Preparation Of Cyclohexenones From Acyclic (pentadienyl)iron(1+) Cations: Synthesis Of Carvone Metabolites And Synthetic Studies Directed Toward Dihydrotachysterols

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PREPARATION OF CYCLOHEXENONES FROM ACYCLIC (PENTADIENYL)IRON(1+) CATIONS: SYNTHESIS OF CARVONE METABOLITES AND SYNTHETIC STUDIES DIRECTED TOWARD DIHYDROTACHYSTEROLS

by

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ABSTRACT
PREPARATION OF CYCLOHEXENONES FROM ACYCLIC (PENTADIENYL)IRON(1+) CATIONS: SYNTHESIS OF CARVONE METABOLITES AND SYNTHETIC STUDIES DIRECTED TOWARD DIHYDROTACHYSTEROLS

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Six-membered carbocycles are abundant in natural products. This structural feature is present in terpenes, secosteroids, antibiotics, and even imbedded in the polycyclic framework of complex alkaloids. A wide variety of methodologies have been utilized for the preparation of six-membered carbocycles including Robinson annulation, Diels-Alder cycloaddition, Dieckmann condensation, ring closing metathesis, photochemical carbonylation of alkenylcyclopropanes, addition of soft nucleophiles to acyclic (η^5-pentadienyl)iron cations, etc.

Acyclic (η^5-pentadienyl)iron(+1) cations were first prepared about 50 years ago. The reactivity of these complexes is of continuing interest, particularly for the synthesis of conjugated polyenes and 2-cyclohexenones. These types of cationic complexes are powerful electrophiles and the site of nucleophilic attack is dependent on substituents on the pentadienyl ligand, the nature of the nucleophile, counter ion and "spectator" ligands on the complex. Tricarbonyl(η^5-1-methylpentadienyl)iron(+1), tricarbonyl(η^5-1-phenylpentadienyl)iron(+1), tricarbonyl(η^5-3-methylpentadienyl)iron(+1), and tricarbonyl(η^5-1,5-dimethylpentadienyl)iron(+1) cations were prepared following literature procedures.

The reactivity of these substituted acyclic (pentadienyl)iron cations with malonate, nitroacetate, sulfonate and phosphonoacetate nucleophiles were examined as potential routes to synthesis of natural product possessing six-membered carbocycles. Addition of stabilized/soft carbon nucleophiles occurs preferentially at the internal positions to afford cyclohexenones via (pentenediyl)iron intermediates. Nucleophilic addition at the terminal positions affords (2,4-dienoate)iron complexes mostly as minor products. This observed regioselectivity was explained mainly on the basis of FMO vs charge control.

In order to synthesize the oxygenated terpene (±)-10-Hydroxycarvone a ketoester was synthesized in five steps starting from commercially available 2,4-hexadienal. Deprotonation of the keteoester followed by DIBAL-reduction gave (±)-10-Hydroxycarvone. Alternatively, saponification of the ketoester afforded (±)-carvonic acid.

Furthermore to synthesize the dihydrotachysterol A-ring fragment, a cyclohexenone was synthesized in five steps from commercially available ethyl 3-methyl-4-oxocrotonate. Luche and catalytic reductions of the cyclohexenone gave

diastereomeric mixture of cyclohexanols. Protection followed by desulfonylation of the diastereomeric mixture gave a single diastereomer. **α**-Selenylation of this diastereomer followed by $NaIO_4$ oxidation gave a racemic mixture dihydrotachysterol A-ring fragments.

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CHAPTER 1

1A.1. General Introduction

The coordination of a tricarbonyl moiety [$Fe(CO)_3$] to conjugated diene ligands results in the formation of complexes (**1** and **2**) (Fig. 1) that are stable for long periods of time, are easy to handle, and are easily prepared on large scales using inexpensive reagents.[1] Donation of electron density from the ligand to the iron tricarbonyl group can activate the diene system and allow reactions such as nucleophilic additions to take place on the ligand which would hitherto not normally occur.[2]

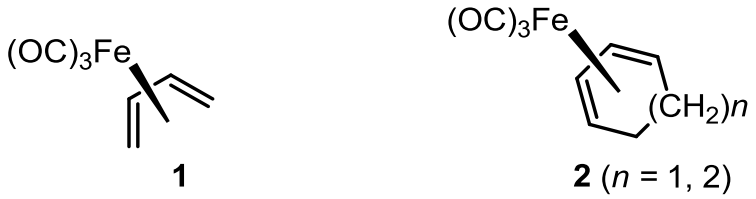


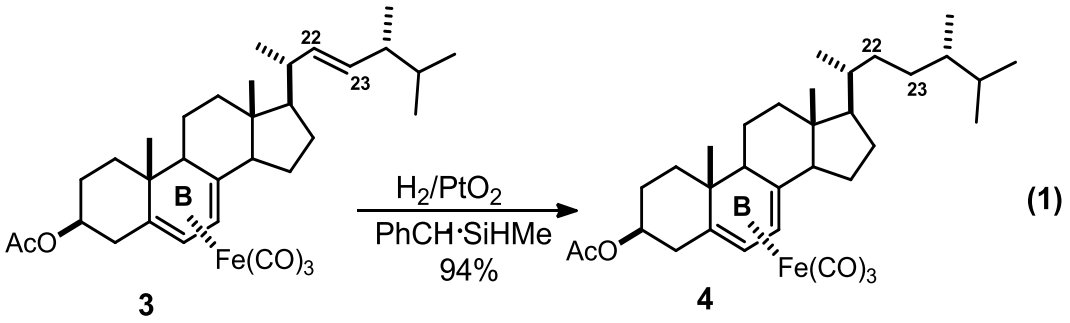
Fig. **1**: Structures of diene-complexes

Additionally, coordination of 1,3-dienes to a $Fe(CO)_3$ group also provides a means of protecting the unsaturated diene system towards catalytic hydrogenation, hydroboration, electrophilic additions and Diel-Alder reactions.[2, 3] The $Fe(CO)_3$ moiety can also influence the reactivity of functional groups attached to the diene system in terms of chemo- and stereoselectivity. [4-7]

1A.2. $Fe(CO)_3$ as Protective Groups for Dienes

The high stability of the $Fe(CO)_3$ moiety towards many chemical reagents makes it particularly useful as a protecting group for 1,3-dienes. Although (diene)$Fe(CO)_3$ complexes can react with strong nucleophiles, radicals, and strong electrophiles, they are unreactive toward many organic transformations such as DIBAL reduction, Swern oxidation, hydroboration, hydration, osmylation, hydrogenation, epoxidation, cyclopropanation. Several examples will be noted below.[8]

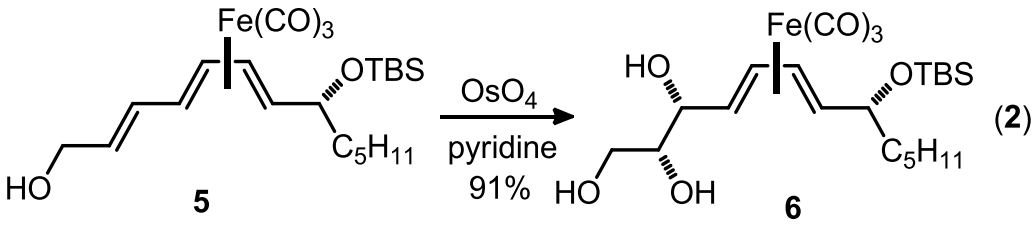
Barton, *et al*.[3] demonstrated that the C22-C23 double bond of ergosteryl acetate **3** can be selectively hydrogenated by the $Fe(CO)_3$ protection of the ring B diene to afford **4** (Eqn. **1**).



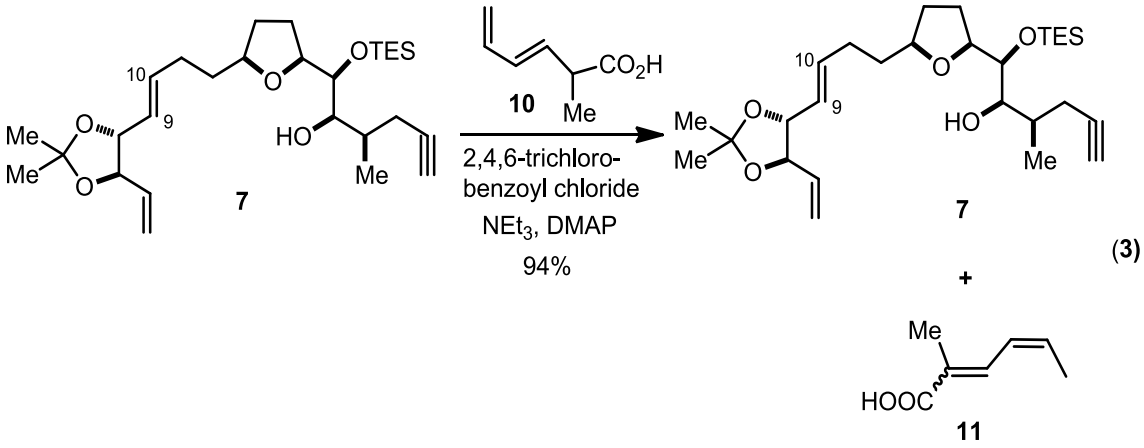
(1)

Formation of the iron tricarbonyl adduct, allowed selective reduction of the C22-C23 double bond by catalytic hydrogenation with retention of the C5-C8 diene system.

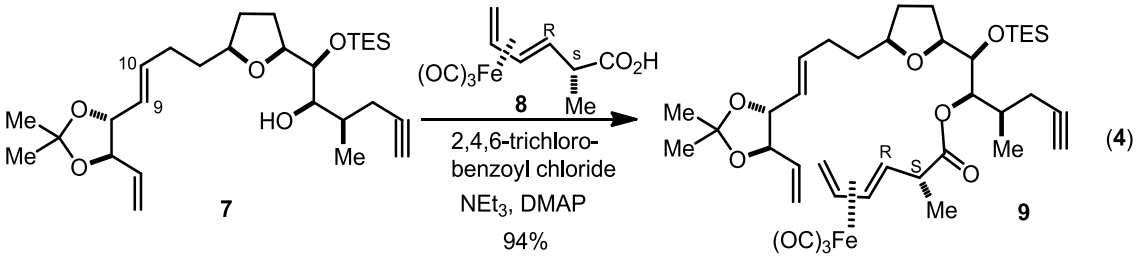
Additionally, Takemoto, *et al*.[9] have reported the dihydroxylation of the uncomplexed olefin in triene **5** with OsO_4 gave the dienediol complex **6** (Eqn. **2**). This reaction was used for the total synthesis of the marine metabolite halicholactone.[10]



Attempts to esterify **7** with 2-methylhexa-3,5-dienoic acid **10** were unsuccessful and generally led to the recovery of **7** and the more thermodynamically stable conjugated diene 2-methylhexa-2,4-dienoic acid **11** (Eqn. 3).



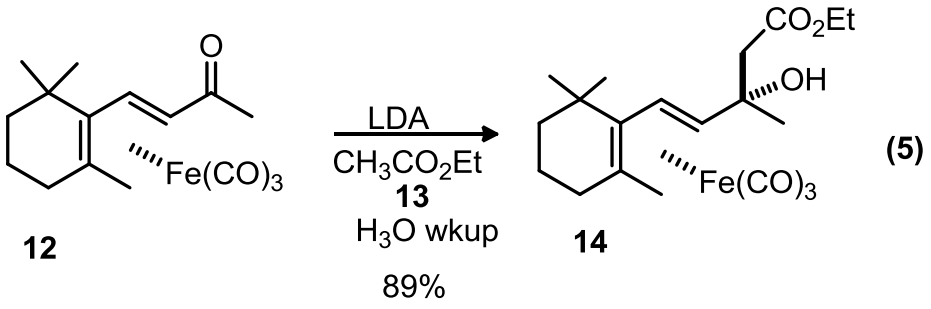
Va and Roush have reported the esterification of **7** with [(2*S*,3*R*)-2-methylhexa-3,5-dienoic acid]$Fe(CO)_3$ **8** to give the complex **9**.[11] In this synthesis the $Fe(CO)_3$ moiety on **8** was utilized to protect the hexa-3,5-dienoic acid against conjugation (Eqn. 4).[10]



1A.3. $Fe(CO)_3$ as Stereo/Regio-directing Groups in Diene Systems

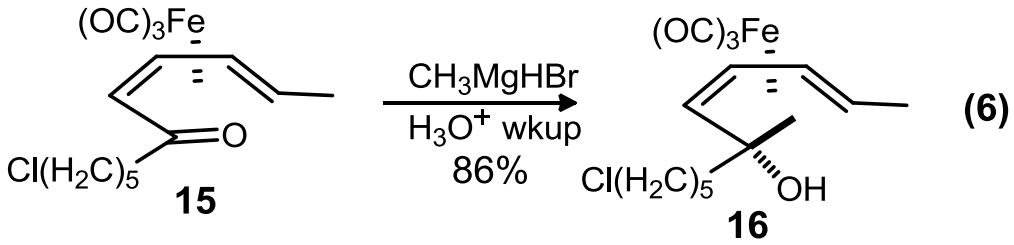
Many reactions of (diene)$Fe(CO)_3$ complexes proceed with a high degree of regio and diastereoselectivty.[12-16] This selectivity is attributed to the steric bulk of the $Fe(CO)_3$ moiety, which forces a wide variety of reagents to approach the diene complex on the face opposite/anti to the $Fe(CO)_3$ and on the least sterically crowded terminal diene carbon. In this regard, the $Fe(CO)_3$ moiety can be used as a stereo-directing group for the functionality in close proximity to the (diene)$Fe(CO)_3$ system.

Wada, *et al*.,[17] have reported the formation of a single product **14** from the reaction of **12** with the lithium enolate of ethyl acetate **13** (Eqn. 5) in the synthesis of retinoic acids.

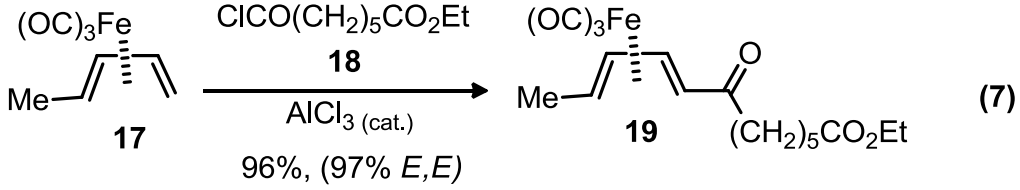


(5)

Iwata and Takemoto[16] have also accomplished the asymmetric syntheses of (+)- and (-)-frontalin,[18-22] an aggregation pheromone of the south pine beetle (*Dendrotonus brevicomis*) starting from a chiral (diene)$Fe(CO)_3$ complex **15**. In this synthesis the diastereoselective addition of MeMgBr to **15** gave the desired tertiary alcohol complex **16** with the methyl group adding anti to the $Fe(CO)_3$ group (Eqn. 6).



(Diene)Fe(CO)$_3$ complexes have also been used for total syntheses of insect pheromones having *(**E**)*- and (***E***,***E***)-l,3-diene skeletons. Knox, *et al*.,[23] have shown that tricarbonyl(butadiene)iron and derivatives undergo electrophilic addition under Friedel-Crafts conditions with the possible formation of stereochemically pure (dienone)Fe(CO)$_3$ complexes.



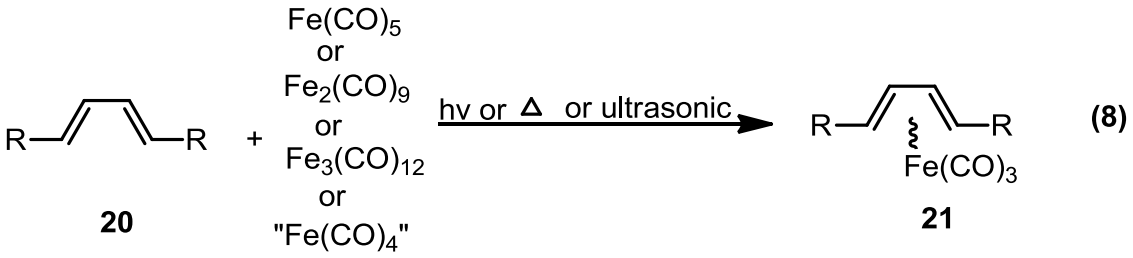
Acylation of tricarbonyl(butadiene)iron **(17)** with the acid chloride **(18)** and AlC1$_3$ gave the (***E***)-syn-keto-ester **(19)**.[23] The presence of the Fe(CO)$_3$ moiety "controls" the reaction, since uncomplexed dienes are usually polymerized under these reaction conditions.[24] The reaction also occurs on the terminal non-substituted carbon, mainly for steric reasons (Eqn. 7).[25]

1A.4. Preparation of Iron Diene Complexes

Reihlen and co-workers first prepared an acyclic (butadiene)(tricarbonyl)iron (**1**) (Fig. **1**) complex in 1930.[26-28] The structure of this complex was confirmed by X-ray

crystallography in 1963.[1] From a synthetic perspective, a variety of methods for the preparation of ironcarbonyl complexes of dienes have been described in the literature.[29] Many of these are restricted to special substrates, e.g., metal-vapor synthesis,[30] rearrangement of ligands,[31-33] reaction of iron carbonyls with halogen compounds,[34-36] and ligand exchange reactions.

The conventional method is to heat or irradiate a mixture of diene (conjugated or non-conjugated) and iron carbonyl, either $Fe(CO)_5$ or $Fe_2(CO)_9$, normally with solvent (Eqn. 8).[37] The use of $Fe_3(CO)_{12}/Fe(CO)_5$ and controlled amounts of Me_3NO has also been reported.[1, 38] In some cases, an improved yield is obtained by using $(dba)Fe(CO)_3$[39, 40] or an 1-azadiene-$Fe(CO)_3$ complex[41] as the $Fe(CO)_3$ donor, or by using iron carbonyl in the presence of an 1-azadiene as catalyst.[42] Recently, a convenient procedure was reported using silica gel as the medium for the complexation.[43]



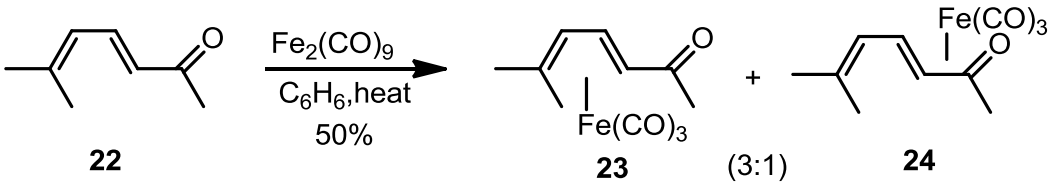
20 **21** **(8)**

The $Fe(CO)_5$/UV method is especially useful for preparing $[Fe(CO)_3(diene)]$ complexes without substituents containing hetero atoms (yields usually 65-85%).[29] However, isomerizations and side reactions tend to occur for ligands which contain a carbonyl group. In this case, the use of $Fe_2(CO)_9$ at elevated temperature provides better results, although yields tend to be somewhat lower (48-80%). In some cases, this

limitation was overcome by the addition of an excess of $Fe_2(CO)_9$ after about half of the reaction time.[29]

The yield of the complexation reaction is mainly controlled by two effects, electron density and steric hindrances in the s-cis-1,3-diene ligand. Yields are lower for dienes with terminal substituents with a (*Z*)-arrangement relative to the central C-C bond. This is attributed to the considerable conformational rearrangement which must occur on complexation. On the other hand, a -CN group attached to the diene dramatically reduces the reactivity of the ligand, even if no steric strain is present. As a general rule, yields decrease as the mesomeric effect of the substituent increases.[29]

In some cases, the tendency to avoid steric strain on complexation results in the formation of unexpected products. Thus, the complexation of (*E*)-6-methyl-3,5-heptadien-2-one (**22**) is presumably hindered by the interference of the CH_3 group with the $Fe(CO)_3$ moiety; in addition to **23** a considerable amount of the unstable dark-red enone complex **24** is formed (Eqn. 9).[2, 29]



(9)

1A.5. Cationic Pentadienyl-Iron Complexes

Acyclic (pentadienyl)iron(1+) cations **25** and **26** were first reported by Pettit and co-workers.[44] The $Fe(CO)_3$ moiety in such cases stabilizes carbocation centers adjacent to

the diene. Complexes of these types (**25** and **26**), have found great utility in the synthesis of natural products (Figure 2).[10]

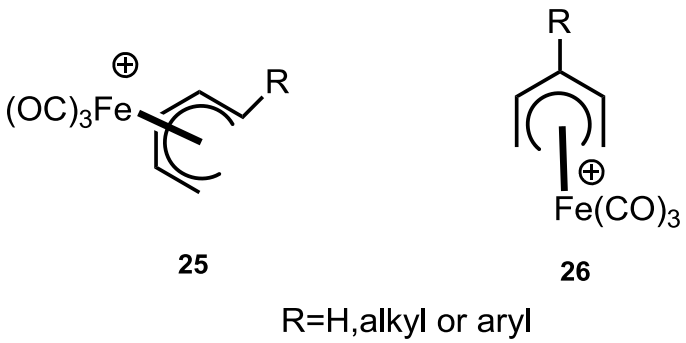
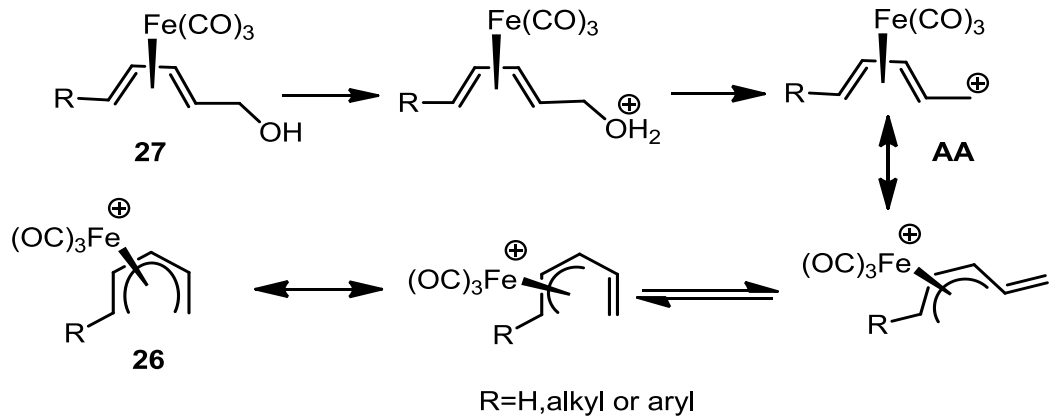


Fig. **2**: Structures of dienyl-iron complexes

The most convenient method for preparing the acyclic (pentadienyl) iron (1+) cations (**25** and **26**) is by acid treatment of a tricarbonyliron complexed pentadienol complex **27** (Scheme 1). Protonation of the alcohol moiety results in the loss of a molecule of water, affording the transoid cation **AA**. The transoid cation rearranges to the cisoid form which is more thermodynamically stable. Hexafluorophosphoric acid is often the acid of choice because it provides a large noncoordinating anion and affords a stable salt. The reaction is easily performed on the laboratory bench top and requires no purification other than precipitation from the reaction mixture and filtration.[44]

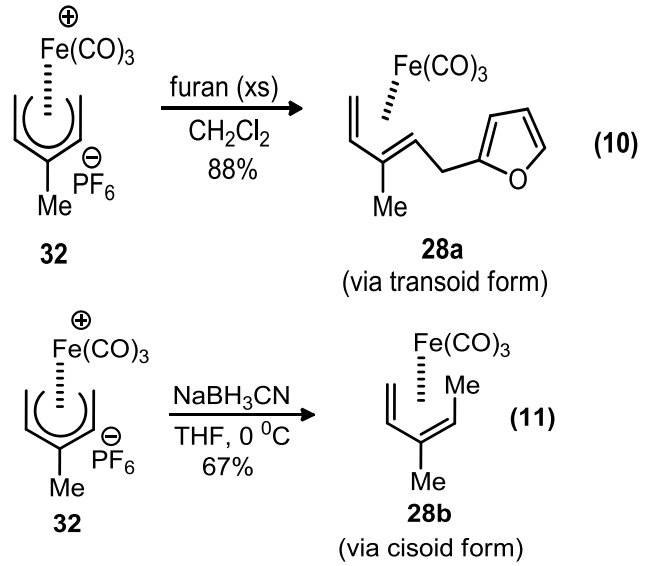


Scheme **1:** Mechanism of preparation of generic acyclic iron cation

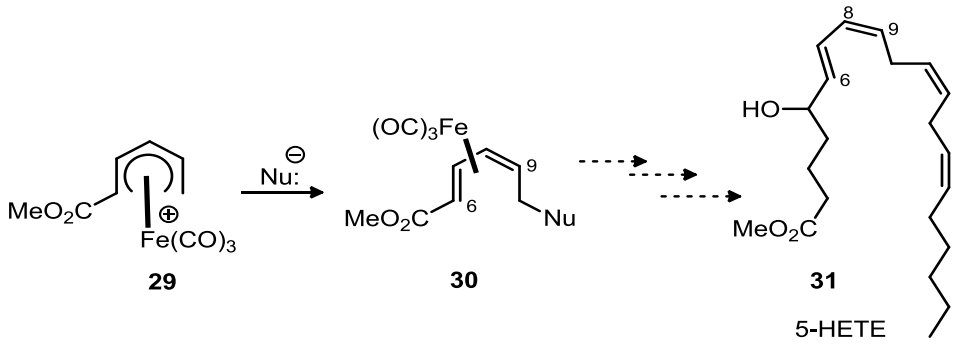
1A.6. Reactivity of acyclic (pentadienyl) iron cations

Nucleophilic attack on coordinated polyenes is one of the paradigms of π-organometallic chemistry.[45] The regioselectivity of nucleophilic attack depends on the nucleophile, substituents present on the pentadienyl ligand, and "spectator" ligands on iron.[46]

In solution, acyclic (pentadienyl) iron cations exist in an equilibrium between the cisoid form and the corresponding less stable transoid form.[47] Nucleophilic attack can take place on the cisoid form at either terminus, to afford *E,Z*-diene complexes or on the internal atoms of the ligand. Alternatively, because the transoid form exists in equilibrium with the cisoid form, nucleophilic attack on the transoid pentadienyl cation generates *E,E*-diene complexes only. Examples of nucleophilic attack at the terminal position of acyclic (pentadienyl) iron cations are illustrated in the following (Eqns. 10, 11).[48]

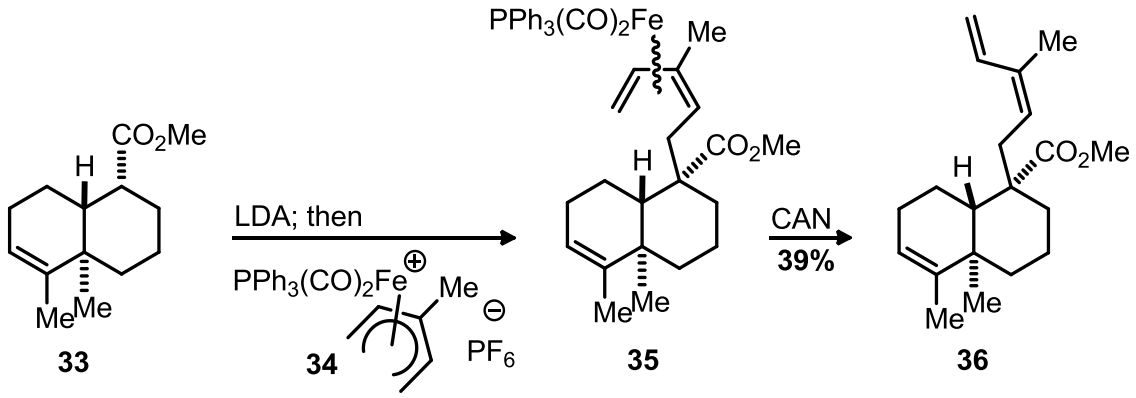


Nucleophilic addition to the terminal position of a pentadienyl cation is also exemplified in Donaldson's synthesis of the leukotriene, 5-hydroxyeicosatetranoic acid (Scheme 2).[49] The *E,Z*-stereochemistry of the 6,8-diene portion is established by nucleophilic addition to the (pentadienyl)$Fe(CO)_3$ cation **29** which resulted in iron complex **30** (Scheme 2)



Scheme **2**: Donaldson's synthesis of 5-HETE-methyl ester

A similar regioselective nucleophilic addition to a pentadienyl cation is exemplified in Donaldson's synthesis of the (3*Z*)-3-methyl-1,3-dienyl side-chain of the originally proposed structure[50-52] of heteroscyphic acid A **(**Scheme 3**)**.

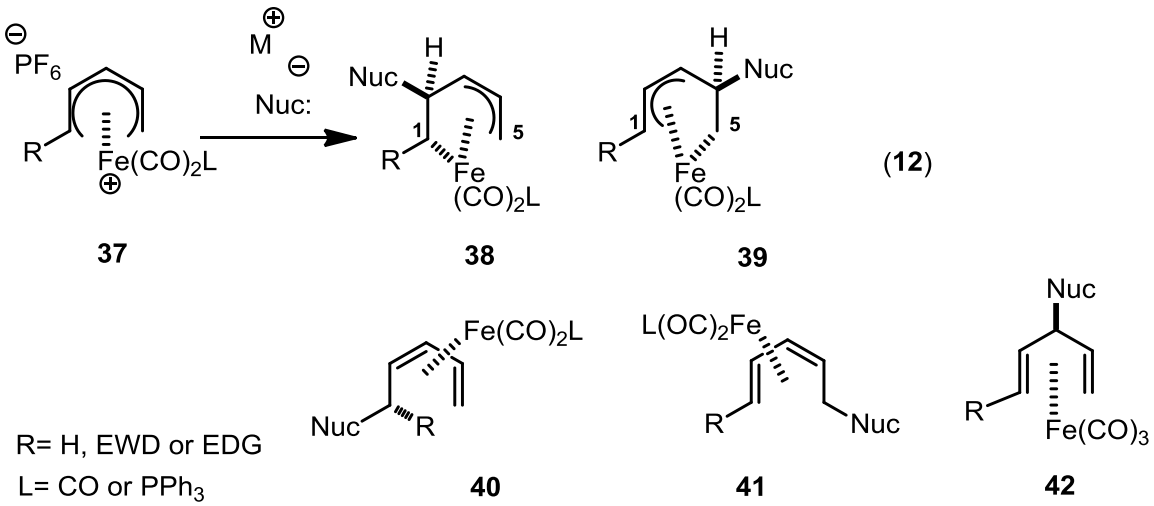


Scheme **3**: Donaldson's synthesis of the (3*Z*)-3-methyl-1,3-dienyl diterpene skeleton

Generation of the ester enolate anion from **33** and addition to the $Fe(CO)_2PPh_3$-ligated pentadienyl cation **34** gave complex **35**. As in 5-HETE, nucleophilic attack at one of the pentadienyl terminal carbons of **34** afforded iron complex **35**. Oxidation of the iron with cerium ammonium nitrate liberated the diene **36** (Scheme 3).[10, 46]

1A.7. (3-Pentene-1,5-diyl)iron Complexes

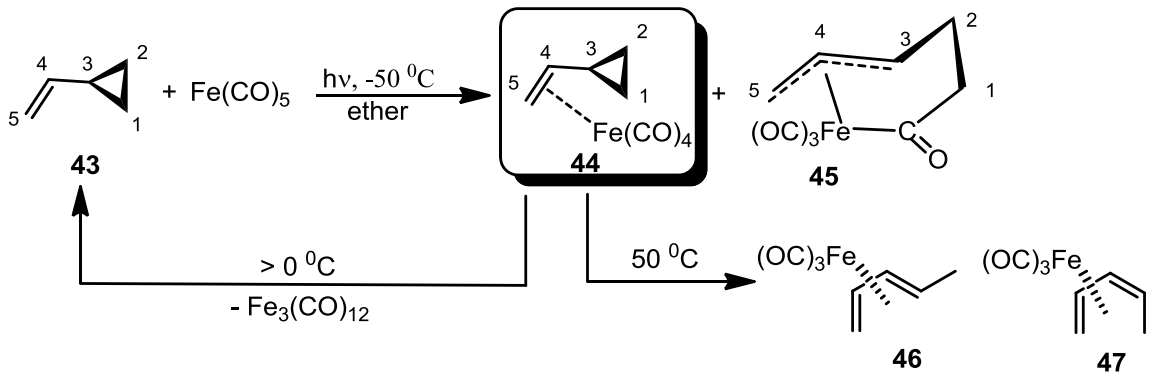
While much less common than tricarbonyl(diene)iron complexes, tricarbonyl(3-pentene-1,5-diyl)iron complexes of the general structure **38** and **39** (Eqn. 12) have recently begun to be utilized in organic synthesis. A variety of routes to these complexes has been reported and will be discussed below.[10, 48, 53-56]



1A.8. Preparation and Stability of (3-Pentene-1,5-diyl) complexes

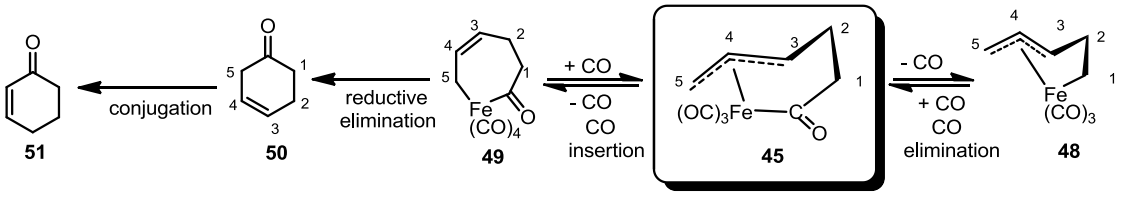
Aumann in 1974[57] synthesized and successfully isolated two thermally unstable iron carbonyl complexes from the reaction of vinylcyclopropane system **43** with iron carbonyls. These included 4,5-η-vinylcyclopropaneiron tetracarbonyl **44** which possessed an intact cyclopropane ring and 3,4,5,6-η-hex-4-en-3,6-yl-6-one-iron tricarbonyl **45** resulting from the cleavage of a C-C bond of the cyclopropane ring (Scheme 4**)**. Complexes **44** and **45** were isolated at -20 ^{0}C and their structures corroborated by NMR, IR, MS and elemental analysis. The fact that **44** does not rearrange to **45** suggest that **44** and **45** are formed by competing reactions of **43** with different iron carbonyl species generated on photolysis of $Fe(CO)_5$[58, 59] in ether.

The tetracarbonyliron complex **44** decomposes to **43** and $Fe_3(CO)_{12}$ at temperatures above 0 ^{0}C. Additionally, **44** on prolonged warming under CO-deficient conditions gave the (1,3-pentadiene)$Fe(CO)_3$ complexes **46** and **47** (Scheme 4).[57]



Scheme **4**: Reaction of vinylcyclopropane with iron carbonyl

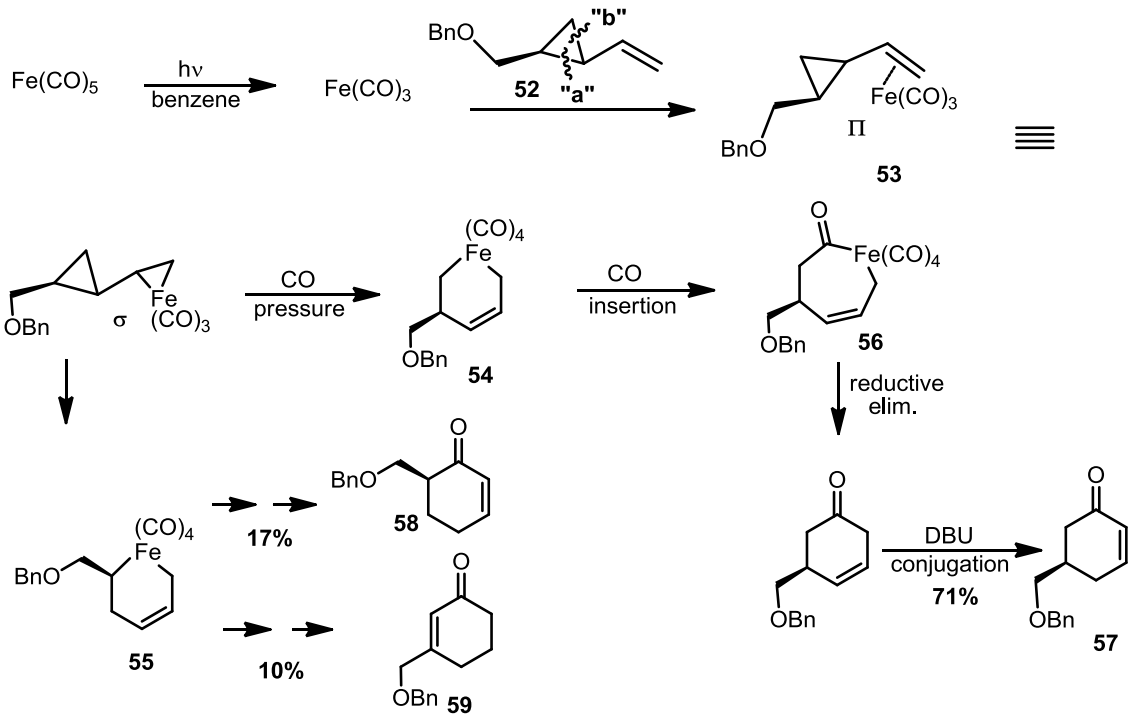
CO saturated hexane solutions of **45** decompose reversibly by loss of CO at 25 ^{0}C to give 1,3,4,5-η-pent-4-ene-3,1-yliron tricarbonyl complex (**48**). Furthermore, solutions of **45** may also decompose to 2-cyclohexenone (**51**) under the influence of air or if a positive pressure of CO (20 atm) is applied (Scheme 5).



Scheme **5**: Reactivity of (3,4,5,6-η-hex-4-en-3,6-yl-6-one)iron complex **45**

In 1978, Sarel and coworkers[60] reported an alternative route to cyclohexenones through a photochemically initiated ring rearrangement-carbonylation of alkenylcyclopropanes. This reaction proceeds through oxidative insertion of iron into one of the proximal vinylcyclopropane bonds ("b" or "a") of **52** to generate (pentenediyl)iron

intermediates **54** and **55**, respectively.[10, 61] The reaction typically gives three regioisomers from the photochemically initiated $Fe(CO)_5$ carbonylation (Scheme 6).[62]

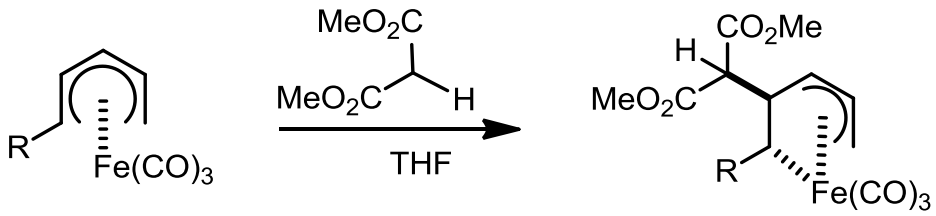


Scheme **6**: Generation of cyclohexenones via Fe-mediated carbonylation of **52**

Cleavage of the less substituted vinyl cyclopropane bond "b" is favored and results in the formation of 5-benzyloxymethylene cyclohexenone **57** as the major product (61%) via the (pentenediyl)iron intermediate **54**. Cleavage of the "a" bond results in the formation of 6-benzyloxymethylene cyclohexenone **58** as a minor product (17%) via intermediate **55**. "Fe-H" isomerization of **52** results in the formation of the 3-benzyloxymethylene cyclohexenone **59** (10%) also as a minor product. The formation of the latter is significantly reduced by running the reaction in 2-propanol.[61-63] Because the major product (**57**) arises from the cleavage of the less substituted vinylcyclopropane

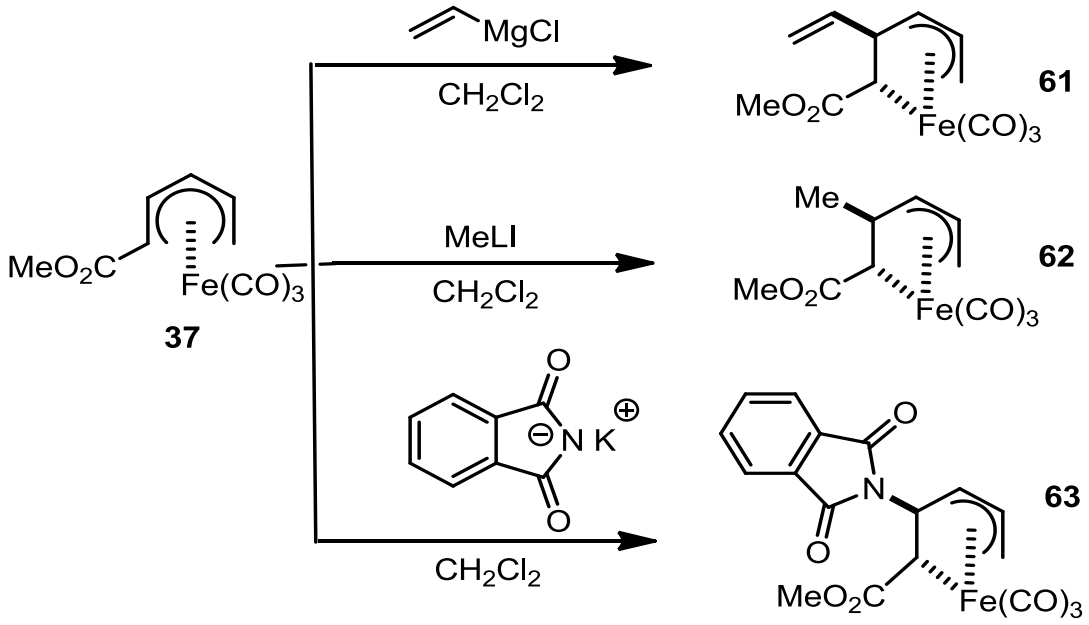
bond “b”, use of the enantiomerically enriched (>99% ee) vinylcyclopropane **52** as starting material led to (+)-**57** in enantiomerically form (95% ee).[10, 61]

(3-Pentene-1,5-diyl)iron complexes **60**-**63** have been prepared by addition of stabilized carbon and nitrogen nucleophiles to unsymmetrical (pentadienyl)iron (+1) cation **37** (Scheme 7).[10, 64] The selectivity of nucleophilic addition to **37** depends on several factors including the strength of nucleophile,[64] substituents on the diene ligand, nature of peripheral ligand L,[65] solvent,[66] steric bulk of nucleophile, nucleophile-counter ion,[46, 48]. Examples of these are below (Scheme 7):



37 **60**

R= CO_2Me, Me or Ph



Scheme **7**: Synthesis of (3-pentene-1,5-diyl)iron complexes

Nucleophilic addition to the (1-methoxycarbonyl pentadienyl)iron (1+) cation **37** with soft nucleophiles such as malonate anions results the in the formation of (pentenediyl)iron complexes via attack at C-2 (e.g. **60-63** Scheme 7). 2-Methyl and 2-vinyl substituted (pentenediyl)iron complexes **62** and **63** were also prepared by reaction of **37** with organolithium or Grignard reagents.

The differences in regioselectivity for addition of stabilized/soft nucleophiles to **37** are qualitatively rationalized as follows: the strongly electron withdrawing methoxycarbonyl substituent (CO_2Me) lowers the relative energy of the pentadienyl LUMO, thus allowing for a better energy match with the metal d-orbitals. This effects a greater transfer of electron density from the metal to the pentadienyl ligand at C1, C3, and C5. Thus, formation of the pentenediyl products **38** and **39** from nucleophilic attack at C2 of **37** is the result of charge control (i.e., greater δ+ charge at C2/C4).[10, 64]

Additionally, the values of the ^{13}C NMR data[67] for **37** indicate that C2 and C4 appear at the lowest chemical shift (Figure **3a**). While the ^{13}C NMR chemical shift of a particular carbon depends on several factors, downfield chemical shifts generally correspond to less electron density at the atom in consideration. Similarly, calculations of the charge distribution over the pentadienyl ligand by density functional theory (B3LYP method, Fig. **3b**) are in concert with the ^{13}C NMR data.[68] Hence, "soft" carbon-stabilized nucleophiles would attack the most electron deficient carbon-2/4.

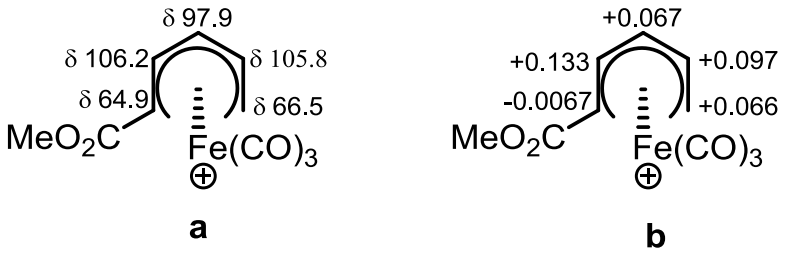
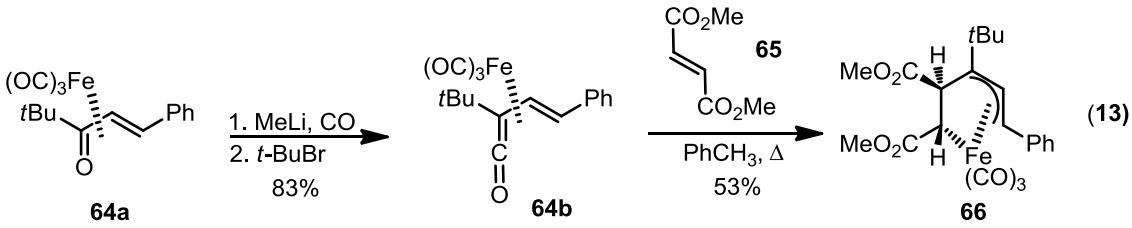


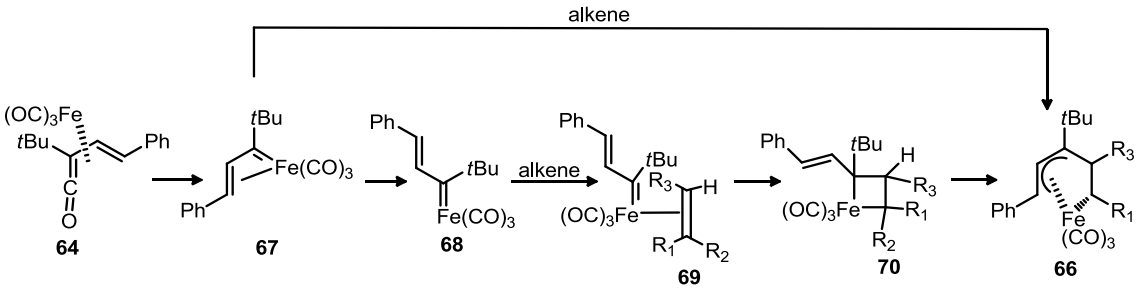
Fig. **3**: (a) ^{13}C NMR spectral data and (b) calculated partial charges

(3-Pentene-1,5-diyl)iron complex **66** may also be generated from the thermal reaction between the (vinylketene)iron complex **64b** and an electron-deficient olefin **65** **(**Eqn. 13).[10, 69, 70]



Mechanistically the reaction between vinylketene **64b** and an electron-deficient alkene proceeds as follows: Decarbonylation of the vinylketene complex **64b** gives the η^3-vinylcarbene intermediate **67**.[71] This is the rate determining step and requires temperature greater than 80 ^{0}C. Formation of the vinylcarbene complex **67** is followed by styryl dissociation to give the 16-electron η^1-vinylcarbene complex **68**, external alkene coordination to give **69** and a formal [2+2] cycloaddition to give the 16-electron ferracyclobutane **70**. This then collapses to the 18-electron (pentenediyl)iron complex **71** (Scheme 8).[70]

Alternatively, direct interaction between the vinylcarbene intermediate **64b** and the external alkene would lead straight to the (pentenediyl)iron complex **66**.



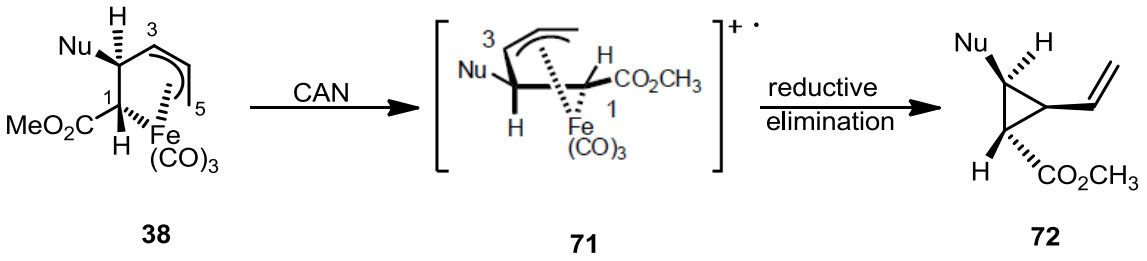
Scheme **8**: Generation of (3-pentene-1,5-diyl)iron complex **66**

1A.9. Oxidative decomplexation of Isolable (pentenediyl)iron complexes

Treatment of (diene)iron complexes **40** and **41** with oxidizing agents (e.g. CAN) liberates the $Fe(CO)_3$ from the (diene)iron complexes to afford free diene ligand.[72, 73] However, oxidation of (3-pentene-1,5-diyl)iron complexes bearing an electron

withdrawing group at C1 (e.g. **38**) leads to the formation of the vinylcyclopropane carboxylate **72** (Scheme 9). [55, 74, 75]

The oxidation of complex **38** with Ce^{4+} results in reactive intermediate **71** which undergoes reductive elimination to give the **72**. The reductive elimination step proceeds with retention of configuration at C1 and C3 such that the nucleophile group is trans to the ester group and cis to the vinyl group. The present of an electron withdrawing group (e.g. methoxycarbonyl group) at C1 of **38** slows the rate of CO insertion compared to the rate of reductive elimination.[74, 75]

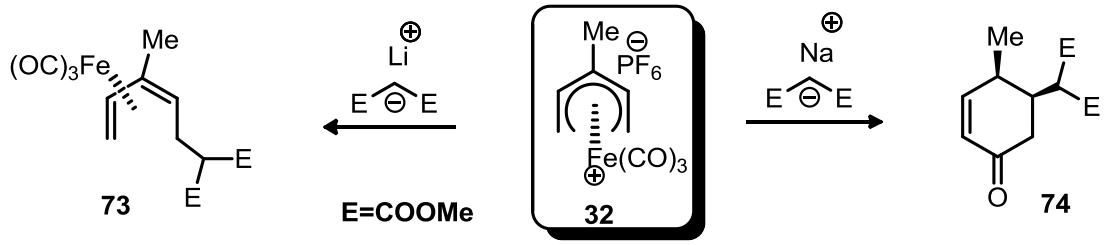


38 **71** **72**

Scheme **9**: CAN-mediated oxidation of **38**

1A.10. Reactivity of tricarbonyl(3-methylpentadienyl)iron (+1)

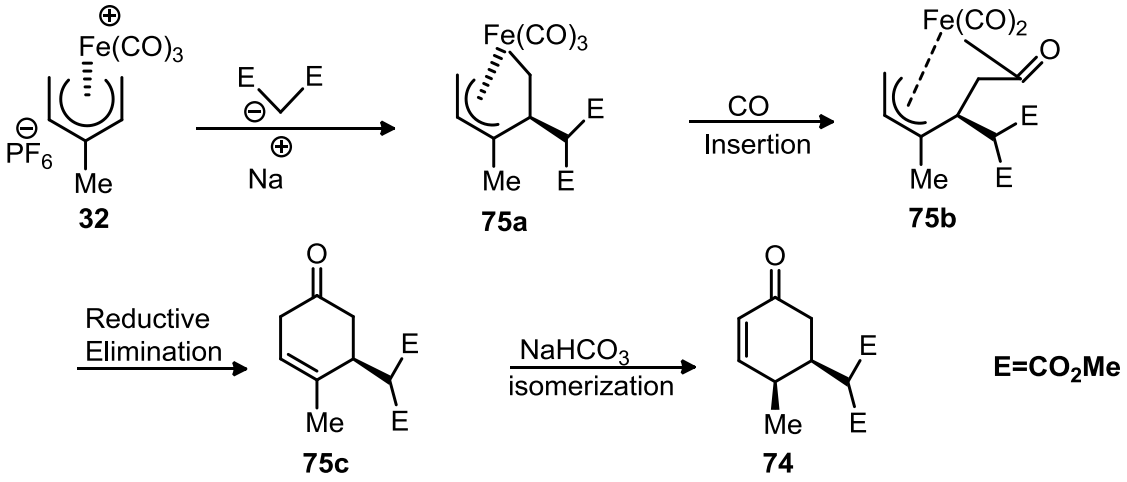
As part of a program to develop synthetic methodology for the rapid introduction of a 3-methyl-1,3-(Z)-pentadienyl side chain present in certain terpene natural products, a previous coworker examined the reactivity of tricarbonyl(3-methylpentadienyl)iron (+1) (**32**) (Scheme 10) with dimethyl malonate anion.[48]



Scheme **10**: Reaction of **32** with sodium and lithium dimethyl malonate

These studies revealed that: (1) nucleophilic attack by dimethyl malonate anion gave two products **73** and **74** and (2) the regioselectivity of the nucleophilic attack depended largely on the nature of the counterion.[49] Thus reaction of **32** with lithium dimethyl malonate gave the 1,3-Z-diene complex **73** while the 4,5-disubstituted cyclohexenone **74** was formed when sodium was used as a counterion (Scheme 10).[10]

The (1,3-Z-diene)iron complex (**73**) arises from a nucleophilic attack at the terminal either C1/C5 of **32** whilst the cyclohexenone (**74**) is formed by a nucleophilic attack at either C2/C4 internal carbon (Scheme 11). The mechanistic rational for the formation of **74** is that the addition of the malonate anion occurs on the face of the cation anti to the $Fe(CO)_3$ group to generate **75a**. Rapid carbonyl insertion affords the pi-sigma acyl complex **75b**. Reductive elimination gives cyclohex-3-en-1-one (**75c**). Workup with methanolic $NaHCO_3$ then effects conjugation of the C2-C3 double bond of **75c** to give the 4,5-disubstituted cyclohexenone **74** (Scheme 11).[10, 48]



Scheme **11**: Mechanistic rational for formation of **74**

The difference in regioselectivity for nucleophilic attack (i.e. C1 vs. C2) is due to the degree of association of the malonate anion with the counterion. Generally strongly associated counterions (e.g., Li^+ or Zn^{2+}) attack at C1/C5 of cation **32** to give complex **73** whilst weakly associated counterions (e.g., Na^+ or Li^+/12-crown-4) afford cyclohexenone (**74**) from nucleophilic attack at C2/C4 of **32**. It was proposed that for the weakly associated malonate nucleophile that nucleophilic attack takes places on the dienyl carbon bearing the greatest partial positive charge. ^{13}C NMR spectroscopy correlation studies[67, 76] and DFT calculations[77] have revealed that the C2 and C4 carbons of the pentadienyl ligand of **32** bear a greater partial positive charge than C1, C3 and C5 carbons.

Alternatively for the more strongly associated counterion, nucleophilic attack was proposed to be under frontier orbital control. The LUMO coefficients derived from MO calculations of dienyl(iron)cation indicate greater orbital contribution from C1 and C5 than from C2 and C4 carbons.[78, 79]

The aim of this research is to expand the scope of this cyclohexenone formation reaction, extend range of nucleophiles, and prepare dihydrotachysterol A-ring fragments as well as terpene metabolites.

1B.1. The Chemistry of the D vitamins

The D vitamins have received considerable chemical and biochemical attention over the past decades.[80-84] The generic term "Vitamin D", refers to a molecule of the general structure derived from cyclopentanoperhydrophenanthrene ring structure (**76**) for steroids with differing side chain structures (Fig. 4).

Technically vitamin D is a seco-steroid. Seco-steroids are molecules wherein one of the rings of the cyclopentanoperhydrophenanthrene ring structure has been broken, and in vitamin D, the C9-C10 bond of the ring B is broken, and it is indicated by the inclusion of "9,10-seco" in the official nomenclature. The structural features combined with their biological activity makes vitamin D and structural analogs appealing synthetic targets.

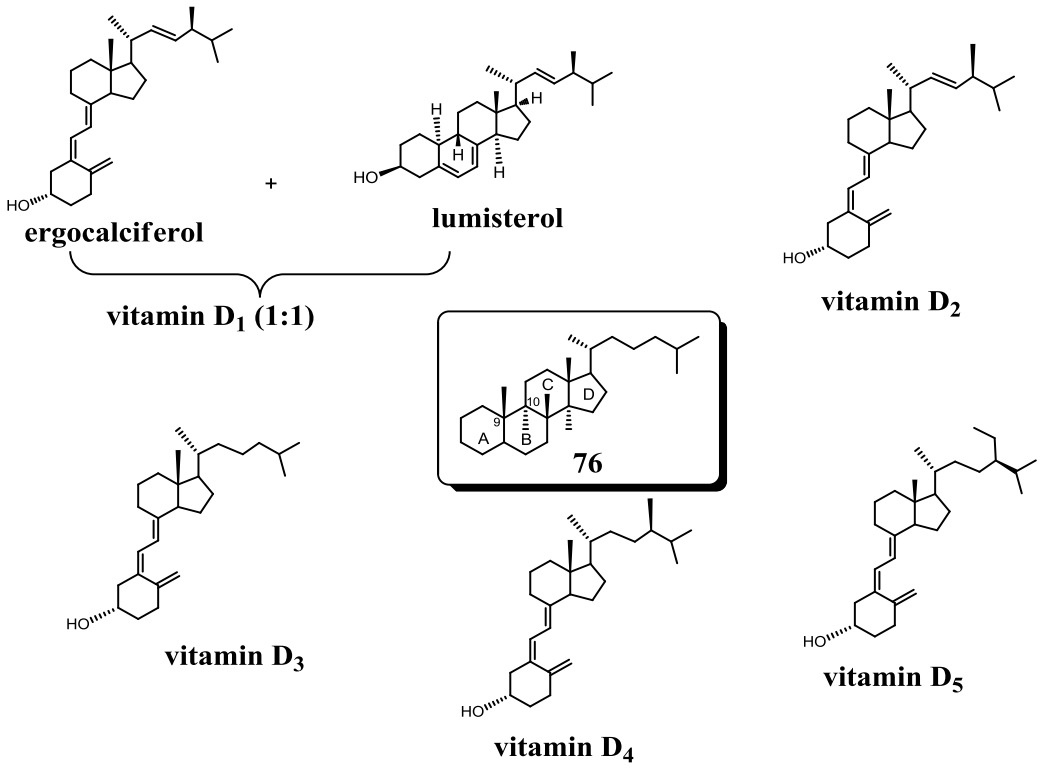


Figure **4**: Forms of Vitamin D showing the basic steroidal (**76**) skeleton

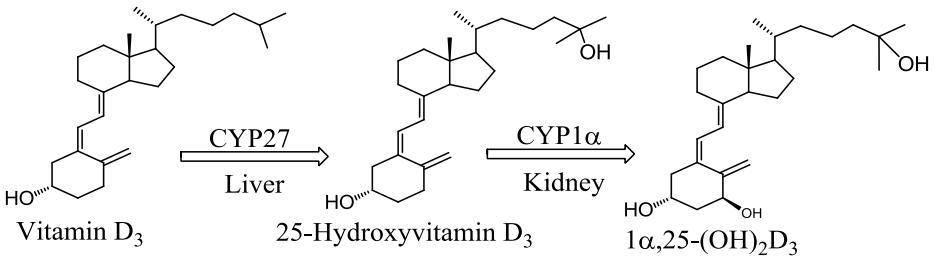
1B.2. Discovery, Sources and Biological Activity of vitamins D_2 and D_3

In 1931 Askew and coworkers isolated vitamin D_2 from ergosterol by ultraviolet irradiation.[85, 86] Windaus, *et al*., successfully synthesized 7-dehydrocholesterol, and from this substance isolated vitamin D_3 after UV irradiation.[87, 88] These two represent the truly natural and nutritionally relevant forms of vitamin D and exhibit similar antirachitic potency in man.

In addition to dietary sources, Vitamin D_3 (cholecalciferol) can also be derived from 7-dehydrocholesterol in the skin following exposure to sunlight (270-300 nm range).[89, 90] Similarly Vitamin D_2 (ergocalciferol) is obtained from ergosterol in the skin upon UV irradiation. The structural difference between vitamin D_2 and vitamin D_3 is in

their side chains. The side chain of vitamin D_2 contains a double bond between C22 and C23, and a methyl group on C24.[84, 91]

Vitamin D in its natural form requires activation to its hormonal form in order to perform its homeostasis role.[92] The activation processes involve first, 25-hydroxylation in the liver, followed by 1α-hydroxylation in the kidney, to make the biologically active hormones 1α,25-$(OH)_2D_3$ and 1α,25-$(OH)_2D_2$, respectively (Scheme 12).[90] There is little evidence that these two active forms differ in their mode of action.



Scheme **12**: Steps involved in activation of vitamin D_3.[93]

1B.3. The Dihydrovitamins D and Dihydrotachysterols (DHT)

Dihydrovitamins D are a class of compounds derived by reduction of the natural vitamin D_3 (**77**), vitamin D_2 (**78**), and their unnatural 5-(E) isomers (5,6-trans derivatives) (Fig. 5).[94] Among them, dihydrotachysterol$_2$ (DHT_2, **79**), first isolated by von Werder in 1939[95] by reduction of tachysterol$_2$ with sodium in propanol,[96] is considered an interesting analog of 1α,25-dihydroxyvitamin D_3 (**81**), the hormonal form of vitamin D_3, because the former's 3β-OH group has a similar topological orientation to that of the latter's 1α-OH.[97, 98]

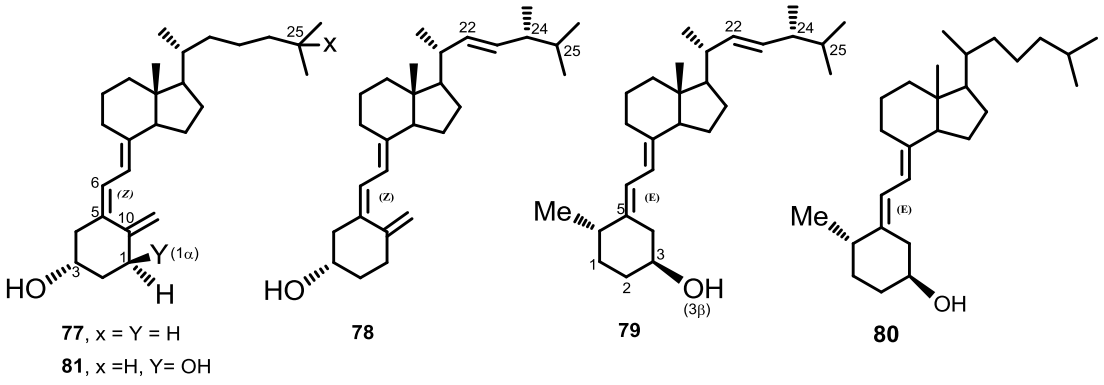
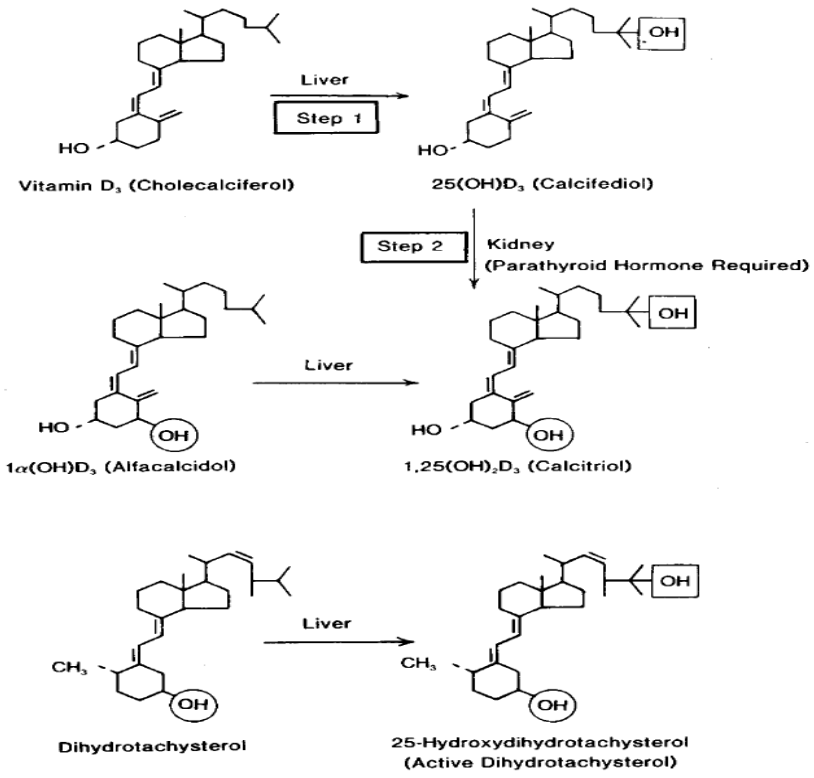


Fig. **5**: Vitamin D (**77** and **78**) and DHT (**79** and **80**).

The dihydrotachysterols [DHT_2 (**79**) and DHT_3 (**80**)], may collectively be considered to be reduction products of the D vitamins and can be produced by direct reduction of vitamin D.[99] The resultant conjugated diene bears an A-ring inverted 180^0 with respect to parent vitamin D. Of the many possible reduction products of the vitamin D triene, the dihydrotachysterol diene is the only known biologically active configuration.

Dihydrotachysterols, like vitamin D, requires hepatic enzymatic hydroxylation in position C-25 before it becomes biologically effective, however unlike vitamin D this transformation is not under feedback control.[96, 100] This distinction may explain why DHT_3 has a greater hypercalcemic effect than vitamin D at high dosages.[101] In the absence of further 1-hydroxylation by the kidney, chemically synthesized 25-(OH)-DHT_3 possesses an affinity for intestinal and bone receptor sites equal to that of 1α,25-$(OH)_2D_3$ (Scheme 13). Chemically synthesized 25-(OH)-DHT_3 is thus more potent, faster acting and more antirachitic than DHT_3 and vitamin D_3 in the mobilization of bone, renal and intestinal calcium.[102, 103]

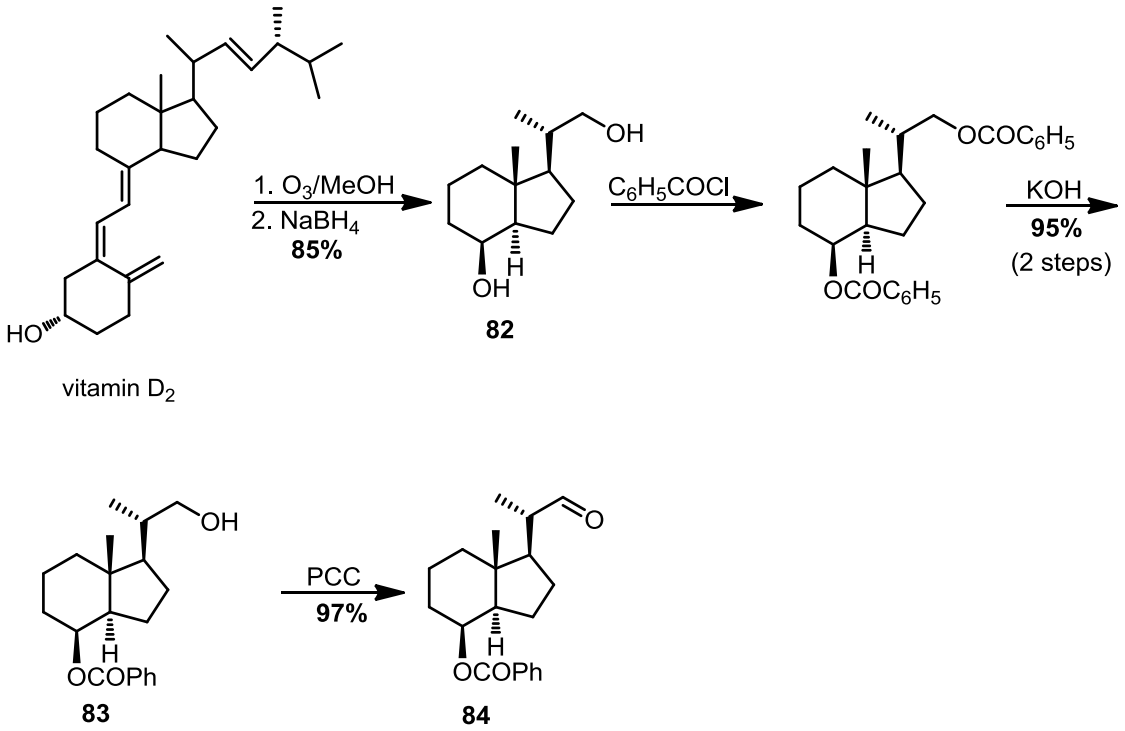


Scheme **13**: Metabolic Activation of Vitamin D_3, 1α,-(OH) D_3 and DHT_2.[103]

1B.4. Previous Synthetic Studies of Dihydrotachysterols

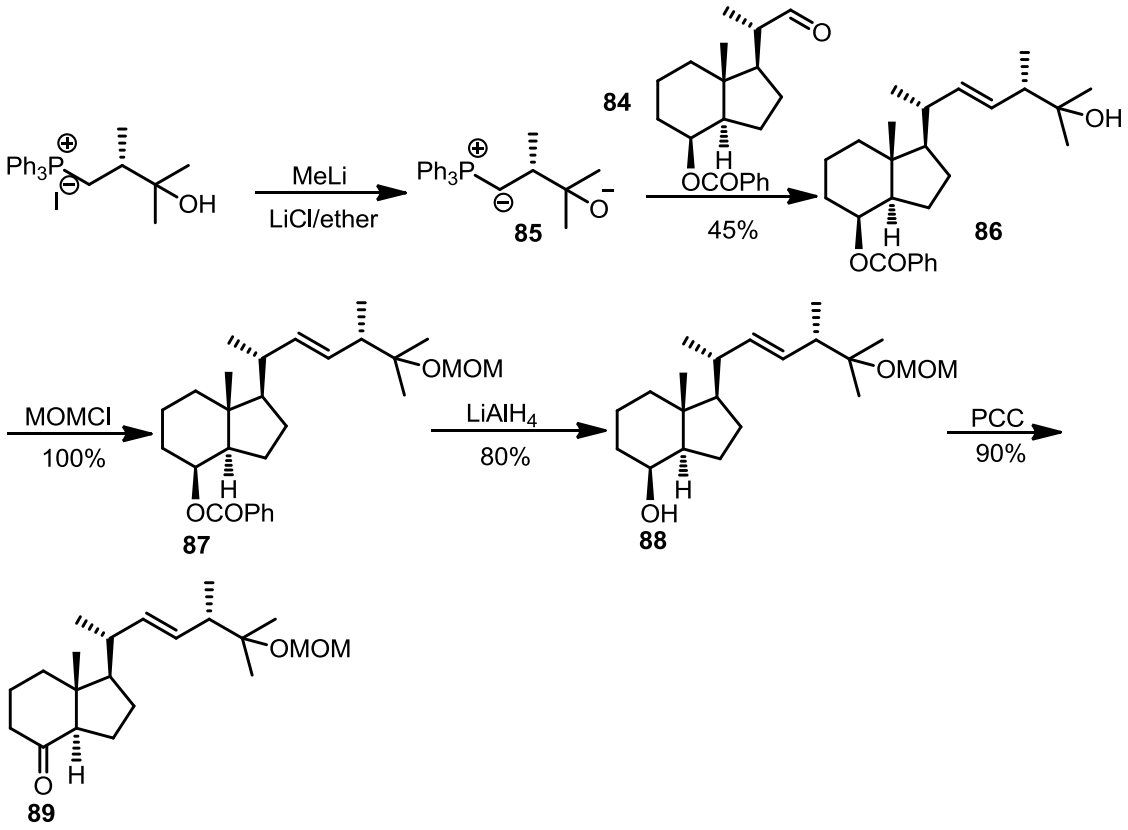
Several synthesis of DHT_2 (**79**) and DHT_3 (**80**) and other closely related hydrovitamins D have been reported. Summaries of these follow:

In 1992, a synthesis of 25-(OH)-DHT_2 was reported by Hanekamp, *et al*. [104] The synthesis started with vitamin D_2. Ozonolysis of natural vitamin D_2 followed by borohydride reduction afforded the C and D rings as diol (**82**). Benzoylation of **82** and subsequent selective debenzoylation of the 1^0 benzoate group with ethanolic potassium hydroxide gave **83**. Pyridinium chlorochromate oxidation of **83** afforded **84** (4 steps, 78%, Scheme 14).[105]



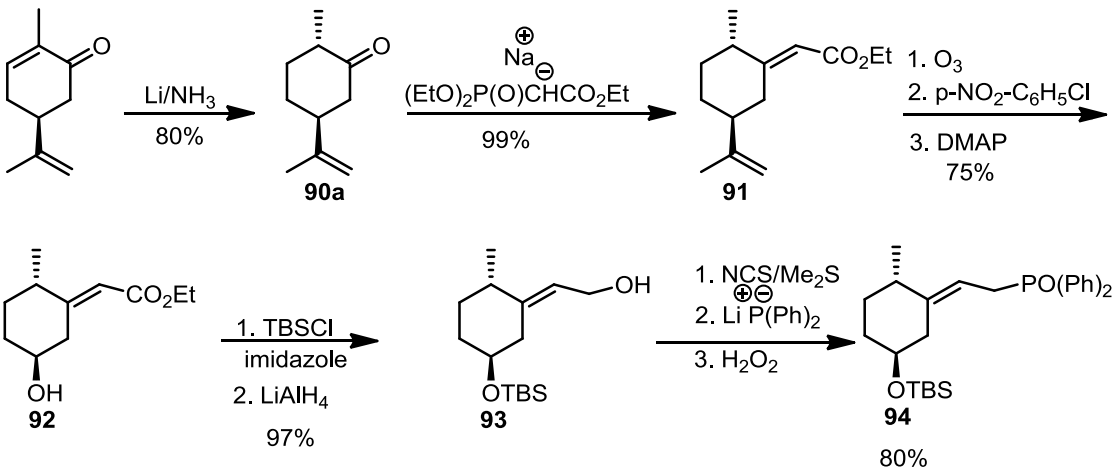
Scheme **14**: Synthesis of the CD-ring of 25-(OH)-DHT_2

Wittig olefination of **85**[106] with **84** gave **86** (Scheme 15). Protection of the tertiary hydroxyl group followed by subsequent removal of the benzoate group with lithium aluminum hydride gave **88**. Oxidation of **88** with pyridinium chlorochromate afforded the MOM-protected 25-OH Windaus and Grundmann's ketone **89**.



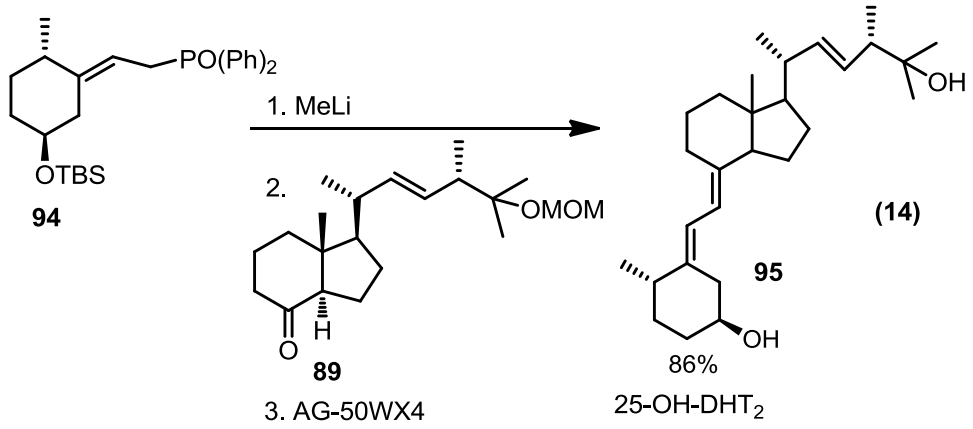
Scheme **15**: Synthesis of Windaus and Grundmann's ketone (**89**)

The Hanekamp, *et al*., synthesis of the A-ring fragment of 25-(OH)-DHT_2 started with reduction of commercially available S-(+)-carvone (Scheme 16).[107] The preparation of **91** via Wittig-Horner reaction of **90a** with ethyl (diethyloxyphosphinyl)acetate proceeded cleanly in near quantitative yield. Conversion of the isopropenyl group to a hydroxyl group, protection of the secondary hydroxyl group, followed by hydride reduction gave allylic alcohol **93**. Conversion of **93** to an allyl diphenylphosphine followed by peroxide oxidation afforded the phosphine oxide **94**.



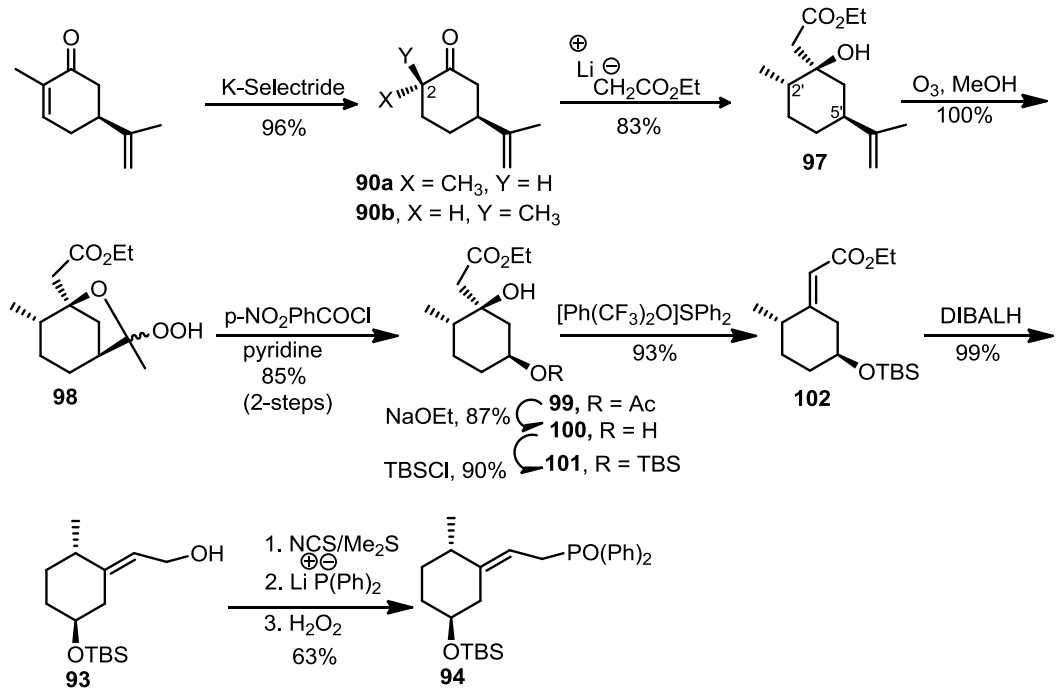
Scheme **16**: Synthesis of TBS-Protected A-ring

Finally, coupling of ketone **89** with the anion generated from phosphine oxide **94** afforded a bis-protected 25-OH-DHT$_2$ (Eqn. 14).[108, 109] Removal of methoxymethyl- and tert-butyldimethylsilyl protective moieties afforded the 25-hydroxylated dihydrotachysterol$_2$ **95**.



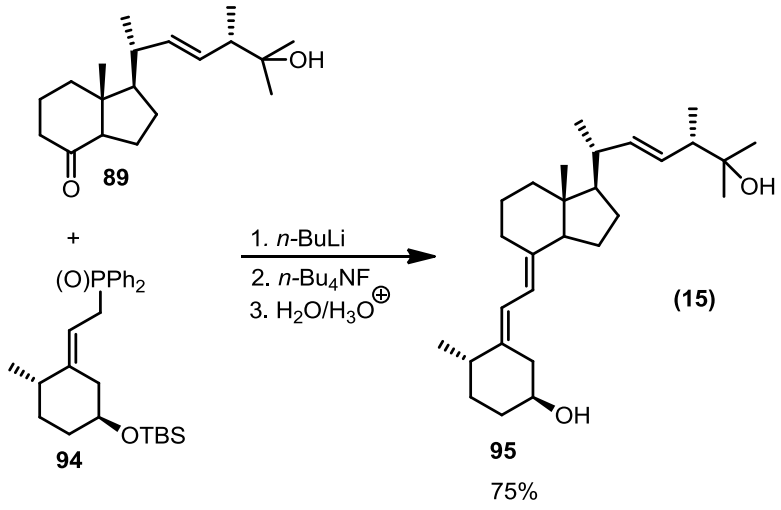
A second synthesis of 25-(OH)-DHT$_2$ was reported by Mourino *et al*. in 1992.[110] This synthesis like Hanekamp, *et al*.'s was based on Wittig-Horner coupling of a TBS-protected A-ring (**94**) and the Windaus and Grundmann's ketone.[80, 111]

Addition of lithium ethyl acetate[112] to trans-dihydrocarvone (**90**a)[113] gave **97** (Scheme 17). Ozonolysis **97** in MeOH afforded the hydroperoxy ketal **98**.[110] Acylation of **98** with *p*-nitrobenzoyl chloride and subsequent Criegee rearrangement[114, 115] gave the acetate **99** which on hydrolysis afforded diol **100**. The selective protection of 2^0-OH group of **100** gave **101** which on dehydration with Martin's sulfurane[116] gave the (*E*)-unsaturated ester **102**. Reduction of **102** with diisobutylaluminum hydride afforded the allylic alcohol **93** (Scheme 17). Transformation of **93** to a TBS-protected A-ring (**94**)[117] was accomplished in 63% yield as in Hanekamp's synthesis.[80]

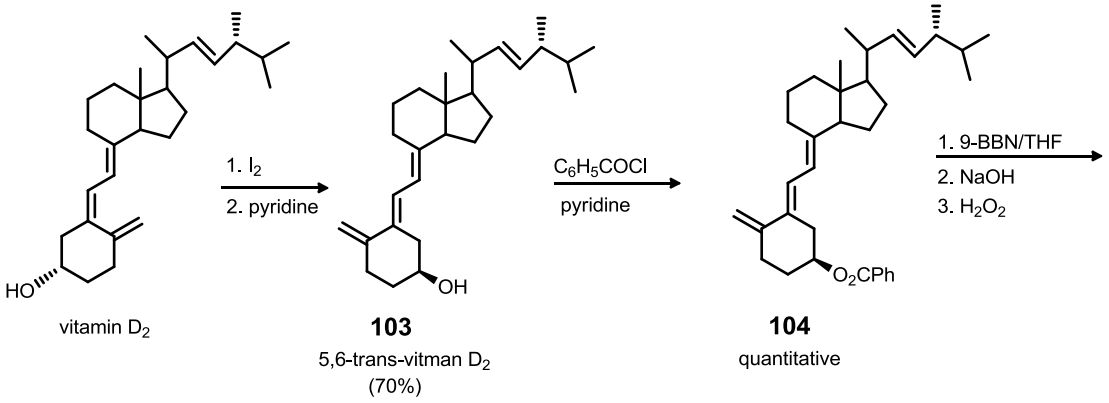


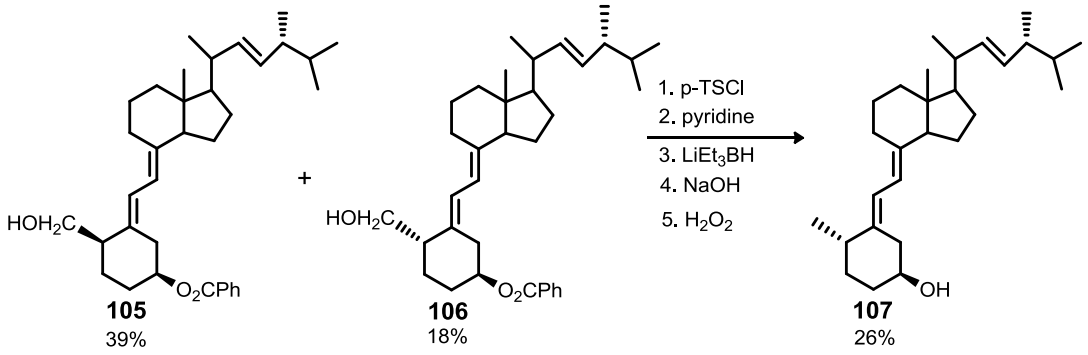
Scheme **17**: Synthesis of TBS-Protected A-ring

Coupling of ketone **89** and **94** afforded a bis-protected 25-OH-DHT_2 in 60% yield. Removal of methoxymethyl- and tert-butyldimethylsilyl protective moieties afforded the 25-hydroxylated dihydrotachysterol$_2$ **95** (Eqn.15).[94]



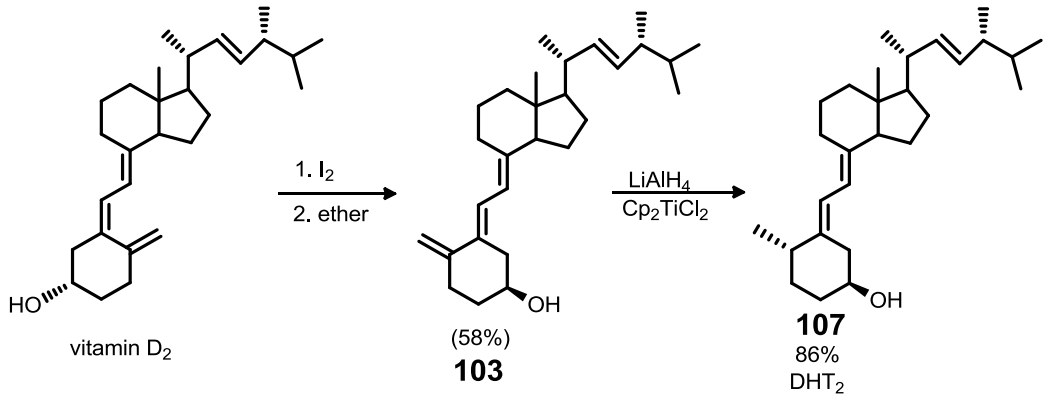
A synthesis of DHT_2 was reported by Okamura and Mourinò in 1977[118, 119] involving iodine-catalyzed[120] isomerization of vitamin D_2 to 5,6-trans-vitamin D_2 (**103**, Scheme 18). Benzoylation of **103** gave **104** which on selective hydroboration[121] afforded **105** and **106**. Tosylation of **106** followed by reduction and hydrolysis of the benzoate ester gave **107** in 26% yield (Scheme 18).[95, 118]





Scheme **18**: Synthesis of DHT_2

Another synthesis of DHT_2 was reported by Castedo *et al*. in 1998[94] involving selective Ti-catalyzed hydrogenation[122-126] of 5,6-trans-vitamin D_2[118] **103** to give **107** as the major product (Scheme 19).[94]

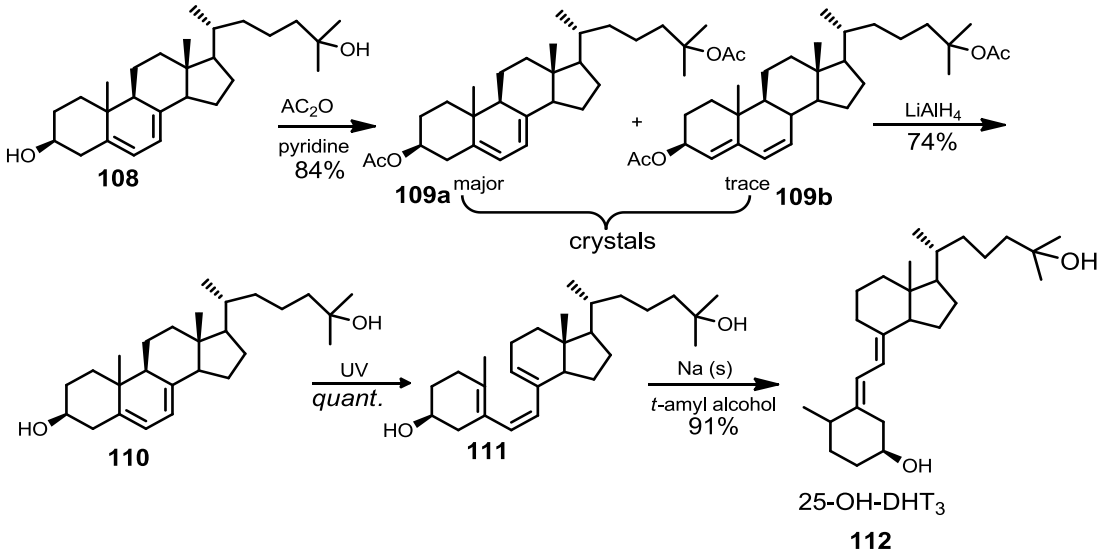


Scheme **19**: Synthesis of DHT_2

In 1969 DeLuca and Blunt reported the synthesis of 25-(OH)-DHT_3.[127-129]

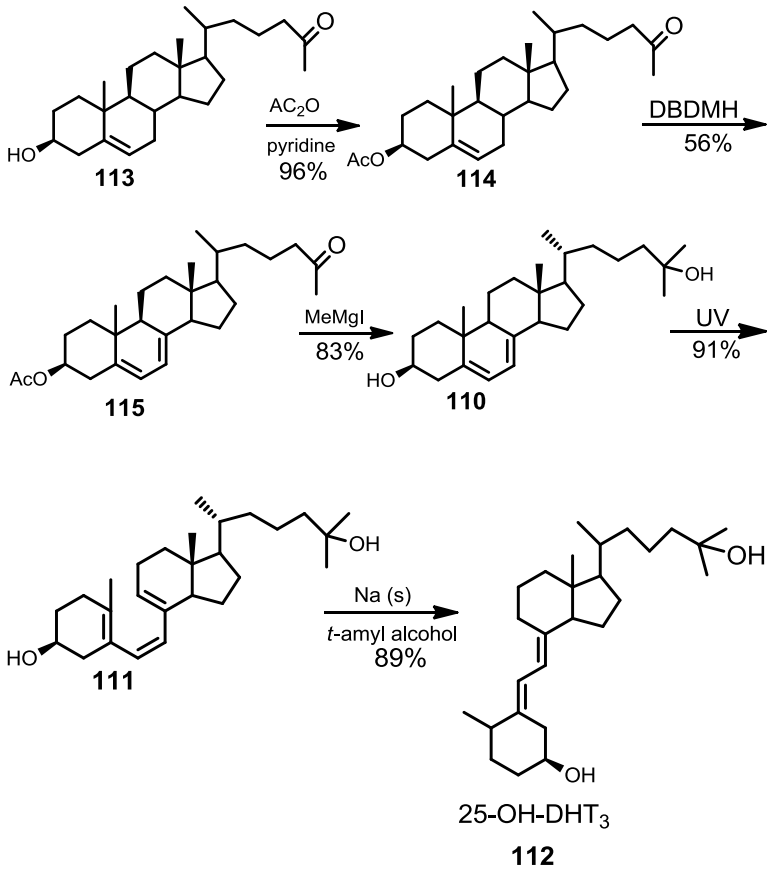
Acetylation of 25-(OH)-7-dehydrocholesterol (**108**)[129, 130] gave **109a** as the major diacetate product (Scheme 20). Lithium aluminum hydride reduction of **109a** gave diol

110 which on irradiation and reductive rearrangement gave 25-(OH)-DHT_3 (**112**) in 32% overall yield.



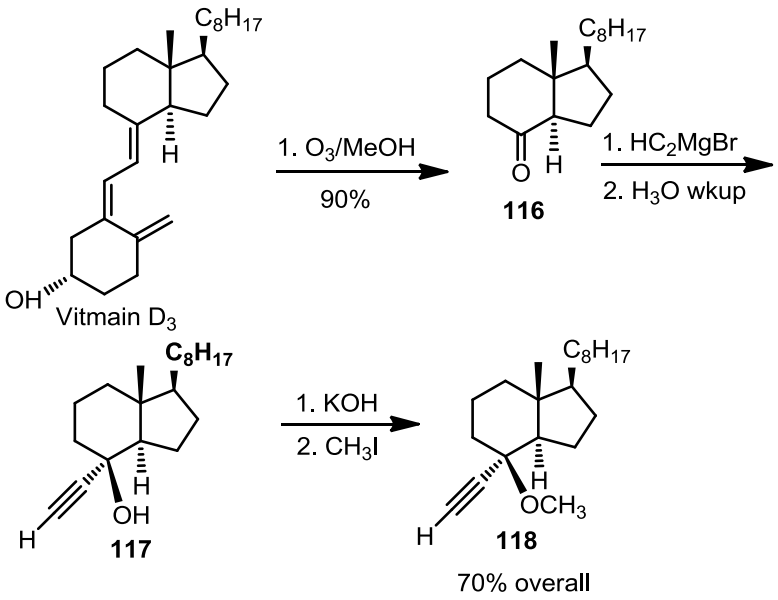
Scheme **20**: Synthesis of 25-(OH)-DHT_3

A second synthesis of 25-(OH)-DHT_3 **112** was reported by DeLuca and Suda *et al.*[131] in 1970 starting from 26-nor-cholesten-3β-ol-25-one (**113**, Scheme 21). Acetylation of **113** gave **114** which upon bromination/dehydrobromination[132] followed by nucleophilic addition of methyl magnesium iodide afforded cholesta-5,7-diene-3β,25-diol (**110**). UV irradiation of diol (**110**) gave tachysterol **111** which upon reduction afforded 25-OH-DHT_3 (**112**) (Scheme 21).[130, 131]



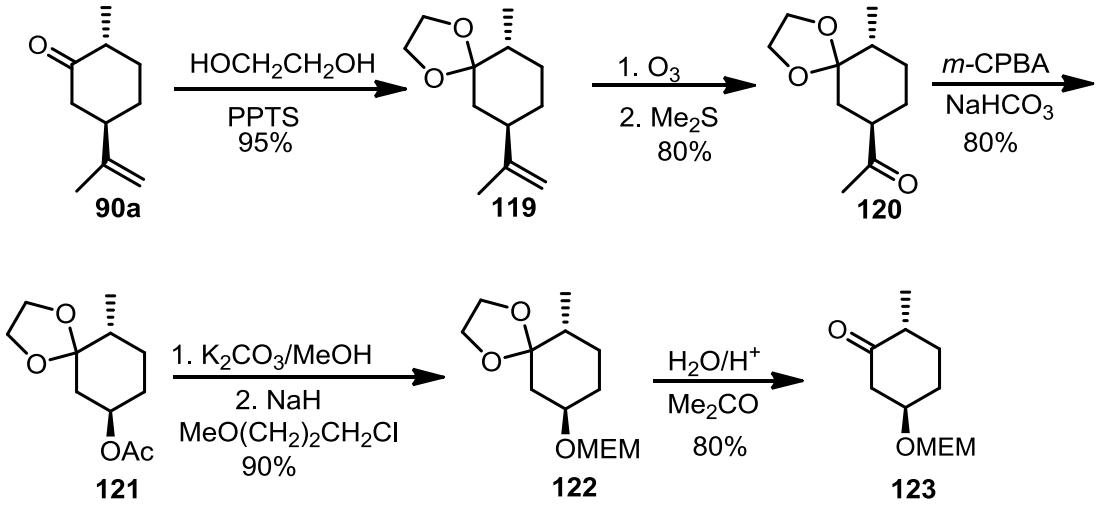
Scheme **21**: Synthesis of 25-(OH)-DHT_3

In 1986, Solladié and Hutt[133] reported the total synthesis of 25-OH-DHT_3 based on a low-valent titanium-induced reductive elimination (Scheme 22).[120, 134] The synthesis started with natural vitamin D_3. Ozonolysis of vitamin D_3 gave Grundmann's ketone[135] **116** in 90% yield. Addition of ethynyl magnesium bromide gave **117** which on methylation afforded **118** (Scheme 22).



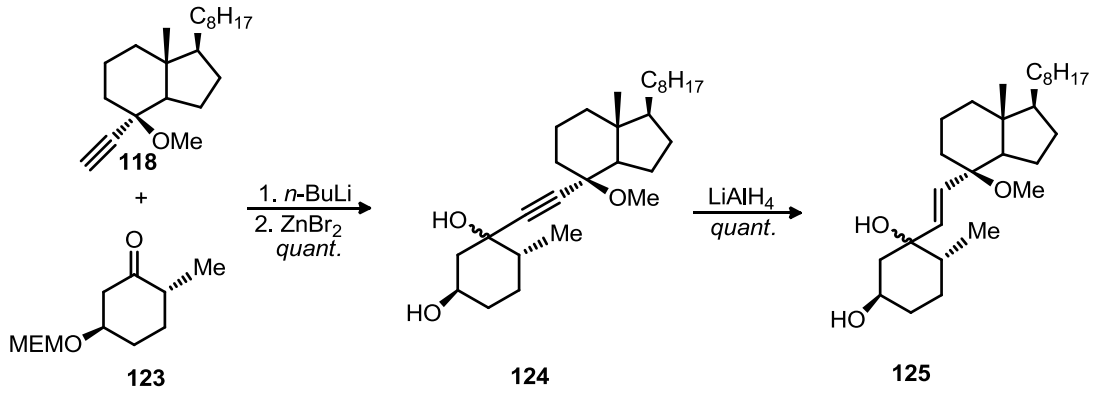
Scheme **22**: Construction of CD-fragment of DHT_3

The Solladié, *et al*., synthesis of the A-ring fragment started with reduction of commercially available S-(+)-carvone to trans-dihydrocarvone **90a** which on acetalation gave **119** (Scheme 23).[133] Ozonolysis of **119** afforded ketone **120**. Baeyer-Villiger oxidation of **120** with meta-chloroperbenzoic acid (*m*-CPBA) gave the desired acetate **121** with complete retention of configuration. Hydrolysis of the acetate group of **121** followed by protection of the OH group afforded **122**. Deacetalation of **122** gave the MEM-protected A-ring (**123**) (5 steps total, 85 % overall). [133]



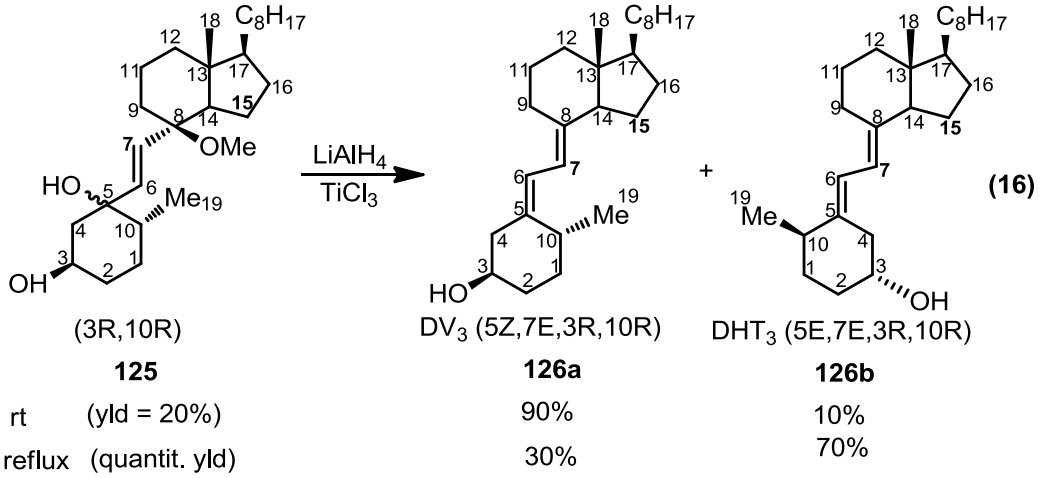
Scheme **23**: Synthesis of MEM-Protected A-ring

Addition of the anion derived from **118** to **123** followed by removal of the methoxyethoxymethyl (MEM) protecting group on the A-ring afforded **124** as a mixture of two diastereomers resulting from the non-stereospecific addition **118** to the carbonyl group of **123**. Reduction of the triple bond of **124** with lithium aluminum hydride gave **125**.[133]

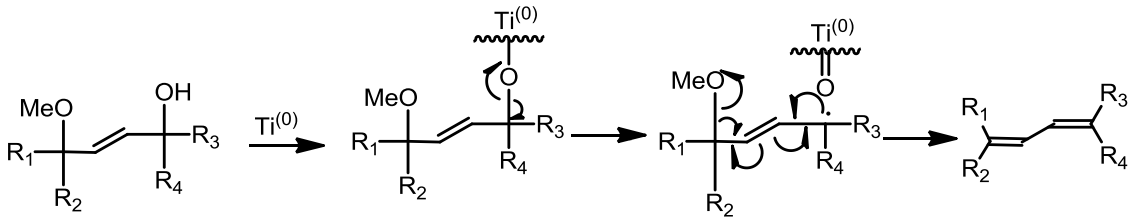


Scheme **24**: Synthesis of intermediate **125**

$Ti^{(0)}$ catalyzed reductive elimination of **125** gave a mixture of (5*Z*,7*E*)-dihydrovitamin D_3 (**126a**) and (5E,7E)-DHT_3 (**126b**) (Eqn. 16).[135-138]

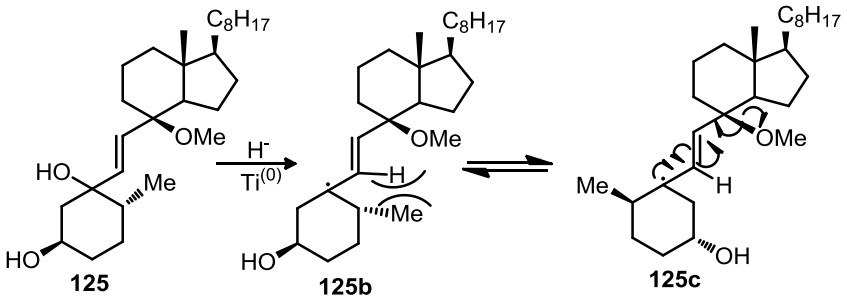


Mechanistically, $Ti^{(0)}$ is the active catalytic species in this reduction reaction which occurs by a single electron transfer on the $Ti^{(0)}$ surface.[118, 139, 140] A generic $Ti^{(0)}$ induced reductive elimination mechanism is shown in Scheme 25.



Scheme **25**: Generic $Ti^{(0)}$ induced reductive elimination

The formation of **126b** at elevated temperature arises from rotation about the C5-C6 bond of the allylic radical **125b** prior to elimination of –OMe thereby releasing steric interactions between C10-Me and C7-H groups to form **125c** (Scheme 26).[140, 141]



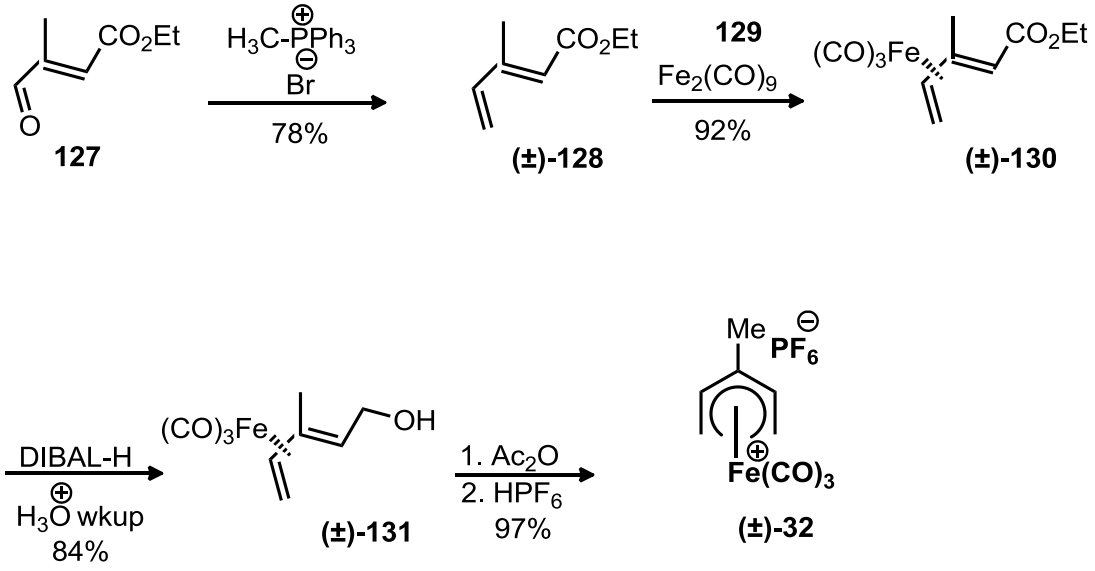
Scheme **26**: Formation of DHT_3

CHAPTER 2

2A.1. Racemic A-Ring Synthons

In an effort to prepare protected DHT A-ring fragments, cation **32** was prepared from ethyl-3-methyl-4-oxo-2-butenoate **127** following the literature procedure.[48] Ethyl (*E*)-3-methyl-2,4-pentadienoate (±)-**128** was prepared from the commercially available ethyl-3-methyl-4-oxo-2-butenoate **127** via a modification to the literature procedure. The following modifications led to significantly improved yields (from 47%[48] to 78-83%): (1) addition of *n*-butyllithium to a suspension of methyltriphenylphosphonium bromide in tetrahydrofuran at -78 ^{0}C instead of 0 ^{0}C,[29] (2) addition of **127** to the resulting wine-red methylenetriphenylphosphorane solution at -78 ^{0}C instead of 0 ^{0}C and (3) allowing the reaction mixture to rise to room temperature with vigorous stirring for 4 h instead of refluxing for 24 h. These modifications ensured shorter reaction times and easier/cleaner work-up. The diene product (±)-**128** thus obtained was sufficiently pure and was used in the complexation step without further purification. Complexation of diironnonacarbonyl[142] **129** with (±)-**128** gave tricarbonyl(ethyl-3-methyl-(2E)-penta-2,4-dienoate)iron (±)-**130**. Much lower yields (26-31%) of the (diene)iron complex (±)-**130** were obtained when the solvent was changed from tetrahydrofuran to diethyl ether (Et_2O).

Reduction of the (diene)iron complex **130** followed by dehydration of (±)-**131** gave a carbocation which was trapped as the hexafluorophosphorate salt (±)-**32** (5-steps total, 59%, Scheme 27). The structures of (±)-**128**, (±)-**130**, (±)-**131** and (±)-**32** were assigned by comparison of their NMR spectral data with the literature values.[29, 48]

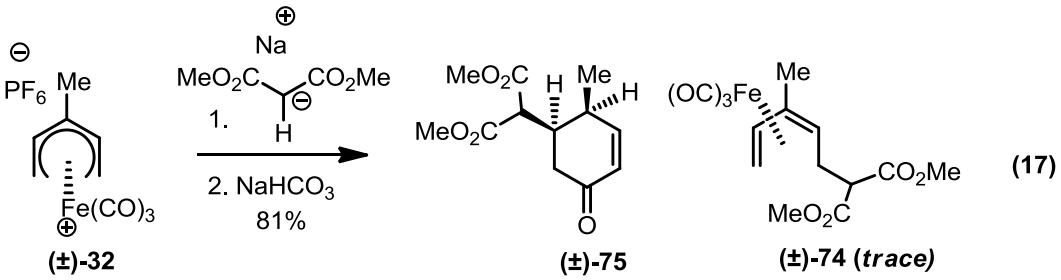


Scheme **27**: Synthesis of (pentadienyl)iron cation (±)-**32**

Previously in chapter 1 (sec. **A.10**), we discussed the mechanistic rational for formation of cyclohexenone (±)-**75** from the reaction of (±)-**32** with sodium dimethyl malonate. To test the scope of the cyclohexenone formation from the reaction of stabilized nucleophiles with (±)-**32** as well as their application to synthesis of protected DHT A-ring fragments, the reaction of cation (±)-**32** with anions of malonate, phosphonoacetate and sulfonyl acetate nucleophiles was examined (Eqns. 18 and 20).

2A.2. Synthesis of A-Ring synthon (±)-142

Nucleophilic attack of sodium dimethyl malonate at either C2/C4 internal positions of the symmetric cation (±)-**32** gave cyclohexenone (±)-**75** as the major regioisomer along with a trace of the (1,3*Z*-diene)iron complex (±)-**74** (Eqn. 18).



The identity of (±)-**75** was confirmed by comparison of its NMR spectral data with the literature values.[48] In particular, the signals at δ 6.11 (dd, J = 6.1, 10.1 Hz, 1H) ppm and δ 5.81 (d, J = 10.1 Hz, 1H) ppm were diagnostic of H^3 and H^2 olefinic protons respectively. These chemical shifts were consistent with the literature values[143] for cis-4,5-dimethyl-2-cyclohexenone (±)-**132** (Fig. 6).

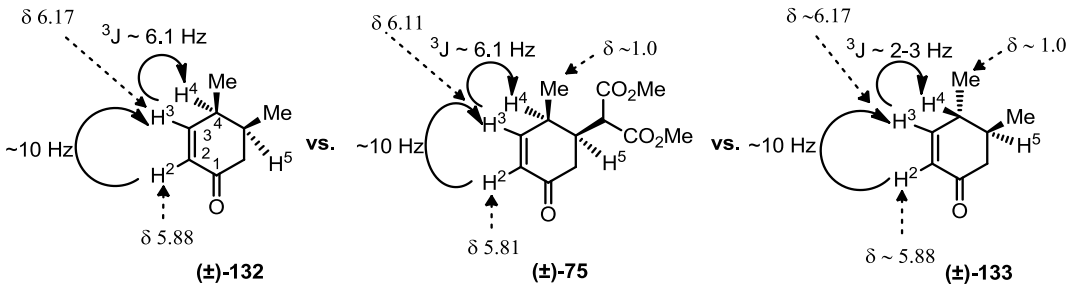


Fig. **6**: Characteristic ^{1}H NMR data for 4,5-disubstituted-2-cyclohexenone

Furthermore, the ^{3}J = 6.1 Hz coupling constant was consistent with a pseudo-equatorial disposition for H^4.[143] A smaller $^3J_{H^3\text{-}H^4}$ coupling constant (~ 2-3 Hz) would have been indicative of pseudo-axial deposition for H^4.[48, 143] The implication of this is that the C4 and C5 side bonds will be cis to each other (Fig. 6). Such an arrangement of the C3-methyl group and the C4-propanedioate group minimizes the steric repulsions of the gauche pentane interactions between these groups (Fig. 7).

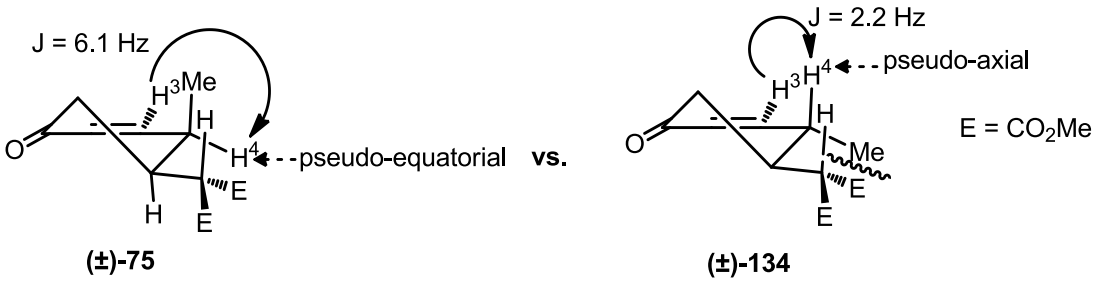
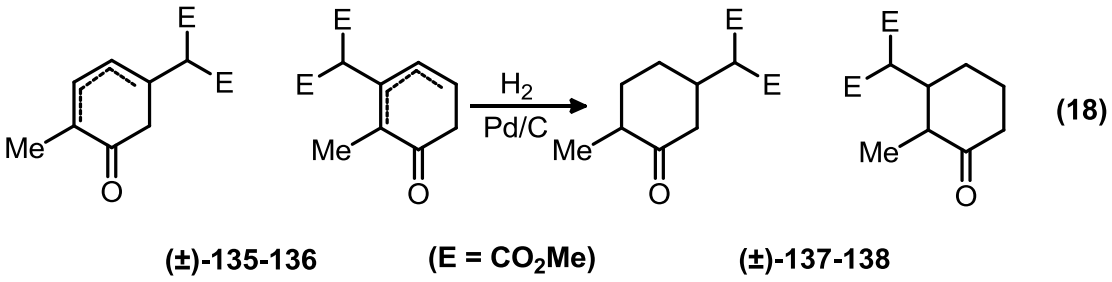


Fig. **7** Coupling constants for H^3 (*cis* vs *trans* 4,5-disubstituted cyclohexenones

It is also noteworthy to mention that for the known *trans*-4,5-dimethyl-2-cyclohexenone (±)-**133**, the H^3 signal (δ 5.90 ppm) appears as ddd (*J* = 10.2, 2.2, 0.7 Hz), where 2.2 Hz coupling is the characteristic of the pseudo-axial disposition of H^4.[144]

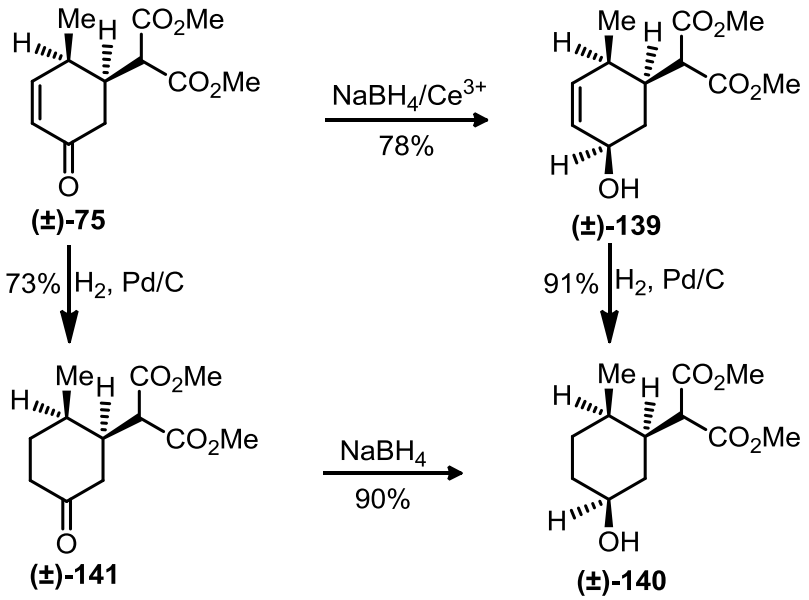
The absence of a methyl-singlet at ca. δ 1.70-1.90 ppm, rules out the isolation of either 3-cyclohexenone or 4-cyclohexenone (±)-**135-(**±)-**136** products both of which have been reported under similar reaction conditions with substituted (pentadienyl)iron cations (Eqn. 17).[64]



Reduction of cyclohexenone **(±)-75** under Luche conditions[145] gave cyclohexenol (±)-**139** as a single diastereomer. Hydride addition to C=O is anticipated under these conditions due to the coordination of Ce^{3+} to both C=O and BH_4^-.The C2-C3 double

bond of **(±)-139** was smoothly reduced with activated palladium on carbon and hydrogen gas at 45 psi to give cyclohexanol (±)-**140** as a single diasteroisomer (Scheme 28).

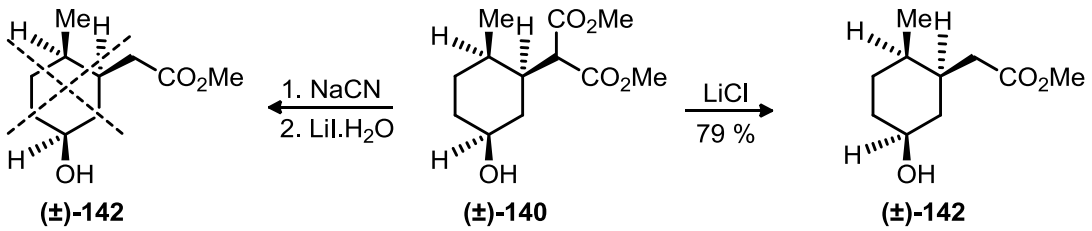
Alternatively, catalytic hydrogenation of cyclohexenone (±)-**75** gave the cyclohexanone (±)-**141** which upon hydride reduction with $NaBH_4$ gave the same cyclohexanol **(±)-140**. The overall yields for these two step sequences (68% compared to 71%) are comparable.



Scheme **28**: Synthesis of cyclohexanol (±)-**140**

The relative stereochemistry about the ring of cyclohexanol **(±)-140** was assigned on the basis of its ^{1}H NMR spectral data. In particular, the signal for the alcohol methine proton of **(±)-140** which appears at δ 3.60 ppm, exhibited two large couplings (δ 3.60, tt, J = 2.8, 10.3 Hz) which were assigned as axial-axial couplings indicating that the hydroxyl group occupies an equatorial orientation. It was further assumed that the lowest

energy conformation of (±)-**140** would have the more bulky propanedioate substituent in an equatorial orientation and the cis C-2 methyl group in an axial orientation.

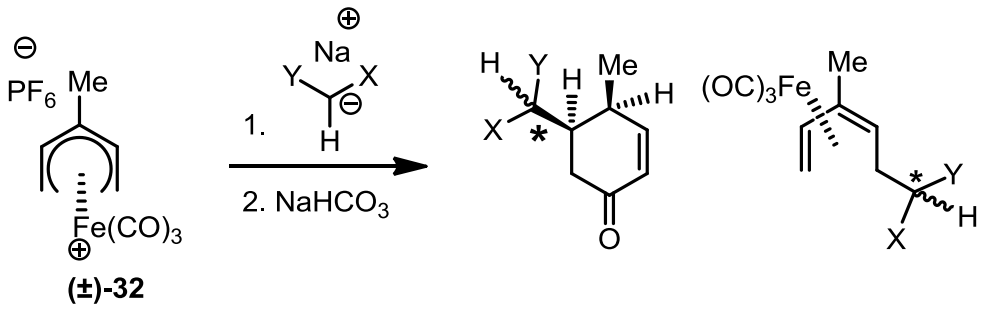


Scheme **29**: Krapcho decarbomethoxylation of cyclohexanol (±)-**140**

Preliminary efforts at decarbomethoxylation of cyclohexanol (±)-**140** with sodium cyanide and lithium iodide[146] were unsuccessful with eventual decomposition of the starting material on prolonged heating. In general, dimethyl and diethyl cyclohexylmalonates reportedly exhibit very little tendency to decarbomethoxylate under Krapcho conditions.[146] Substituents adjacent to the carbon bearing the geminal diester groups sterically inhibit water attack at one of the ester carbonyl groups. Additionally nucleophilic substitution of the hydroxyl functionality by either iodide or cyanide anions could possibly be a competing side reaction (Scheme 29).

In contrast, decarbomethoxylation[146] of cyclohexanol **(±)-140** proceeded smoothly with lithium chloride in refluxing dimethyl sulfoxide (Scheme 29) to afford methyl (cyclohexyl)acetate (±)-**142**. Structural assignment of **(±)-142** was made on the basis of its ^{1}H and ^{13}C NMR spectral data. In particular, signals at δ 2.36-2.17 (m, 2H) ppm in the ^{1}H NMR spectrum and δ 36.1 ppm in the ^{13}C NMR spectrum of **(±)-142** were assigned to the methylene protons alpha to the CO_2Me group. Additionally, the signal at δ 174.0 ppm

was assigned to the CO_2Me group compared to δ 169.3 ppm and δ 168.9 ppm for the precursor propanedioate.



X = CO_2Et, Y = $P(O)(OEt)_2$	(±)-**143** (84%)	(±)-**144** (trace)
X = SO_2Ph, Y = $P(O)(OEt)_2$	(±)-**145** (72%)	--
X = SO_2Ph, Y = CO_2Me	(±)-**146** (72%)	(±)-**147** (trace)

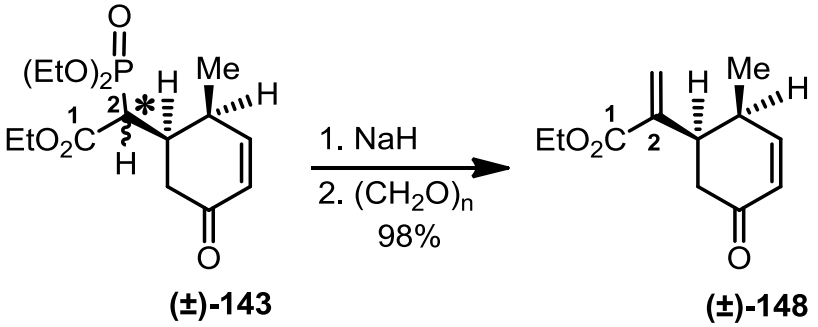
Scheme **30**: Reaction of cation **32** with stabilized nucleophiles

Treatment of cation **32** with sodium triethyl phosphonoacetate, sodium diethyl (phenylsulfonyl)methanephosphonate, or sodium methyl (phenylsulfonyl)acetate [prepared from sodium hydride and appropriate precursor] in anhydrous THF gave the cyclohexenones (±)-**143**, (±)-**145** and (±)-**146** respectively in good yields along with a trace of the C1/C5 nucleophilic addition products (±)-**144** or (±)-**147** (Scheme 30). Cyclohexenones (±)-**143**, (±)-**145** and (±)-**146** were each isolated as a mixture of two diastereomers at the indicated (*) carbon.

The structures of (±)-**143**, (±)-**145** and (±)-**146** were assigned based on their NMR spectral data. The signals at ca. δ 6.95-7.05(dd, 1H) ppm and ca. δ 5.9-6.0 (d, J = 6 Hz, 1H) ppm were assigned to the sp^2 olefinic hydrogens of each. The $^3J_H{}^3{}_{-H}{}^4 \sim 6$ Hz coupling constant for each was consistent with a pseudo-equatorial disposition for H^4 proton and

thus a cis arrangement of the C3-methyl and C4-substituent was assigned. These assignments are consistent with that for the product obtained for the reaction of cation **32** with sodium dimethylmalonate, (±)-**75**.

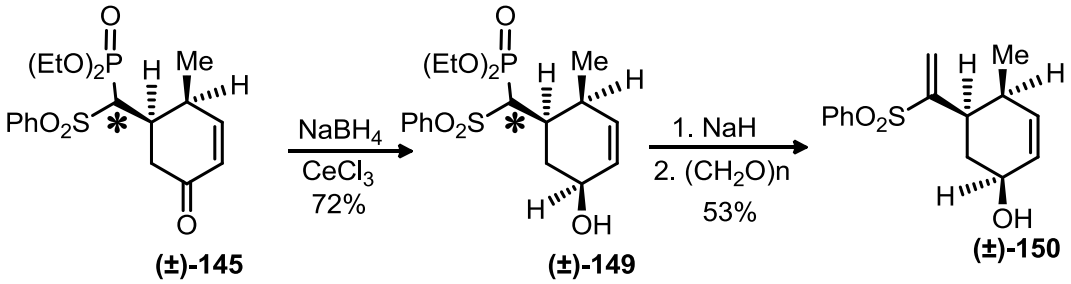
It was not possible to assign the signals in the ^{13}C NMR spectrum of **(±)-143** or (±)-**145** to each of the carbon atoms due to the presence of two sets of signals and further complicated by coupling with the phosphorus atom in each.



(±)-143 **(±)-148** **(20)**

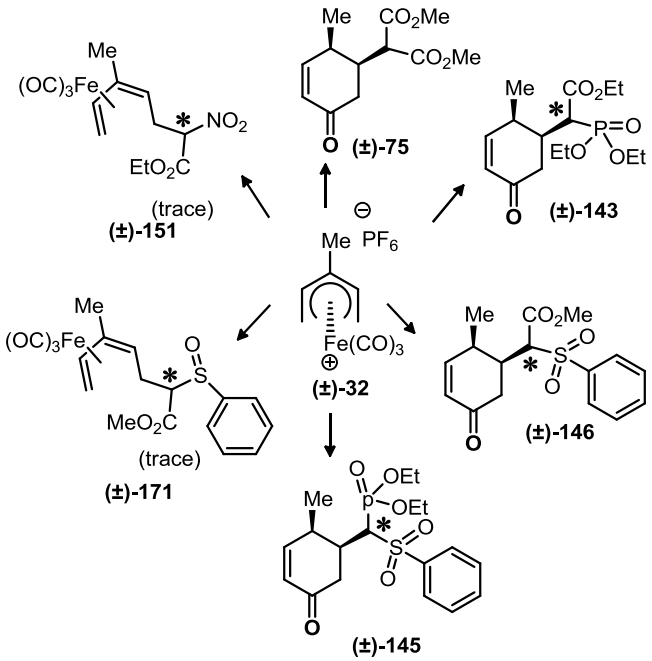
Horner-Emmons olefination of the mixture of diastereomer (±)-**143** with paraformaldehyde in anhydrous THF gave the enoate (±)-**148** (Eqn. 18). Since carbon 2 is not a chiral center, **(±)-148** was isolated as a single diastereomer instead of a mixture of diastereomers. The structure of **(±)-148** was assigned based on its NMR spectral data. The ^{1}H NMR spectrum of **(±)-148** evidenced signals at δ 6.39 (s, 1H) ppm and δ 5.48 (s, 1H) ppm which were assigned to the diastereotopic methylene olefinic hydrogens. Additionally, the signals at δ 7.02 ppm (dd, J = 4.1, 9.5 Hz, 1H) ppm and δ 5.99 ppm (d, J = 9.5 Hz, 1H) were assigned to the two sp^2 cyclohexenyl protons. The magnitude of the H^3-H^4 vicinal coupling (J = 4.1 Hz) is intermediate to that anticipated for cis-3,4-disubstituted and trans-3,4-disubstituted 2-cyclohexenones (6 Hz vs. 2 Hz). While this

coupling was not diagnostic in assigning the relative ring stereochemistry it was deemed unlikely that the Horner-Emmons reaction conditions would lead to epimerization at either C3 or C4. The signals at δ 155.6, 140.9, 127.6, 125.3 ppm in the ^{13}C NMR spectrum of **(±)-148** corresponded to the four olefinic carbons.



Scheme **21**: Horner-Emmons olefination of (±)-**149**

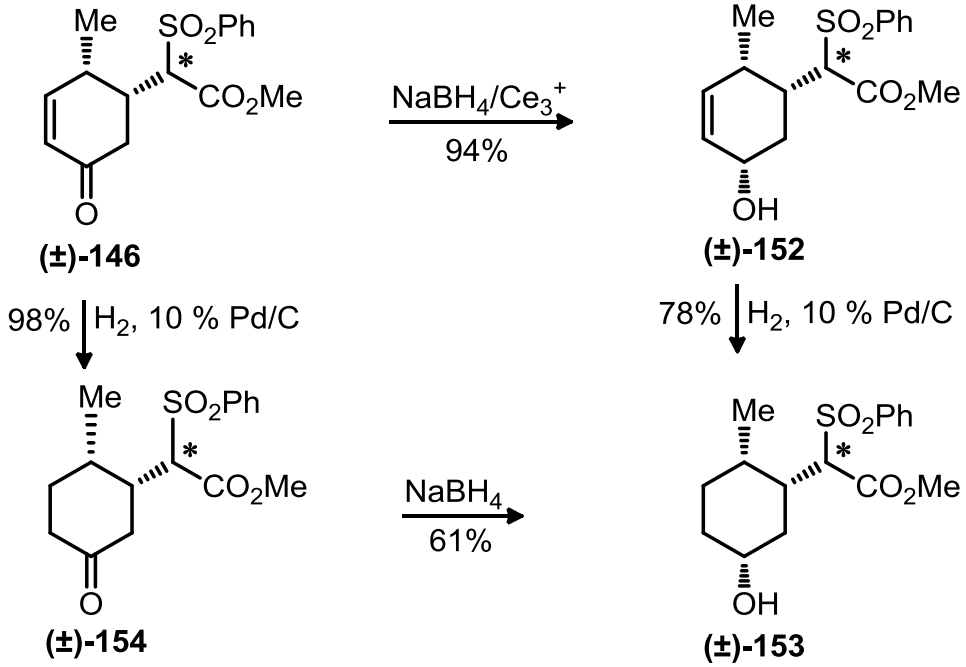
Luche reduction[145] of **(±)-145** gave cyclohexenol **(±)-149** which was subjected Horner-Emmons olefination to afford (±)-**150** (Scheme 21). The structure of (±)-**150** was assigned based on its ^{1}H and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of (±)-**150** had signals at ca. δ 6.39 (s, 1H) and 5.48 (s, 1H) ppm which were assigned to the diastereotopic sp^2 hydrogens. Additionally, the signals at δ 5.66 ppm (dddd, 1H) and δ 5.54 (dd, 1H) ppm were assigned to the two sp^2 cyclohexenyl protons. Assignment of the ^{13}C NMR signals to individual carbons was not attempted due to the presence of two sets of signals and further complications arising from coupling to the phosphorus atom.



Scheme **22**: Summary of nucleophilic addition products of cation **32**

2B.1. Synthesis of Protected DHT A-ring Fragments

Elaboration of the cyclohexenone **(±)-146** to a DHT A-ring fragment was attempted (Scheme 31). To this end, Luche reduction of the diastereomeric mixture of cyclohexenones (±)-**146** gave the cyclohexenol **(±)-152** as a as a mixture of diastereomers at the C* position. Catalytic hydrogenation of (±)-**152** gave the cyclohexanol **(±)-153** also as a mixture of diastereomers. Alternatively, the cyclohexanol **(±)-153** was prepared by catalytic hydrogenation of the diastereomeric mixture of cyclohexenones **(±)-146** to afford the cyclohexanones **(±)-154**, followed by hydride reduction to afford (±)-**153** as a mixture of diastereomers. While these compounds were isolated as a mixture of diastereomers at the exocyclic carbon, a clean sample of one or both diastereomers was isolated for **(±)-146**, (±)-**152** and **(±)-153** after careful column chromatography.

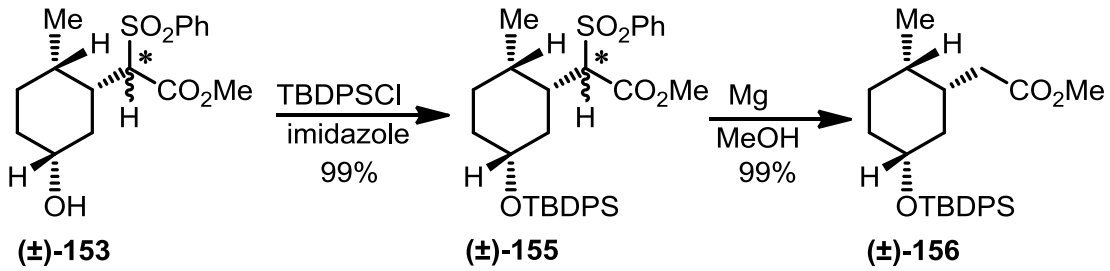


Scheme **31**: Synthesis of cyclohexanol **(±)-153**

The structures of the cyclohexenol **(±)-152** and cyclohexanone **(±)-154** intermediates were established on the basis of their IR, ^{1}H and ^{13}C NMR spectral data. In particular, the signals in the ^{1}H NMR spectrum of **152** at δ 5.76 (ddd, *J* = 1.2, 4.5, 10.2 Hz, 1H) ppm and δ 5.61 (d, *J* = 10.2 Hz, 1H) ppm were assigned to the two olefinic protons. Additionally the absence of a carbonyl signal at ca. δ 190-210 ppm in the ^{13}C NMR spectrum of cyclohexenol **(±)-152** was consistent with reduction of the cyclohexenone **(±)-146**. For cyclohexanone **(±)-154** the absence of olefinic signals at ca. δ 5.0-6.0 ppm in the ^{1}H NMR spectrum as well as the absence of signals at δ 156.9 and 127.8 ppm in the ^{13}C NMR spectrum also confirmed the saturation of the C2-C3 double of the starting cyclohexenone (±)-**146**.

The structure of cyclohexanol **(±)-153** was assigned based on its ^{1}H and ^{13}C spectral data. In particular signals at δ 167.7 [166.7] ppm in the ^{13}C NMR spectrum were assigned to the diastereomeric carbomethoxyl carbons of (±)-**153**. While the cluster of signals at ca. δ 140-129 ppm correspond to the aromatic carbons, and signals at ca. δ 70-71 ppm corresponded to the 6-membered alcohol carbon. The ^{1}H NMR spectrum of **(±)-153** had signals in the range of δ 7.9-7.6 ppm which integrated to five protons corresponded to the aromatic protons. The relative stereochemistry about the cyclohexyl ring of cyclohexanol (±)-**153** was assigned on the basis of its ^{1}H NMR spectral data. In particular, the signal for the alcohol methine proton of cyclohexanol (±)-**153** exhibited two small couplings and two large couplings (δ 3.58, tt, *J* = 2.8, 10.3 Hz). These larger values correspond to axial-axial couplings indicating that the hydroxyl group occupies an equatorial orientation. The signal for the alcohol methine proton of the other diastereomer of cyclohexanol **(±)-153** is relatively broad and appears at a similar chemical shift δ

(3.68-3.57, m) indicative of an equatorial orientation for the alcohol functionality in this diastereomer as well.



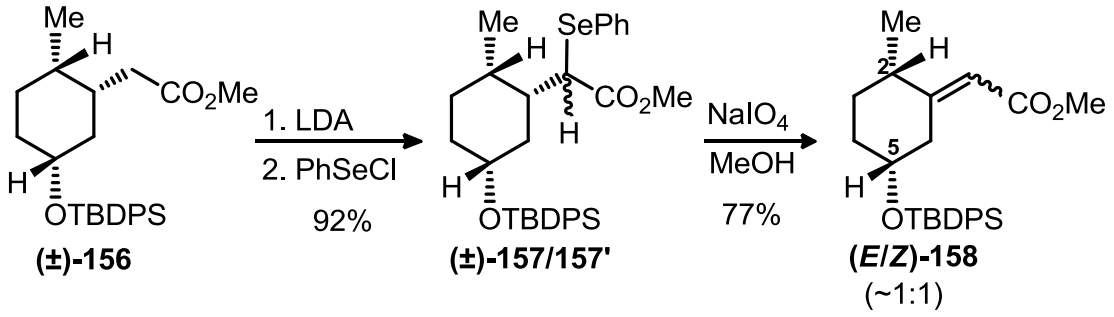
Scheme **32**: Desulfonylation of cyclohexanol (±)-**153**

Reaction of the mixture of diastereomers **(±)-153** with *t*-butyldiphenylsilyl chloride afforded the silyl ether **(±)-155** as a mixture of diastereomers. While the diastereomeric mixtures could be separated by careful column chromatography in certain cases, it was more convenient to carry these mixtures forward. Notably, reductive desulfonylation of the mixture of diastereomers **(±)-155** gave **(±)-156** as a single diastereomer (Scheme 32).

The structure of **(±)-156** was assigned on the basis of its ^{1}H and ^{13}C NMR spectral data. In particular, signals in the range of 7.8-7.3 ppm in the ^{1}H NMR spectrum which integrated to 10 protons were assigned to the aromatic protons, while the sharp singlet at δ 1.09 (s, 9H) ppm was assigned to the *t*-butyl group. Additionally, the signals at δ 51.5 ppm in the ^{13}C NMR spectrum and δ 2.26-2.20 (2xdd, 2H) ppm in the ^{1}H NMR spectrum were assigned to the α-methylene carbon and its attached protons.

Deprotonation of **(±)-156**, followed by reaction with phenylselenyl chloride gave a mixture of diastereomeric α-phenylselenyl esters **157/157'**, which upon oxidation and

syn elimination of phenylselenic acid gave an equimolar mixture of stereoisomeric enoates **(*Z*)-158** and **(*E*)-158** (Scheme 33).



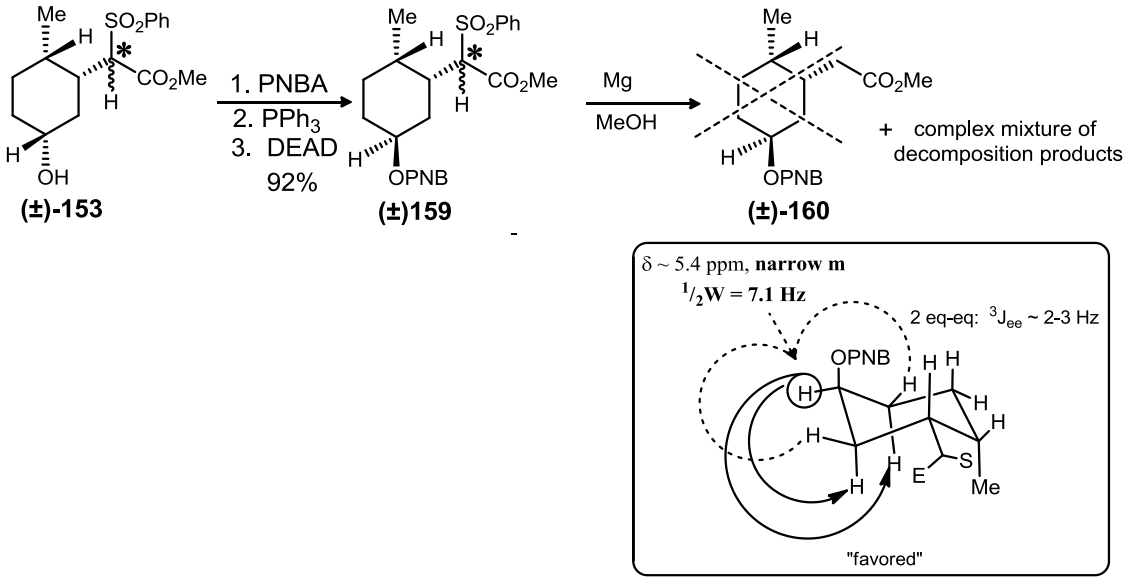
Scheme **33**: Attempted synthesis of protected DHT A-ring fragment (*E*/*Z*)-(±)-**158**

The structure of the α-phenylseleno esters **(±)-157/157'** was assigned based on its ^{1}H and ^{13}C NMR spectral data. In particular, the signals at δ 3.37 (d, *J* = 12.0 Hz, 1H) ppm and 3.39 (d, *J* = 11.8 Hz, 1H) ppm were assigned to the α-selenyl proton for each of the two diastereomers, while signals at ca. δ 49.3 [49.2] ppm in the ^{13}C NMR spectrum were assigned to the α-seleno acetate carbon.

The structural assignment for (*E*/*Z*)-**(±)-158** was based on its ^{1}H and ^{13}C NMR spectral data. In particular, the pair of singlets at δ 5.73 (s, 1H) and δ 5.36 (s, 1H) ppm were assigned to the α-olefinic protons, while the pair of multiplets at δ 4.05 (m, 1H) and δ 3.98 (s, 1H) ppm were assigned to the H-5 protons. Additionally the signals at 3.64 (s, 3H) and 3.63 (s, 3H) ppm were each assigned to the carbomethoxyl protons. Signals at δ 1.07 (s, 9H) and δ 1.04 (s, 9H) ppm corresponded to the *t*-butyl protons. The signals at δ 1.13 (d, *J* = 7.8 Hz, 3H) and δ 1.11 (d, *J* = 6.0 Hz, 3H) ppm were assigned to the C2-methyl protons.

2B.2. Protected DHT A-ring fragments

Next we sought to prepare a DHT A-ring synthon that had the C-2-methyl and C-5 hydroxyl groups mutually trans. To this end reaction of diastereomeric mixture of cyclohexanols **(±)-153** with *p*-nitrobenzoic acid under Mitsunobu conditions[147] gave an equimolar mixture of benzoate esters **(±)-159** which were diastereomeric at the * carbon (Scheme 34). These reaction conditions are known to proceed with inversion at the carbinol carbon.

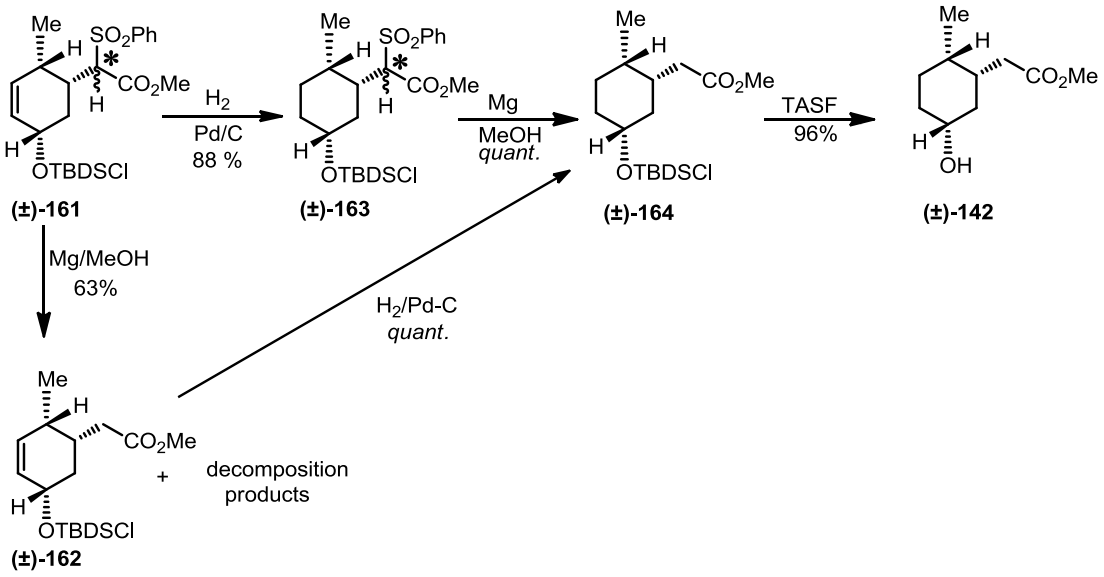


Scheme **34**: Desulfonylation of cyclohexanol **(±)-153**

The structural assignment for (±)-**159** was based on its ^{1}H and ^{13}C NMR spectral data (Scheme 4). In particular narrow multiplets at δ 5.41-5.40 and δ 5.31-5.30 ppm with half-width of 7.4 Hz in the ^{1}H NMR spectrum of (±)-**159** was assigned to the H^5 proton. The narrowness of these signals reflects the lack of any large axial-axial couplings and thus H^5 was assigned an equatorial orientation (therefore OPNB is axial). Additionally,

sets of signals at δ 4.02 (br s, 1H) and δ 4.00 (dd, J = 3.3 Hz, 1H) ppm corresponded to the epimeric α-phenylsulfonyl methine protons. The C-4 methyl protons corresponded to the signals at δ 1.05 (d, J = 7.0 Hz, 3H) and δ 0.96 (d, J = 7.0 Hz, 3H) ppm. In the ^{13}C NMR spectra of **(±)-159** the signals at δ 71.3 [70.9] ppm were assigned to the C5 carbinol carbons of each diastereomer.

The attempted desulfonylation of a diastereomeric mixture of cyclohexanols (±)-**159** gave a complex [148]mixture of decomposition products. The Mg/MeOH desulfonylation system has also been reported to effect smooth removal of *p*-benzoate groups (Scheme 34).[149, 150]

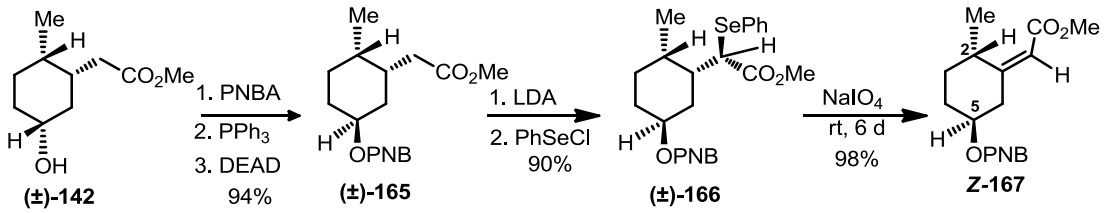


Scheme **35**: Synthesis of methyl (cyclohexyl)acetate (±)-**142**

Reductive desulfonylation of the diastereomeric mixture of silyl protected cyclohexanols (±)-**163** gave (±)-**164** as a single diastereomer in quantitative yield

(Scheme 35). Deprotection of (±)-**164** with TASF gave the cyclohexanol **(±)-142** (Scheme 35).

Reaction of cyclohexanol **142** with *p*-nitrobenzoic acid under Mitsunobu conditions gave (±)-**165** as a single diastereomer (Scheme 36). **α**-Deprotonation of (±)-**165**, followed by reaction with phenyl selenyl chloride gave α-phenylselenyl ester **(±)-166**, which upon oxidation and elimination of phenylselenic acid afforded the enoate (*Z*)-**167** only (Scheme 36).

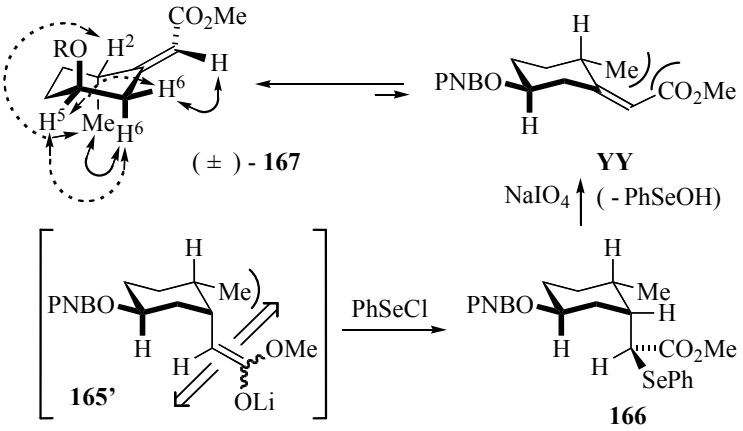


Scheme **36**: Attempted synthesis of protected DHT A-ring fragment (*Z*)-(±)-**167**

The structural assignment for (±)-**167** was based on its ^{1}H NMR spectral data. In particular, the singlet at δ 5.61 ppm which integrated to one proton was assigned to the α-olefinic proton, while the multiplet at δ 5.44 ppm was assigned to H-5. The assignment of this latter signal was further supported by COSY crosspeaks with the signal for H-6ax and H-6eq (δ 2.78 and 2.46 ppm respectively). Assignment of the broad multiplet at δ 4.25-4.15 ppm to H-2 was aided by a COSY crosspeak with the Me-2 doublet at δ 1.22 ppm.

The lack of any NOESY crosspeaks between the α-olefinic proton signal (δ 5.61 ppm) and the signals for Me-2 or H-2, and the appearance of a crosspeak with H-6eq

(δ 2.46 ppm) lead to the assignment of the *Z*-stereochemistry for the exocyclic olefin (Scheme 37). Enoate (±)-**167** exits predominantly in the Me-2/OPNB diaxial conformer is evidenced by (i) the narrow half-width of the signal for H-5 (½W = 7.4 Hz) indicative of a lack of axial-axial couplings, (ii) a NOESY crosspeak between the signal for Me-2 and H-6ax, and (iii) the relatively large downfield shift for H-2 due to the deshielding anisotropy of the **Z**-enoate functionality. A similar methyl axial conformational preference has been reported for (*Z*)-(2-methylcyclohexylidene)acetic acid.[151] The higher energy of the Me-2/OPNB diequatorial conformer **YY** is due to the 1,3-allylic strain between the ester substituent and Me-2 present in this conformer; this strain is absent in the Me-2/OPNB diaxial conformer (±)-**167**.



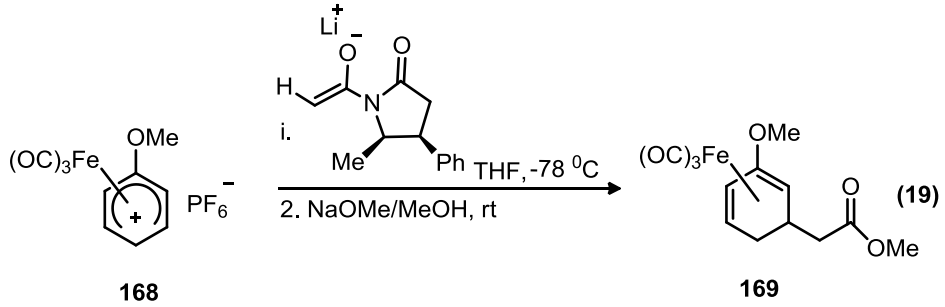
Scheme **37**: Structure of (*Z*)-**167** (Solid double-headed arrows correspond to COSY interactions; dashed double-headed arrows correspond to NOESY interactions

Exclusive formation of the ***Z***-stereoisomer is rationalized in the following manner. Electrophilic attack of the phenylselenyl chloride on the ester enolate (±)-**165'** derived from (±)-**165** occurs preferentially on the face opposite to the steric bulk of the

Me-2 substituent to afford the *α*-selenyl ester (±)-**166**. Oxidation of (±)-**166** leads to an *α*-selenyloxide which undergoes a *syn* elimination to generate **YY**, which undergoes a chair-chair inversion to the more stable conformer (±)-**167**.

2C.1. Preliminary Efforts at Chiral Cyclohexenones Synthesis

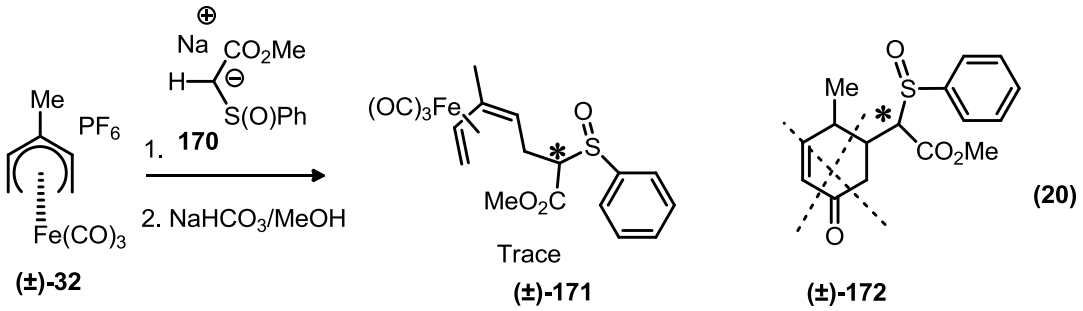
Chiral phosphine ligands on iron and chiral nucleophiles have been used in the desymmetrization of symmetrical (cyclohexadienyl) and (cycloheptadienyl)iron(1+) cations.[152] Deprotonation of the *N*-acyloxazolidinone, reaction with the (cyclohexadienyl) cation **168** and removal of the chiral auxiliary afforded the methyl ester **169** in 77% yield and 57% enantiomeric excess (Eqn. **19**).[153]



168 **169**

77%, 57% ee

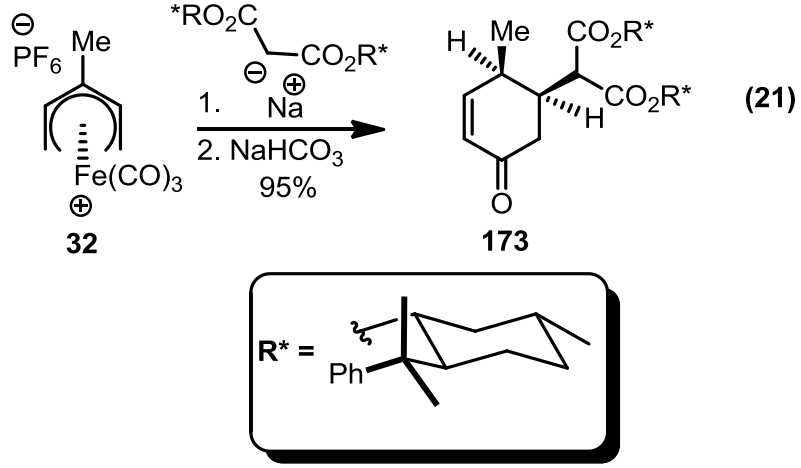
The reaction of symmetrical cation **32** with chiral (±)-methyl phenylsulfinyl acetate anion (**±)-170** was examined (Eqn. **20**). The pK_as of malonates (16.4)[154] and phenylsulfinyl acetates (18.3)[155] are relatively similar and as such cyclohexenone formation was anticipated. However the reaction afforded mainly the unreacted nucleophile and a trace amount of the (1,3-*Z*-pentadienyl)iron complex (±)-**171** arising from nucleophilic attack at C1/C5 of **32**.



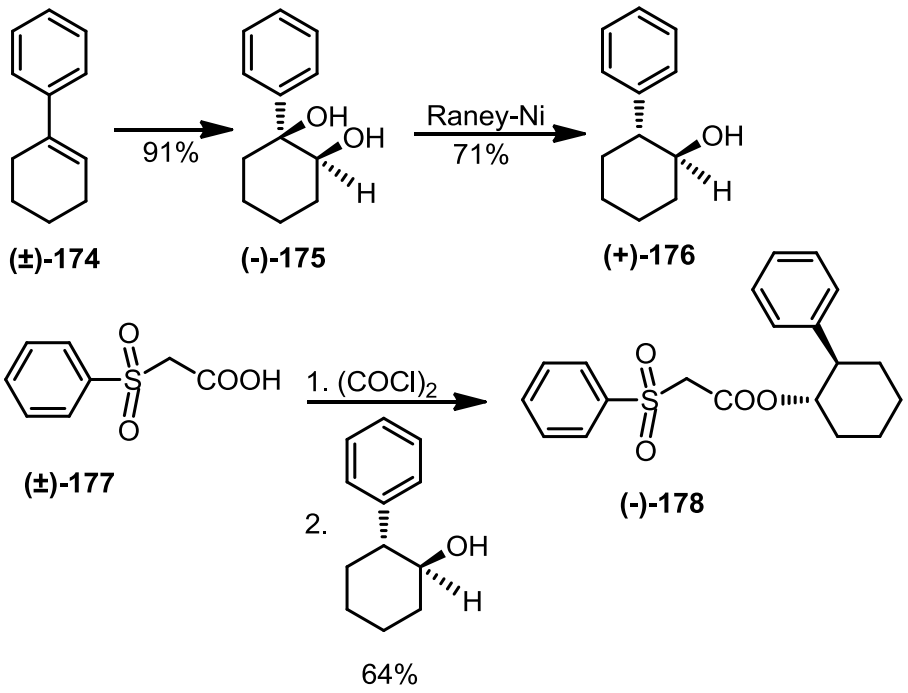
Surprisingly, cyclohexenone formation was also not observed with ethyl nitro acetate, the reaction affording only a trace of the (1,3-*Z*-pentadienyl)iron complex (±)-**151** (Scheme 22).

2C.2. Chiral Protected DHT A-ring Synthons

A previous group member had discovered that the reaction of cation **32** with the sodium salt of bis(8-phenylmenthyl) malonate[152] gave an enantiomerically pure cyclohexenone (**173**) in good yield as a single diastereomer (Eqn. **21**).[64] However, the absolute configuration at the C4 cyclohexenone methyl group was opposite to that required for the correct configuration of DHT_2.



Since *ent*-8-phenyl menthol is not commercially available and is difficult and laborious to prepare, an alternative route was designed based on the 2-phenyl cyclohexyl group.

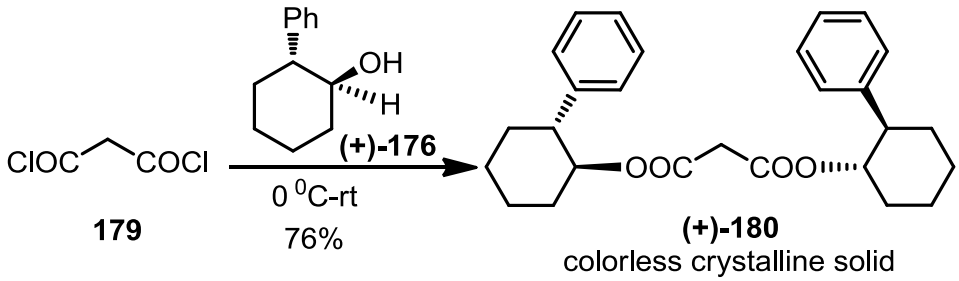


Scheme **38**: Preparation of precursor chiral nucleophile (-)-**178**

To synthesis the chiral A-ring fragments, chiral nucleophile (-)-**178** was prepared in three steps from the commercially available achiral 1-phenylcyclohexene. Diol (-)-**175** was obtained by dihydroxylation of 1-phenylcyclohexene (**174**) under Sharpless conditions.[156, 157] Reduction of diol (-)-**175** with Raney nickel gave (+)-**176** in moderate yield. Structural assignment of (+)-**176** was based mainly on comparison of its ^{1}H and ^{13}C NMR spectral data with literature values.[148]

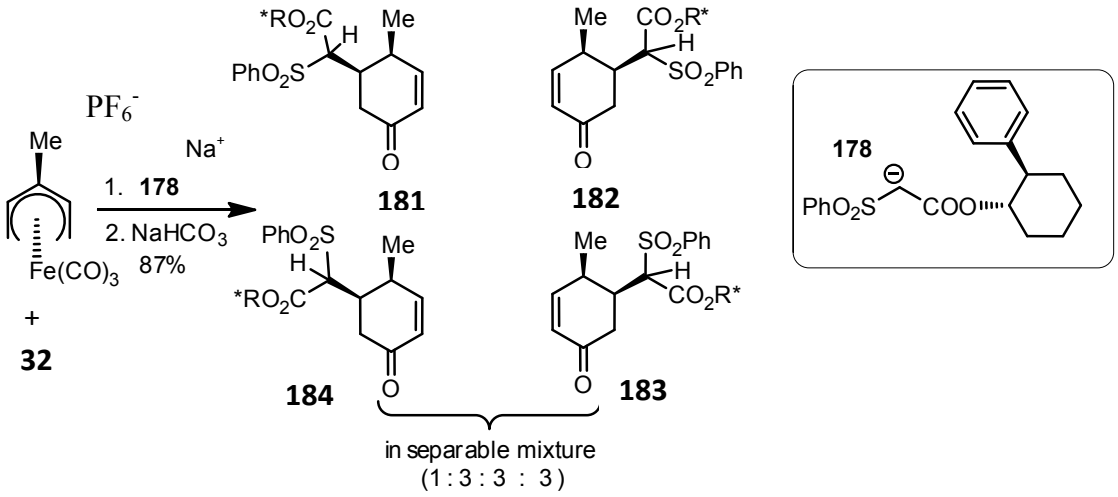
The reaction of phenyl sulfonyl acetic acid **177** with oxalyl chloride gave phenyl sulfonylacetyl chloride which was further reacted with 2-phenyl cyclohexenol (+)**-176** to afford (-)-**178** as a single enantiomer in moderate yield (Scheme 38). The structure of (-)-**178** was assigned based on its ^{1}H and ^{13}C NMR spectral data. The signals at ca. δ 7.8-7.4 ppm in the ^{1}H NMR spectra were assigned to the aromatic protons of the phenylsulfonyl group whilst those at δ 7.18 (m, 5H) ppm corresponded to the aromatic protons of other phenyl group. Notably, the signals at δ 4.86 (dt, J = 4.2, 10.5 Hz, 1H) ppm were assigned to the carbinol methine proton whilst the two diastereotopic α-methylene protons appear at δ 3.76 ppm and δ 3.70 ppm as second order doublets (J = 14.4 Hz). Similarly, the signals at δ 78.8 ppm and 62.0 ppm in the ^{13}C NMR spectra corresponded to the carbinol and α-methylene carbons whilst the signal at δ 49.0 ppm was assigned to the other methine carbon.

Additionally, the chiral nucleophile (+)-**180** was successfully prepared via a modified literature procedure.[48, 152] Reaction of commercially available malonyl dichloride **179** with chiral alcohol (+)-**176** gave the chiral nucleophile (+)-**180** in moderate yield (Scheme 39).



Scheme **39**: Preparation of precursor chiral nucleophile (+)-**180**

Structural assignment for (+)-**180** was based on its ^{1}H and ^{13}C NMR spectral data. Notably, the signals at ca. δ 7.22 ppm in the ^{1}H NMR spectra which integrated to 10 were assigned to the aromatic protons whilst those at δ 4.98 (dt, J = 4.2, 10.6 Hz, 2H) ppm corresponded to the carbinol methine protons of the cyclohexyl ring. The two α-methylene protons were assigned to the signal at δ 2.78 (s, 2H) ppm. Additionally, the signal at δ 2.61 (dt, J = 3.4, 11.6 Hz, 2H) ppm were assigned to the H-2 protons of the cyclohexyl ring. The cluster of signals ranging from ca. δ 2.0-1.2 ppm in the ^{1}H NMR spectra of (+)-**180** which integrated to 16 corresponded to the methylene protons of the cyclohexyl rings. Furthermore, the signals at δ 166.0 ppm in the ^{13}C NMR spectra of (+)-**180** was assigned to the C=O functionality whilst those ranging from ca. δ 143-126 ppm corresponded to the aromatic carbons of the phenyl ring. The carbinol signal was at δ 77.2 ppm whilst the α-methylene carbon corresponded to the signal at δ 49.6 ppm in the ^{13}C NMR spectra. The signal at δ 41.7 ppm was assigned to the methine carbon of the cyclohexyl ring whilst the remaining 4 signals ranging from ca. δ 34-25 ppm corresponded to the four methylene carbons of the cyclohexyl ring.



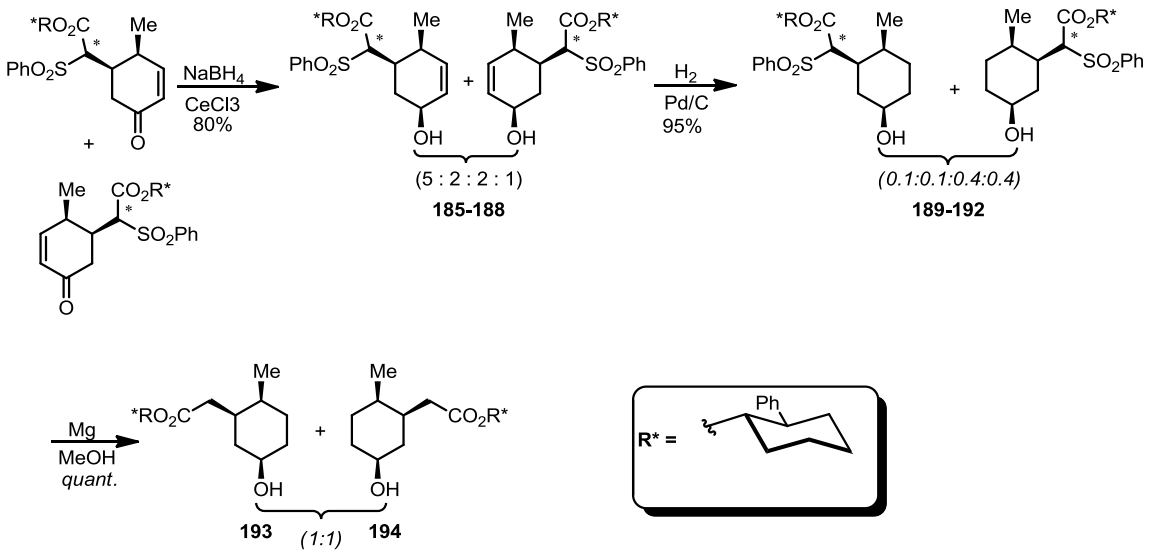
Scheme **40**: Synthesis of chiral cyclohexenones

Reaction of cation **32** with the sodium enolate of (-)-**178** was carried as in previous cyclohexenone syntheses to afford a mixture of diastereomeric cyclohexenones **181**, **182**, **183** and **184** in good yield (Scheme 40). While diastereomers **181**-**184** were obtained as an inseparable mixture, signals in the ^{1}H NMR spectrum of a single isolated diastereomer of this mixture aided the assignment of the cyclohexenone fragments. In particular, the signals at ca. δ 7.8 ppm and ca. δ 5.8 ppm in the ^{1}H NMR spectrum corresponded to the two olefinic protons, while signals at ca. δ 197 ppm in the ^{13}C NMR spectra was diagnostic for the C=O of the ketone functionality.

Due to the inseparable nature of this mixture we deemed more convenient to reduce the number of possible diastereomers by further chemical manipulation. As such, the mixture of cyclohexenones **181**-**184** was reduced under Luche conditions to afford a mixture of four diastereomeric cyclohexenols **185**-**188** in good yield. This mixture was used without further characterization. Catalytic reduction of **185**-**188** proceeded smoothly

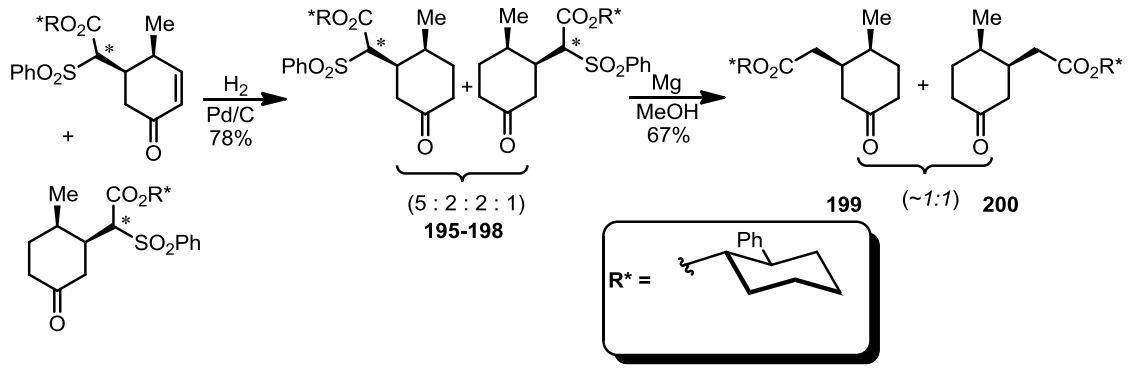
in excellent yield to afford an inseparable mixture of diastereomer **189-192**. Desulfonylation of this diastereomeric mixture afforded an inseparable equimolar mixture of two diastereomeric ester **193** and **194** in quantitative yield (Scheme 41).

Structural assignment for **193** and **194** was based on its ^{1}H NMR spectral data. Notably, the signals at ca. δ 7.28 ppm in the ^{1}H NMR spectra of **193** and **194** which integrated to 10 protons corresponded to the aromatic protons of the two enantiomers. Additionally, δ 5.16-4.99 (m, 2H) ppm signal corresponded to the carbinol methine proton of the chiral side group whilst the signal at δ 3.31 ppm which integrated to 1 proton corresponded to the carbinol methine proton of the cyclohexyl ring. Most importantly, the C-4 methyl groups of the two diastereomers gave rise to two doublets at δ 0.72 and δ 0.59 ppm both of which integrated to 3 protons each.



Scheme **41**: Synthesis of DHT A-ring synthons **193/194**

Alternatively, the diastereomeric mixture of chiral cyclohexenones **181**-**184** was reduced catalytically using H_2 and palladium on carbon to afford a mixture cyclohexanones **195-198** (5 : 2 : 2 : 1 *ratio*) in moderate yield. This mixture was treated with Mg/MeOH to effect desulfonylation. The latter step afforded an inseparable nearly equimolar mixture of two diastereomeric cyclohexanols **199**/**200** in moderate yield (Scheme 42).

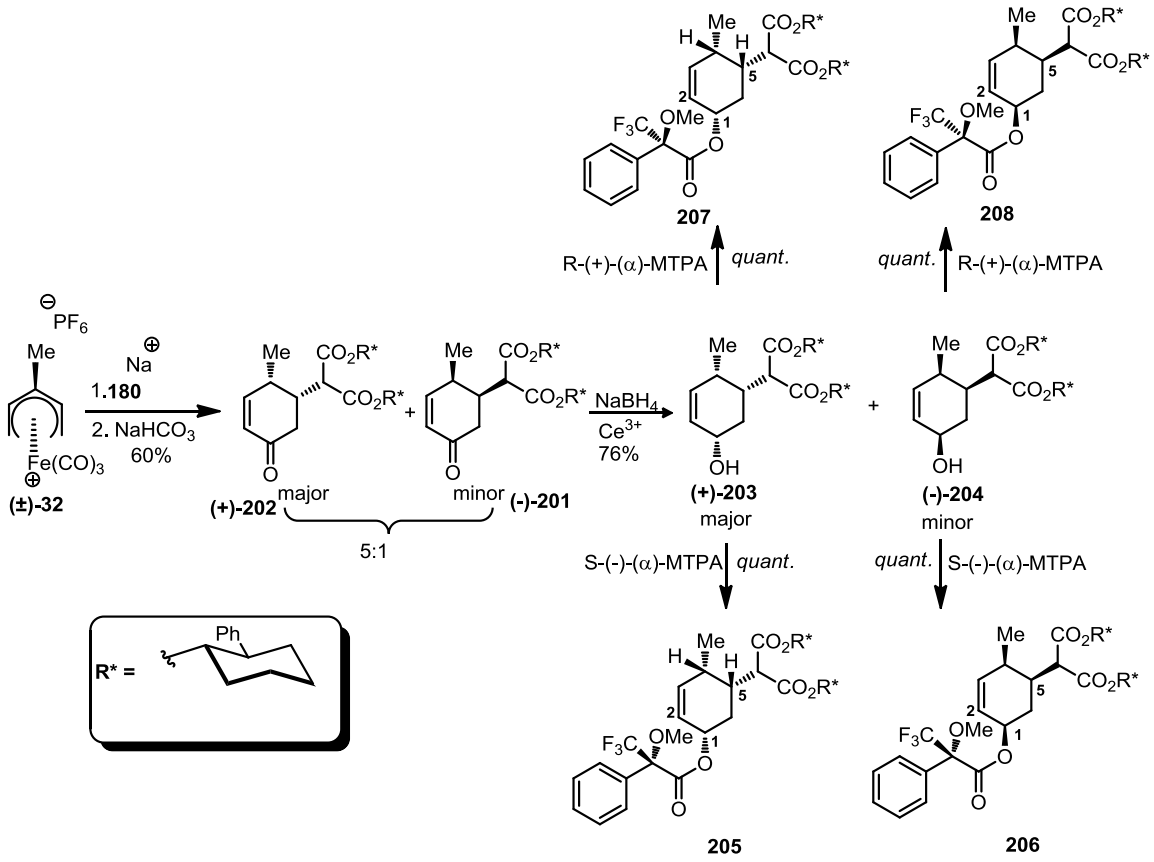


Scheme **42**: Synthesis of DHT A-ring synthons **199**/**200**

Structural assignments for **199**/**200** were based on their ^{1}H and ^{13}C NMR spectral data. In particular, signals at δ 7.24 ppm in the ^{1}H NMR spectra of **199**/**200** which integrated to 10 protons were assigned to the aromatic protons of the two diastereomers. The signals at δ 5.08-4.94 (m, 2H) ppm in the ^{1}H NMR spectra corresponded to the carbinol protons of the 2-phenylcyclohexyl group of **199**/**200**. Most importantly, the signals at δ 0.79 (d, J = 6.8 Hz, 3H) ppm and δ 0.65 (d, J = 6.9 Hz, 3H) ppm corresponded to the C-4 methyl protons of the diastereomers **199**/**200**. Integration of these signals indicated that they are formed in nearly equimolar ratio.

2C.3. The Synthesis of Protected Chiral DHT A-Ring Fragment

Reaction of the chiral malonate nucleophile (+)-**180** (sodium salt) with **32** was carried out in a fashion similar to the reaction with dimethyl malonate anion. This reaction gave a diastereomeric mixture of two cyclohexenones **201** (less polar/minor) and **202** (more polar/major) in moderate yield and selectivity (Scheme 43). While the mixture of diastereomers was not separable by column chromatography, the structures of **201** and **202** were assigned by comparison of their ^{1}H and ^{13}C NMR spectral data with that of other cyclohexenones previously described. The signals at δ 6.66 (dd, J = 4.0, 6.5, Hz, 1H) and δ 5.73 (d, J = 10.9 Hz, 1H) ppm in the ^{1}H NMR spectra of **202** corresponded to the cyclohexenone olefin protons. The signal at δ 2.74 (d, J = 13.1 Hz, 1H) ppm corresponded to the α-methine proton of the propanedioate group. Of particular role is the far upfield shifted signal for the C4-methyl protons which appeared at δ 0.14 (d, J = 7.0 Hz, 3H) ppm. This upfield shift is attributed to the anisotropy of the aromatic portion of the 2-phenylcyclohexyl groups. Additionally, signals at δ 198.9 and δ 166.9 ppm in the ^{13}C NMR spectrum of **202** corresponded to the C=O functionality of the ketone and ester groups. Similar chemical shifts for diastereomer **201** led to its structural assignment.



Scheme **43**: Synthesis and Derivatization of (-)-**201** and (+)-**202**

Luche reduction of the diastereomeric mixture of **201** and **202** gave a mixture of diastereomeric cyclohexenols (+)-**203** and (-)-**204** in moderate yield which were completely separable by column chromatography (Scheme 43). The structural assignments of the cyclohexenol fragments of **203** and **204** were made by comparison of their ^{1}H NMR spectral data with that for (±)-**161**.

Assignment of the absolute stereochemistry at the carbinol carbon of (+)-**203** was accomplished by ^{1}H NMR analysis of the corresponding (S)- and (R)-Mosher esters. Reaction of the more polar cyclohexenol (+)-**203** with S-(-)-(α)- and R-(+)-(α)-Mosher acids following literature procedures [158] gave the Mosher esters **205** and **207** respectively

in quantitative yields (Scheme 43). Transformation of the less polar cyclohexenol (-)-**204** to its corresponding S-(-)-(α)- and R-(+)-(α)-Mosher esters **206** and **208** respectively was accomplished in similar fashion in excellent yields.

The stereochemical assignment of the carbinol methine proton of (+)-**203** was made based on the relative chemical shifts of the alkenyl proton (H^2) of the derived (S)- and (R)-Mosher esters **205** and **207** (δ 5.42 and 5.32 ppm, respectively). These relative chemical shifts are consistent with an (*S*)-stereochemical assignment at C1-carbinol carbon and therefore C5 is assigned as (*R*).[158] Since the minor diastereomer (-)-**204** originated from the same 1S,2R-2-phenylcyclohexanol auxiliary the cyclohexenone ring formed may be inferred to have an opposite stereochemical relationship to (+)-**203**.

The difference in diastereoselectivity for the addition of the chiral phenylsulfonyl acetate and malonate nucleophiles to cation **32** is rationalized in the following fashion (Figs. **8** and **9**). Nucleophilic attack occurs on the face of the pentadienyl ligand opposite to the Fe metal and the C2 chiral malonate anion is aligned synclinal with respect to the electrophilic π-system (i.e., the C1-C2 bond) (Fig. **8**). Steric interaction between the phenyl substituent and the pentadienyl ligand present in **TS2** is expected to raise the energy of this transition state compared to **TS1**.

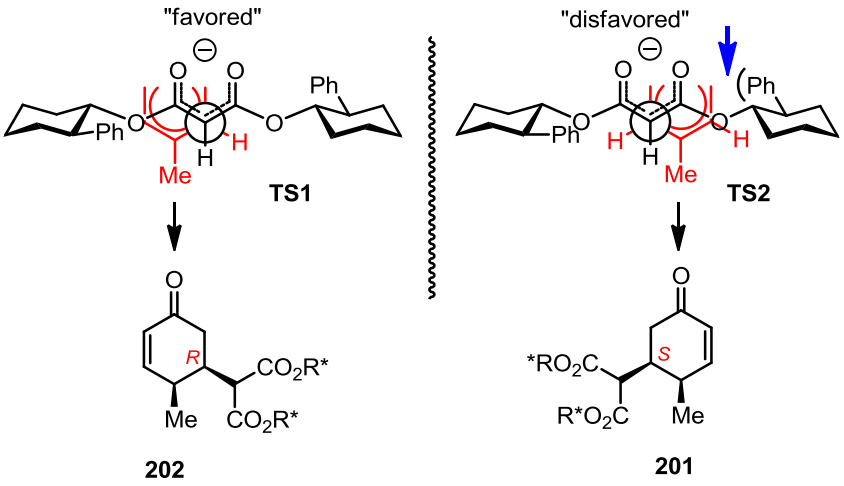


Fig. **8**: Diastereomeric transition states for formation of **201** and **202**

For the chiral phenylsulfonyl acetate nucleophile (-)-**178**, reaction can proceed via approach on the *re*-face (i.e., **TS3** and **TS4**) or on the *si*-face (**TS5** and **TS6**) (Fig. **9**). It is anticipated that approach of the nucleophile from either *re*- or *si*-faces is equally probable, and that once nucleophilic attack begins that the reaction proceeds irreversibly. For approach on the *re*-face of the nucleophile, steric interaction between the phenylsulfonyl group and the pentadienyl ligand in **TS4** results in this being a higher energy/"disfavored" pathway compared to **TS3**. Alternatively, for approach on the *si*-face of the nucleophile, the steric interaction between the phenylsulfonyl group and the pentadienyl ligand in **TS5**, and the steric interaction between the phenyl group of the 2-phenyl cyclohexyl ester in **TS6** would seem to indicate that the two transition states are relatively similar in energy. Thus a lack of diastereoselectivity for reaction of (-)-**178** with cation **32** is due to only minor differences in the energies of these transition states.

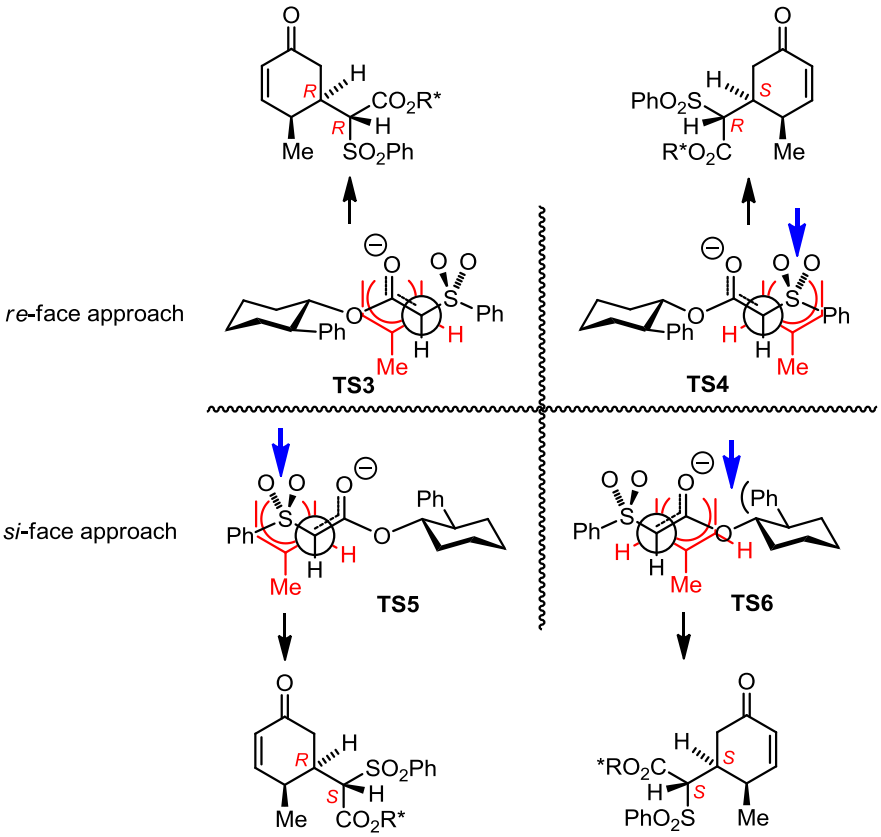
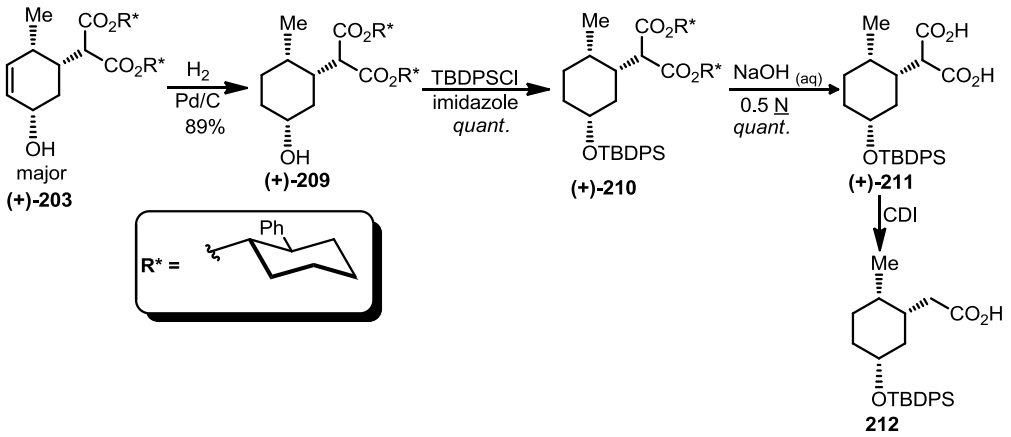


Fig. **9**: Diastereomeric transition states for formation of (±)-**181**-**184**

Catalytic reduction of cyclohexenol (+)-**203** proceeded smoothly to afford cyclohexanol (+)-**209** in good yield as a single diastereomer. Protection of the hydroxyl group of (+)-**209** with *t*-butyldiphenylsilyl chloride gave (+)-**210** in quantitative yield also as a single diastereomer (Scheme 44).

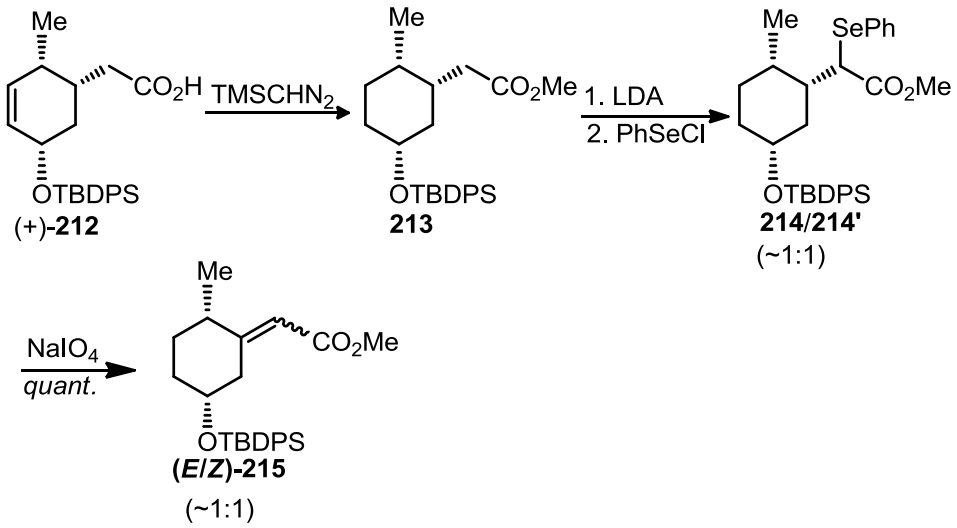


Scheme **44**: Synthesis of Chiral Protected DHT A-ring synthon **212**

Structural assignment of the protected cyclohexyl portion of (+)-**210** was made by comparison of its ^{1}H NMR spectral data with that previously obtained for (±)-**155**. Notably, the signals at ca. δ 7.70-7.30 ppm in the ^{1}H NMR spectra of (+)-**210** which integrated to a total of 10 were assigned to aromatic protons of the *t*-butyldiphenylsilyl group whilst those at δ 7.29-7.07 (m, 10H) ppm corresponded to the aromatic protons of chiral auxiliary. The signals at δ 5.01-4.81(m, 2H) were assigned to the carbinol methine protons of the chiral auxiliary. The carbinol methine proton and the C-4 methyl protons of the cyclohexyl ring were assigned the signals at ca. δ 3.44 ppm and δ 0.11 ppm respectively.

Preliminary efforts at hydrolysis of (+)-**210** under acidic conditions with aqueous hydrochloric acid (0.5 N) at room temperature or reflux resulted in the removal of the *t*-butyldiphenylsilyl group. Furthermore, the use of LiOH with tetrahydrofuran, methanol or water also resulted in the deprotection of (+)-**210**. Similar results were obtained with KOH and methanol. Hydrolysis of (+)-**210** was however achieved albeit with deprotection of the starting material to a lesser extent in refluxing (85-95 ^{0}C) aqueous

sodium hydroxide (~0.5 N) solution to give the diacid (+)-**211** quantitatively as a single diastereomer. The structure of (+)-**211** was assigned based on its ^{1}H and ^{13}C NMR spectral data. In particular, signals at δ 7.70-7.30 ppm in the ^{1}H NMR spectrum of (+)-**211** which integrated to 10 was assigned to the aromatic protons of the phenyl groups. The carbinol methine proton was assigned the signal at δ 3.50 (m, 1H) whilst the C-4 methyl protons were assigned the signal at δ 0.81 (br s, 3H). Additionally, the signals at δ 175.5 ppm and δ 174.4 ppm in the ^{13}C NMR spectrum of (+)-**211** corresponded to the two C=O functionalities. The cluster of 8 signals ranging from ca. δ 135-128 ppm was assigned to the aromatic carbons whilst the carbinol carbon of the cyclohexyl ring was assigned the signal at δ 73.0 ppm. Furthermore, the α-methylene carbon of (+)-**211** was assigned the signal at δ 50.9 ppm in the ^{13}C NMR spectrum. The diacid (+)-**211** was converted to the monoacid -**212** upon reaction with 1,1′-carbonyldiimidazole with great difficulty owing to the removal of the *t*-butyldiphenylsilyl during the course of the reaction resulting in very low yields of the anticipated product. As such the monoacid **212** (26 mg) was carried forward without further purification. Partial structural assignment of -**212** was made on the basis of its ^{1}H and ^{13}C NMR spectral data. In particular, the signals at ca. δ 7.70-7.30 ppm in the ^{1}H NMR spectrum of -**212** which integrated to 10 were assigned to the aromatic protons of the two phenyl rings. Similarly, the multiplet at δ 4.61 (m, 1H) ppm corresponded to the carbinol methine proton of the cyclohexyl ring. The C4-methyl protons were also assigned to the signal at δ 0.85 (d, J = 6.2 Hz, 3H) ppm. Additionally, the signal at δ171.5 ppm in the ^{13}C NMR spectrum of **212** was assigned to the C=O functionality of the carboxylic acid.

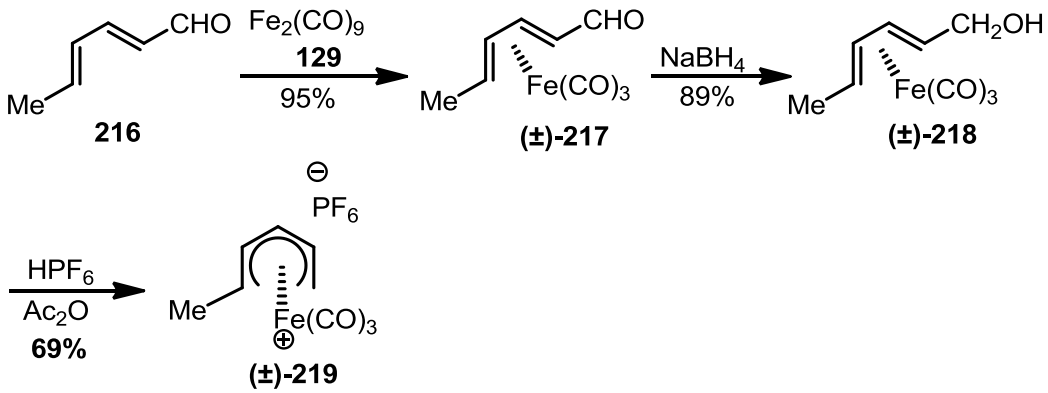


Scheme **45**: Synthesis of chiral protected A-ring fragments (*E*/*Z*)-**215**

Reaction of the monoacid **212** with excess trimethylsilyldiazomethane solution afforded **213** which after filtration through a celite pad was carried forward to the next step without further purification. Deprotonation of **213**, followed by reaction with phenylselenyl chloride gave an equimolar mixture of diastereomeric α-phenylselenyl esters **214**/**214'**, which upon oxidation and elimination of phenylselenic acid gave an inseparable equimolar mixture of stereoisomeric enoates (*Z*)-**215** and (*E*)-**215** in quantitative yield (Scheme 45). The structures of (*Z*)-**215** and (*E*)-**215** were assigned based on their ^{1}H and ^{13}C NMR spectral data which were identical with that previously obtained for the racemic protected DHT A-ring fragment (±)-**158**.

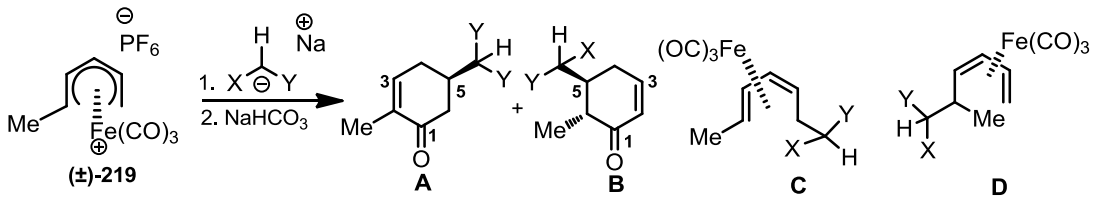
2D.1. Preparation of 2-methyl-2-cyclohexenones

The reaction of stabilized carbon nucleophiles with the (1-methylpentadienyl)iron(+1) cation **219** were also examined. Cation **219** was prepared starting from the commercially available 2,4-hexadienal **216** following literature procedure (Scheme 46).[49] Complexation of diironnonacarbonyl **129** with **216** gave tricarbonyl(η^4- 2,4-hexadienal)iron (±)-**217** in excellent yield. Hydride reduction of **217** gave **(±)-218**. Dehydration of **218** with acetic anhydride gave a carbocation which was trapped as the hexafluorophosphorate salt (±)-**219** (3-steps total, 58%, Scheme 46).



Scheme **46**: Synthesis of cation **(±)-219**

The reactions of cation **219** with phosphorus stabilized nucleophiles to form cyclohexanones were examined as potential synthons for the synthesis of carvone metabolites and DHT A-ring synthons (Scheme 47).



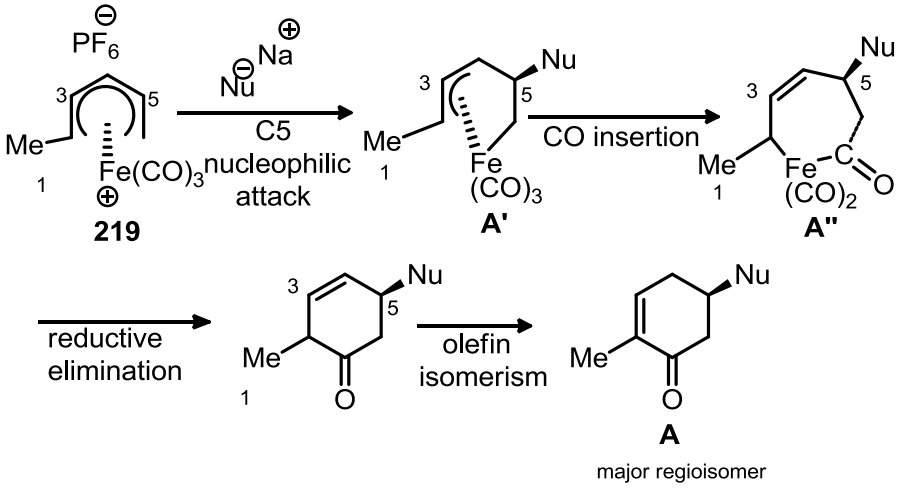
(±)-220. X = P(O)(OMe)$_2$ Y = CO_2Me , 87% (*1:0.3*)
(±)-221. X = P(O)(OEt)$_2$ Y = CO_2Et , 68% (*1.0:1.0*)
(±)-222. X = P(O)(OEt)$_2$ Y = C(O)Me , 74% (*1.0:0.1*)
(±)-223. X = P(O)(OEt)$_2$ Y = SO_2Ph , 76% (*1.0:0.3*)
(±)-224. X = P(O)(OEt)$_2$ Y = CN , 76% (*1.0:1.0*)

Scheme **47**: Synthesis of cyclohexenones from phosphorous-stabilized nucleophiles

Thus reaction of cation **219** with sodium trimethyl phosphonoacetate [prepared from the reaction of trimethyl phosphonoacetate and sodium hydride] afforded an inseparable mixture of regioisomeric cyclohexenones (±)-**220a** and (±)-**220b** in good yield and selectivity. No (diene)iron complexes **C** or **D** were isolated after column chromatography. Cyclohexenone **220a** arises from the nucleophilic attack at the C5 (Scheme 48) whilst **220b** is formed by the nucleophilic attack at the C3 position of cation **219** (Scheme 49).

The structural assignment for the major cyclohexenone **220a** was made based on its ^{1}H NMR spectral data. In particular, the multiplet at δ 6.73-6.63 (m, 1H) ppm was assigned to the C-3 olefinic proton. The methyl ester protons corresponded to the signals at ca. δ 3.77 ppm which integrated to 9. The α-methine proton was also assigned to the signal at δ 3.03-2.92 (dd, J = 8.3, 8.5 Hz, 1H) ppm. Owing to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum of **220a** was not attempted.

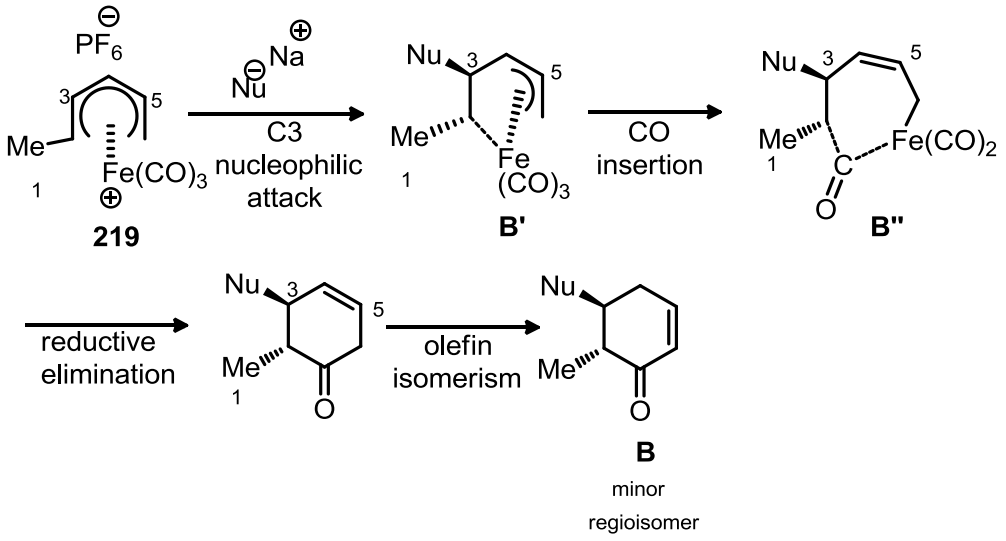
Cyclohexenones **221a/b - 224a/b** were also prepared following a similar protocol (Scheme 47). The structures of the other cyclohexenones were assigned based on their ^{1}H NMR spectral data and by comparison with previously reported 2-methyl-2-cyclohexenones.



Scheme **48**: Mechanistic ration for formation of cyclohexenone **A**

Nucleophilic attack at the C5 position generates the (pentenediyl)iron complex **A'**. The absence of a strongly electron-withdrawing substituent at C1 implies that the relative rate of carbonyl insertion into the Fe-C σ-bond will be faster than reductive elimination of the $Fe(CO)_3$ group.[64] Thus rapid CO insertion into the Fe-C σ-bond affords the π-allyl-σ-acyl complex **A''**. Reductive elimination followed by conjugation affords cyclohexenone **A**.

Conversely, attack at the C3 position of cation **219** will lead to cyclohexenone **B** (Scheme 12). Nucleophilic attack at either of the terminal C2/C6 positions of cation **219** will result in (diene)iron complexes **C** and **D**. [64]



Scheme **49**: Mechanistic ration for formation of cyclohexenone **B**

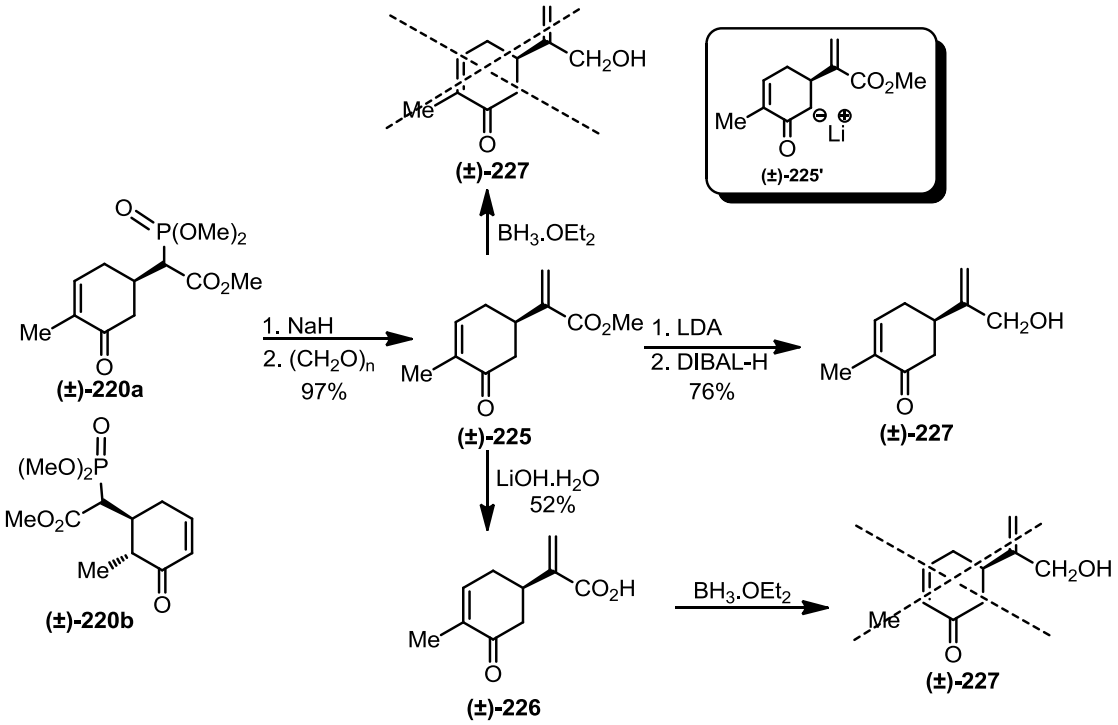
2D.2. Synthesis of Carvone Metabolites: 10-Hydroxycarvone and Carvonic acid

10-Hydroxycarvone has been isolated from *Hyssopus cuspidatus*, a plant used in Chinese folk medicine for the treatment of fever and broncusus asthma.[159] This terpene has also been isolated as a minor carvone metabolite from cultured cells of the Madagascar periwinkle, *Catharanthus roseus*,[160] and as an excreted metabolite of carvone in the urine of rabbits,[161] and human volunteers,[162, 163] while carvonic acid has also been isolated as a human metabolite of carvone.[162, 163]

Horner-Emmons olefination[164] of **220a**/**b** with paraformaldehyde afforded (±)-**225** as a single diastereomer in excellent yield (Scheme 50). The structure of **225** was assigned based on its ^{I}H and ^{13}C NMR spectral data.

In particular, the signal at δ 6.73 (m, 1H) ppm in the ^{1}H NMR spectrum of **225** was assigned to the C-3 olefinic proton of the cyclohexenone ring whilst the pair of

singlet signals at δ 6.26 and 5.57 ppm were assigned to the exocyclic olefinic protons. Furthermore, the signals at δ 199.0 ppm and δ 166.8 ppm in the ^{13}C NMR spectrum of **225** were assigned to the C=O functionality of the ketone and ethyl ester groups respectively. The cluster of four signals from ca. δ 144.0-124 ppm was assigned to the olefinic carbons.



Scheme **50**: Syntheses of carvone metabolite (±)-**226** and (±)-**227**

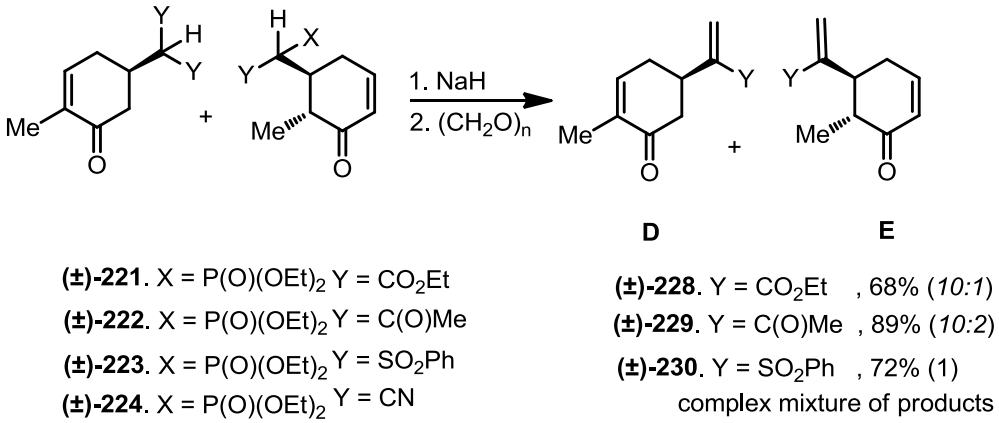
Hydrolysis of (±)-**225** proceeded smoothly to afford carvonic acid (±)-**226** in moderate yield. Structural assignment of **226** was made based on its ^{1}H and ^{13}C NMR spectral data. Notably, the signals at δ 6.76 (m, 1H) ppm in the ^{1}H NMR spectrum of **226** corresponded to the C-3 cyclohexenone olefinic proton. Similarly, the two exocyclic diastereotopic exocyclic protons were assigned to the singlets at δ 6.44 and 5.72 ppm.

The absence of the methoxyl protons at δ 3.70 ppm was also confirmative. These assignments were also consistent with literature values.[162, 163]

To synthesize 10-hydroxycarvone (±)-**227**, we initially explored the reduction of carvonic acid **226** with borane. This reaction however gave a complex mixture of reaction products (Scheme 50). 10-Hydroxycarvone (**227** was eventually prepared by α-deprotonation of **225** with lithium diisopropylamide to afford the enolate **225'** which was reduced in situ with diisobutylaluminum hydride. Aqueous workup of the reaction mixture gave 10-hydroxycarvone **227** as a single diastereomer. The structural assignment of **227** was based on its ^{1}H and ^{13}C NMR spectral data. In particular, the signal at δ 4.15 (s, 2H) ppm in the ^{1}H NMR spectrum of **227** corresponded to the allylic carbinol protons. The signal at δ 65.1 ppm in the ^{13}C NMR spectrum was also assigned to the carbinol carbon. The ^{1}H and ^{13}C NMR spectral data of **227** were also consistent with literature values.[162, 163]

2D.3. Synthesis of 5-alkenyl-2-methyl-2-cyclohexenones via Horner-Emmons Olefination

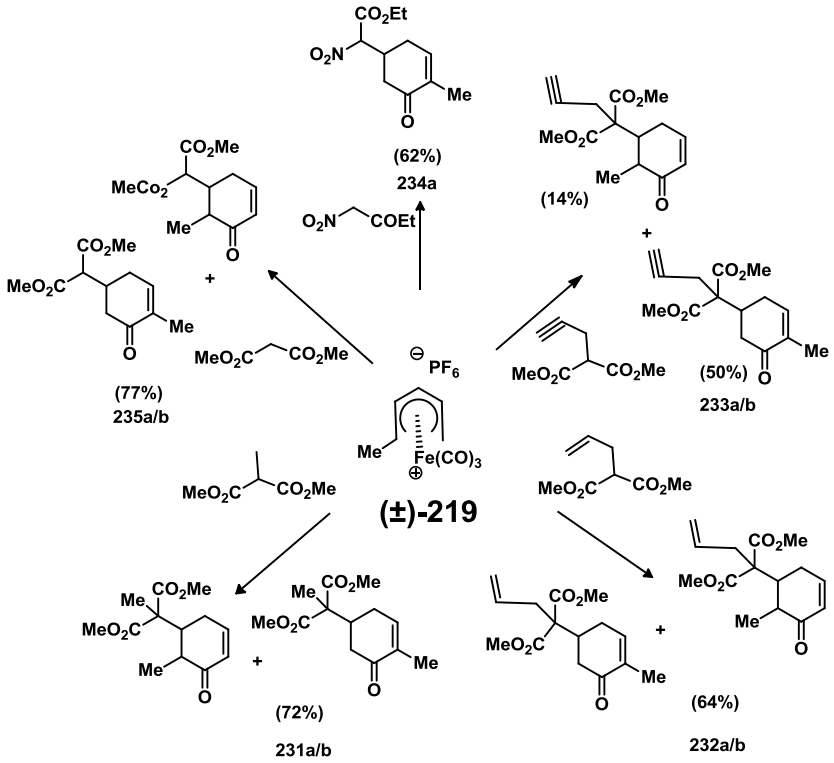
With the successful synthesis of oxygenated carvones we sought to utilize the other phosphonates **221**-**224** in Horner-Emmons olefination[164] reactions. Thus reaction of the anions of **221**-**223** with paraformaldehyde gave the olefin products **228**-**230** respectively. Unfortunately, attempted olefination with **224** led to a complex mixture of products (Scheme 51).



Scheme **51**: Synthesis of Carvone Synthons

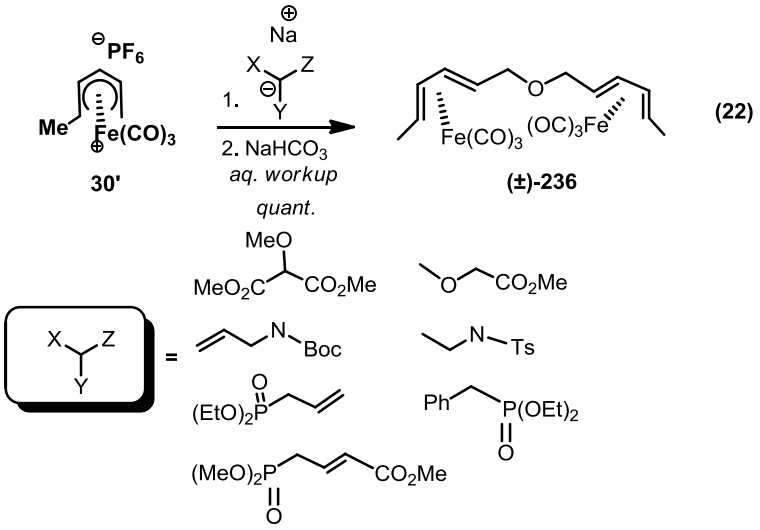
The structure assignments of the oxygenated products (±)-**228**-**230** were made by comparison of their ^{1}H and ^{13}C NMR spectral data with that obtained for **225**. In particular, the C-3 cyclohexenone olefinic protons were assigned to the signal at ca. δ 6.70 ppm whilst the two exocyclic diastereotopic protons were assigned to the signals ranging from ca. δ 6.50-5.50 ppm in the ^{1}H NMR spectra. The C4-methyl protons were assigned to the signals ranging from ca. δ 1.60-1.80 ppm.

The reaction of cation **219** with stabilized carbon nucleophiles was also examined. The results are summarized in Scheme 52. The attack of "soft" nucleophiles to cation **219** proceeded at both terminal and internal carbons of the pentadienyl ligand to give mixtures of pentenediyl complexes **A'**/**B'** and (diene)iron complexes **C**/**D**. In general, increasing the substitution on the malonate nucleophile (e.g. dimethyl malonate vs. dimethylpropagyl malonate) led to a small decrease in the percent nucleophilic attack at the pentadienyl terminus.[64] Also the regioselectivity of nucleophilic attack was largely independent of the nucleophile counterion used as was the case when Li^{+} and K^{+} were used counterions.



Scheme **52**: Synthesis of cyclohexenones from stabilized malonate nucleophiles

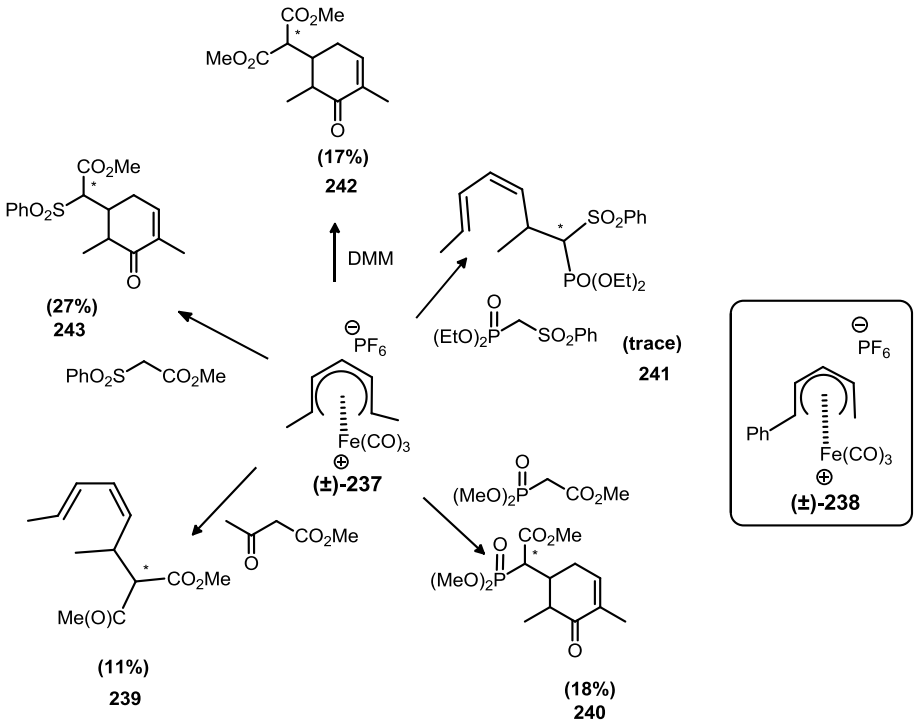
The reaction of cation **219** with nitrogen-stabilized and other stabilized carbon nucleophiles all resulted in the formation of the dimeric (diene)iron complex (±)-**236** (Eqn. 22).



The reactivity of tricarbonyl(η^5- 1,5-dimethylpentadienyl)iron cation (+1) (±)-**237** and tricarbonyl(η^5-5-phenylpentadienyl)iron cation (+1) (±)-**238** with stabilized nucleophiles was also examined. To this end cations **237**[165] and **238**[49, 166] were prepared in 58 % and 59 % yields respectively following literature procedures. Generally the yields of products arising via for nucleophilic addition to these cations were significantly lower compared to cations **32** and **219** (Scheme 53).

Nucleophilic attack at the internal (C3/35) positions of cation **237** afforded cyclohexenones albeit in significantly low yields. Formation of (diene)iron products from the terminal (C2/C6) nucleophilic attack was sterically disfavored (Scheme 53).

No nucleophilic attack was observed for reactions of cation **238** with nucleophiles used. In all cases the tricarbonyl(η^4-5-phenyl-2,4-pentadienol)iron complex was isolated as the major fraction after column chromatography.

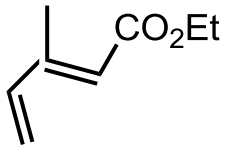


Scheme **53**: Synthesis of cyclohexenones

EXPERIMENTAL

General Data

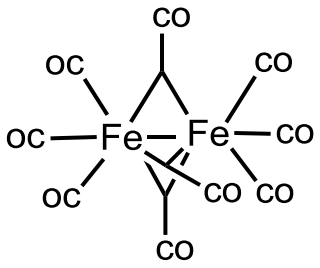
All non-aqueous reactions were carried out under a nitrogen atmosphere. Spectrograde solvents were used without purification with the exception of dry diethyl ether which was distilled from calcium hydride. Dichloromethane was distilled from calcium hydride (CaH_2) whilst tetrahydrofuran was distilled from sodium and benzophenone. Anhydrous *N,N*-dimethylformamide (DMF), anhydrous dimethyl sulfoxide (DMSO), and anhydrous toluene were purchased from VWR. Column purification was performed on silica gel 60 (60-200 mesh Dynamic Adsorbents, Inc.). Thin layer chromatography plates were detected by one of the following methods; ultraviolet light or iodine vapor. Melting points were obtained on a Mel-Temp melting apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet Magna IR 560 Spectrometer. All ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury Series 300 or Varian Inova Series 400 Spectrometers at the appropriate frequency. High resolution mass spectra were obtained from Old Dominion University COSMIC Lab, Norfolk, Virginia.



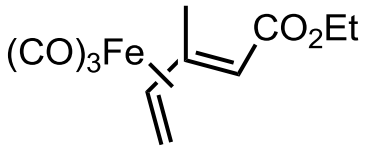
Ethyl 3-methyl-(2E)-2,4-pentadienoate (128): In a 250 mL flame-dried round bottom flask was suspended methyltriphenylphosphonium bromide (8.1 g, 22 mmol) in dry tetrahydrofuran (75 mL). The suspension was then maintained under N_2 and cooled to -78 ^{0}C using an acetone-liquid nitrogen bath. A solution of n-BuLi (2.50 M in hexanes, 9.2 mL, 23 mmol) was added dropwise by means of a syringe. The mixture was warmed to 0 ^{0}C and stirred for 1 h. The reaction mixture was cooled again to -78 ^{0}C and 3-methyl-4-oxocrotonate (3.0 g, 21 mmol) (**127**) added dropwise. The mixture was stirred at this temperature for 2 h after which it was warmed to room temperature and stirring continued overnight. The reaction was quenched with H_2O, extracted several times with Et_2O, dried ($MgSO_4$) and concentrated. The crude extracts were purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 0-5% gradient) to afford **128** as a yellowish oil (2.3 g, 78%).

IR (neat) 2926, 1716, 1659, 1605, 988, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.41 (dd, *J* = 10.6, 17.3 Hz, 1H), 5.79 (s, 1H), 5.61 (d, *J* = 17.3 Hz, 1H), 5.39 (d, *J* = 10.6 Hz, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 152.1, 140.2, 120.1, 119.5, 60.0, 14.6, 13.3.

The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[29]



Diiron nonacarbonyl (129): A 1000 mL round bottom flask was charged with glacial acetic acid (500 mL). The solvent was deoxygenated by bubbling N_2 through for about 10-15 min. Iron pentacarbonyl (100 mL) was added and the solution irradiated with a medium pressure mercury vapor lamp for 4 h. Diiron nonacarbonyl formed as thin golden flakes which were then separated by suction filtration through a sintered glass funnel. The residue collected was washed with diethyl ether and stored in an amber glass container at 0-5 ^{0}C. The acetic acid-iron pentacarbonyl filtrate was resubjected to UV irradiation and the procedure repeated several times. From the 100 mL of iron pentacarbonyl, 80 g of diiron nonacarbonyl was obtained. This compound was used without further characterization.

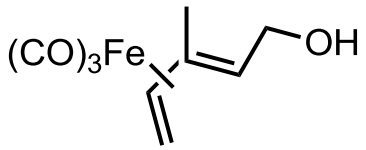


Tricarbonyl(ethyl 3-methyl-(2*E*)-penta-2,4-dienoate)iron (130): To a 500 mL round bottom flask equipped with a reflux condenser and a magnetic stirring bar was added a solution of dienoate **128** (2.47 g, 17.6 mmol) in benzene (150 mL). Nitrogen was bubbled through this solution for 15 min and diiron nonacarbonyl **129** (16.0 g, 44.1 mmol) was added. The mixture was gently heated at reflux until TLC confirmed disappearance of

all starting material. The mixture was subsequently concentrated under reduced pressure, redissolved in CH_2Cl_2, filtered through a pad of celite and the pad washed several times with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 5-10% gradient) to afford **130** as a yellowish oil (4.01 g, 81%).

IR (neat) 2058, 1985, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.23 (br t, *J* = 7.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.84 (dd, *J* = 2.6, 6.8 Hz, 1H), 1.28 (br t, *J* = 7.1 Hz, 3H), 0.72 (s, 1H), 0.52 (dd, *J* = 2.6, 9.1 Hz, 1H); ^{13}C NMR $CDCl_3$, 75 MHz) δ 209.2, 171.9, 104.6, 86.0, 60.3, 48.8, 38.6, 19.0, 14.5.

The ^1H, ^{13}C and IR spectra matched those reported in the literature.[29]

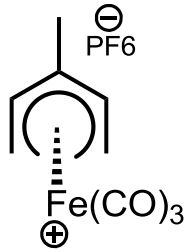


Tricarbonyl(3-methyl-2(*E*),4-pentadien-1-ol)iron (131): In a flame dried 250 mL round bottom flask, **3** (7.31 g, 26.1 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and the solution cooled to -78 ^0C in a dry ice-acetone bath under an N_2 atmosphere. A solution of DIBAL in hexanes (1.00 M, 80 mL, 80 mmol) was added slowly and carefully via syringe. The reaction mixture was stirred at -78 ^0C for 2 h. After this time methanol (20 mL) was added, followed by water. The mixture was warmed to room temperature and extracted several times with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The bright yellow semi-solid residue was purified by flash column

chromatography (SiO_2, ethyl acetate-hexane = 0-20% gradient) to afford **131** as pale yellow oil (6.1 g, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.15 (t, *J* = 8.1 Hz, 1H), 3.77 (m, 2H), 2.40 (br s, 1H), 2.19 (s, 3H), 1.66 (dd, *J* = 2.7, 7.0 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 1H), 0.25 (dd, *J* = 2.7, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.3, 102.7, 83.7, 61.8, 61.7, 37.8, 18.3.

The ^{1}H and ^{13}C spectra matched those reported in the literature.[29]

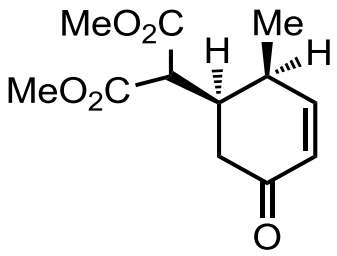


Tricarbonyl(η^5-3-methylpentadienyl)iron(+1) hexafluorophosphate (32): To a cold stirring solution of **131** (6.1 g, 25 mmol) in ether (30 mL) was added dropwise acetic anhydride (13 mL). The reaction mixture was stirred at 0 ^{0}C for 20 min after which a solution of hexafluorophosphoric acid (60.0% w/w solution, 8.6 mL) in acetic anhydride (13 mL) was added. The mixture was stirred for 30 min at 0 ^{0}C during which time a pale yellow precipitate appeared. The reaction mixture was transferred into ether (200 mL) to induce precipitation. The precipitate was isolated by suction filtration to give **32** as a bright yellow solid (7.9 g, 85%).

mp 130-135 ^{0}C (decomposes); IR (KBr) 2119, 2068 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.49 (t, *J* = 11.5 Hz, 2H), 3.81 (dd, *J* = 3.2, 10.1 Hz, 2H), 2.87 (s, 3H), 2.44 (dd,

J = 2.9, 12.6 Hz, 2H); ^{13}C NMR (acetone-d_6, 75 MHz): δ 117.9, 104.5, 64.2, 22.4. The signal for Fe-CO was not observed.

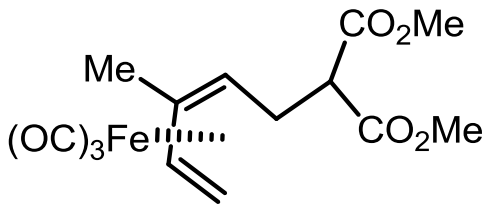
The spectral data matched those reported in literature.[48]



Reaction of cation 5 with sodium dimethyl malonate (±)-75: To an ice-cold stirring suspension of NaH (37 mg, 0.92 mmol) in dry THF (10 mL) was added dimethyl malonate (0.081 g, 0.62 mmol). The mixture was stirred at 0 ^{0}C for 10-15 min, the solid cation **32** (0.150 g, 0.410 mmol) was added in one portion and reaction mixture stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated solution of methanolic $NaHCO_3$ (10 mL), and stirred overnight at room temperature. The reaction was quenched with H_2O, extracted several times with CH_2Cl_2, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 50-75% gradient) to afford **75** as a light yellow oil (80 mg, 81%) and a trace of **74** (diene).

IR (neat) 1734, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.11 (dd, J = 6.1, 10.1 Hz, 1H), 5.81 (d, J = 10.1 Hz, 1H), 3.31 (d, J = 10.9 Hz, 1H), 3.23 (s, 3H), 3.20 (s, 3H), 3.03 (m, 1H), 2.47 (dd, J = 3.8, 16.7 Hz, 1H), 2.31 (m, 1H), 2.10 (dd, J = 13.5, 16.7 Hz, 1H), 0.55 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.6, 167.9, 167.8, 153.5, 127.9, 54.6, 52.2, 52.1, 37.5, 37.3, 31.6, 12.2.

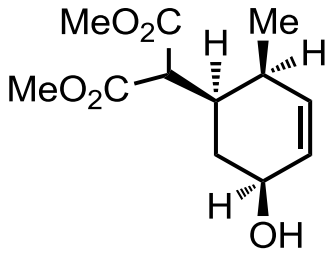
The ^{1}H and ^{13}C spectra matched those reported in the literature.[48]



74

IR (neat) 2046, 1966, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.33 (t, J = 8.4 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.29 (dd, J = 6.1, 8.8 Hz, 1H), 2.40 (dd, J = 1.5, 4.3 Hz, 1H), 2.17 (m, 1H), 2.09 (s, 3H), 1.73 (dd, J = 3.3, 7.6 Hz, 1H), 1.61 (m, 1H), 1.28 (dd, J = 3.2, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.6, 169.1, 168.9, 104.2, 90.8, 57.1, 54.3, 52.8, 52.7, 37.7, 29.0, 25.7.

The ^{1}H and ^{13}C spectra matched those reported in literature.[48]

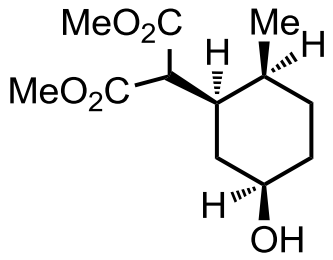


Dimethyl 2-(5-hydroxy-2-methylcyclohex-3-en-1-yl)propandioate (±)-139: To a stirring solution of **(±)-75** (33 mg, 0.14 mmol) in methanol (2.5 mL) was added $CeCl_3.7H_2O$ (57 mg, 0.15 mmol). The mixture was stirred until all the inorganic salt had dissolved completely. Solid $NaBH_4$ (25 mg, 0.65 mmol) was added in one portion and the solution stirred at room temperature for 2 h. The reaction was quenched with H_2O,

extracted several times with ether, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 0-75% gradient) to afford **(±)-139** as a pale yellow oil (26 mg, 78%).

IR (neat) 3404, 2856, 2877, 1735, 1435, 1315, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.70 (dd, *J* = 1.7, 10.5 Hz, 1H), 5.60 (dd, *J* = 1.9, 10.5 Hz, 1H), 4.26 (ddd, *J* = 1.9, 4.0, 9.9 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.37 (d, *J* = 6.7 Hz, 1H), 2.56 (dqd, *J* = 1.7, 6.6, 9.9 Hz, 1H), 2.32 (dddd, *J* = 2.1, 6.7, 9.9, 10.1 Hz, 1H) 1.77 (ddd, *J* = 2.1, 4.0, 13.5 Hz, 1H), 1.68 (br s, 1H), 1.45 (ddd, *J* = 9.9, 10.1, 13.5 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 168.5, 134.6, 129.9, 68.2, 55.2, 52.9, 52.8, 36.3, 31.3, 30.8, 14.6.

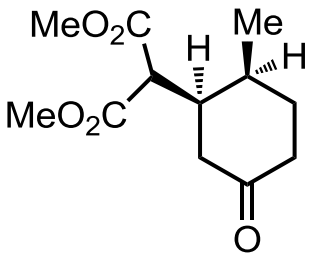
These spectral data were compared to those of a similar compound reported by our group.[48]



Dimethyl 2-(5-hydroxy-2-methylcyclohexyl)propandioate (±)-140: The cyclohexenol **(±)-139** (56 mg, 0.23 mmol) was dissolved in methanol (8 mL) and the resultant solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 10 mg) was added and the flask was connected to a Parr hydrogenation apparatus. The reaction mixture was maintained under H_2 (45 psi) and stirred for 5 h after

which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate (10 mL) and filtered through a pad of celite. The filter bed was washed several times with ethyl acetate and the extracts concentrated under reduced pressure to afford **(±)-140** as a colorless oil (52 mg, 91%).

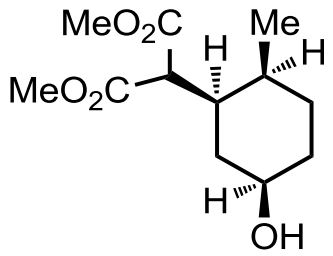
IR (neat) 3471, 2910, 1675, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (s, 6H), 3.60 (tt, *J* = 2.8, 10.3 Hz, 1H), 3.31 (d, *J* = 5.5 Hz, 1H), 2.32 (tdd, *J* = 2.8, 5.5, 10.3 Hz, 1H), 1.83 (m, 1H), 1.70 (m, 3H), 1.57 (m, 2H), 1.51 (br s, 1H), 1.39 (m, 1H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 168.9, 70.7, 55.7, 52.7, 39.6, 33.7, 31.0, 29.5, 28.4, 12.2.



Dimethyl 2-(2-methyl-5-oxocyclohexyl)propandioate (±)-141: The cyclohexenone **(±)-75** (112 mg, 0.467 mmol) was dissolved in methanol (10 mL) and the resultant solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 15 mg) was added and the flask was connected to a Parr hydrogenation apparatus. The reaction mixture was maintained under H_2 (45 psi) and stirred for 24 h after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate and filtered through a pad of celite. The filter bed was washed several times with ethyl acetate and the extracts concentrated under reduced pressure.

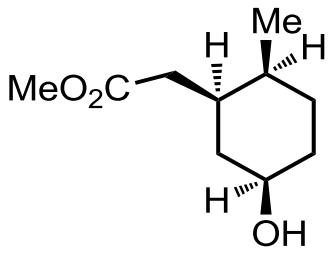
The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 15-30% gradient) to afford **(±)-141** as a pale yellow oil (82 mg, 73%).

IR (neat) 3439, 2957, 2085, 1990, 1735, 1666, 1435, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H), 3.72 (s, 3H), 3.39 (d, *J* = 5.7 Hz, 1H), 2.72 (dd, *J* = 10.2, 15.8 Hz, 1H), 2.48 (m, 1H), 2.31 (m, 1H), 2.25 (m, 2H), 1.12 (m, 1H), 1.87 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.5, 169.3, 168.4, 55.5, 52.9, 49.3, 40.9, 36.5, 31.7, 28.8, 11.9.



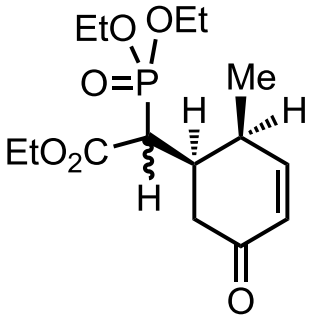
Dimethyl 2-(5-hydroxy-2-methylcyclohexyl)propandioate (±)-140: To a stirring solution of the cyclohexanone **(±)-141** (36 mg, 0.15 mmol) in methanol (5 mL) was added solid $NaBH_4$ (6 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred for a further 2 h under room temperature. The reaction was quenched with H_2O, extracted several times with ether, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 30-50% gradient) to afford **(±)-140** as a pale yellow oil (31 mg, 93%).

The ^1H and ^{13}C NMR spectra for this product were identical to those previously obtained.



Methyl 2-(5-hydroxy-2-methylcyclohexyl)acetate (±)-142: To a stirring solution of **(±)-140 (**40 mg, 0.17 mmol) in DMSO (10 mL) was added LiI (70 mg, 1.4 mmol) and H_2O (70 mg, 3.9 mmol). The reaction mixture was stirred at room temperature until all the inorganic salts had dissolved and then heated to reflux at 150 ^{0}C for 24 h. After completion the reaction mixture was cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with 10% aqueous HCl (15 mL) followed by saturated aqueous $NaHCO_3$ (38 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **(±)-142** as a colorless oil (23 mg, 79%).

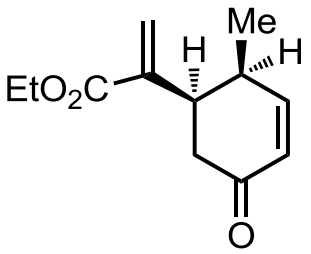
IR (neat) 2965, 1723, 1467, 1311, 1186 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.68-3.57 (m, 1H), 2.36-2.17 (m, 2H), 2.14-1.99 (m, 1H), 1.88-1.78 (m, 8H), 0.86 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 70.8, 51.8, 38.8, 36.1, 36.0, 30.8, 30.4, 29.8, 12.5. ESI-HRMS m/z 209.1148 (calcd. for $C_{10}H_{18}O_3Na$ (M+Na) m/z 209.1148).



Triethyl 2-(2-methyl-5-oxocyclohex-3-en-1-yl)phosphonoacetate (±)-143 a/b: To an ice-cold stirring suspension of NaH (13.5 mg, 0.546 mmol) in dry THF (10 mL) was added triethyl phosphonoacetate (0.122 mg, 0.546 mmol). The mixture was stirred at 0 ^{0}C for 10-15 min. Solid cation **32** (0.20 g, 0.55 mmol) was added in one portion and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and saturated methanolic $NaHCO_3$ (10 mL each) and stirred overnight at room temperature. Water (20 mL) was added and the mixture extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 0-50% gradient) to afford **143a** as a yellowish oil (164 mg, 84%) as well as an unquantified trace of **143b** (diene)**.**

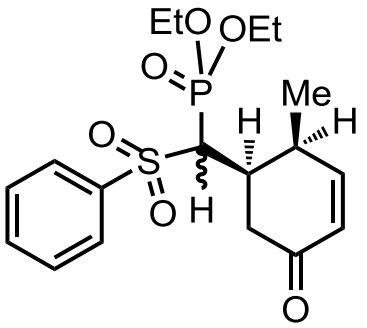
IR (neat) 2960, 2890, 1730, 1680, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (dd, *J* = 6.1, 10.1 Hz, 1H), 5.92 (d, *J* = 6.1 Hz, 1H), 4.32-4.03 (m, 6H), 3.08-2.73 (m, 5H), 1.37-1.19 (m, 9H), 1.10 (d, *J* = 6.7 Hz, 3H). ESI-HRMS m/z 355.1281 (calcd. for $C_{12}H_{25}O_6PNa$ (M+Na) m/z 355.1285).

Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.



Ethyl 2-(2-methyl-5-oxocyclohex-3-en-1-yl)propenoate (±)-148: To an ice-cold stirring suspension of NaH (43 mg, 0.11 mmol) in dry THF (5 mL) was added **143a** (40 mg, 0.11 mmol). The mixture was stirred at 0 ^{0}C for 30 min, and paraformaldehyde (3.2 mg, 0.11 mmol) added. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted H_2O (10 mL) and extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 0-25% gradient) to afford **(±)-148** as a pale yellowish oil (20 mg, 98%).

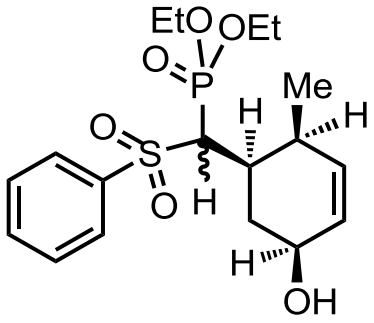
IR (neat) 2964, 2874, 1714, 1252, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (dd, *J* = 4.1, 9.5 Hz, 1H), 6.39 (s, 1H), 5.99 (d, *J* = 9.5 Hz, 1H), 5.48 (s, 1H), 4.22 (q, *J* = 7.5 Hz, 2H), 3.54-3.41 (m, 1H), 2.94-2.81 (m, 1H), 2.66-2.53 (m, 1H), 2.39-2.28 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 168.0, 155.6, 140.9, 127.6, 125.3, 60.9, 38.1, 37.1, 32.1, 14.2, 12.6. ESI-HRMS m/z 439.2091 (calcd. for $(C_{12}H_{16}O_6)_2Na$ (M+Na) m/z 439.2100).



Diethyl [(2-methyl-5-oxocyclohex-3-en-1-yl)(phenylsulfonyl)methyl]phosphonate (±)-145: To an ice-cold stirring suspension of NaH (28.4 mg, 0.710 mmol) in dry THF (13 mL) was added diethyl (phenylsulfonyl)methanephosphonate (0.16 g, 0.55 mmol). The mixture was stirred at 0 ^{0}C for 10-15 min, solid cation **32** (0.20 g, 0.55 mmol) was added in one portion and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (13 mL), a saturated solution of methanolic $NaHCO_3$ (26 mL) was added, and the mixture was stirred overnight at room temperature. Water (20 mL) was added, and the mixture was extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 0-90% gradient) to afford **(±)-145a** as a bright green oil (108 mg, 61%) and an unquantifiable amount of diene complex **14b**.

IR (neat) 2925, 1675, 1448, 1311, 1255, 1156, 1021 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05-7.94 (m, 2H), 7.72-7.64(m, 1H), 7.62-7.53 (m, 2H), 6.96 (dd, *J* = 5.7, 9.5 Hz, 1H), 5.96 (d, *J* = 9.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.63 (d, *J* = 6.4 Hz, 1H), 3.33-3.16 (m, 1H), 3.02-2.87 (m, 1H), 2.84-2.72 (m, 1H), 2.60 (dd, *J* = 2.6, 15.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.17 (d, *J* = 7.2 Hz, 3H).

Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.

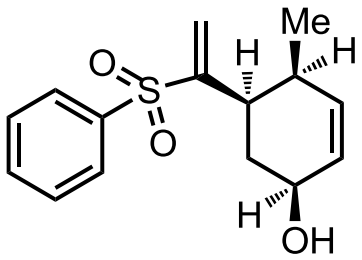


Diethyl [(5-hydroxy-2-methylcyclohex-3-en-1-yl)(phenylsulfonyl)methyl]phosphonate (±)-149: The cyclohexenone **145a** (147 mg, 0.367 mmol) and $CeCl_3$. $8H_2O$ (136.7 mg, 0.3670 mmol) were dissolved in MeOH (10 mL). The mixture was stirred until all the inorganic salt had dissolved completely. Solid $NaBH_4$ (14 mg, 0.38 mmol) was added in one portion and the solution stirred at room temperature. The reaction mixture was stirred for a further 2 h under room temperature. The reaction was quenched with water (50 mL) and the mixture extracted several times with ether. The combined extracts were dried ($MgSO_4$) and concentrated. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 0-75% gradient) to afford **(±)-149** as a pale green oil (106 mg, 72%).

IR (neat) 3422, 3055, 2983, 1652, 1558, 1265, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02-7.94 (m, 2H), 7.68-7.61 (m, 1H), 7.57-7.50 (m, 2H), 5.63 (dd, *J* = 6.2, 10.9 Hz, 1H), 5.56 (d, *J* = 11.1 Hz, 1H), 4.24-4.16 (m, 1H), 4.14-4.03 (m, 4H), 3.63-3.50 (m, 1H), 2.77-2.64 (m, 1H), 2.95-2.34 (m, 1H), 2.24-2.14 (m, 1H), 2.13-2.03 (m, 1H), 1.84-1.70 (m,

1H), 1.33-1.25 (m, 6H), 1.00 (d, J = 7.2 Hz, 3H). ESI-HRMS m/z 425.1158 (calcd. for $C_{18}H_{27}O_6PSNa$ (M+Na) m/z 425.1162).

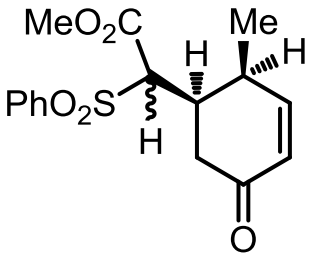
Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.



4-Methyl-5-[1-(phenylsulfonyl)ethenyl]cyclohex-2-enol (±)-150: To an ice-cold stirring suspension of NaH (8.20 mg, 0.205 mmol) in dry THF (8 mL) was added (±)-**149** (55 mg, 0.14 mmol). The mixture was stirred at 0 ^{0}C for 30 min, and then paraformaldehyde (8.2 mg, 0.27 mmol) was added slowly at such a rate that the temperature remained below 30 ^{0}C and then reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether-hexanes = 0-75% gradient) to afford **(±)-150** as a pale yellowish oil (20 mg, 53%).

IR (neat), 3426, 2925, 2853, 1447, 1302, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (ddd, J = 0.8, 1.5, 8.0 Hz, 2H), 7.64 (tt, J = 1.5, 7.5 Hz, 1H), 7.61 (ddd, J = 0.8, 7.5, 8.0 Hz, 2H), 6.46 (d, J = 2.3 Hz, 1H), 5.71 (d, J = 2.3 Hz, 1H), 5.66 (dddd, J = 1.9, 6.2, 10.4, 10.9 Hz, 1H), 5.54 (dd, J = 1.8, 10.3 Hz, 1H), 4.23-4.17 (m, 1H), 2.78 (dddd, J = 7.7, 8.8,

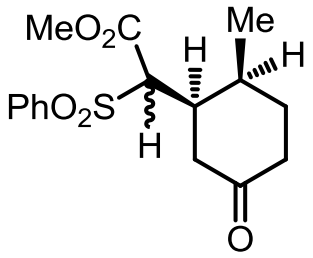
15.2, 19.7 Hz, 1H), 2.40 (qdd, *J* = 1.9, 3.9, 6.9 Hz, 1H), 1.73-1.65 (m, 1H), 1.63-1.52 (m, 2H), 0.72 (d, *J* = 6.9 Hz, 3H). ESI-HRMS m/z 579.1846 (calcd. for $(C_{15}H_{18}O_3S)_2Na$ (M+Na) m/z 579.1855).



Methyl 2-(3'-methyl-6'-oxo-1'-cyclohexen-4'-yl)-2-phenylsulfonylacetate (±)-146a/b: To a stirring suspension of NaH (33 mg, 0.82 mmol) in freshly distilled THF (13 mL) at 0 ^{0}C was added dropwise methyl phenylsulfonylacetate. The reaction mixture was stirred at this temperature under N_2 for 1 h. Tricarbonyl(η^5-3-methyl-pentadienyl)iron(+1) hexafluorophosphate cation **32** (200 mg, 0.546 mmol) was added in one portion and the mixture stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 (13 mL) and saturated $NaHCO_3$/MeOH (26 mL) and stirred at room temperature for 24 h. The reaction was finally quenched with water and the organic components extracted into CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 4:1) to afford a mixture of two diastereomeric cyclohexenones **146a** and **146b** (~ 1:1) partially separable on silica (126 mg, 72%) as a yellow oil in addition to an unquantifiable trace of iron diene product **147**.

IR (neat) 2954, 1739, 1482, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) **146a** δ 7.85 (d, *J* = 7.6 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.13 (dd, *J* = 5.8, 10.4 Hz, 1H), 5.98 (d, *J* = 10.4 Hz, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 3.46 (s, 3H), 3.21-3.15 (m, 2H),

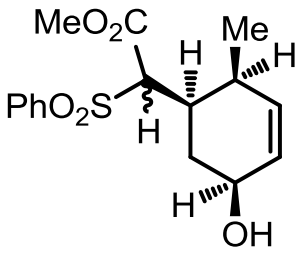
2.37 (dd, *J* = 13.4, 16.8 Hz, 1H), 2.13 (dd, *J* = 3.6, 16.8 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 167.3, 156.9, 138.5, 135.2, 129.1, 127.8, 72.4, 53.2, 38.7, 36.4, 31.8, 31.7, 12.4; ^{1}H NMR ($CDCl_3$, 300 MHz) **146b** δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 6.85 (dd, *J* = 6.3, 9.9 Hz, 1H), 5.98 (d, *J* = 9.9 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 3.44 (s, 3H), 3.19 (dd, *J* = 13.4, 16.5 Hz, 1H), 3.12-2.98 (m, 1H), 2.52 (dd, *J* = 13.5, 17.1 Hz, 1H), 2.27-2.41 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.8, 166.1, 154.2, 137.5, 134.8, 129.6, 128.3, 74.1, 53.3, 36.7, 36.3, 31.9, 31.2, 12.3. ESI-HRMS m/z 345.0767 (calcd. for $C_{16}H_{18}O_5SNa$ (M+Na) m/z 345.0772).



Methyl 2-(2'-methyl-5'-oxocyclohexyl)-2-(phenylsulfonyl)acetate (±)-154a/b: The mixture of diastereomeric cyclohexenones **146a** and **146b (**378 mg, 1.17 mmol) was dissolved in MeOH (20 mL) and the solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 115 mg) was added and the flask connected to a Parr hydrogenation apparatus. The mixture was maintained under H_2 (45 psi) with stirring for 24 h after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate (25 mL) and filtered through a celite pad. The filter bed was washed several times with ethyl acetate and the extracts concentrated. The residue was purified by flash column chromatography (SiO_2, ethyl

acetate-hexanes = 0-80% gradient) to afford a mixture of two diastereomeric cyclohexanones **(±)-154a/b** inseparable on silica as a green oil (370 mg, 98%).

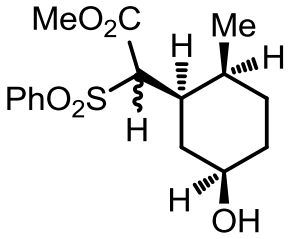
^{1}H NMR ($CDCl_3$, 400 MHz) **154a/b** δ 7.89 (d, *J* = 8.6 Hz, 4H), 7.69 (t, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 4H), 4.07 (d, *J* = 11.9 Hz, 1H), 4.02 (d, *J* = 11.1 Hz, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 3.07 (br d, *J* = 17.1 Hz, 1H), 2.91-2.82 (m, 1H), 2.79-2.69 (m, 2H), 2.44-2.35 (m, 3H), 2.34-2.24 (m, 3H), 2.05 (br d, *J* = 12.5 Hz, 1H), 1.94-1.77 (m, 5H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **20c/d** δ 208.3 [208.2], 166.3 [166.1], 137.8 [137.6], 134.7 [134.6], 129.6 [129.5], 129.5 [129.4], 75.1 [73.0], 53.2 [53.1], 40.5 [40.3], 39.9 [39.8], 36.6 [35.9], 31.4 [31.2], 29.2 [28.7], 11.9 [11.8]. Diastereomeric signals in brackets. ESI-HRMS m/z 347.0924 (calcd. for $C_{16}H_{20}O_5SNa$ (M+Na) m/z 347.0921).



Methyl 2-(3'-methyl-6'-hydroxy-1-cyclohexen-4'-yl)-2-phenylsulfonylacetate (±)-152a/b: To a solution of diastereomeric cyclohexenones **146a** and **146b** (83 mg, 0.26 mmol) in methanol (10 mL) was added cerium chloride heptahydrate (97 mg, 0.26 mmol). The mixture was stirred until the cerium salt had dissolved completely. Solid $NaBH_4$ (10 mg, 0.28 mmol) was added slowly with vigorous stirring. After addition was complete, the mixture was stirred under N_2 for 3 h. The reaction was quenched with water (5 mL) and the organic components extracted several times with diethyl ether. The

combined extracts were washed (brine), dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (SiO_2, hexanes-ethyl acetate = 20:1 → 4:1 gradient) afforded an inseparable mixture of diastereomers (**152a** and **152b**, ~3:4) as a pale yellow oil (78 mg, 94% yield). A pure diastereomer (**152a**) could be isolated by careful rechromatography:

ν_{max} (CH_2Cl_2)/cm^{-1} 3397, 2955, 1739, 1447, 1310, 1144; ^{1}H NMR ($CDCl_3$, 300 MHz) **152a** δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 5.76 (ddd, *J* = 1.2, 4.5, 10.2 Hz, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 4.35-4.25 (br m, 1H), 4.09 (d, *J* = 9.6 Hz, 1H), 3.49 (s, 3H), 2.80-2.68 (m, 2H), 1.70-1.55 (m, 2H), 1.44 (dt, *J* = 10.2, 12.3 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **152a** δ 166.8, 166.7, 138.2, 138.0, 134.6, 129.4, 129.3, 73.2, 68.4, 53.0, 35.7, 31.5, 31.2, 14.8. ESI-HRMS m/z 347.0924 (calcd. for $C_{16}H_{20}O_5SNa$ (M+Na) m/z 347.0921).

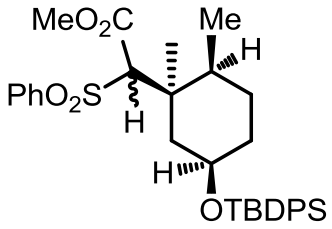


Methyl 2-(2'-methyl-5'-hydroxy-1-cyclohexyl)-2-phenylsulfonyl)acetate (±)-153a/b: The mixture of diastereomeric cyclohexenols **(±)-152a/b** (35 mg, 0.11 mmol) was dissolved in MeOH (5 mL) and the solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 15 mg) was added and the flask connected to a Parr hydrogenation apparatus. The mixture was maintained under H_2 (45 psi) with stirring for 5 h after which the pressure was released and the solvent

removed. The residue was suspended in ethyl acetate (25 mL) and filtered through a celite pad. The filter bed was washed several times with ethyl acetate and the extracts concentrated. The residue was purified by flash column chromatography (SiO_2, hexanes-ethyl acetate = 20:1 → 1:1 gradient) to afford a mixture of two diastereomeric cyclohexanols (**153a** and **153b**) partially separable on silica as a pale yellow oil (27 mg, 78%).

ν_{max} (CH_2Cl_2)/cm^{-1} 3446, 2952, 1740, 1652, 1448, 1325, 1145; ^{1}H NMR ($CDCl_3$, 300 MHz) **153a** δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 4.02 (d, *J* = 10.1 Hz, 1H), 3.63-3.48 (m, 1H), 3.44 (s, 3H), 2.54-2.41 (m, 2H), 1.79-1.21 (m, 7H), 0.98 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) **153a** δ 167.0, 138.5, 134.9, 129.4, 129.3, 73.7, 70.7, 52.8, 38.6, 33.4, 30.9, 29.3, 28.3, 12.1; ^{1}H NMR ($CDCl_3$, 300 MHz) **153b** δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 4.00 (d, *J* =11.7 Hz, 1H), 3.71-3.58 (m, 1H), 3.42 (s, 3H), 2.57-2.42 (m, 2H), 1.80-1.21 (m, 7H), 0.88 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **153b** δ 166.7, 138.2, 134.5, 129.4, 129.3, 75.1, 70.3, 25.9, 38.5, 33.6, 30.8, 29.4, 28.9, 12.5.

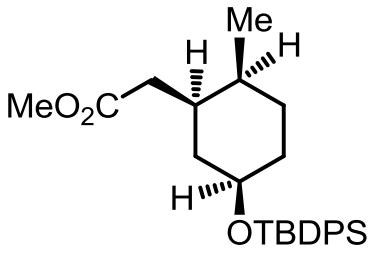
ESI-HRMS m/z 349.1080 (calcd. for $C_{16}H_{22}O_5SNa$ (M+Na) m/z 349.1080).



Methyl 2-[5'-(*t*-butyldiphenylsilyl)oxy-2'-methylcyclohexyl]-2-phenylsulfonylacetate (±)-155a/b: To a solution of diastereomeric cyclohexanols **153a/b** (435 mg, 1.33 mmol)

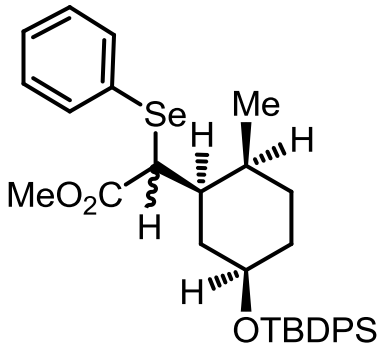
in CH_2Cl_2 (50 mL) at 0 ^{0}C was added imidazole (182 mg, 2.67 mmol). The reaction mixture was stirred under N_2 for 15 min. Liquid *t*-butyldiphenylsilyl chloride (561 mg, 2.00 mmol) was added slowly with vigorous stirring. After addition was complete the mixture was stirred at room temperature overnight and quenched with water. The resulting mixture was extracted several times with Et_2O, and the combined extracts dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-acetone = 20:1 → 4:1 gradient) to afford a mixture of protected cyclohexanols **155a** and **155b** as a colorless oil **(**744 mg, 99%) partially separable on silica.

^{1}H NMR ($CDCl_3$, 300 MHz) **155a** δ 7.75-7.35 (m, 15H), 3.96 (d, *J* = 11.4 Hz, 1H), 3.55-3.45 (s & m, 4H total), 2.47 (br d, *J* = 12.9 Hz, 1H), 2.20-2.15 (m, 1H), 1.63-1.20 (m, 6H), 1.08 (s, 9H), 0.87 (d, *J* = 7.2 Hz, 3H); ^{1}H NMR ($CDCl_3$, 300 MHz) **155b** δ 7.85-7.30 (m, 15H), 3.97 (d, *J* = 10.5 Hz, 1H), 3.65-3.53 (m, 1H), 3.30 (s, 3H), 1.65-1.20 (m, 8H), 1.02 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **155a/b** δ 167.9 [167.8], 139.6 [139.3], 137.06 [137.0], 136.9 [136.8], 135.7 [135.6], 135.5 [135.4], 135.4 [131.2], 131.0 [130.4], 130.4 [130.3], 130.2 [129.0], 128.9 [128.7], 76.1 [74.3], 73.7 [73.3], 53.3 [53.2], 40.0 [39.9], 34.9 [34.4], 31.8 [31.7], 30.7 [30.5], 30.4 [29.7], 27.7 [27.6], 20.1 [20.0], 12.6 [12.5]. Diastereomeric signals in brackets. ESI-HRMS m/z 587.2258 (calcd. for $C_{32}H_{40}O_5SiSNa$ (M+Na) m/z 587.2256).



Methyl 2-[5'-(*t*-butyldiphenylsilyl)oxy-2'-methylcyclohexyl]acetate (±)-156: To a solution of cyclohexanols **155a**/**b** (68 mg, 0.12 mmol) in MeOH (10 mL) was added Mg metal (21 mg, 0.87 mmol). The reaction mixture was heated at 50 ^{0}C until gas evolution started at which stage the heating source was removed and stirring continued at room temperature. Additional Mg metal (21 mg, 6X) was added at 50 ^{0}C successively until all starting material had been consumed as indicated by TLC. The solvent was removed and the mixture redissolved in CH_2Cl_2. The mixture was filtered, washed with brine, dried ($MgSO_4$) and concentrated to give **(±)-156** as a single diastereomer (54 mg, *quant.*). This compound was used in the next step without further purification.

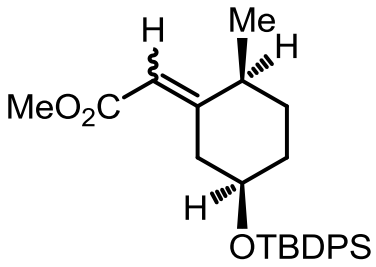
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75-7.70 (m, 4H), 7.40-7.35 (m, 6H), 3.70-3.62 (s & m, 4H total), 2.26 (dd, *J* = 7.8, 15.0 Hz, 1H), 2.20 (dd, *J* = 8.1, 15.0 Hz, 1H), 2.00-1.85 (m, 1H), 1.79-1.30 (m, 7H), 1.09 (s, 9H), 0.88 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 136.0, 135.8, 134.9, 129.7, 129.6, 127.7, 127.6, 127.5, 72.2, 51.5, 38.6, 36.3, 36.0, 30.6, 30.3, 30.1, 27.2, 19.3, 12.6. ESI-HRMS m/z 447.2326 (calcd. for $C_{26}H_{36}O_3SiNa$ (M+Na) *m/z* 447.2324).



Methyl 2-[5'-(*t*-butyldiphenylsilyl)oxy-2'-methylcyclohexyl]-2-phenylselenylacetate (±)-157a/b: To a stirring solution of LDA (2.0 M in heptanes, 0.08 mL, 0.2 mmol) in dry THF (2 mL) at -78 ^{0}C was added dropwise a solution of crude **(±)-156** (30 mg, 0.071 mmol) in dry THF (2 mL). The mixture was stirred at -78 ^{0}C under N_2 for 30 min. A solution of PhSeCl (27 mg, 0.14 mmol) in dry THF (0.5 mL) was added dropwise rapidly with vigorous stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h under N_2. The reaction was quenched with water. The resulting mixture was extracted several times with Et_2O, and the combined extracts washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 20:1) to afford a mixture of two diastereomeric phenylseleno compounds **157a** and **157b** (~1:1) (38 mg, 92%) partially separable on silica as a bright green oil.

^{1}H NMR ($CDCl_3$, 300 MHz) **157a** δ 7.78-7.70 (m, 4H), 7.50-7.20 (m, 11H), 3.57 (s, 3H), 3.58-3.48 (m, 1H), 3.37 (d, *J* = 12.0 Hz, 1H), 2.31 (br d, *J* = 12.0 Hz, 1H), 1.75-1.20 (m, 7H), 1.08 (s, 9H), 0.82 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **157a** δ 172.9, 136.2, 136.0, 134.8, 134.7, 129.8, 129.7, 129.1, 128.7, 128.1, 127.8, 127.7, 72.7, 52.0, 49.3, 40.3, 34.1, 31.2, 29.3, 27.2, 19.4, 12.0; ^{1}H NMR ($CDCl_3$, 75 MHz, deconvoluted

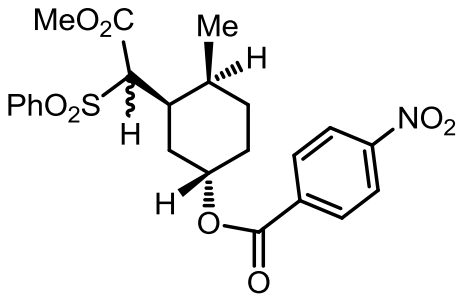
from **157a/b**) **157b** δ 7.68-7.54 (m, 7H), 7.46-7.19 (m, 8H), 3.63-3.61 (m, 1H), 3.45 (s, 3H), 3.39 (d, J = 11.8 Hz, 1H), 2.25-2.17 (m, 1H), 1.90-1.23 (m, 7H), 1.04 (s, 9H), 0.85 (d, J = 4.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, deconvoluted from **157a/b**) **157b** δ 173.0, 136.1, 136.0, 134.9, 134.8, 129.9, 129.8, 129.7, 129.4, 129.3, 129.2, 72.4, 52.1, 49.2, 40.2, 35.0, 31.1, 29.3, 27.3, 19.4, 11.9. ESI-HRMS m/z 603.1804 (calcd. for $C_{32}H_{40}O_5SiSeNa$ (M+Na) m/z 603.1802).



(E/Z)- Methyl 2-[5'-(*t*-butyldiphenylsilyl)oxy-2'-methylcyclohexylidene]acetate (158a/b): To a stirring solution of the phenylseleno compounds **157a**/**b** (27 mg, 0.046 mmol) in MeOH (3 mL) was added $NaIO_4$ (23 mg, 0.11 mmol). The mixture was stirred vigorously under N_2 overnight. The reaction was quenched with water. The resulting mixture was extracted several times with Et_2O, and the combined extracts washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 20:1) to afford a mixture of unsaturated esters **158a** and **158b** (~1:1) as a colorless oil inseparable on silica (15 mg, 77%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (br d, J = 7.8 Hz, 8H), 7.48-7.33 (m, 12H), 5.73 (br s, 1H), 5.36 (br s, 1H), 4.05-3.98 (m, 1H), 3.91-3.80 (m, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 2.61-2.40 (m, 2H), 2.27-2.11 (m, 2H), 1.77-1.47 (m, 10H), 1.13 (d, J = 6.0 Hz, 3H), 1.11

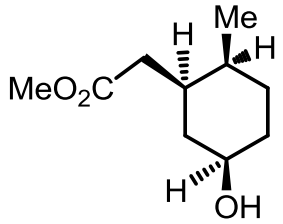
(d, J = 7.8 Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6 [166.9], 164.7 [163.6], 136.1 [136.0], 135.9 [134.9], 134.54 [134.52], 134.4 [134.3], 129.9 [129.8], 129.7 [128.8], 127.7 [127.6], 114.3 [113.8], 73.2 [71.2], 51.1 [51.0], 42.9 [42.8], 39.4 [39.3], 36.8 [32.3], 31.2 [30.3], 29.9 [29.8], 29.7 [29.4], 27.2 [27.1], 19.4 [19.3], 18.6 [18.4]. Diastereomeric signals in brackets. ESI-HRMS m/z 445.2169 (calcd. for $C_{26}H_{34}O_3SiNa$ (M+Na) m/z 445.2168).



3-(2-Methoxy-2-oxo-1-(phenylsulfonyl)ethyl)-4-methylcyclohexyl-4-nitrobenzoate (±)-159a/b: To a mixture of cyclohexanols **153a/b** (172 mg, 0.526 mmol) was added 4-nitrobenzoic acid (353 mg, 2.11 mmol) and triphenylphosphine (554 mg, 2.11 mmol). Freshly distilled THF (10 mL) was added and the mixture stirred at room temperature until homogeneous. The mixture was cooled to 0 ^{0}C and diethyl azodicarboxylate (1.03 mL, 2.1 mmol, 40 w/v in toluene) was added slowly over a 30 min period with stirring. After addition was complete the reaction mixture was slowly warmed to room temperature and stirred for 16 h under N_2. The reaction mixture was then stirred at 40 ^{0}C for 4 h. The reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude residue was suspended in Et_2O (10 mL) and allowed to stand overnight and the by-products precipitated by addition of hexane. The

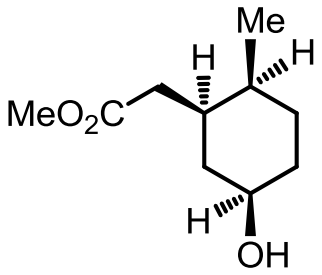
mixture was filtered and concentrated and the residue purified by column chromatography (SiO_2, hexanes-Et_2O = 5:1) to afford a mixture of *p*-nitro benzoate esters **159a/b** (~1:1) as a colorless oil (230 mg, 92%).

^{1}H NMR ($CDCl_3$, 300 MHz, deconvoluted from **159a/b**) **159a** δ 8.34-8.26 (m, 4H), 7.94-7.64 (m, 5H), 5.41-5.40 (m, 1H), 4.02 (br s, 1H), 3.56 (s, 3H), 3.04-2.93 (m, 1H), 2.66-2.61 (m, 1H), 2.08-1.79 (m, 6H), 1.05 (d, *J* = 7.0 Hz, 3H); ^{1}H NMR ($CDCl_3$, 300 MHz, deconvoluted from **159a/b**) **159b** δ 8.25-8.13 (m, 4H), 7.63-7.37 (m, 5H), 5.31-5.30 (m, 1H), 4.00 (d, *J* = 3.3 Hz, 1H), 3.41 (s, 3H), 2.84-2.73 (m, 1H), 2.60-2.56 (m, 1H), 1.78-1.44 (m, 6H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **159a/b** δ 166.8 [166.6], 164.1 [164.0], 150.8 [150.7], 138.1 [137.8], 136.3 [136.2], 134.5 [134.4], 131.1 [130.9], 130.0 [129.4], 129.2 [129.1], 123.9 [123.8], 75.5 [73.6], 71.3 [70.9], 53.1 [52.9], 35.2 [35.0], 29.6 [29.4], 28.3 [28.2], 27.9 [27.8], 24.0 [23.7], 11.7 [11.6]. Diastereomeric signals in brackets.



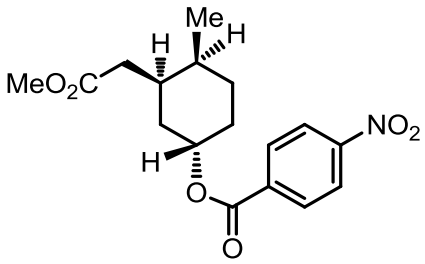
Methyl 2-(5-hydroxy-2-methylcyclohexyl)acetate (±)-160: To a mixture of cyclohexanols **153a/b** (230 mg, 0.480 mmol) in methanol (30 mL) was added activated Mg metal (85 mg, 3.5 mmol). The reaction mixture was heated at 50 ^{0}C until gas evolution started at which stage the heating source was removed and the reaction stirred at room temperature. Additional Mg metal (85 mg, 3.5 mmol, 8X) was added at 50 ^{0}C

until all starting material had been consumed as indicated by TLC. The solvent was removed and the mixture redissolved in Et_2O. The mixture was filtered, washed with brine, dried ($MgSO_4$) and concentrated to give the crude product as a single diastereomer (120 mg). The residue was purified by column chromatography (hexanes-ethyl acetate = 3:1) to afford a single diastereomer as a brown oil (39 mg 25%) in addition to a complex mixture of unidentifiable reaction products. The ^1H and ^{13}C NMR spectral data for this product are consistent with those obtained for a product formed via a different route (*vide supra*).



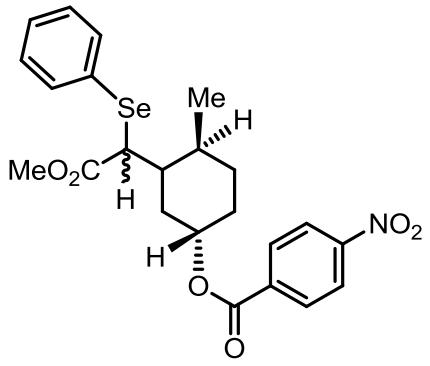
Methyl 2-(5'-hydroxy-2'-methylcyclohexyl)acetate (±)-142: To a stirring solution of the protected silyl ether **(±)-155a/b** (57 mg, 0.13 mmol) in DMF (2 mL) at 0 ^0C was added TSAF (60 mg, 0.22 mmol). The reaction mixture was stirred at 0 ^0C for 2 h after which the ice bath was removed and stirring continued at room temperature for 24 h. Upon completion of the reaction, as indicated by TLC the solvent was removed under an N_2 stream and the mixture applied to a silica pad. The product was eluted (ethyl acetate-hexanes = 1:5) to afford the unprotected cyclohexanol **(±)-142** as a colorless oil (24 mg, 96%).

The ^1H and ^{13}CNMR spectra for this compound matched with those previously obtained.

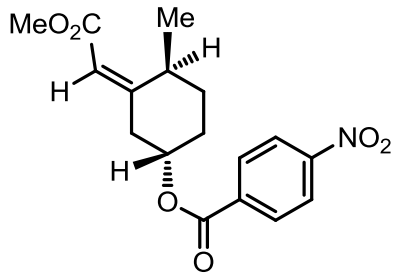


3-(2-Methoxy-2-oxoethyl)-4-methylcyclohexyl 4-nitrobenzoate (±)-165: To **(±)-142** (27 mg, 0.15 mmol) was added *p*-nitrobenzoic acid (99.3 mg, 0.594 mmol) and triphenylphosphine (156 mg, 0.594). Freshly distilled THF (5 mL) was added and the mixture stirred at room temperature under N_2 for 15 min until homogeneous. The reaction mixture was cooled to 0 ^{0}C and a solution of diethyl azodicarboxylate (259 mg, 40 % wt solution in toluene) added slowly over a 10 min period. The mixture was then stirred vigorously at 0 ^{0}C for 30 min after which the cold bath was removed and stirring continued at room temperature for 24 h. Upon completion of the reaction, as indicated by TLC, the solvent was removed under a N_2 stream and the residue applied to a silica pad. The product was eluted (ethyl acetate-hexanes = 0-40% gradient) to afford **(±)-165** as a pale green oil (46 mg, 94%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33-8.17 (m, 4H), 5.30-5.21 (m, 1H), 3.68 (s, 3H), 2.55-2.42 (m, 3H), 1.99-1.64 (m, 6H), 1.48-1.36 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ 173.5, 164.5, 150.9, 136.2, 131.6, 124.6, 72.1, 51.9, 36.3, 33.5, 32.3, 31.6, 28.1, 26.6, 14.2. ESI-HRMS m/z 358.1261 (calcd. for $C_{17}H_{21}NO_6Na$ (M+Na) m/z 358.1260).

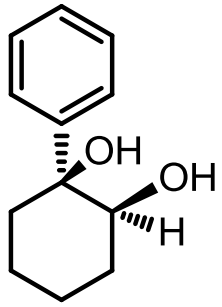


3-(2-Methoxy-2-oxo-1-(phenylselenyl)ethyl)-4-methylcyclohexyl 4-nitrobenzoate (±)-166: To a stirring solution of LDA (2.0 M in heptane, 0.26 mL, 1.3 mmol) in dry THF (1 mL) at -78 ^{0}C was added dropwise a solution of the crude (±)-**165** (35 mg, 0.10 mmol) in dry THF (2 mL). The mixture was stirred at -78 ^{0}C under N_2 for 30 min. A solution of PhSeCl (40 mg, 0.21 mmol) in dry THF (0.5 mL) was added dropwise rapidly with vigorous stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h under an N_2. The solvent was removed under N_2 stream and the residue purified by column chromatography (SiO_2, hexanes-ethyl acetate = 0-20% gradient) to afford a mixture of two diastereomeric phenylseleno compounds as a green oil (46 mg, ~1:1 *ratio*, 90%). Owing to the susceptibility of the latter to slow oxidation by air the crude compound **(±)-166** was used without thorough column purification.



(*Z*)-3-(2-Methoxy-2-oxoethylidene)-4-methylcyclohexyl 4-nitrobenzoate (±)-167: To a stirring solution of the crude phenylseleno compound (15 mg, 0.031 mmol) in MeOH (2 mL) was added $NaIO_4$ (13 mg, 0.61 mmol). The mixture was stirred vigorously under N_2 for 6 d. The reaction was quenched with water. The resulting mixture was extracted several times with Et_2O, dried ($MgSO_4$) and concentrated under a N_2 stream. The residue was purified by column chromatography (SiO_2, diethyl ether-hexanes = 0-10% gradient) to afford **(±)-167** as a single isomer as a pale yellow oil (10 mg, 98%).

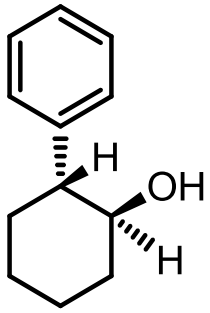
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31-8.12 (m, 4H), 5.61 (s, 1H), 5.46-5.40 (m, 1H), 3.69 (s, 3H), 2.81-2.72 (m, 1H), 2.48-2.39 (m, 2H), 2.07-1.87 (m, 4H), 1.22 (d, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 164.2, 162.2, 150.8, 136.2, 131.0, 123.8, 116.1, 73.2, 51.3, 36.8, 30.4, 29.9, 27.4, 18.2. ESI-HRMS m/z 356.1105 (calcd. for $C_{17}H_{19}NO_6Na$ (M+Na) m/z 356.1104).



(1*S*,2*S*)-1-Phenylcyclohexane-1,2-diol (-)-175: To a flame dried 1000 mL 3-necked round bottom flask was added H_2O (166 mL), $K_3Fe(SCN)_6$ (109.3 g), K_2CO_3 (46 g), $CH_3SO_2NH_2$ (11 g), $K_2OsO_4 \cdot 2H_2O$ (24 mg) and (DHQ)PHAL (216 mg). The mixture was stirred vigorously at room temperature for 20 min. The reaction mixture was cooled to 0 ^{0}C and 1-phenyl-1-cyclohexene (16.5 g, 0.104 mol) added with stirring. The mixture was kept stirring at 0 ^{0}C and the progress of the reaction monitored by TLC. The reaction was quenched with water and the organic components extracted into ethyl acetate. The organic extracts were washed with 5 M KOH, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (SiO_2, ethyl acetate-hexanes 0-50% gradient) afforded the diol **(-)-175** as a colorless solid (18.3 g, 91%).

$[\alpha]_D^{20}$ = – 16.4 (*c* = 0.0184, benzene) [Lit.[3] $[\alpha]_D = -16.0$ (*c* = 1.0, benzene)]

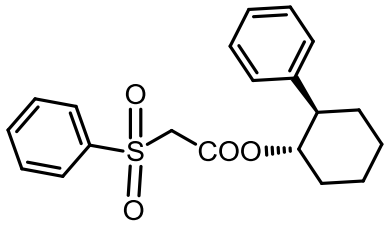
mp 117-120 ^{0}C (Lit.[156] 122-123 ^{0}C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56-7.23 (m, 5H), 3.98 (dd, *J* = 4.8, 4.6 Hz, 1H), 1.88-1.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.2, 128.5, 126.6, 124.1, 76.8, 68.9, 39.7, 28.9, 25.0, 22.8.



(1*S*,2*R*)-2-Phenylcyclohexanol (+)-176: Into an oven dried 3-necked round bottom flask was added a slurry of Raney nickel (100 g) in water. The (1*S*,2*S*)-1-phenylcyclohexan-1,2-diol (19.0 g, 98.4 mmol) was added. A solution of absolute ethanol (140 mL) in water (60 mL) was added and the mixture stirred mechanically for 15 min at room temperature. The mixture was heated at reflux vigorous with stirring for 7 d. The mixture was filtered through a celite pad. The pad was washed several times with absolute ethanol and ethyl acetate. The organic extracts were separated, washed (brine), dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (SiO_2, ethyl acetate-hexanes = 0-20% gradient) afforded the alcohol (+)-**176** as a colorless crystalline solid (12.3g, 71%).

$[\alpha]_D^{20}$ = + 43.5 (*c* = 0.119, MeOH) [Lit.[3] $[\alpha]_D$ = +59.4 (*c* = 1.0, meOH)]

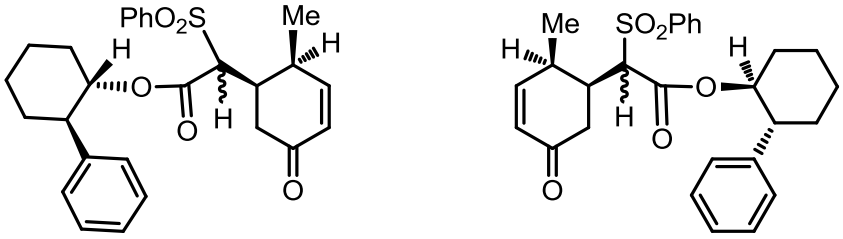
mp 58-60 ^{0}C (Lit.[156] 64-66 ^{0}C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.38 (m, 5H), 3.64 (m, 1H), 2.41 (m, 1H), 2.16 (m, 1H), 1.83-1.78 (m, 3H), 1.49-1.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.2, 128.8, 128.0, 126.9, 74.4, 53.2, 34.5, 33.3, 26.0, 25.0.



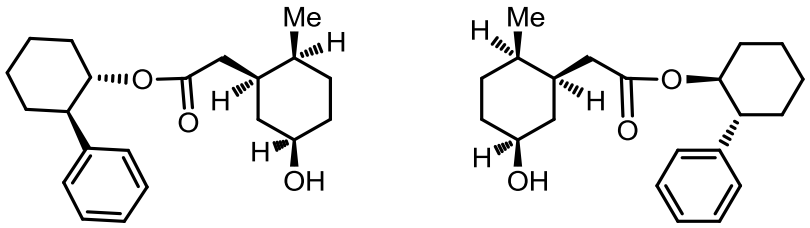
(1*S*,2*R*)-2-Phenylcyclohexyl 2-(phenylsulfonyl)acetate (-)-178: Into a 100 mL round bottom flask was added phenylsulfonyl acetic acid **177** (100 mg, 0.499 mmol). Oxalyl chloride (78 mg, 0.050 mmol) was added dropwise with stirring. The mixture was stirred at room temperature under a nitrogen atmosphere for 1 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride used without further purification. The residue was redissolved in benzene (5 mL). The (1*S*,2*R*)-2-phenylcyclohexanol (105 g, 0.599 mmol) prepared previously was added in one portion and the resulting mixture heated to reflux for 48 h. The solvent was removed under vacuum and the residue purified by column chromatography (ethyl acetate-hexanes = 0-20% gradient) to afford **(-)-178** a dark brown viscous oil (115 mg, 64%).

$[\alpha]_D^{20} = -5.1$ (c = 0.0049, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.5 Hz, 2H), 7.62-7.43 (m, 3H), 7.24-7.13 (m, 5H), 4.98-4.85 (m, 1H), 3.76 (d, J = 14.4 Hz, 1H), 3.70 (d, J = 14.4 Hz, 1H), 2.62-50 (m, 1H), 2.19-1.88 (m, 1H), 1.85-1.64 (m, 3H), 1.49-1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.5, 144.3, 138.6, 134.8, 129.6, 128.0, 127.2, 126.4, 178.6, 78.8, 62.0, 48.9, 34.8, 32.5, 26.3, 25.0. ESI-HRMS m/z 381.1131 (calcd. for $C_{20}H_{22}O_4SNa$ (M+Na) m/z 381.1127).



(1*S*,2*R*)-2-Phenylcyclohexyl 2-(2-methyl-5-oxocyclohex-3-en-1-yl)phenylsulfonylacetate (±)-181-184: To a stirring suspension of NaH (83 mg, 2.1 mmol) in freshly distilled THF (34 mL) at 0 ^{0}C was added dropwise (1*S*,2*R*)-2-phenylcyclohexyl phenylsulfonyl acetate **(-)-178** (542 mg, 1.51 mmol). The reaction mixture was stirred at this temperature under a N_2 for 1 h. Solid (3-methylpentadienyl)iron(+) cation **32** (500 mg, 1.37 mmol) was added in one portion and the mixture stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 (34 mL) and saturated $NaHCO_3$/MeOH (44 mL) and stirred at room temperature for 24 h. The reaction was finally quenched with water and the organic components extracted into CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 4:1) to afford a mixture of 4 diastereomeric cyclohexenones **A**, **B**, **C** and **D** (*0.1: 0.3: 0.3:0.3 ratio*) as a dark brown oil inseparable on silica (560 mg, 87%). This mixture was used in the next step without further characterization.



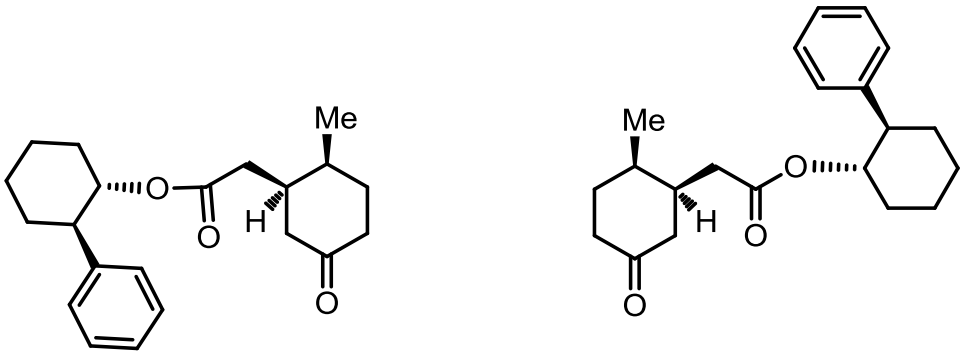
(1*S*,2*R*)-2-Phenylcyclohexyl 2-[(1*S*,2*S*,5*R*)-5-hydroxy-2-methylcyclohexyl]acetate and **(1*S*,2*R*)-2-Phenylcyclohexyl 2-[1*R*,2*R*,5*S*)-5-hydroxy-2-methylcyclohexyl]acetate (±)-193/194:** To a solution of the isomeric cyclohexenones **A**, **B**, **C** and **D** (146 mg, 0.312 mmol) in methanol (10 mL) was added cerium trichloride heptahydrate (1.49 g, 4.0 mmol). The mixture was stirred until the cerium salt had dissolved completely. Solid $NaBH_4$ (18 mg, 0.47 mmol) was added slowly with vigorous stirring. After addition was complete, the mixture was stirred under N_2 for 3 h. The reaction was quenched with water and the organic components extracted several times with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (SiO_2, hexanes-ether = 0-25% gradient) afforded an inseparable mixture of 4 diastereomeric cyclohexenols (*0.1:0.1:0.4:0.4 ratio*) as a colorless foamy solid (118 mg, 80%). This material was used in the next step without further characterization.

The mixture of isomeric cyclohexenols (118 mg, 0.252 mmol) was dissolved in MeOH (10 mL) and the solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (100 mg, 10 % w/w) was added and the flask connected to a Parr hydrogenation apparatus. The mixture was maintained under H_2 (40-45 psi) with stirring for 12 h after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate (150 mL) and filtered through a celite pad. The

filter bed was washed several times with ethyl acetate and the extracts concentrated. The residue was purified by flash column chromatography (SiO_2, acetone-hexanes = 0-20 gradient) to afford a mixture of 4 diastereomeric cyclohexanols **A**, **B**, **C** and **D** (*0.1:0.1:0.4:0.4 ratio*) as a colorless foamy solid (113 mg, 95%). This material was used in the next step without further characterization.

To an isomeric mixture of cyclohexanols **A**, **B**, **C** and **D** (63 mg, 0.081 mmol) in MeOH (10 mL) was added activated Mg (15 mg, 0.62 mmol). The reaction mixture was stirred at 50 ^{0}C until gas evolution started at which stage the heating source was removed and the reaction stirred at room temperature. Additional Mg (63 mg, 0.081 mmol, 6X) was added at 50 ^{0}C until all starting material had been consumed as indicated by TLC. The solvent was removed and the mixture redissolved in CH_2Cl_2. The mixture was filtered, washed with brine, dried (Na_2SO_4) and concentrated to give the crude product (120 mg). The residue was purified by column chromatography (hexanes-ethyl acetate = 4:1) to afford an inseparable mixture of 2 diastereomers (±)-**193**/**194** (*1:1 ratio*) (*quant.*) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.18 (m, 10H), 5.16-4.99 (m, 2H), 3.40-3.22 (m, 2H), 2.66-2.60 (ddd, *J* = 3.4, 3.5, 4.0 Hz, 2H), 2.18-1.65 (m, 12H), 1.64-1.20 (m, 24H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.59 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 173.2, 143.7, 143.5, 127.8, 127.6, 125.7, 76.2, 71.4, 71.2, 50.1, 50.0, 39.7, 39.6, 37.2, 36.1, 36.0, 35.2, 35.0, 33.5, 32.1, 32.0, 31.9, 31.7, 26.5, 26.0, 12.7, 12.5. ESI-HRMS m/z 353.2087 (calcd. for $C_{21}H_{30}O_3Na$ (M+Na) m/z 353.2083).

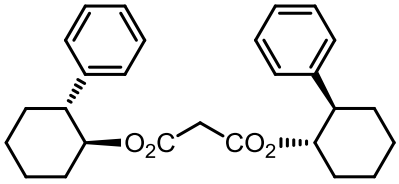


(1*S*,2*R*)-2-Phenylcyclohexyl 2-(2-methyl-5-oxocyclohexyl)acetate (±)-199/200: The mixture of 4 isomeric cyclohexenones **A**, **B**, **C** and **D** (182 mg, 0.388 mmol) was dissolved in MeOH (20 mL) and the solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (100 mg, 10 % w/w) was added and the flask connected to a Parr hydrogenation apparatus. The mixture was maintained under H_2 atmosphere (40-45 psi) with stirring overnight after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate (150 mL) and filtered through a celite pad. The filter bed was washed several times with ethyl acetate and the extracts concentrated. The residue was purified by flash column chromatography (SiO_2, acetone-hexanes = 0-25 gradient) to afford an inseparable mixture of 4 isomeric cyclohexanones **A**, **B**, **C** and **D** (0.5, 0.2, 0.2, 0.1 *ratios*) as a colorless foamy solid (141 mg, 78%). This mixture was used in the next step without further characterization.

To the above isomeric mixture of cyclohexanones (145 mg, 0.309 mmol) in MeOH (10 mL) was added activated Mg (54.2 mg, 2.25 mmol). The reaction mixture was stirred at 50 ^{0}C until gas evolution started at which stage the heating source was removed and the reaction stirred at room temperature. Additional Mg (54.2 mg, 2.25 mmol, 7X) was added at 50 ^{0}C until all starting material had been consumed as indicated by TLC. The solvent

was removed and the mixture redissolved in Et_2O. The mixture was filtered, washed (brine), dried ($MgSO_4$) and concentrated to give the crude product (88 mg). The residue was purified by column chromatography (SiO_2, ethyl acetate- hexanes = 1:4) to afford an inseparable mixture of 2 diastereomers **(±)-199/200** (~1:1*)* as a colorless oil (68 mg, 67%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.12 (m, 10H), 5.08-4.94 (m, 2H), 2.73-2.57 (m, 2H), 2.27-2.17 (m, 2H) 2.15-1.69 (m, 17H), 1.65-12.5 (m, 17H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.9, 210.8, 171.8, 171.5, 143.4, 143.3, 128.6, 128.5, 127.7, 127.6, 126.8, 126.7, 77.5, 76.3, 50.1, 50.0, 43.9, 43.6, 38.4, 38.3, 38.0, 37.9, 37.5, 37.0, 34.4, 34.3, 32.6, 33.2, 33.1, 32.5, 31.7, 31.3, 30.9, 30.3, 26.0, 25.0, 13.5, 12.8. ESI-HRMS m/z 351.1926 (calcd. for $C_{21}H_{28}O_3Na$ (M+Na) m/z 351.1926).

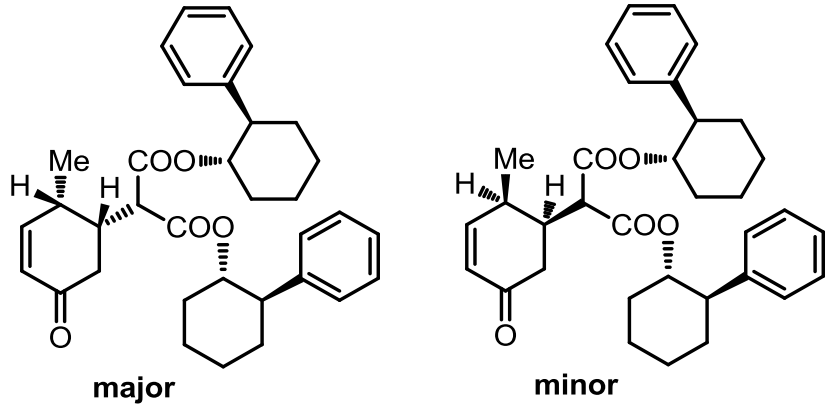


Bis-(2-Phenylcyclohexyl) malonate (+)-180: To a stirring solution of the chiral alcohol **(+)-176** (360 mg, 2.03 mmol) in freshly distilled CH_2Cl_2 at 0 ^{0}C was added triethylamine (206 mg, 2.03 mmol). The reaction mixture was stirred at 0 ^{0}C under N_2 for 1 h. Malonyl dichloride (143 mg, 1.02 mmol) was added dropwise over a 5 min period. Upon complete addition the mixture was stirred at 0 ^{0}C for 30 min and at room temperature for 24 h. On completion of the reaction as indicated by TLC the solvent was removed under a N_2

stream. The residue was purified by column chromatography (SiO_2, ethyl acetate-hexanes = 1:5) to afford the ester **(+)-180** as a colorless crystalline solid (208 mg, 76%).

$[\alpha]_D^{20}$ = + 13.5 (c = 0.0169, CH_2Cl_2)

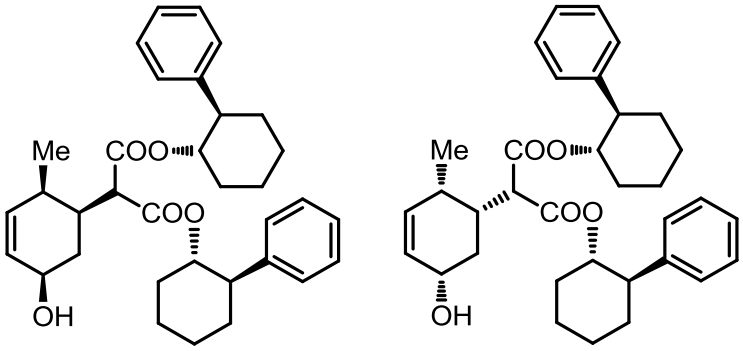
mp 114-116 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.11 (m, 10H), 4.98 (dt, J = 4.2, 10.6 Hz, 2H), 2.78 (s, 2H), 2.61 (dt, J = 3.4, 11.6 Hz, 2H), 2.15-205 (m, 2H), 1.98-1.73 (m, 6H), 1.66-1.25 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0, 143.1, 128.5, 127.7, 126.7, 77.2, 49.6, 41.7, 34.0, 32.2, 25.9, 24.9. ESI-HRMS m/z 443.2193 (calcd. for $C_{27}H_{32}O_4Na$ (M+Na) m/z 443.2193).



Bis((1*R*,2*S*)-2-phenylcyclohexyl)-2-((1*S*,2*R*)-2-methyl-5-oxocyclohex-3-en-1-yl)propanediaote (±)-201/202: To a cold stirring suspension of NaH (48 mg, 1.1 mmol) in freshly distilled THF (10 mL) at 0 ^{0}C was added a solution of the chiral ester (320 mg, 0.761 mmol) in THF (3 mL) dropwise. The reaction mixture was stirred at 0 ^{0}C and under N_2 atmosphere for 1 h. Solid (3-methylpentadienyl)iron(+1) cation **32** (418 mg, 1.14 mmol) was added in one portion. The reaction mixture was stirred at 0 ^{0}C for 2 h. The mixture was then diluted with CH_2Cl_2 (13 mL) and saturated methanolic $NaHCO_3$ (15

mL) and stirred at room temperature for 24 h. The reaction was quenched with H_2O and extracted several times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexanes = 0-25% gradient) to afford an inseparable mixture of two diastereomeric cyclohexenones **(±)** as a colorless crystalline solid (241 mg, *1:0.*2 *ratio*, 60%).

mp 144-146 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz, major isomer) **(+)-202** δ 7.35-7.04 (m, 10H), 6.66 (dd, *J* = 4.0, 6.5 Hz, 1H), 5.73 (d, *J* = 10.9 Hz, 1H), 4.97-4.84 (m, 2H), 2.74 (d, *J* = 13.1 Hz, 1H), 2.64-2.46 (m, 2H), 2.28-2.01 (m, 3H), 1.94-1.67 (m, 8H), 1.49-1.23 (m, 9H), 0.14 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, major isomer) **(+)-202** δ 198.9, 166.9, 155.3, 143.4, 143.2, 129.4, 129.0, 128.4, 128.2, 127.3, 125.9, 125.2, 55.5, 49.8, 49.2, 38.3, 35.8, 35.6, 32.4, 32.0, 31.6, 25.7, 25.2. ESI-HRMS m/z 551.2768 (calcd. for $C_{34}H_{40}O_5Na$ (M+Na) m/z 551.2757).



less polar/a more polar/b

Bis((1R,2S)-2-phenylcyclohexyl)-2-((1S,2R)-5-hydroxy-2-methylcyclohex-3-en-1-yl)malonate 203/204: To the mixture of chiral cyclohexenones (**201** and **202**, 100 mg, 0.189 mmol) in MeOH (10 mL) at 0 ^{0}C was added $CeCl_3.7H_20$ (1.49 mg, 4.00 mmol).

The mixture was stirred vigorously until homogeneous (~15 min). Solid $NaBH_4$ (29 mg. 0.76 mmol) was added in small portions and stirring continued at room temperature for 3 h. The reaction was quenched with H_2O, extracted several times with Et_2O, and the combined extracts dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate-hexanes = 0-40% gradient) afforded two completely separable diastereomeric cyclohexenols **(-)-204** (less polar, 21 mg, 24%) and **(+)-203** (more polar, 65 mg, 76%) both as colorless oils.

More Polar isomer/(+)-203:

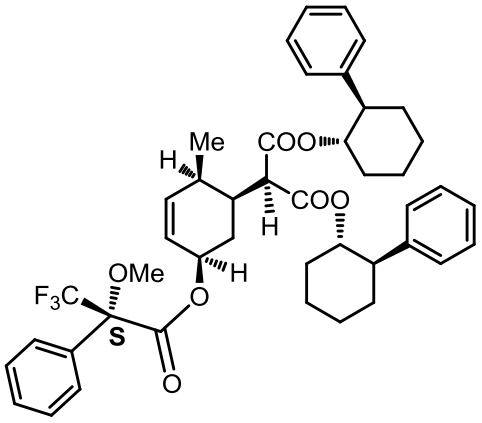
$[\alpha]_D^{20} = +\ 20.6$ (c = 0.00156, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16-7.38 (m, 10H), 5.39 (s, 2H), 5.28-4.97 (m, 2H), 3.42 (m, 1H), 2.60 (d, J = 6.4 Hz, 1H), 2.58-2.45 (m, 2H), 2.15-1.63 (m, 9H), 1.62-1.20 (m, 10H), 0.86-0.75 (m, 1H), 0.63-0.43 (m, 1H), 0.09 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 166.0, 144.2, 143.0, 139.9, 128.6, 128.2, 126.6, 126.1, 125.8, 125.3, 78.2, 77.3, 68.5, 56.3, 49.8, 49.6, 35.2, 35.0, 34.8, 33.7, 32.6, 30.7, 25.3, 24.8, 14.9.

Less Polar Isomer/(-)-204:

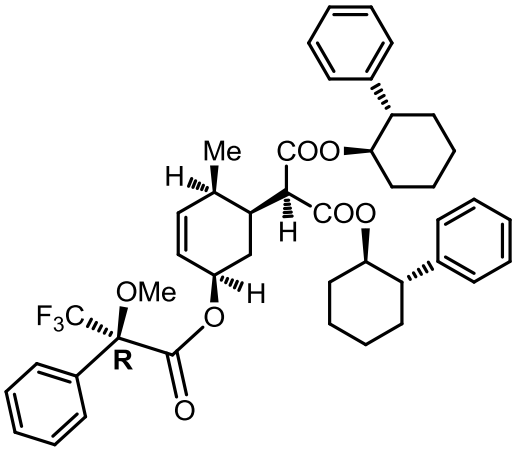
$[\alpha]_D^{20} = -\ 31$ (c = 0.0014, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18-7.35 (m, 10H), 5.38-5.13 (m, 2H), 5.14-4.89 (m, 2H), 3.81(t, J = 5.2 Hz, 1H), 2.79 (d, J = 7.9 Hz, 1H), 2.65-2.57 (m, 2H), 2.14-1.65 (m, 9H), 1.58-1.10 (m, 11H), 0.57-0.42 (m&d, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 166.5, 144.0, 143.7, 130.1, 128.6, 128.4, 127.3, 127.0, 126.8, 126.3, 77.5, 77.1, 68.5, 51.3, 49.6, 49.0, 35.1, 35.0, 34.9, 33.5, 33.3, 30.6, 30.1, 25.3, 25.0, 14.8.



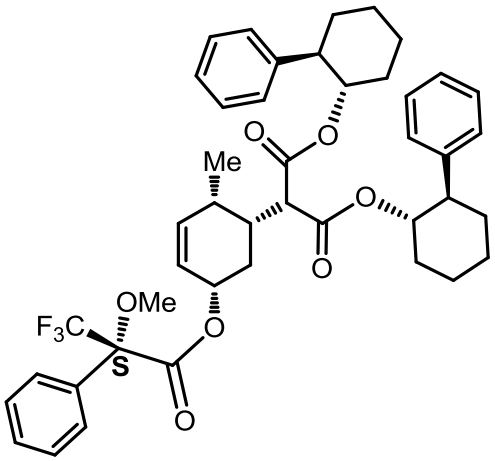
Reaction of (-)-204 with S-(-)-(α)-MTPA: To a solution of the less polar cyclohexenol **(-)-204** (15 mg, 0.028 mmol) in freshly distilled THF (3 mL) was added S-(-)-(α)-MTPA (26 mg, 0.11 mmol). The mixture was homogenized. DCC (23 mg, 0.11 mmol) and DMAP (0.5 mg, 0.004 mmol) were added successively with stirring. After 4 h the reaction mixture was heated at reflux for 12 h. Upon completion consumption of the starting material the solvent was removed under N_2 stream. The residue was purified by column chromatography (SiO_2, ethyl acetate-hexanes = 0-20% gradient) to afford a colorless oil *quantitatively.*

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58-6.98 (m, 15H), 5.41-5.36 (m, 1H), 5.34-5.21 (m, 2H), 5.13-4.96 (m, 2H), 3.53 (s, 3H), 2.65 (d, *J* = 7.4 Hz, 1H), 2.63-2.58 (m, 2H), 2.12-1.75 (m, 8H), 1.48-1.18 (m, 10H), 1.11-0.65 (m, 2H), 0.52 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 166.4, 166.0, 143.8, 143.5, 138.7, 133.5, 129.8, 129.0, 128.6, 127.2, 126.8, 122.8, 78.3, 73.7, 55.1, 54.9, 50.1, 49.8, 35.8, 35.0, 34.8, 33.2, 33.0, 31.0, 30.8, 27.2, 25.3, 25.0, 14.9.



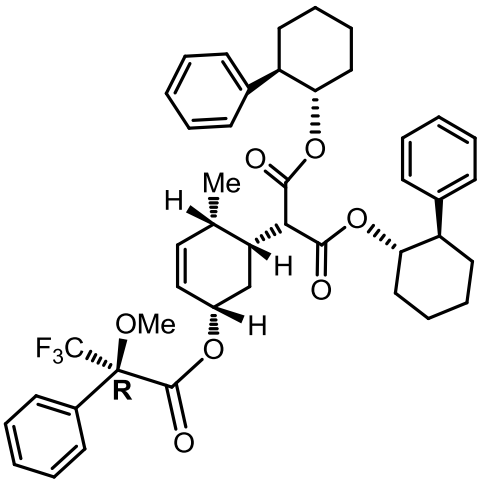
Reaction of (-)-204 with R-(+)-(α)-MTPA: Esterification of the less polar cyclohexenol **(-)-204** (15 mg, 0.028 mmol) with R-(+)-(α)-MTPA (26 mg, 0.11 mmol) was carried out in a fashion similar to that for formation of the (S)-MTPA ester. The product was purified by column chromatography (SiO_2, ethyl acetate-hexanes = 0-40 % gradient) to afford a colorless crystalline solid *quantitatively.*

mp 132-135 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57-6.85 (m, 15H), 5.43-5.28 (m, 3H), 5.71-4.88 (m, 2H), 3.55 (s, 3H), 2.69-2.51 (d & m, 3H), 2.02-1.70 (m, 9H), 1.54-1.26 (m, 8H), 1.13-1.03 (m, 1H), 0.95-0.70 (m, 2H), 0.48 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 167.0, 166.3, 143.2, 142.8, 138.4, 132.6, 129.8, 128.9, 128.6, 128.4, 127.7, 127.6, 127.5, 126.8, 126.7, 123.2, 77.6, 77.0, 73.4, 55.9, 55.6, 49.8, 49.4, 35.1, 34.4, 34.0, 32.0, 31.9, 29.7, 25.9, 24.8, 13.6.



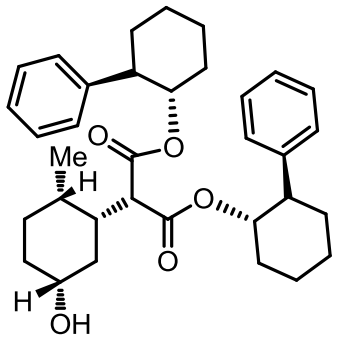
Reaction of (+)-203 with S-(-)-(α)-MTPA: Esterification of the more polar cyclohexenol **(+)-203** (15 mg, 0.028 mmol) with S-(-)-(α)-MTPA (26 mg, 0.11 mmol) was carried out in a fashion similar to the reaction of **(-)-204** with (S)-MTPA. The product was purified by column chromatography (SiO_2, ethyl acetate-hexanes = 0-40% gradient) to afford a colorless oil *quantitatively.*

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58-7.16 (m, 15H), 5.49 (dd, *J* = 5.2, 6.4 Hz, 1H), 5.42 (d, *J* = 7.0 Hz, 1H), 5.13-4.95 (m, 3H), 3.56 (s, 3H), 2.71 (d, *J* = 7.4 Hz, 1H), 2.66-2.60 (m, 2H), 2.17-1.65 (m, 10H), 1.54-0.89 (m, 10H), 0.00 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 167.0, 166.3, 143.2, 143.1, 138.6, 132.2, 129.7, 129.5, 128.4, 128.0, 127.9, 123.3, 78.3, 77.9, 73.8, 55.1, 55.0, 50.2, 50.0, 35.3, 35.0, 34.9, 34.8, 34.63, 33.6, 33.4, 30.1, 25.1, 25.0, 24.9, 13.8.



Reaction of (+)-203 with R-(+)-(α)-MTPA: Esterification of the more polar cyclohexenol **(+)-203** (15 mg, 0.028 mmol) with R-(+)-(α)-MTPA (26 mg, 0.11 mmol) was carried out in a fashion similar to **(-)-204** with (S)-MTPA. The product was purified by (SiO_2, ethyl acetate-hexanes = 0-40% gradient) to afford a colorless solid *quantitatively.*

mp 130.0-132.0 ^{0}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56-7.14 (m, 15H), 5.57 (dd, J = 5.4, 6.0 Hz, 1H), 5.32 (d, J = 6.8 Hz, 1H), 5.16-4.85 (m, 3H), 3.57 (s, 3H), 2.78-2.56 (d & m, 3H), 2.16-1.65 (m, 10H), 1.47-0.89 (m, 10H), 0.00 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 167.4, 166.8, 143.2, 143.0, 138.4, 132.5, 129.9, 129.8, 128.4, 128.0, 129.9, 123.6, 78.0, 77.6, 73.8, 55.0, 51.4, 51.0, 35.1, 35.0, 33.2, 33.0, 30.1, 26.0, 25.0, 13.7.



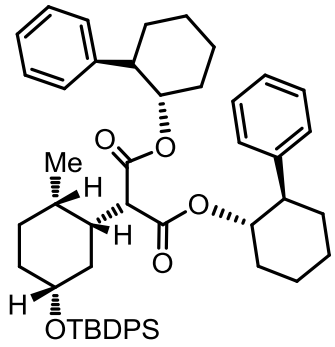
Bis[(1*S*,2*R*)-2-Phenylcyclohexyl] 2-[5(*R*)-hydroxy-2(*S*)-methyl-1(*R*) cyclohexyl]propanedioate (+)-209: The more polar (major isomer) cyclohexenol **(+)-203** (320 mg, 0.603 mmol) was dissolved in MeOH (10 mL) and the solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 150 mg) was added and the flask connected to a Parr hydrogenation apparatus. The mixture was maintained under H_2 (45 psi) with stirring for 24 h after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate (50 mL) and filtered through a celite pad. The filter bed was washed several times with ethyl acetate and the extracts concentrated. The residue was purified by flash column chromatography (SiO_2, ether-hexanes = 0-50% gradient) to afford a cyclohexanol **(+)-209** as a colorless solid (284 mg, 89%).

mp 135-138 ^{0}C;

$[\alpha]_D^{20}$ = + 14 (c = 0.0080, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.11 (m, 10H), 5.12-4.97 (m, 2H), 2.95-2.81 (m, 1H), 2.78-2.55 (d & m, 3H), 2.08-1.98 (m, 1H), 1.92-1.68 (m, 8H), 1.50-1.18 (m, 9H), 1.15-0.94 (m, 4H), 0.90-0.80 (m, 1H), 0.74-0.56 (m, 1H), 0.73-0.28 (m, 1H), 0.09 (d, J = 7.1

Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 167.0, 143.3, 143.0, 128.7, 128.5, 127.7, 127.6, 126.9, 126.7, 77.6, 76.7, 55.5, 49.7, 49.5, 40.0, 39.8, 36.1, 34.7, 34.6, 32.3, 31.9, 31.1, 27.7, 25.9, 24.8, 11.1.

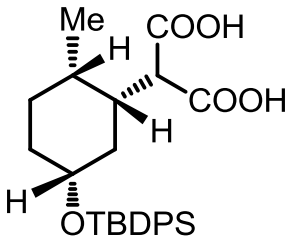


Bis [(1*S*,2*R*)-2-Phenylcyclohexyl] 2-[5(*R*)-(*t*-butyldiphenylsilyl)oxy-2(*S*)-methyl-1(*R*)-cyclohexyl]propanedioate (+)-210: To a solution of the pure cyclohexanol **(+)-209** (250 mg, 0.469 mmol) in CH_2Cl_2 (10 mL) at 0 ^{0}C was added imidazole (64 mg, 0.94 mmol). The reaction mixture was stirred under N_2 for 15 min. *t*-Butyldiphenylsilyl chloride (194 mg, 0.704 mmol) was added slowly with vigorous stirring. After addition was complete the mixture was stirred at room temperature overnight and quenched with water. The resulting mixture was extracted several times with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, acetone-hexanes = 0-5% gradient) to afford the protected cyclohexanol **(+)-210** as a colorless oil **(**359 mg, *quant.*).

$$[\alpha]_D^{20} = +27.2 \ (c = 0.00187, CH_2Cl_2)$$

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.64 (m, 4H), 7.49-7.34 (m, 6H), 7.29-7.07 (m, 10H), 5.01- 4.81 (m, 2H), 3.51-3.37 (m, 1H), 2.76-2.41 (d & m, 3H), 2.09-1.99 (m, 1H), 1.98-

1.69 (m, 6H), 1.62-1.20 (m, 11H), 1.16-0.87 (m & s, 15H), 0.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 167.4, 143.4, 143.3, 136.0, 135.9, 135.0, 134.9, 129.8, 197.7, 128.6, 128.5, 127.8, 127.7, 127.65, 127.6, 126.6, 126.5, 76.3, 72.4, 55.4, 49.5, 49.4, 39.5, 34.9, 34.8, 33.6, 32.3, 31.7, 30.8, 29.7, 27.6, 27.2, 26.1, 26.0, 24.9, 24.8, 19.4, 11.6.

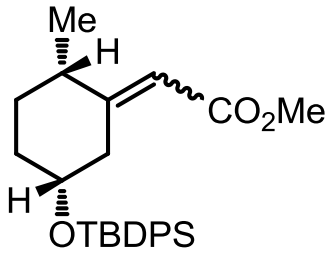


2-([5(*R*)-((tert-Butyldiphenylsilyl)oxy)-2(*S*)-methyl-1(*R*)-cyclohexyl)malonic acid (+)-211: To a solution of the diester (+)-**210** (95 mg, 0.16 mmol) in methanol (5 mL) was added NaOH (93 mg, 2.3 mmol). The reaction mixture was heated at reflux (85-95 ^{0}C) for 4 d. Upon completion of the reaction, as indicated by TLC, the mixture was acidified with 6 M HCl (6 mL) and the mixture extracted several times with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, methanol-ethyl acetate = 0-40% gradient) gave the diacid **(+)-211** as a pale colorless semi solid quantitatively.

$[\alpha]_D^{20}$ = + 9.3 (c = 0.00075, CH_2Cl_2)

^{1}H NMR (d_6-DMSO, 300 MHz) δ 7.65-7.55 (m, 4H), 7.52-7.34 (m, 6H), 3.57-3.43 (m, 1H), 2.62 (br d, J = 11.0 Hz, 1H), 1.95-1.08 (m, 8H), 0.97 (s, 9H), 0.81 (br s, 3H). The signals for the COO<u>H</u> protons were not observed; ^{13}C NMR (DMSO, 75 MHz) δ 175.5,

174.4, 135.9 135.8, 134.8 134.4, 130.4 130.3, 128.4 128.3, 73.0, 50.9, 44.8, 36.3, 33.7, 33.5, 31.3, 27.5, 20.1, 19.4.



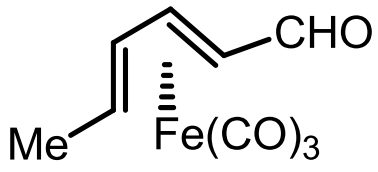
(*E*/*Z*)-Methyl 2-(5-((tert-Butyldiphenylsilyl)oxy)-2-methylcyclohexylidene)acetate (215): To a solution of the diacid (+)-**211** (36 mg, 0.079 mmol) in freshly distilled THF (3 mL) was added CDI (28 mg, 0.17 mmol). The mixture was vigorously stirred at room temperature for 2 h. Aqueous NaOH (3N, 2 mL) was added at this stage and stirring continued for 6 h. On completion of the reaction, as indicated by TLC, the reaction mixture was acidified with 6 M HCl (10 mL), extracted several times with CH_2Cl_2, dried (Na_2SO_4) and concentrated to afford a brown oil. The crude product (+)-**212** (26 mg) was used without further purification.

To a solution of the acid (+)-**212** (26 mg, 0.063 mmol) in dry toluene (2.4 mL) and anhydrous methanol (1.6 mL) was added a solution of trimethylsilyldiazomethane (2.0 *M* in hexane, 0.1 mL, 0.20 mmol) slowly. The reaction mixture was stirred at room temperature and the progress of the reaction monitored by TLC. Upon completion the solvent was removed, the residue redissolved in CH_2Cl_2 and filtered through a silica pad to afford 33 mg of the crude product (+)-**213** which was used for the next step without purification.

To a stirring solution of LDA (2.0 M in heptane, 0.2 mL, 032 mmol) in dry THF (2 mL) at -78 ^{0}C was added dropwise a solution of the crude **(+)-213** (33 mg, 0.080 mmol) in dry THF (2 mL). The mixture was stirred at -78 ^{0}C under N_2 for 30 min. A solution of PhSeCl (31 mg, 0.16 mmol) in dry THF (0.5 mL) was added dropwise rapidly with vigorous stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h under N_2. Upon completion of the reaction (as indicated by TLC) the solvent was removed under an N_2 stream and the crude product **214/214'** (19 mg) used for the next step without purification

To a stirring solution of the crude phenylseleno compound (19 mg, 0.033 mmol) in MeOH (4 mL) was added NaIO4 (150 mg, excess). The mixture was stirred vigorously under N_2 over night. The reaction mixture was concentrated and the residue purified by column chromatography (SiO_2, hexanes- ethyl acetate 20:1) to afford a mixture of unsaturated esters (***E/Z*)-215** as colorless oil inseparable on silica (15 mg, quantitative~1:1).

The ^{1}H and ^{13}C NMR spectral data for this product were identical with that previously obtained for the racemic material.

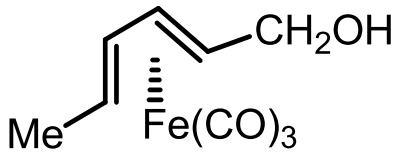


Tricarbonyl(η^4-2,4-hexadienal)iron (217): A flame dried round bottom flask was charged with 2,4-hexadienal (6.00 g, 62.2 mmol). Benzene (140 mL) was added and the

system flushed with N_2 for 15 min. Diirron-nonacarbonyl (30 g, 81 mmol) was added. The mixture was heated at reflux under a N_2 atmosphere for 2 h. The reaction mixture was cooled to room temperature and additional diirron-nonacarbonyl (16 g, 44 mmol) added. The reaction mixture was heated at reflux until no starting material was left as indicated by TLC. The reaction mixture was cooled to room temperature, filtered through celite pad and concentrated. Careful vacuum distillation at room temperature afforded an orange viscous liquid (14 g, 95%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.24 (d, J = 4.8 Hz, 1H), 5.80-5.78 (m, 1H), 5.30-5.26 (m, 1H), 1.78-1.62 (m, 1H), 1.55 (s, 3H), 1.23-1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.1, 90.2, 82.3, 64.3, 55.7, 19.9. The signal for the Fe-CO was not observed.

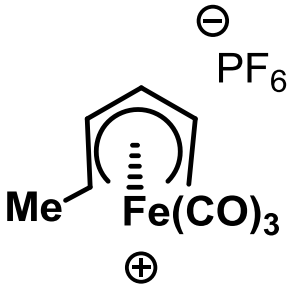
These spectral data are consistent with the literature values.[49]



Tricarbonyl(η^4-2,4-hexadienol)iron (218): To a solution of **217** (13 g, 55 mmol) in methanol (80 mL) at room temperature was added $NaBH_4$ (3.5 g, 80 mmol) in small quantities with the evolution of hydrogen gas. The reaction mixture was stirred at this temperature for 2 h after which TLC indicated all starting material had been consumed. The reaction was quenched with MeOH/H_2O (1:1, 50 mL), extracted several times with ether, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (SiO_2, ethyl acetate-hexane = 2:3) afforded **218** a yellow oil (11.7, 89%).

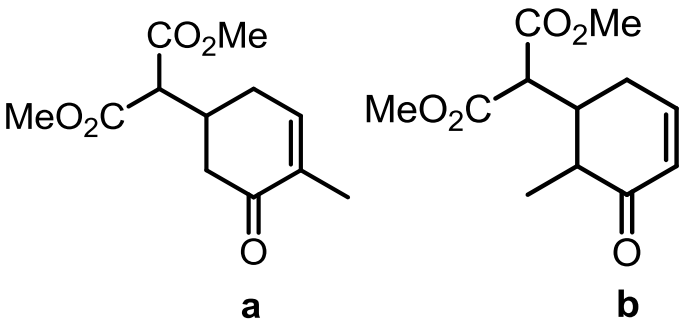
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.21-5.01 (m, 2H), 3.79-3.59 (m, 2H), 1.65-1.48 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H), 1.35-1.20 (m, 1H), 1.18-1.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.0, 88.2, 54.6, 67.3, 61.6, 59.9, 20.0.

These spectral data are consistent with the literature values.[49]



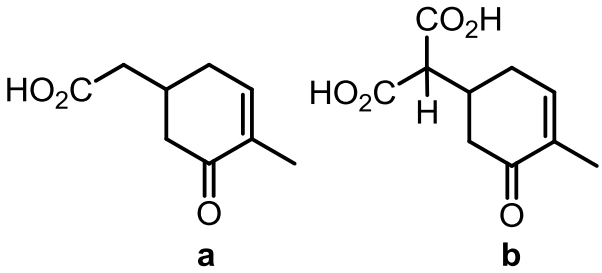
Tricarbonyl(η^5-1-methyl-pentadienyl)iron(+1) hexafluorophosphate (219): To a solution of **218** (11.7 g, 49 mmol) in diethyl ether (70 mL) at 0 ^{0}C was added acetic anhydride (15 mL). The mixture was stirred for 15-20 min and a solution of hexafluorophosphoric acid (60 % w/w, 10 mL) and acetic anhydride (9 mL) was added slowly. A yellow solid began to precipitate after about 20 min of stirring. The reaction mixture was stirred at 0 ^{0}C for an additional 30 min. The thick yellow mixture was poured into ether (1 L) and filtered through a sintered glass funnel to afford a bright yellow solid (11.9 g, 69%).

These spectral data are consistent with the literature values.[49]



Dimethyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)propanedioate (235a) and dimethyl 2-(2-methyl-3-oxocyclohex-4-en-1-yl)propanedioate (235b): To an ice cold stirring suspension of NaH (25 mg, 0.62 mmol) in freshly distilled THF (10 mL) was added dimethylmalonate (55 mg, 0.41 mmol) slowly. The resultant mixture was stirred at 0 ^{0}C for 45 mins. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-25% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones (76 mg, *~1:0.0.2 ratio*, 77%).

^{1}H NMR major isomer, deconvoluted from the mixture ($CDCl_3$, 300 MHz) **235a** δ 6.75 (br s, 1H), 3.71 (s, 6H), 3.38 (d, *J* = 7.4 Hz, 1H), 2.75-2.79 (m, 1H), 2.57-2.38 (m, 2H), 2.30-2.17 (s & m, 2H), 1.72 (s, 3H); ^{13}C NMR major isomer, deconvoluted from the mixture ($CDCl_3$, 75 MHz) **235a** δ 198.1, 168.1, 144.0, 135.9, 56.0, 52.8, 41.9, 35.2, 30.1, 15.9.

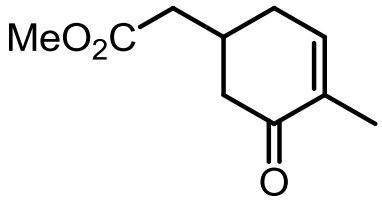


Hydrolysis of (±)-235a/b: To mixture of the two isomeric cyclohexenones **235a/b** (2.1 g, 8.7 mmol) was added aqueous HCl (~1N, 10 mL). The mixture was heated at reflux (85-95 ^{0}C) and the progress of the reaction monitored by TLC. When all starting material had been consumed (3 d) the mixture was concentrated under a N_2 stream. The organic components were extracted into ether, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate-hexanes = 0-60% gradient) afforded the **244a** (1.42 g, 97%) as a brown oil and **244b** (24 mg, 1%) as a dark brown oil.

244a: ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.90 (br s, 1H), 2.67-2.22 (m, 7H), 1.81 (s, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 198.3, 172.8, 144.6, 135.3, 43.9, 39.5, 32.6, 31.8, 14.9.

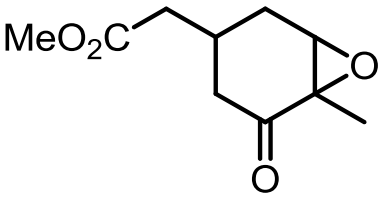
244b: ^{1}H NMR (acetone-d_6, 75 MHz) δ 6.91 (br s, 1H), 3.53 (d, *J* = 6.4 Hz, 1H), 2.87-2.36 (m, 5H), 1.79 (s, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 197.3, 170.0, 144.4, 135.3, 55.8, 42.2, 35.4, 32.8, 15.1.

The signals for the COO<u>H</u> protons were not observed.



Methyl 2-(4-methyl-5-oxocyclohex-3-en-1-yl) acetate (±)-245: To a solution of the crude monoacid **(±)-244** (37 mg, 0.22 mmol) in a methanol:toluene solvent system (2:3, 4 mL) was added dropwise an excess of trimethylsilyldiazomethane solution (0.35 mL, 2.0 M in hexanes, 0.70 mmol). The reaction mixture was stirred vigorously and the progress of the reaction monitored by TLC. Upon completion of the reaction, 1 h, the mixture was concentrated and the residue purified by flash column chromatography (ethyl acetate-hexanes = 0-40% gradient) to afford **(±)-245** as bright yellow oil (39 mg, 97%).

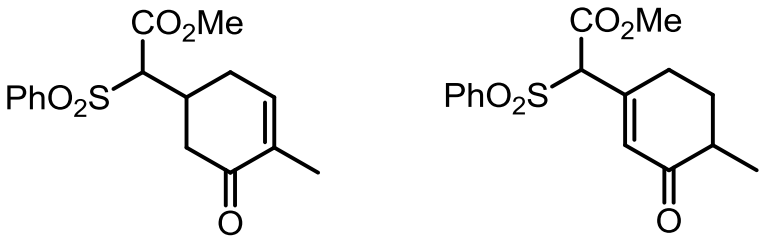
^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.71 (br s, 1H), 3.69 (s, 3H), 2.64-2.42 (m, 3H), 2.38 (d, *J* = 6.1 Hz, 2H), 2.26-2.06 (m, 2H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.2, 172.6, 144.0, 135.9, 52.2, 44.2, 40.0, 32.7, 32.0, 16.0.



Methyl 2-(6-methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl) acetate(±)-246: To a solution of **(±)-245** (37 mg. 0.20 mmol) in MeOH (0.8 mL) was added 2 M aqueous NaOH (0.04 mL, 0.08 mmol). The mixture was stirred at 0 ^{0}C for 20 min under N_2 atmosphere. Hydrogen peroxide (0.08 ml, 50% v/v) was added dropwise with stirring at 0 ^{0}C. The mixture was stirred at this temperature and the progress of the reaction monitored

by TLC. Upon completion as indicated by TLC (~4 h) the mixture was diluted with H_2O, extracted several times with Et_2O and concentrated. The residue was purified by column chromatography (SiO_2, ethyl acetate-hexanes = 0-50% gradient) to afford the epoxide as a colorless liquid (35 mg, 87%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 3.41-3.39 (m, 1H), 2.70-2.53 (m, 2H), 2.42-2.23 (m, 3H), 1.93-1.69 (m, 2H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.1, 172.4, 61.3, 59.1, 52.0, 42.5, 39.7, 29.8, 26.0, 15.5.

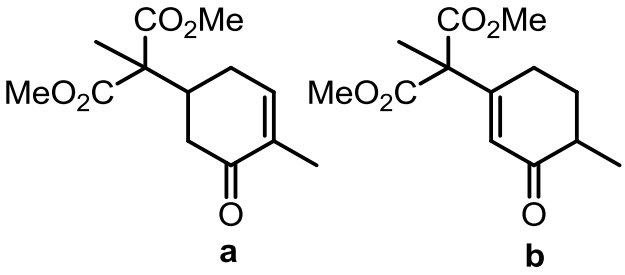


Methyl 2-(4-methyl-5-oxocyclohex-3-en-1-yl)-2-(phenylsulfonyl)acetate (±)-247a/b: To a stirring suspension of methyl phenylsulfonylacetate (117 mg, 0.546 mmol) in THF (10 mL) at 0 ^{0}C was added dropwise a solution of butyl lithium (2.5 M in hexanes, 0.26 mL, 0.66 mmol). The solution was stirred at this temperature under nitrogen atmosphere for 30 min during which a pale white precipitate formed. The solid cation **219** (200 mg, 0.546 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash

column chromatography (SiO_2, ethyl acetate-hexane = 0-60% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones as a pale green oil (46 g, 26%).

^{1}H NMR ($CDCl_3$, 300 MHz) **247a/b** δ 7.97-7.83 (m, 4H), 7.74-7.64 (m, 2H), 7.63-7.52 (m, 4H), 6.96-6.88 (m, 1H), 6.77-6.62 (m, 1H), 6.01 (d, J = 10.8 Hz, 1H), 4.16-4.10 (m, 1H), 4.03-3.94 (m, 1H), 3.71-3.37 (m, 6H), 3.24-2.74 (m, 5H), 2.57-2.19 (m, 4H), 1.76 (s, 3H), 1.26-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) **247a/b** δ 200.4, 198.2, 164.9, 168.5, 139.2, 138.6, 137.1, 136.0, 135.5, 134.5, 133.7, 133.6, 129.7, 128.9, 128.3, 128.0, 76.2, 72.9, 54.8, 56.1, 40.1, 38.3, 28.3, 29.6, 16.4, 16.0, 15.3, 15.8**.**

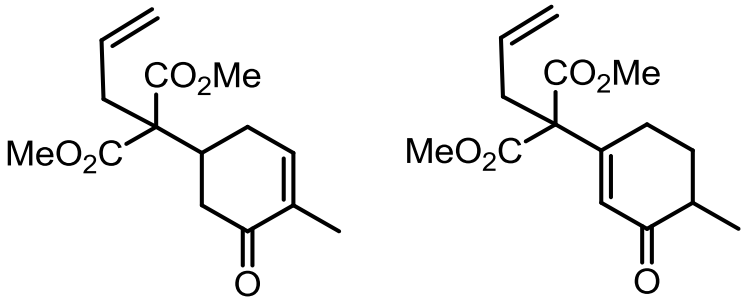
The reaction was repeated using sodium methyl phenylsulfonylacetate (127 mg, 72%) and potassium methyl phenylsulfonylacetate (65 mg, 49%).



Dimethyl 2-methyl-2-(4-methyl-3-oxocyclohex-4-en-1-yl)propanedioate (231a/b): To an ice cold stirring suspension of NaH (25 mg, 0.60 mmol) in freshly distilled THF (10 mL) was added slowly dimethyl methylmalonate (60.5 mg, 0.409 mmol). The resultant mixture was stirred at 0 ^{0}C for 1 h. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The

organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-30% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **231a** and **231b** (*1.0:0.3 ratio*) (72 mg, 69%).

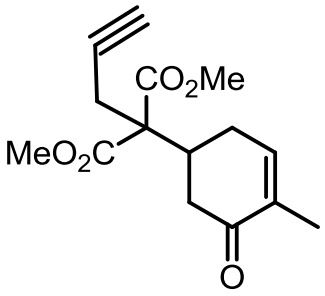
^{1}H NMR major isomer, deconvoluted from the mixture ($CDCl_3$, 300 MHz) δ 6.69 (s, 1H), 3.68 (s, 6H), 2.84-2.70 (m, 1H), 2.48-2.21 (m, 4H), 1.72 (s, 3H), 1.38 (s, 3H); ^{13}C NMR major isomer, deconvoluted from the mixture ($CDCl_3$, 75 MHz) δ 199.1, 171.5, 171.4, 144.7, 135.7, 56.5, 52.9, 40.2, 39.8, 28.0, 17.6, 15.8.



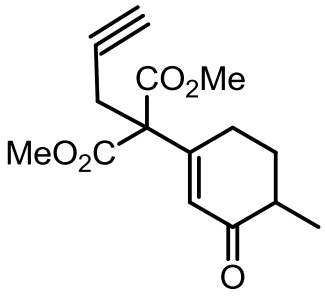
Dimethyl 2-allyl-2-(4-methyl-3-oxocyclohex-4-en-1-yl)propanedioate (±)-(232a) and **dimethyl 2-allyl-2-(4-methyl-3-oxocyclohex-1-enyl)propanedioate (±)-(232b)**: To an ice cold stirring suspension of NaH (25 mg, 0.66 mmol) in freshly distilled THF (10 mL) was added dropwise dimethyl allylmalonate (72 mg, 0.01 mmol). The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The mixture was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4)

and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-30% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **(±)-232a** and **(±)-232b** (*~1:1 ratio*) (64 mg, 56%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.75-6.70 (m, 1H), 5.99 (m, 1H), 5.94-5.59 (m, 2H), 5.17-5.06 (m, 3H), 3.80-3.70 (m & s, 11H), 2.87-2.00 (m, 12H), 1.76 (s, 3H), 1.14 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.8, 198.7, 170.4, 170.2, 169.1, 169.0, 157.9, 144.5, 135.4, 132.7, 132.2, 128.0, 119.3, 119.1, 64.4, 60.6, 25.9, 25.4, 41.2, 40.4, 38.4, 38.2, 37.6, 31.1, 27.7, 15.6, 14.9.



A

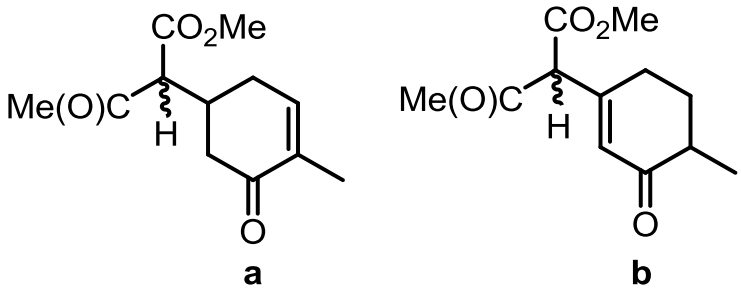


B

Dimethyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)-2-(prop-2-yn-1-yl)propanedioate (233a) and **Dimethyl 2-(4-methyl-3-oxocyclohex-1-enyl)-2-(2-propyn-1-yl)propanedioate (233b)**: To a solution of sodium dimethyl propargylmalonate [prepared from sodium hydride (25 mg, 0.62 mmol) and dimethyl propargylmalonate] (73 mg, 0.40 mmol)] in THF (10 mL) at 0 ^{0}C was added solid cation **219** (150 mg, 0.409 mmol). The mixture was stirred at room temperature for 2 h. Saturated methanolic $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added and the reaction mixture stirred for 24 h. Water (10 mL) was added and the mixture extracted several times with CH_2Cl_2. The

combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (SiO_2, acetone-hexanes = 0-25% gradient) gave a separable mixture of alkene regioisomers **(±)-233a** (56 mg, 50 %) and **(±)-233b** (16mg, 14%) both as colorless oils.

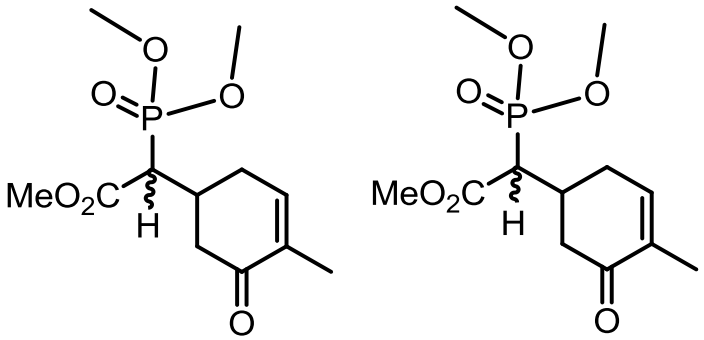
^{1}H NMR ($CDCl_3$, 300 MHz) **233a** δ 6.74 (d, *J* = 6.3 Hz, 1H), 3.75 (s, 6H), 3.06-2.94 (m, 1H), 2.88 (d, *J* = 2.7 Hz, 2H), 2.76-2.67 (m, 1H), 2.62-2.49 (m, 1H), 2.34-2.15 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.8, 169.9, 169.8, 144.8, 135.6, 78.5, 72.4, 59.6, 53.1, 53.0, 40.6, 37.8, 28.1, 23.1, 15.8; ^{1}H NMR ($CDCl_3$, 300 MHz) **233b** δ 6.04 (s, 1H), 3.80 (s, 6H), 3.00 (s, 2H), 2.56-2.46 (m, 2H), 2.45-2.32 (m, 1H), 2.16-2.02 (m, 1H), 1.83-1.66 (m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) B δ 200.0, 168.6, 156.8, 128.6, 79.1, 72.1, 63.7, 53.5, 41.4, 31.0, 27.6, 24.7, 15.2. ESI-HRMS m/z 301.1046 (calcd. for $C_{15}H_{18}O_5Na$ (M+Na) m/z 301.1047).



Methyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)-3-oxobutanoate (±)-248a/b: To an ice cold stirring suspension of NaH (25 mg, 0.62 mmol) in freshly distilled THF (10 mL) was added dropwise methyl acetoacetate (53 mg, 0.40 mmol. The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was

diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-25% gradient) afforded an inseparable mixture of diastereomeric cyclohexenones **(±)-248a/b** as a pale yellow oil (48 mg, 52%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74-6.67 (m, 1H), 3.75 (s, 3H), 3.40 (d, *J* = 10.2 Hz, 1H), 2.96-2.79 (m, 1H), 2.57-2.33 (m, 2H), 2.29-2.04 (m & s, 5H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1 [199.0], 195.6 [195.5], 166.3 [166.1], 141.5 [141.2], 133.6 [133.4], 61.8 [61.4], 50.4 [50.3], 39.7 [39.4], 32.3 [32.2], 27.6 [27.4], 27.3 [27.2], 13.2 [13.1]; Diastereomeric signals are in brackets. ESI-HRMS m/z 247.0948 (calcd. for $C_{12}H_{16}O_4Na$ (M+Na) m/z 247.0941).

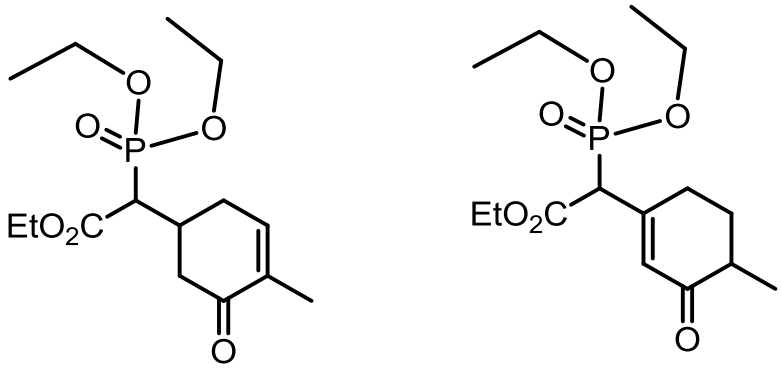


Trimethyl-2-(4-methyl-3-oxocyclohex-4-en-1-yl)phosphonoacetate (±)-220a/b: To an ice cold stirring suspension of NaH (27 mg, 0.67 mmol) in freshly distilled THF (10 mL) was added dropwise trimethyl phosphonoacetate (84 mg, 0.45 mmol). The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (200 mg, 0.450 mmol) was

added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-50% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **220a/b** (114 mg, *~1.0:0.3 ratio*, 87%) as a colorless oil.

IR (neat) 3460, 2958, 1734, 1670, 1437, 1253, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.73-6.63 (m, 1H), 3.82-3.71 (m, 9H), 3.03-2.92 (dd, *J* = 8.3, 8.5 Hz, 1H), 2.84-2.61 (m, 3H), 2.54-2.18 (m, 2H), 1.73 (s, 3H); ESI-HRMS m/z 603.1734 (calcd. for $(C_{12}H_{19}O_6P)_2Na$ (M+Na) m/z 603.1734).

Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.

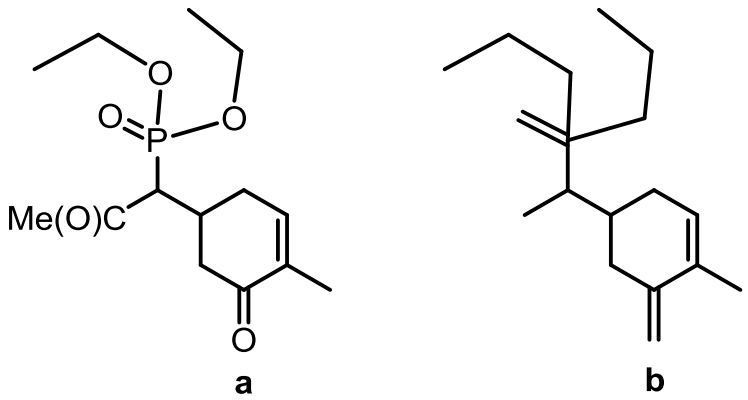


Triethyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)phosphonoacetate (±)-221a and triethyl 2-(4-methyl-3-oxocyclohex-1-enyl)phosphonoacetate **(±)-221b:** Reaction of the sodium

salt of triethyl phosphonoacetate (122 mg, 0.108 mmol) with cation **219** (200 mg, 0.450 mmol) was carried out in a fashion similar to that for the reaction of 35 with trimethyl phosphonoacetate. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-50% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **221a** and **221b** (*~1:1 ratio*) as a greenish oil (124 mg, 68%).

^{1}H NMR ($CDCl_3$, 300 MHz): **221a/b** δ 6.91-6.79- (m, 1H), 6.69-6.60 (m, 1H), 5.93 (d, *J* = 10.9 Hz, 1H), 4.17-4.01 (m, 12H), 3.26-3.02 (m, 1H), 2.93-2.82 (m, 1H), 2.79-2.61 (m, 4H), 2.53-2.14 (m, 5H), 1.68 (s, 3H), 1.28-1.17 (m, 18H), 1.12 (d, *J* = 6.2 Hz, 3H).

Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.

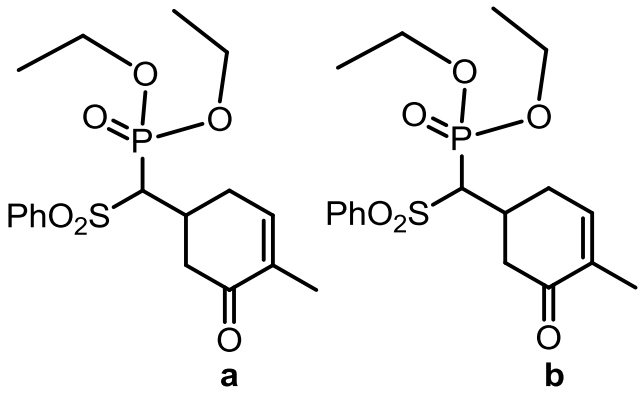


Diethyl (1-(4-methyl-3-oxocyclohex-4-en-1-yl)-2-oxopropyl)phosphonate (±)-222a/b: To an ice cold stirring suspension of NaH (25 mg, 0.62 mmol) in freshly distilled THF (10 mL) was added dropwise diethyl 2-oxopropylphosphonate (79 mg, 0.41 mmol) in drops. The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for

2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate-hexane = 0-60% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **(±)-222a** and **(±)-222b** (*~1.0:0.1 ratio*) as a colorless oil (89.7 mg, 74%).

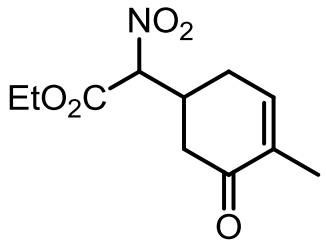
^{1}H NMR ($CDCl_3$, major isomer, 300 MHz) δ 6.75-6.62 (m, 1H), 4.18-4.07 (m, 4H), 3.22 and 3.15 (2xdd, J = 8.7, 9.3 Hz, 1H total), 2.89-2.66 (m, 2H), 2.43-2.21 (m, 3H), 2.33 and 2.29 (2xs, 3H total), 1.75 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H); ESI-HRMS m/z 325.1175 (calcd. for $C_{14}H_{23}O_5PNa$ (M+Na) m/z 325.1175).

Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.



Diethyl ((4-methyl-3-oxocyclohex-4-en-1-yl)(phenylsulfonyl)methyl)phosphonate (±)-223a/b: To an ice cold stirring suspension of NaH (25 mg, 0.62 mmol) in freshly

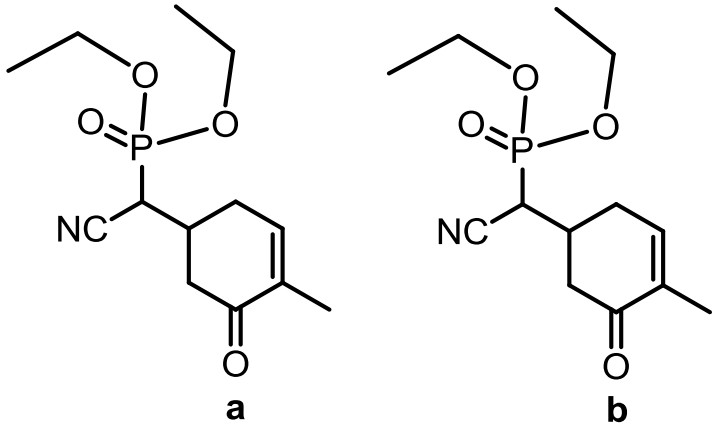
distilled THF (10 mL) was added dropwise diethyl (phenylsulfonyl)methylphosphonate (116 mg, 0.409 mmol). The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate-hexane = 0-80% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **(±)-223a** and **(±)-223b** (*~1.0:0.3 ratio*) as a pale green oil (76 mg, 47%). ESI-HRMS m/z 423.1002 (calcd. for $C_{18}H_{25}O_6SPNa$ (M+Na) m/z 423.1002). This compound was used in the olefination reaction without further characterization.



Ethyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)-2-nitroacetate (±)-234: To an ice cold stirring suspension of NaH (25 mg, 0.62 mmol) in freshly distilled THF (10 mL) was added dropwise ethyl nitroacetate (56 mg, 0.41 mmol). The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (150 mg, 0.409 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was

stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexane = 0-25% gradient) afforded an inseparable mixture of diastereomeric cyclohexenones as a colorless oil (61 mg, 62%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.73 (br s, 1H), 5.08 (t, *J* = 5.9 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.19-3.03 (m, 1H), 2.71-2.25 (m, 4H), 1.81 (s, 3H), 1.32 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.5 [196.4], 163.2 [163.1], 142.7 [142.5], 136.5 [136.4], 90.8 [90.5], 63.7 [63.6], 40.2 [40.1], 36.3 [36.2], 28.4 [28.1], 15.9 [15.8], 14.2 [14.1]; Diastereomeric signals in brackets. ESI-HRMS m/z 264.0842 (calcd. for $C_{11}H_{15}NO_5Na$ (M+Na) m/z 264.0843).

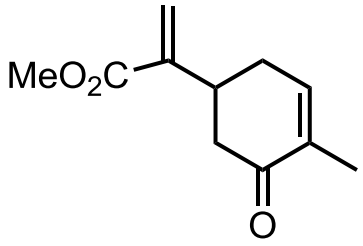


Diethyl (cyano(4-methyl-3-oxocyclohex-4-en-1-yl)methyl)phosphonate (±)-224a/b: To an ice cold stirring suspension of NaH (33 mg, 0.82 mmol) in freshly distilled THF (10 mL) was added dropwise diethyl (cyanomethyl)phosphonate (99 mg, 0.55 mmol). The resultant mixture was stirred at 0 ^{0}C for 45 min. The solid cation **219** (200 mg, 0.546

mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and saturated $NaHCO_3$/MeOH (10 mL). The reaction was stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (SiO_2, acetone-hexane = 0-25% gradient) afforded an inseparable mixture of regioisomeric cyclohexenones **(±)-224a/b** (*~1:1 ratio*) as a pale brown oil (118 mg, 76%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98-6.88 (m, 1H), 6.77-6.68 (m, 1H), 6.11-6.03 (dd, *J* = 2.3, 2.8 Hz, 1H), 4.34-4.16 (m, 8H), 3.29 and 3.21 (2xd, *J* = 2.8 and 3.0 Hz, 1H total), 3.07-2.66 (m, 5H), 2.63-2.38 (m, 5H), 1.77 (s, 3H), 1.44-1.33 (m, 12H), 1.18 (d, *J* = 6.4 Hz, 3H).

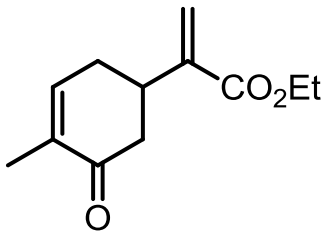
Due to the presence of two diastereomers, as well as ^{31}P coupling, interpretation of the ^{13}C NMR spectrum was not attempted.



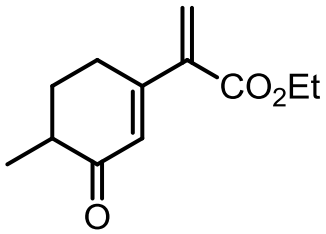
Methyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)acrylate (±)-225: To an ice-cold stirring suspension of NaH (43 mg, 1.1 mmol) in dry THF (20 mL) was added **(±)-220a/b** (210 mg, 0.721 mmol). The mixture was stirred at 0 ^{0}C for 30 min, and then paraformaldehyde

(43.4 mg, 1.447 mmol) was added slowly at such a rate that the temperature remained below 30 ^{0}C and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (20 mL) and the mixture extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether: hexanes = 50-75% gradient) to afford **(±)-225** as a pale yellowish oil (88 mg, 97%).

IR (neat) 3470, 2924, 2853, 1717, 1675 1457, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75-6.71 (m, 1H), 6.26 (s, 1H), 5.57 (s, 1H), 3.76 (s, 3H), 3.28-3.19 (m, 1H), 2.64-2.52 (m, 2H), 2.48-2.39 (m, 1H), 2.34-2.23 (m, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.0, 166.8, 144.3, 142.3, 135.5, 124.6, 52.0, 42.9, 36.7, 31.6, 15.6. ESI-HRMS m/z 411.1786 (cald. for $C_{11}H_{14}O_3Na$ (M+Na) m/z 411.1778S).



a

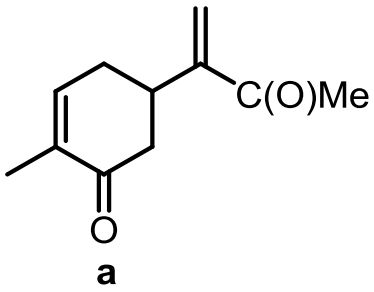


b

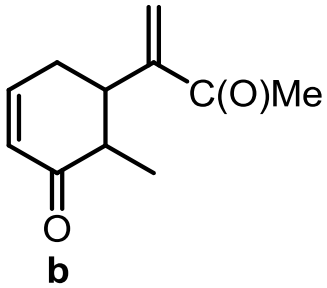
Ethyl 2-(4-methyl-3-oxocyclohex-4-en-1-yl)acrylate (±)-228: To an ice-cold stirring suspension of NaH (21 mg, 0.53 mmol) in dry THF (10 mL) was added **(±)-221a/b** (118 mg, 0.355 mmol). The mixture was stirred at 0 ^{0}C for 30 min, paraformaldehyde **(**15 mg, 0.46 mmol) was added slowly at such a rate that the temperature remained below 30 ^{0}C and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was diluted H_2O (10 mL) and the mixture extracted several times with CH_2Cl_2. The combined

extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexane = 0-60% gradient) to afford an inseparable mixture of regioisomers **228a/b** as a colorless oil (50 mg, *~1:1 ratio*, 68%).

^{1}H NMR **228a** deconvoluted from **228a/b** ($CDCl_3$, 300 MHz) δ 6.78-6.72 (m, 1H), 6.27 (s, 1H), 5.57 (s, 1H), 4.22 (q, *J* = 6.5 Hz, 2H), 3.32-3.119 (m, 1H), 2.67-2.52 (m, 2H), 2.50-2.38 (m, 1H), 2.37-2.23 (m, 1H), 1.80 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR **228a** deconvoluted from **228a/b** ($CDCl_3$, 75 MHz) δ 199.1, 167.8, 141.2, 140.7, 136.1, 125.3, 61.5, 40.9, 30.3, 28.4, 15.9, 14.6.



a

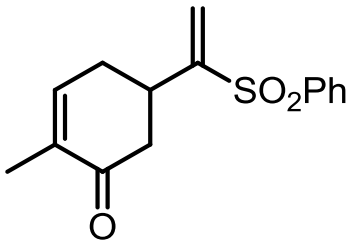


b

2-Methyl-5-(1-methylene-2-oxopropyl)-2-cyclohexenone and 6-Methyl-5-(1-methylene-2-oxopropyl)-2-cyclohexenone (±)-229a/b: To an ice-cold stirring suspension of NaH (12 mg, 0.29 mmol) in dry THF (5 mL) was added **(±)-222a/b** (74 mg, 0.25 mmol). The mixture was stirred at 0 ^{0}C for 30 min, paraformaldehyde **(**14 mg, 0.47 mmol) was added slowly at such a rate that the temperature remained below 30 ^{0}C and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was diluted H_2O (10 mL) and the mixture extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column

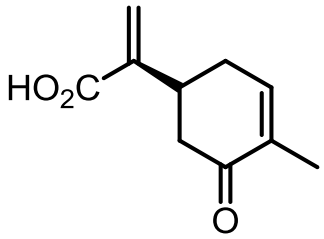
chromatography (SiO_2, ethyl acetate-hexane: 0-60% gradient) to afford an inseparable mixture of regioisomers as a pale green oil (39 mg, *~1.0:0.2 ratio*, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz) **229a** δ 6.75-6.69 (m, 1H), 6.14 (s, 1H), 6.01 (s, 1H), 3.42-3.28 (m, 1H), 2.58-2.42 (m, 2H), 2.41-2.30 (m & s, 4H), 2.26-2.12 (m, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.5, 199.3, 150.7, 144.6, 135.6, 125.2, 43.1, 35.4, 32.1, 26.6, 15.9; spectral data (partial) for minor regioisomer **229b** δ 6.93-6.84 (m), 6.20 (s), 6.05-5.98 (m), 6.87 (s), 3.13-2.99 (m), 2.72-2.60 (m); ESI-HRMS m/z 201.0886 (calcd. for $C_{11}H_{14}O_2Na$ **(**M+Na) m/z 201.0887).



2-Methyl-5-(1-phenylsulfonylethenyl)-2-cyclohexenone (±)-230: To an ice-cold stirring suspension of NaH (6 mg, 0.2 mmol) in dry THF (3 mL) was added **(±)-223** (50 mg, 0.13 mmol). The mixture was stirred at 0 ^{0}C for 30 min, paraformaldehyde **(**14 mg, 0.47 mmol) was added slowly at such a rate that the temperature remained below 30 ^{0}C and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was diluted H_2O (10 mL) and the mixture extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, ethyl acetate-hexane = 0-45% gradient) to afford **(±)-230** as a greenish oil (25 mg, 72%).

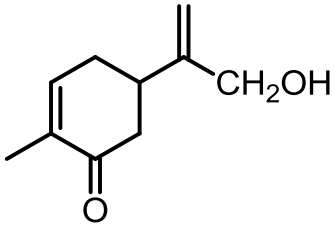
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.65 (t, *J* = 8.3 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 6.66 (d, *J* = 5.8 Hz, 1H), 6.53 (s, 1H), 5.89 (s, 1H), 3.08-2.95 (m, 1H), 2.67-2.55 (m, 1H), 2.43-2.23 (s & m, 3H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.8, 153.1, 143.8, 138.9, 135.8, 134.1, 129.7, 128.3, 124.5, 43.6, 35.6, 33.0, 15.9. ESI-HRMS m/z 299.0712 (calcd. for $C_{15}H_{16}O_3SNa$ (M+Na) m/z 299.0709).



Carvonic acid (±)-226: The ester **(±)-225** (69 mg, 0.46 mmol) was dissolved in a mixture of THF, methanol and water (4 mL, 2:2:1). Lithium hydroxide monohydrate (116 mg, 2.77 mmol) was added in small portions with stirring. The reaction mixture was stirred for 1 h (TLC indicated complete consumption of the starting material). Dilute hydrochloric acid (~1 N) was added slowly until a yellow solution was obtained. The organic portions were extracted several times with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexanes 0-50% gradient) gave the acid **(±)-226** (43 mg, 52%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80-6.72 (m, 1H), 6.44 (s, 1H), 5.72 (s, 1H), 3.32-3.17 (m, 1H), 2.71-2.26 (m, 4H), 1.80 (s, 3H). The signal for the COO<u>H</u> proton was not observed; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1, 170.9, 144.5, 141.7, 135.7, 127.2, 43.1, 36.7, 31.2, 15.9.

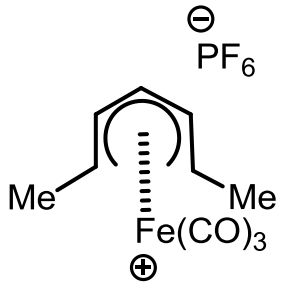
The ^{1}H NMR spectral data for this compound are consistent with literature[162, 167] values.



10-Hydroxycarvone (±)-227: To a stirring solution of LDA (0.91 mL, 1.8 mmol, 2.0 M in heptanes) in THF (5 mL) at -78 ^{0}C was added dropwise a solution of **(±)-225** (91 mg, 0.61 mmol) in THF (1 mL). The reaction mixture was stirred at this temperature for 30 min after which a solution of DIBAL–H (2.8 mL, 1.0 M hexanes, 2.8 mmol) was added slowly. The reaction mixture was stirred at -78 ^{0}C for an additional 3 h after which the cold bath was removed and the mixture stirred at room temperature for 1 h. The reaction was quenched with H_2O, extracted several times with CH_2Cl_2, washed with brine and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexanes = 0-35% gradient) afforded **(±)-227** as a yellow oil (56 mg, 76%).

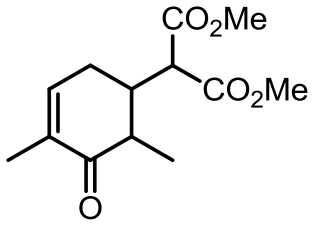
^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79-6.72 (m, 1H), 5.15 (s, 1H), 4.96 (s, 1H), 4.15 (s, 2H), 2.89-2.75 (m, 1H), 2.67-2.34 (m, 5H), 1.78 (s, 3H)**;** ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 150.5, 144.7, 135.7, 110.7, 65.1, 43.4, 38.8, 31.9, 16.0.

The ^{1}H and ^{13}C NMR spectral data for this compound are consistent with literature[162, 167] values.



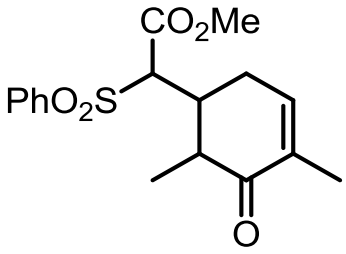
Tricarbonyl(η^5 -1,5-dimethylpentadienyl)iron(+1) hexafluorophosphate (237): The preparation cation **237** started with (η^4-2,4-hexadienal)$Fe(CO)_3$ (**216**) which was prepared as in cation **219**. To a solution of the complexed aldehyde **217** (4.3 g, 18 mmol) in dry ether (60 mL) was added dropwise a solution of methyl magnesium bromide (7.5 mL, 1.0 M in THF, 7.5 mmol). A dark viscous reaction mixture formed which was stirred for 2 h. The reaction mixture was quenched with water, extracted several times with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (ethyl acetate-hexanes = 0-40% gradient) afforded two separable alcohols (3.1 g, 68%). This product was used in the next step without further characterization. A portion of the alcohol complex (2.8 g, 11 mmol) was dissolved in dry ether (30 mL) and cooled to 0 ^{0}C. Acetic anhydride (3.5 mL) was added and the reaction mixture stirred for 20 min. A mixture of hexafluorophosphoric acid (60 % w/w, 3.5 mL) and acetic anhydride (3.5 mL) were added slowly with stirring. A dark brown precipitate formed. The reaction mixture was poured into dry ether (1 L) and filtered through a sintered glass funnel to afford **237** as a light brown solid (1.6 g, 58%).

The spectral data matched those reported in the literature.[165]



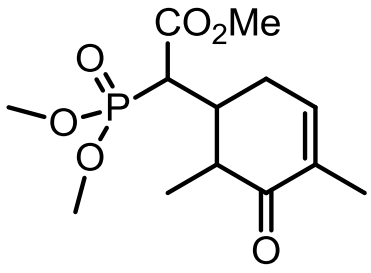
Dimethyl 2-(2,4-dimethyl-3-oxocyclohex-4-en-1-yl)propanedioate (±)-242: To an ice-cold stirring suspension of NaH (36 mg, 0.90 mmol) in dry THF (10 mL) was added dropwise dimethyl malonate (79 mg, 0.60 mmol) in drops. The mixture was stirred at 0 ^{0}C for 30 min. The solid cation **237 (**150 mg, 0.60 mmol) was added and the reaction mixture stirred for 1 h at room temperature. Saturated $NaHCO_3$/MeOH (10 mL) was added and the reaction stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexanes = 0-25% gradient) afforded cyclohexenone as a greenish oil (39 mg, 26%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.63 (br s, 1H), 3.74 (s, 6H), 3.63 (d, J = 5.8 Hz, 1H), 2.64-2.36 (m, 4H), 1.77 (s, 3H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.6, 169.2, 168.6, 142.8, 134.7, 53.3, 52.8, 44.5, 40.9, 27.1, 16.4, 13.8.



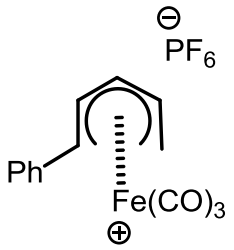
Methyl 2-(2,4-dimethyl-3-oxocyclohex-4-en-1-yl)-2-(phenylsulfonyl)acetate (±)-243: To an ice-cold stirring suspension of NaH (36 mg, 0.90 mmol) in dry THF (10 mL) was added dropwise methyl phenylsulfonylacetate (79 mg, 0.60 mmol). The mixture was stirred at 0 ^{0}C for 30 min. The solid cation **237 (**150 mg, 0.60 mmol) was added and the reaction mixture stirred for 1 h at room temperature. Saturated $NaHCO_3$/MeOH (10 mL) was added and the reaction stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexanes = 0-25% gradient) afforded a diastereomeric mixture of cyclohexenones as a colorless oil (38 mg, 27%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95-7.84 (m, 2H), 7.74-7.53 (m, 3H), 6.66 (br s, 1H), 4.13 (d, J = 3.6 Hz, 1H), 3.60 and 3.40 (2xs, 3H total), 3.15-2.62 (m, 3H), 2.53-2.28 (m, 1H), 1.80-1.74 (2xs, 3H total), 1.22-1.11 (2xd, J = 7.5 Hz, 3H total); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.5, 164.9, 141.8, 137.1, 135.4, 133.7, 129.7, 128.3, 75.8, 51.9, 45.3, 26.2, 21.2, 16.2, 11.7.



Trimethyl 2-(2,4-dimethyl-3-oxocyclohex-4-en-1-yl)phosphonoacetate (±)-240: To an ice-cold stirring suspension of NaH (36 mg, 0.90 mmol) in dry THF (10 mL) was added dropwise trimethyl phosphonoacetate (79 mg, 0.60 mmol). The mixture was stirred at 0 ^{0}C for 30 min. The cation **237 (**150 mg, 0.60 mmol) was added and the reaction mixture stirred for 1 h at room temperature. Saturated $NaHCO_3$/MeOH (10 mL) was added and the reaction stirred for 24 h. The reaction was quenched with water (10 mL). The organic portions were extracted several times with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (SiO_2, acetone-hexanes, 0-25% gradient) afforded cyclohexenone as a brownish oil (32 mg, 18%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.71-6.61 (m, 1H), 3.84-3.76 (m, 9H), 3.38-3.16 (m, 1H), 2.81-2.36 (m, 4H), 1.79 (s, 3H), 1.19 (d, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.9, 171.3, 142.8, 135.4, 53.2, 50.2, 48.2, 44.6, 28.9, 17.2, 14.0, 12.2.



Tricarbonyl(η^5-5-phenylpentadienyl)iron(+1) hexafluorophosphate (238): To flame dried round bottom flask was added 5-phenylpentadienoic acid (10.0 g, 70.7 mmol). Oxalyl chloride (10.7 mg, 84.8 mmol) was added and the reaction mixture stirred for 1 h. Methanol (37 mL) was added and stirring continued until the starting material was completely consumed as indicated by TLC. Purification by flash column chromatography (SiO_2, ethyl acetate- hexanes = 0-20%) afforded a yellow crystalline solid (8.5 g, 64 %). This product was used in the next step without further characterization. A mixture of methyl 5-phenyl-2,4-pentadienoate (13.3 g, 70.7 mmol), $FeCl_3.6H_2O$ (45 mg) and diiron nonacarbonyl (34 g, 91 mmol) in ether (200 mL) was taken in a 500 mL round bottom flask fitted with a reflux condenser. The flask was placed in an ultrasonic cleaning bath and sonolysed under nitrogen for 24 h. The mixture was filtered through celite and the solvent was removed on a rotary evaporator. The crude residue was purified by flash column chromatography (ethyl acetate-hexanes = 15-20% gradient) to afford tricarbonyl(η^4-methyl 5-phenyl-2,4-pentadienoate)iron complex **(**17.2 g, 74% yield). This product was used in the next step without further characterization.

To a solution of tricarbonyl(methyl η^4-5-phenyl-2,4-pentadienoate)iron (17.2 g, 52.3 mmol) in ether (150 mL) was slowly added a solution of DIBAL-H (167 mL, 1.0 M in hexanes, 167 mmol). The reaction mixture was stirred at room temperature for 3 h. Upon completion of the reaction as indicated by TLC, the excess hydride was cautiously

quenched with a mixture MeOH/H_2O (1:1). The organic portions were extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography ((SiO_2, ethyl acetate- hexanes = 1:1) gave the alcohol (9.3 g, 5%) as a bright yellow oil. This product was used in the next step without further characterization.

The tricarbonyl(η^4-5-phenyl-2,4-pentadienol)iron complex (9.3 g, 30 mmol) was dissolved in dry ether (20 mL) and cooled to 0 ^{0}C. Acetic anhydride (18 mL) was added and the reaction mixture stirred for 20 min. A solution of hexafluorophosphoric acid (60 % w/w, 9 mL) in acetic anhydride (9 mL) was added slowly with stirring. A dark brown precipitate formed. The reaction mixture was poured into dry ether (1.5 L) and filtered through a sintered glass funnel to afford **238** (11.6 g, 85%) a bright yellow solid. The ^{1}H NMR spectral data of 56 were consistent with the literature values.[44, 49]

NB: No Nucleophilic attack was observed for reactions of cation **238** with nucleophiles used. In all cases the tricarbonyl(η^4-5-phenyl-2,4-pentadienol)iron complex was isolated as the major fraction after column chromatography.

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