiomeric purity of (*R*)-**30** (*ee* > 99 %) was determined by HPLC employing a chiral stationary phase (Daicel-OD) and by comparison with the racemic material, which was synthesized by an analogous route using the racemic iron complex (1*R/S*,2*R/S*,3*R/S*)-**17**. Palladium catalyzed hydrogenation of the double bond of (*R*)-**30** furnished the saturated sulfone (*R*)-**31** in quantitative yield. Although difficult, the keto group was quantitatively transformed to the dioxolane derivative according to *Noyori's* acetalisation method. The β-keto sulfone (*R/S,R*)-**33** was synthesised as a mixture of diastereomers in a two step procedure with an overall yield of 89 %. Aldol-type reaction of furan-3-aldehyde **29** with the α-lithio derivative of the protected sulfone of (*R*)-**32** at –78 °C furnished a mixture of diastereomeric alcohols with 96 % conversion with respect to the starting material (*R*)-**32** and completed the construction of the carbon skeleton of the target molecule. Subsequent *Swern* oxidation of the diastereomeric secondary alcohols yielded the β-keto sulfone (*R/S,R*)-**33** in 93 % yield and with a moderate diastereomeric excess of only 23 % of one of the α-epimeric sulfones. Simultaneous removal of both the acetal protecting group and the sulfone group of (*R/S,R*)-**33** was achieved by refluxing (*R/S,R*)-**33** in a mixture of ethyl acetate, acetic acid and ethanol (3:1:1) in the presence of zinc dust and a few drops of water to afford the target compound as a pale yellow liquid in 93 % yield, solidifying to a colourless solid in the refrigerator. The enantiomeric excess of (*S*)-**19** (*ee* > 99 %) was determined by HPLC on a chiral stationary phase (Daicel OD) and by comparison with a racemic sample. As clearly shown by the HPLC-plots, the stereogenic centre bearing the methyl branch does not suffer from any significant racemisation during the reaction sequence under the described conditions (figure 2).

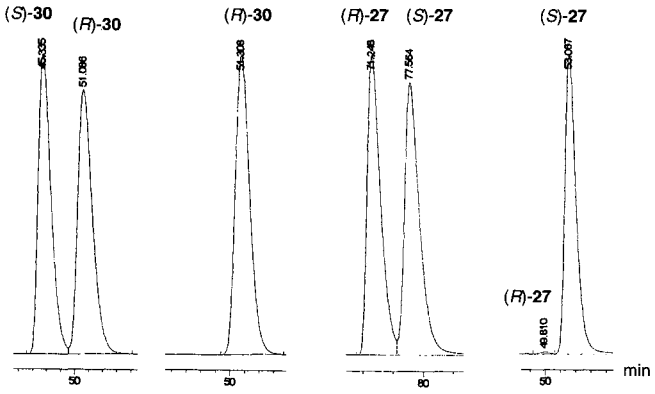
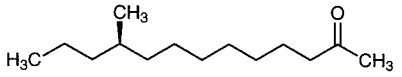


Figure 2

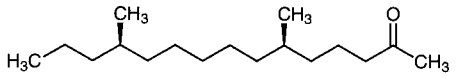
In summary, the naturally occuring hepatotoxic furanosesquiterpene (–)-(*S*)-myoporone has been synthesised straightforward and efficiently in excellent enantiomeric purity (*ee* > 99 %) and in a very high overall yield of 82 % (six steps) from readily available starting materials.[17] This reaction sequence examplifies very nicely the great synthetic value of the phenylsulfonyl-substituted (π-allyl) complex *syn,syn*-(1*R*,2*S*,3*R*)-**17** due to its potential bifunctionality.

3.3 Synthesis of the Sex Pheromones of the Spotted and Banded Cucumber Beetle

The Spotted Cucumber Beetle (SCB) *Diabrotica undecimpunctata howardi* Barber as well as the Banded Cucumber Beetle (BCB) *Diabrotica balteata* LeConte are polyphagous insects (*Coleoptera: Chrysomelidae*) belonging to the *fucata* species group of the genus *Diabrotica*. In general, both species are confined to North America from Canada to Mexico but the Banded Cucumber Beetle is found more often in the warmer southern regions down to Costa Rica and Cuba.[46,47] These beetles are known to cause severe damage to several crop plants due to their action as vectors of a number of plant diseases. In contrast, the larvae of these beetles [e.g. Southern Corn Rootworm (SCR)] are most damaging pests to e.g. seedling curcubits, groundnut, corn and sweet potato.[48] (–)-(*R*)-10-Methyltridecan-2-one [(*R*)-**34**] was identified as the sex pheromone secreted by virgin females of *Diabrotica undecimpunctata howardi* Barber,[48] while the female produced sex pheromone of *Diabrotica balteata* LeConte has been isolated and identified as (–)-(*R*,*R*)-6,12-Dimethylpentadecan-2-one [(6*R*,12*R*)-**35**].[49] The chemical structures of sex pheromones of this species included in the *fucata* group are characterised by the methyl ketone functionality and a methyl branch on the fourth carbon from the hydrocarbon end of the chain (scheme 18).[47,49,50]



(–)-(*R*)-10-methyltridecan-2-one (*R*)-**34**



(–)-(*R*,*R*)-6,12-dimethylpentadecan-2-one (*R*,*R*)-**35**

Scheme 18

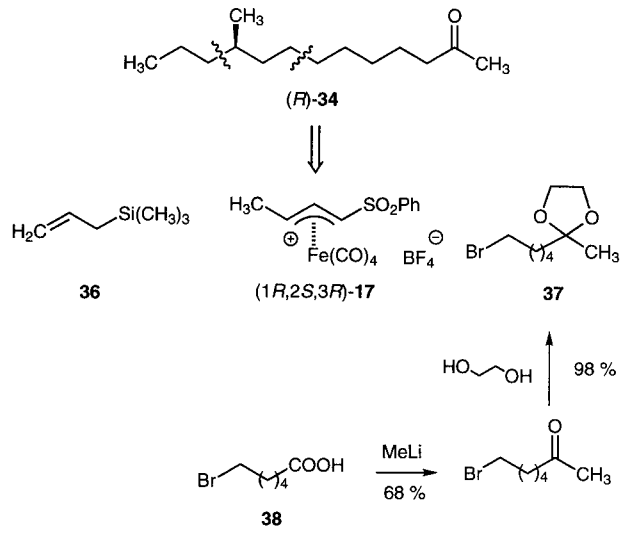
Field trapping experiments directed towards sex pheromones as biotechnical weapons with regard to integrated future pest management programs generally demonstrated that the (*R*)- or the (*R*,*R*)-stereoisomers, respectively, show the highest attractive bioactivity towards males of the SCB or the BCB and closely related species.[48,49] However, only few total syntheses of all possible stereoisomers of **34** and **35** in high enantiomeric purity have been reported so far in the literature, mostly starting from enantiopure methyl-branched building blocks from nature e.g. citronellol.[50-52]

With our method we were able to realize efficient and convergent syntheses of highly enantiomerically enriched (6*R*)-**34** as well as (6*R*,12*R*)-**35** taking advantage of the bifunctionality of the phenylsulfonyl substituted iron complex (1*R*,2*S*,3*R*)-**17**. In the following chapters the straightforward syntheses of both sex pheromones in their naturally occuring absolute configuration are described.

3.3.1 Synthesis of (–)-(*R*)-10-Methyltridecan-2-one

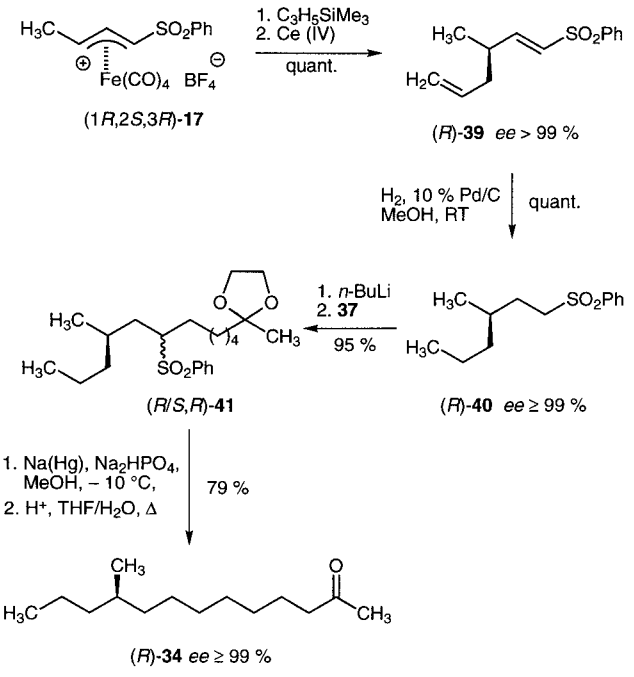
The retrosynthetic analysis of the spotted cucumber beatle sex pheromone is illustrated in scheme 19. The target molecule (*R*)-**34** can be divided into three subunits, the allyl silane **36**, the planar chiral, cationic phenylsulfonyl substituted (η^3-allyl)tetracarbonyl iron complex *syn*,*syn*-(1*R*,2*S*,3*R*)-**17** and the bromide **37**.

The synthesis of the protected electrophile **37** was easily accomplished in two steps starting from commercially available 6-bromo hexanoic acid **38** in 67 % overall yield. Again, the key step of the synthesis is a nucleophilic addition, in this case of allyltrimethylsilane, to the electrophilic iron complex *syn*,*syn*-(1*R*,2*S*,3*R*)-**17**, followed by oxidative cleavage of the tetracarbonyl iron fragment furnishing the γ-propenyl substituted alkenyl sulfone (*R*)-**39** in quantitative yield. The enantiomeric excess of (*R*)-**39** (*ee* = 99.4 %) was determined by GC employing a chiral stationary phase (Lipodex E) and by comparison



Scheme 19

with the appropriate racemic material. Catalytic hydrogenation of (*R*)-**39** yielded (*R*)-**40** virtually without any racemisation as it has been proven again by GC analysis on a chiral stationary phase (Lipodex E). α-Lithiation of the saturated sulfone (*R*)-**40** with *n*-butyllithium and subsequent alkylation of the metalated species with bromide **37** completed the final construction of the carbon skeleton to furnish (*R*/*S*,*R*)-**41** in 95 % yield as a mixture of diastereomers (*de* < 2 %). The sulfonyl group was reductively removed by treatment with an excess of sodium amalgam. Cleavage of the acetal protecting group was accomplished by acid hydrolysis to yield finally the pure pheromone (*R*)-**34** in 79 % yield (scheme 20). As it has been shown for very similar systems no synthetic operation should have affected the stereogenic centre at C-10 during the reaction course and the enantiomeric purity of the pheromone (*R*)-**34** should be identical with that determined for (*R*)-**39** or (*R*)-**40** (*ee* ≥ 99 %).

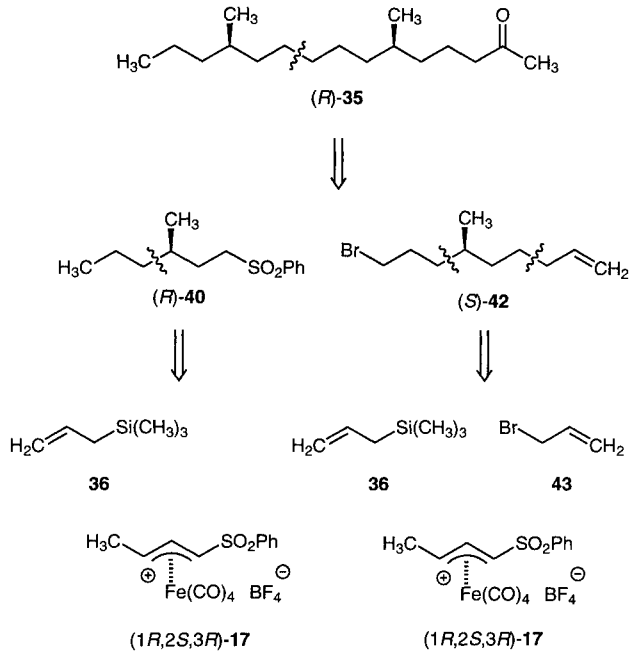


Scheme 20

In conclusion, an efficient and highly convergent synthesis of the sex pheromone of *Diabrotica undecimpunctata howardi* Barber, (–)-(*R*)-10-methyltridecan-2-one, in excellent overall yield (five steps, 75 %) and in high enantiomeric purity (*ee* ≥ 99 %) was realized.[19]

3.3.2 Synthesis of (–)-(*R*,*R*)-6,12-Dimethylpentadecan-2-one

Retrosynthetic analysis of the target molecule by C-9/C-10 disconnection leads to the sulfone (*R*)-**40** and the bromide (*S*)-**42**, which can be subsequently further disconnected to five readily accessible allylic subunits as illustrated in scheme 21.

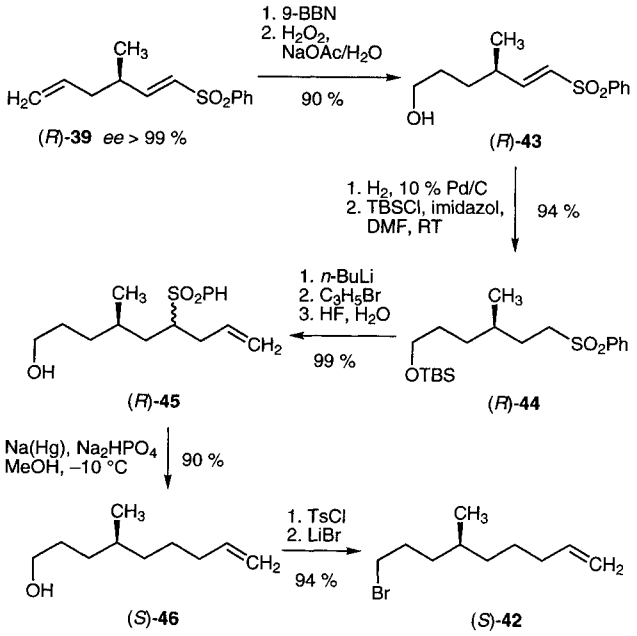


Scheme 21

The synthesis of the sulfone (*R*)-**40** has already been described in the previous section (*vide supra*), while the bromide (*S*)-**42** can be synthesised from allyltrimethylsilane **36**, the iron complex *syn,syn*-(1*R*,2*S*,3*R*)-**17** and allyl bromide. The crucial step for the construction of the carbon chain of the title compound was the alkylation of the sulfone (*R*)-**40** with the bromide (*S*)-**42**.

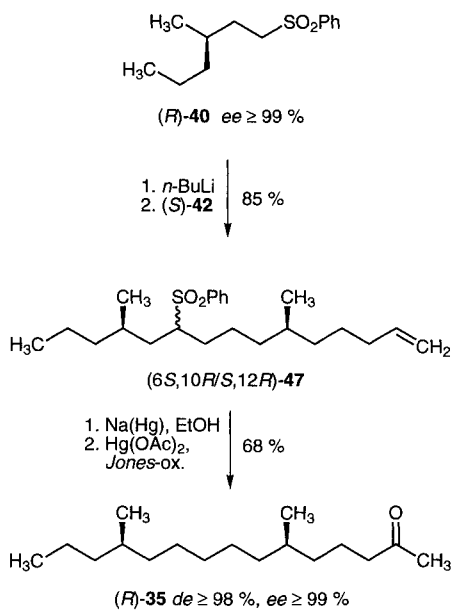
The building block (*R*)-**40** was prepared in three steps and practically quantitative yield starting from iron complex *syn,syn*-(1*R*,2*S*,3*R*)-**17** as described earlier (*ee* ≥ 99 %). For the preparation of the subunit (*S*)-**42** the regioselective hydroboration of the terminal double bond of (*R*)-**39** was achieved by treatment with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup with H_2O_2 furnishing the alcohol (*R*)-**43** in 90 % yield. Palladium catalyzed hydrogenation of the remaining double bond and protection of the free hydroxy functionality as the corresponding *t*-butyldimethylsilyl-ether furnished the sulfone (*R*)-**44** in 94 % overall yield. The α-lithio derivative of (*R*)-**44** was alkylated with allyl bromide affording the alkylated sulfone. The crude alkylation product was directly deprotected with aqueous hydrofluoric acid/acetonitrile furnishing the hydroxy sulfone (*R*/*S*,*R*)-**45** in 99 % yield over three steps. The reductive removal of the sulfonyl group of (*R*/*S*,*R*)-**45** was achieved by treatment with an excess of sodium amalgam. The resulting alcohol (*S*)-**46** was converted in two steps to the corresponding bromide (*S*)-**42** according to literature procedures (scheme 22).

The final construction of the carbon skeleton was achieved by alkylative connection of the two enantiopure building blocks (*R*)-**40** and (*S*)-**42** under the standard conditions described before (scheme 20). The reductive removal of the phenylsulfonyl group of the resulting alkylation product (6*S*,10*R*/*S*,12*R*)-**47** and the *Wacker*-type conversion of



Scheme 22

the terminal double bond into the methyl ketone functionality furnished the pure pheromone (6*R*,12*R*)-**35** in 68 % yield (scheme 23) and in excellent diastereo- and enantiomerical purity (*de* ≥ 98 %, *ee* ≥ 99 %).



Scheme 23

In conclusion, starting from readily available, inexpensive starting materials, the first stereocontrolled, efficient and highly convergent synthesis of the sex phereomone (–)-(*R*,*R*)-6,10-dimethylpentadecan-2-one was accomplished in good overall yield (13 steps, 39 %) and in high diastereo- and enantiomeric purity (*de* ≥ 98 %, *ee* ≥ 99 %).[18] There remains to be mentioned that the sign of the optical rotations of the final products (*S*)-**27** myoporone, (*R*)-**34** and (6*R*,12*R*)-**35** were identical with those reported for the authentical natural samples in the literature, which demonstrates that we have synthesised all compounds in their naturally occurring configurations. These results

also verify the overall stereochemical outcome of our "chirality transfer" process according to the proposed mechanism with double inversion (net retention) at the stereogenic centre with respect to the starting materials. The synthesis of the corresponding optical antipodes or diastereomers may be easily performed in the same manner by employing the other enantiomer of the iron complex **17**.

4 Conclusion

We presented in this paper a "chirality transfer" process in iron mediated allylic substitution reactions. Starting from enantiopure precursors from the "chiral pool", the formation of the enantiopure tetracarbonyl(η^3-allyl)iron(1+) complexes proceeds with virtually complete "chirality transfer" from the allylic starting material with central chirality to the corresponding tetracarbonyl(η^3-allyl)iron(1+) complexes owing planar chirality. During the subsequent nucleophilic addition to the electrophilic iron complexes a new stereogenic center is formed with inversion of the configuration at the involved carbon atom. Thus, the whole reaction sequence proceeds with overall retention (double inversion) of the stereochemistry of the stereogenic centre with respect to the starting materials (*S*)-**12** and (*S*)-**15**. In addition, the reaction proceeds with complete γ-regioselectivity and with conservation of the (*E*)-double bond geometry. Although this "chirality transfer" process in allylic substitution reactions proceeds *via* stoichiometric tetracarbonyl(η^3-allyl)iron(1+) complexes, the great variability in the substitution patterns of the allylic subunit, the broad range of employable nucleophiles in this sequence and the possibility of preparing both enantiomers of a target molecule display the great synthetic potential and value of this protocol. Highly functionalized and stereochemically well defined compounds of high enantiomeric purity are of increasing significance and represent valuable building blocks in the synthesis of bioactive compounds. The presented methodology should be regarded as a useful supplement to alternative (catalytical) variants in allylic subsitution reactions, which are often more limited in their range of nucleophilic components and allylic substrates.

Acknowledgement. D. E. would like to express his sincere thanks to the following former coworkers, whose experimental skill and enthusiasm have contributed to the successful development of the iron mediated allylic substitution project: Dr. Peter Fey, Dr. Thomas Schmitz, Dr. Udo Frank, Dr. Braj Bhushan Lohray and Dr. Michael Finkam. This work was supported by the Volkswagen-Stiftung, the Fonds der Chemischen Industrie, the European Community (Human Capital and Mobility Network: Metal Mediated and Catalyzed Organic Synthesis) and the Deutsche Forschungsgemeinschaft (Leibniz award). We thank BASF AG, Bayer AG, Boehringer Mannheim AG, Degussa AG, Hoechst AG, Schering AG and Wacker Chemie for generously providing us with chemicals.

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