# Enantioselective Synthesis of (9*R*,10*S*)-Dihydrosterculic Acid: Overcoming Unanticipated Challenges in α,β-Unsaturated 1,1-Bis(Sulfoxides)

by

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## Abstract

A diastereoselective Corey-Chaykovsky cyclopropanation of 1,1-alkylidene bis(sulfoxides) is applied to enantioselective syntheses of natural products (9*R*,10*S*)-dihydrosterculic acid (**1**) and methyl (9*R*,10*S*)-dihydrosterculate (**2**). The synthesis of **1** was achieved in 16.1% yield over eight steps and the synthesis of **2** was achieved in 17.3% yield over seven steps, both prepared from commercially available 9-decen-1-ol. Featured in the main synthetic route is a regioselective C-S bond cleavage and alkylation sequence to construct the *cis* relationship of the cyclopropane ring and improved conditions for the hydrolysis of **2**. Future work on this project includes the identification of cyclopropane desaturase from *Sterculia* and the determination of the cryptoregiochemicastry and stereoselectivity for the $\Delta^9$ desaturation of **1**.

"With the victory and all they sought for we were one among the fence."

From *In Keeping Secrets Of Silent Earth: 3* by Coheed & Cambria

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This paragraph goes out to the Palko fam jam (Mom, Dad, Nicholas Picholas, Bradlina, Awex, Crick, Nevek, Steve, Ginger, Kikko, Taz, Sophie, Daisy, Jack and Steve French). This may be the only string of sentences they'll understand in this entire book so

I made sure it spread over two pages. Thank you for all the love and support. I'm proud to be the smartest derp of us all.

Thanks goes out to all the friends I've made around the department who have not had the unfortunate pleasure of working with me in the lab. You don't want to know what you've missed out on.

A shout out goes to all my friends from the bingo hall in Niagara Falls for all the good times! I dedicate this work to our friend Jennifer Cheevers who will be forever missed by us all.

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## List of Abbreviations

| | |
|---|---|
| 1,2-DCE | 1,2-Dichloroethane |
| ACP | Acyl carrier protein |
| BBN | Borabicyclo[3.3.1]nonane |
| brsm | Based on recovered starting materials |
| CFA | Cyclopropane Fatty Acid |
| CoA | Coenzyme A |
| d | Doublet |
| DHP | 3,4-Dihydro-*2H*-pyran |
| DIBAL-H | Di-*iso*-butylaluminum hydride |
| DIPT | Di-*iso*-propyl tartrate |
| DME | Dimethoxyethane |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DPTI | Diphenyltriflylimidazolidinone |
| *dr* | Diastereomeric ratio |
| *ee* | Enantiomeric excess |
| Enz | Enzyme |
| EWG | Electron Withdrawing Group |
| GC | Gas chromatography |
| GCMS | Gas chromatography mass spectrometry |
| HMPA | Hexamethylphosphoramide |
| HMPT | Hexamethylphosphorous triamide |

| | |
|---|---|
| HWE | Horner-Wadsworth-Emmons reaction |
| imid | Imidazole |
| IUPAC | International Union of Pure and Applied Chemistry |
| KHMDS | Potassium hexamethyldisilylazide |
| KIE | Kinetic isotope effect |
| LDA | Lithium di-*iso*-propylamide |
| LG | Leaving Group |
| m | Multiplet |
| menth | menthyl |
| *m*-CPBA | *meta*-perchlorobenzoic acid |
| Morpho-CDI | N-Cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-*para*-toluenesulfinate |
| MIRC | Michael-induced ring closure |
| MS | Mass spectrometry |
| NADPH | Nicotinamide Adenine Dinucleotide Phosphate |
| NMR | Nuclear magnetic resonance |
| Oxone® | $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ |
| PCC | Pyridinium chlorochromate |
| PDC | Pyridinium dichromate |
| PL | Phospholipid |
| PTSA | *para*-toluenesulfonic acid monohydrate |
| PG | Protecting group |
| pyr | Pyridine |

| | |
|---|---|
| q | Quartet |
| s | Singlet |
| SAM | S-Adenosyl methionine |
| t | Triplet |
| TBAF | Tetra-*n*-butylammonium fluoride |
| TBHP | *t*-Butyl hydroperoxide |
| THF | Tetrahydrofuran |
| THP | Tetrahydropyranyl |
| TMS | Trimethylsilyl |
| Tr | trityl; triphenylmethyl |
| TS | Transition State |
| UFA | Unsaturated Fatty Acid |
| UV | Ultraviolet |
| X | Halide or Pseudohalide |

# 1 Chapter: An Introduction to Dihydrosterculic Acid

## 1.1 Historical Background

The discovery of cyclopropane containing fatty acids isolated from lactic acid bacteria by Hofmann[1] in 1952 prompted widespread investigation to elucidate the structures of these unusual fatty acids. Dihydrosterculic acid and its cyclopropenyl analogue, sterculic acid, were first isolated with structural assignment by Nunn from the seed oil of the tropical tree *Sterculia foetida* for which its name is derived.[2,3] Dihydrosterculic acid and other cyclopropane fatty acids have been isolated from other plant species including Bombaceae, Tilaceae, Gnetaceae and Spindaceae.[4] Other unique examples include U-106305, an antifungal metabolite found in a Streptomyces strain,[5] α-mycolic acid, a hydroxylated, long chain fatty acid found in Mycobacteria (Figure 1).[6] Other examples of cyclopropane fatty acids have been reported.[3,7,8]

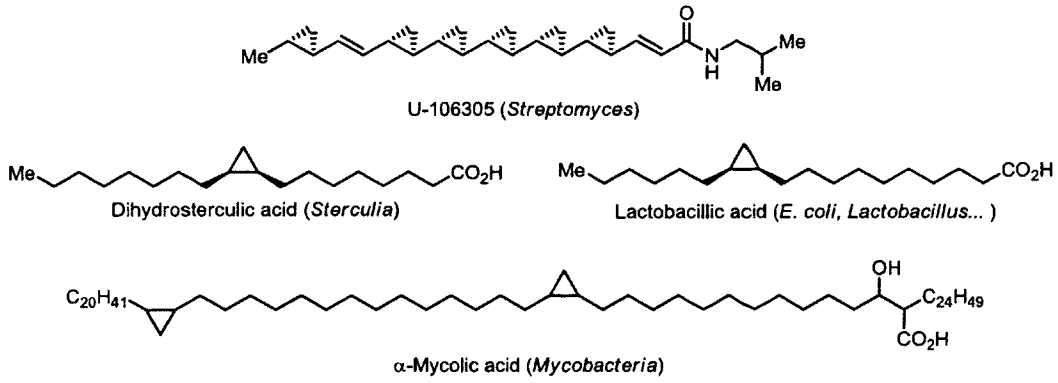



**Figure 1: Examples of some naturally occurring cyclopropane fatty acids**

Initial degradation studies of sterculic acid by Hilditch and co-workers[9] incorrectly assigned its structure as 12-methyloctadeca-9,11-dienoic and was later correctly assigned by Nunn based on the absence of bands characteristic of conjugated

C=C bonds from its UV absorption spectrum. Early characterization methods of sterculic acid had been used to deduce a formula of $C_{19}H_{34}O_2$. Its purified oil polymerized readily at room temperature after low-temperature crystallization from acetone and was also found to absorb one equivalent of hydrogen over Pd-$CaCO_3$. The data for the resulting low-melting solid was in agreement with the spectra obtained for dihydrosterculic acid while additionally absorbing one equivalent of hydrogen in the presence of Adams' catalyst ($PtO_2$). This fully hydrogenated mixture produced a formula of $C_{19}H_{38}O_2$ after elemental analysis and a melting point range of 63 to 66.5 °C. The authors of these studies concluded that this mixture contained *n*-nonadecanoic acid and two methyl-substituted octadecanoic acids (Figure 2). When sterculic acid was subjected to oxidation with $KMnO_4$ in acetone, a mixture of pelargonic and azelaic acids was obtained. Upon oxidation with $H_2O_2$ in AcOH, pelargonic and azelaic acid were obtained as the only fission products, but the remaining portion of the crude extract gave a deep red colour with ferric chloride. The absorption spectrum of this compound was characteristic of a 1,3-dione while with a formula of $C_{19}H_{34}O_4$ and concluded to be 9,11-diketononadecanoic acid, providing the basis for structural reassignment.

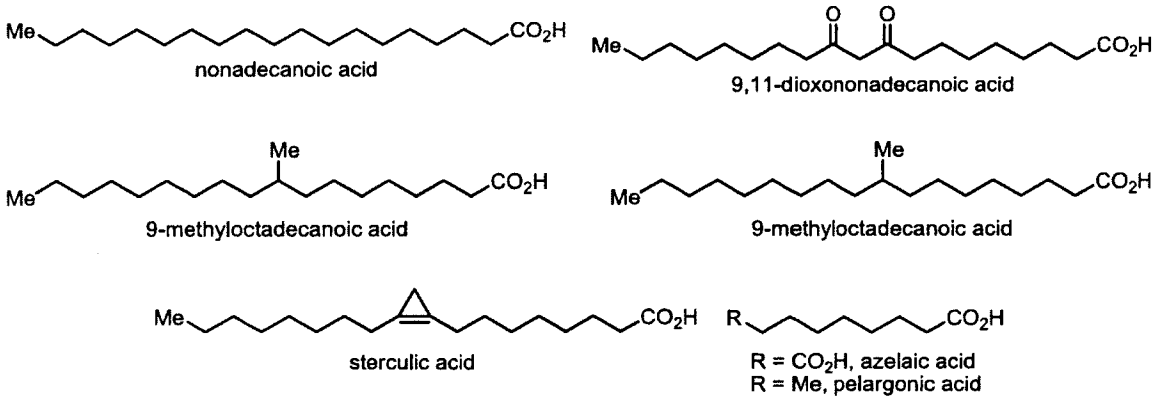



**Figure 2: Various degradation products of sterculic acid**

The structure of dihydrosterculic acid was confirmed by both chemical synthesis[2] and comparison to the reported degradation studies and then supported later when sophisticated NMR techniques became available.[10] Nunn had postulated that hydrogenation of sterculic acid would result in predominantly *cis*-addition to the double bond. To confirm its identity, he described a synthesis of (±)-*cis*-9,10-methyleneoctadecanoic acid. Degradation and synthetic studies were also performed on the structurally similar natural product lactobacillic acid. These studies concluded that this newly isolated compound was in fact (±)-*cis*-11,12-methyleneoctadecanoic acid.[11] Decades later, an accurate determination of absolute stereochemistry for cyclopropane fatty acids was developed in the Tocanne group by comparison of α-keto cyclopropane fatty acids[12] to synthetic standards.[13]

Contributions by the Buist group, using Tocanne's protocol, have determined the absolute stereochemistry of methyl dihydrosterculate[14] isolated from *Litchi chinensis* and methyl lactobacillate[15] isolated from *Escherichia coli*. They found both compounds to have an absolute stereochemistry of 9*R*,10*S* following the IUPAC numbering system for cyclopropane fatty acids (Figure 3).

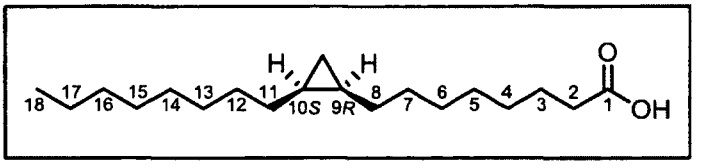



**Figure 3: Generally accepted numbering system of (9*R*,10*S*)-dihydrosterculic acid (1)**

## 1.2 Biological Activity

Cyclopropane fatty acids are unique. The presence of their cyclopropyl ring confers physical and chemical properties characteristic of unsaturated fatty acids with the oxidative stability displayed by saturated fatty acids making them of considerable industrial interest.[16] Cyclopropenoid fatty acids are well-known inhibitors of fatty acid desaturation in animals,[17] by inhibition of both stearoyl-CoA desaturase and interfere with the maturation and reproduction of some insect species suggesting that they are a defence weapon in plants in addition to their traditional role as storage lipids.

## 1.3 Biosynthesis of Cyclopropane Fatty Acids

Biosynthesis of cyclopropane rings in natural compounds has been recently reviewed.[18] Cyclopropane fatty acids (CFA) are derived biosynthetically from the corresponding unsaturated fatty acid (UFA) phospholipids while these UFAs derive from the acetate pathway, a well-understood route in biosynthesis.[19]

The acetate pathway involves an initial conversion of a malonyl group, in the form of malonyl CoA, to an enzyme-bound acyl derivative (Figure 4). Malonyl-ACP undergoes a decarboxylative Claisen condensation process, followed by a stereoselective reduction of the ketone, dehydration to the corresponding $\alpha,\beta$-unsaturated acyl derivative, and hydrogenation of the C=C bond. This process is then repeated until the desired chain length is achieved. As a consequence, most long chain fatty acyl derivatives isolated from natural sources contain an even number of carbons. To complete the biosynthesis of oleic acid, the corresponding fatty acyl derivative, acyl-ACP, undergoes a stereoselective $\Delta^9$ desaturation.

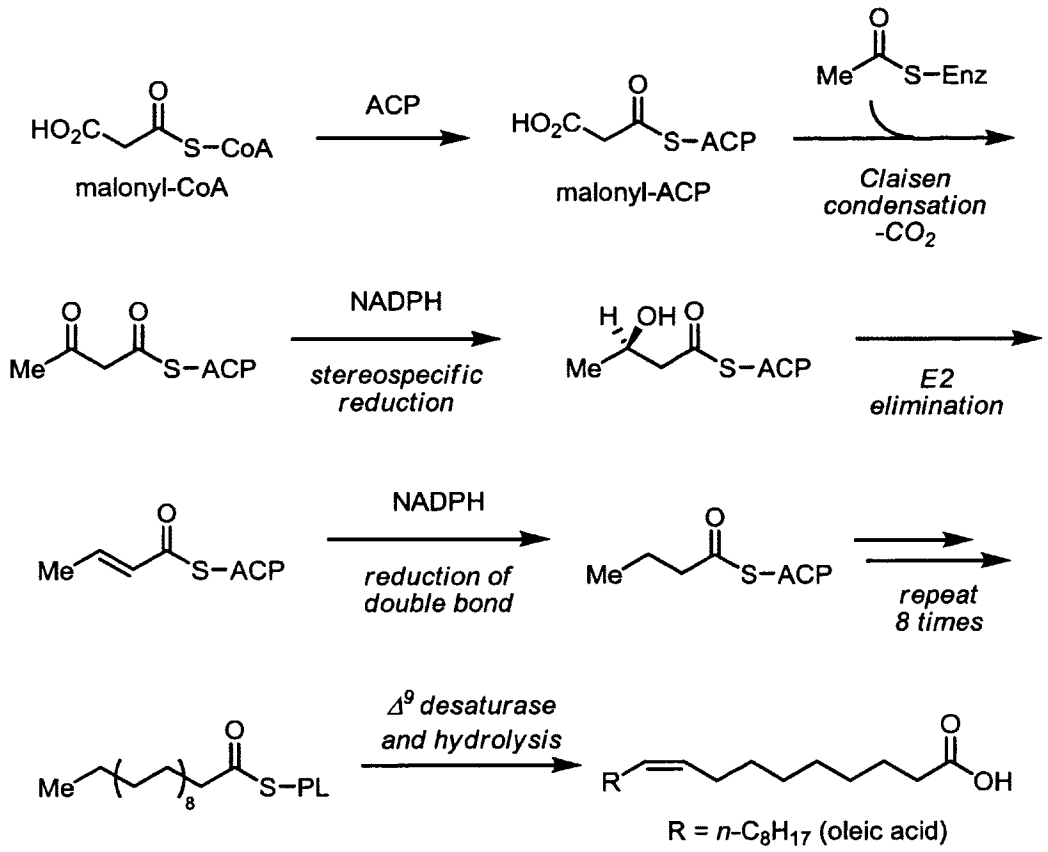



**Figure 4: Biosynthesis of oleic acid**

Olefinic fatty acids undergo a wide range of bio transformations (Figure 5). The most intriguing of these transformations is the stereoselective cyclopropanation of the olefin. A long chain unsaturated fatty acid such as oleic acid undergoes a stereospecific S-adenosyl methionine methylation which has been subject to extensive studies and reviewed.[16] The cyclopropane ring en route to dihydrosterculic acid is formed by CFA synthase while the source of the cyclopropane methylene carbon is the methyl group of S-adenosyl methionine (SAM). The mechanism for reaction describes a SAM-dependent cyclopropane ring formation first proposed by Lederer.[20] The first event in the mechanism is an $S_N2$ attack by the olefin in enzyme bound oleic acid onto SAM resulting in carbocation formation. This is followed by a deprotonation event and rapid ring

closure. Other mechanisms that have been proposed involve a sulfur ylide or metal carbenoid formation. Meanwhile, crystal structures of a number of cyclopropane synthases involved in mycolic acid biosynthesis have shown the presence of a SAM binding motif and a bicarbonate ion in the hydrophobic pocket in the enzyme and are believed to play a vital role.[21]

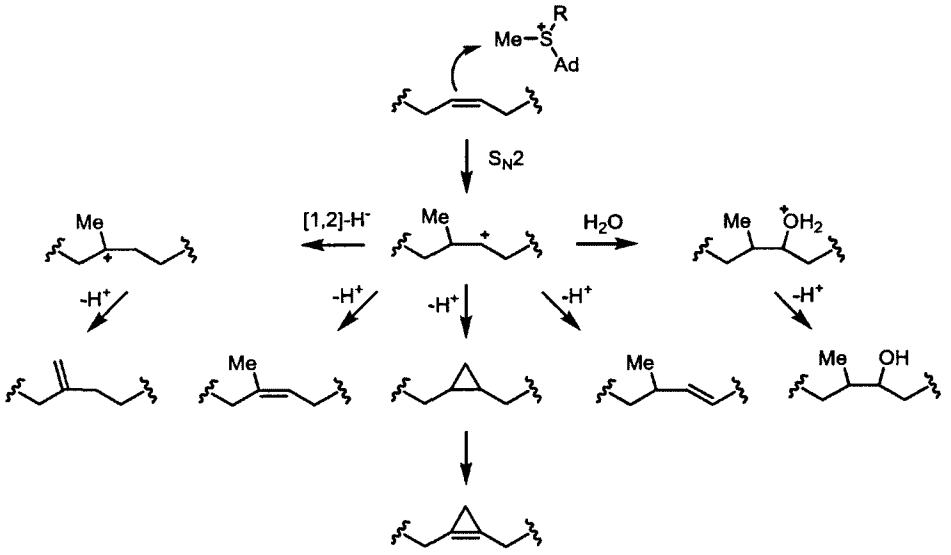



**Figure 5: Various biosynthetic pathways for SAM methylation of olefins**

## 1.4 Mechanistic Aspects of Desaturases

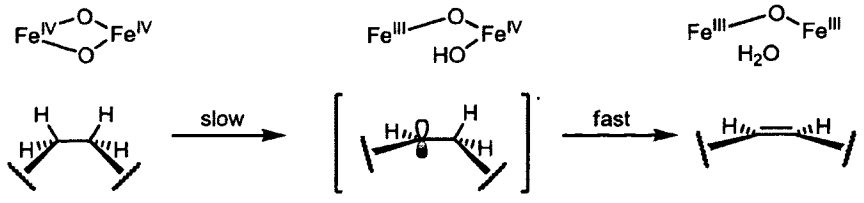
Bioorganic chemists who investigate enzymatic desaturation reactions rely on mechanistic probes that have similar physical and chemical properties to the substrate in question.[16] Common probes used for these investigations include isotopic labels (such as $^{1}H$ and $^{13}C$) and isosteric replacement of methylene groups with oxygen or sulfur and hydrogen with fluorine. These probes must be compatible with the enzymes: it must fit in the enzyme pocket, undergo thioester or glycerolipid formation, and undergo the desaturation reaction. Two important mechanistic issues must be addressed by bioorganic

chemists: cryptoregiochemistry and stereochemistry. $\Delta^9$ desaturation has been long regarded as the prototypical reaction for this class of oxidation reactions because of its presence in almost all aerobic organisms.

### 1.4.1 Cryptoregiochemistry

The site of initial oxidation in a general desaturation reaction is referred to as cryptoregiochemistry. This fundamental aspect of a bioenzymatic mechanism is often determined through KIE methodology based on the difference in bond dissociation energies between, most commonly, C-H and C-D. Initial C-H bond cleavage is energetically more difficult while the elimination of a hydrogen radical to form a C=C bond is an energetically favourable process (Scheme 1). For $O_2$-dependent desaturation, H abstraction is considered the slow process generating an alkyl radical followed by rapid elimination event forming a C=C bond.

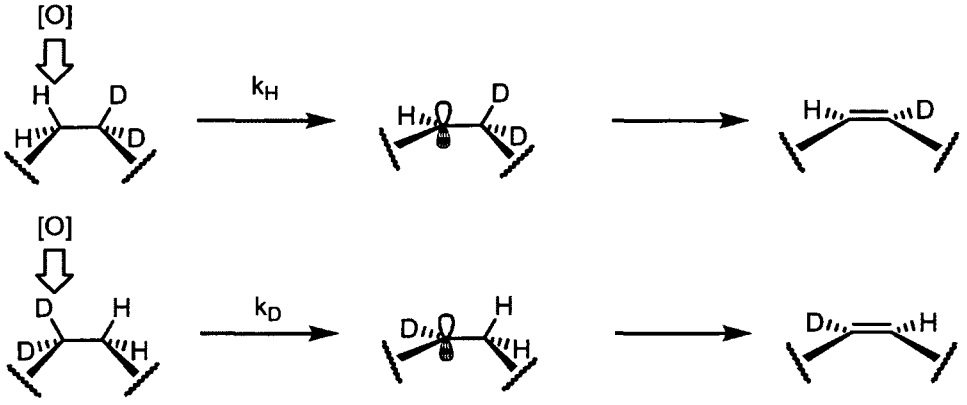
Most frequently used measurement of primary KIE for C-H cleavage in desaturation reactions involves a 1:1 mixture of regiospecific doubly deuterated substrate and its non-deuterated parent compound. The $d_1/d_0$ ratio of the olefinic product is compared to the $d_2/d_0$ ratio of the starting mixture.




**Scheme 1: General mechanism for the desaturase-mediated formation of unsaturated fatty acids**

### 1.4.2 Enantioselectivity / Stereoselectivity

The enantioselectivity of desaturation reactions is often investigated by the use of KIE methodology. No stereospecifically labeled substrates since prochiral centres are being oxidized. However, for cyclopropane desaturation, oxidation occurs at adjacent chiral centres. To overcome this challenge, a highly stereoselective route to cyclopropane fatty acids is required.




**Scheme 2: KIE effects on the rate limiting step of desaturation**

# 2 Chapter: Synthesis of Cyclopropane Fatty Acids

## 2.1 Introduction

This chapter describes general methods for the synthesis of 1,2-*cis* disubstituted cyclopropanes for the assembly of *cis*-cyclopropane fatty acyl derivatives. Here, we will not survey the various stereoselective methods for our target compounds, but simply have directed the reader to relevant reviews. These methods include the synthesis of natural products containing cyclopropane rings fused to cyclic systems,[22] heavily substituted or aryl substituted cyclopropanes,[23] and vinyl cyclopropanes as precursors to fragmentation and cycloaddition reactions.[24]

The general methods subsections briefly describe relevant properties and reactions but also reference relevant reviews and book chapters. This is followed by a section of selected syntheses of cyclopropane fatty acids with an emphasis on retrosynthetic analysis, cyclopropane formation, and stereoselectivity. This chapter will not include modern methods of cyclopropane / cyclopropene formation and synthesis of chiral auxiliaries examined experimentally during the course of this project.

## 2.2 General Methods of the Synthesis of Cyclopropanes

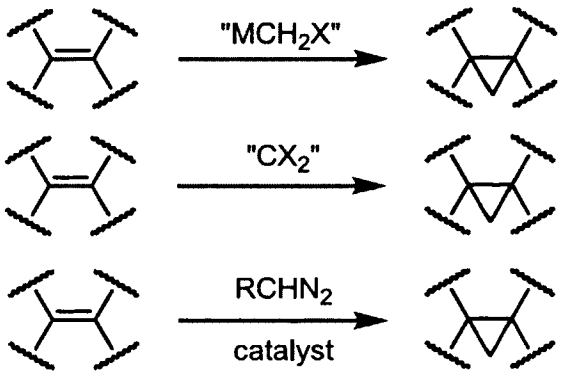
Cyclopropanes are strained three-membered carbocyclic structures with interesting properties and reactivity. Cyclopropanes have unique properties such as bond angle, bond length, strain energy, electron population at hydrogen (Table 1) and are found in a wide range of naturally occurring compounds.

**Table 1: Properties of some cycloalkanes**

| | △ | □ | ⬡ |
|---|---|---|---|
| bond length (C-C, Å) | 1.497 | 1.548 | 1.533 |
| bond length (C-H, Å) | 1.076 | 1.082 | 1.088 |
| bond angle (H-C-H) | 114.2 | 108.2 | 106.8 |
| $e^-$ population (H, 6-31G*) | 1.052 | 1.076 | 1.094 |
| strain energy (kcal $mol^{-1}$) | 27.5 | 26.5 | 0.0 |

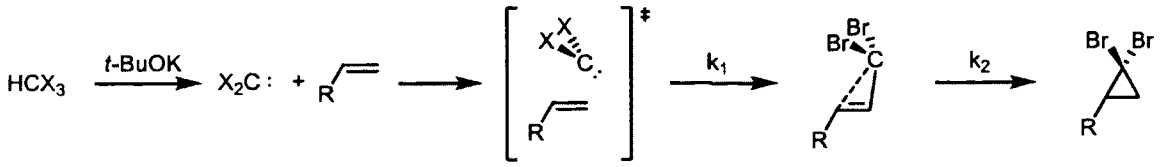
A number of orbital models for cyclopropyl rings have been proposed and studied experimentally and by theoretical calculations. The Forster-Coulson-Moffitt model[25] recognizes that strongly bent bonds lead to poor orbital overlap and weak C-C bonds. This model predicts maximal bond strength and overlap when the C-C bonds have 20% s and 80% p character and the C-H bonds have 30% s and 70% p character.

Cyclopropanes are valuable structures in the pharmaceutical industry and versatile building blocks in the synthesis of more functionalized cycloalkanes. There are a number of general methods for their preparation that can be classified as carbene or carbenoid addition across a C=C bond (Scheme 3) and Michael-induced ring closure (MIRC) reactions (Scheme 6). The former can further be categorized as addition across olefins using: (a) halomethyl-metal-mediated carbenes, (b) dihalocarbenes, and (c) transition metal-catalyzed decomposition of diazo compounds.




**Scheme 3: General methods for the synthesis of cyclopropanes by addition across C=C bonds**

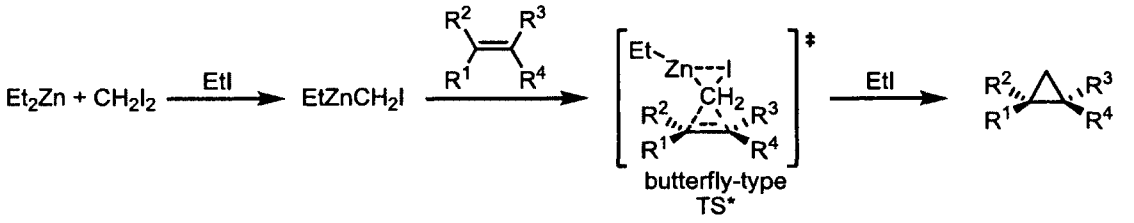
First published by Doering in 1954, dihalocarbene addition to olefins is the most reliable method to form dibromocyclopropanes.[26] This report was the first structural evidence for the formation of dibromocarbenes, prepared by mixing haloforms with KO*t*-Bu and bases with similar $pK_b$ values may also be used. Debromination is typically carried out by catalytic hydrogenation with Raney nickel or reduction with sodium metal in alcoholic solvents. Regioselective monodebromination is also known to proceed under radical conditions ($Et_3B$, $Ph_3SnH$).[27] Mechanistically, singlet carbene addition to olefins is a concerted cycloaddition although a symmetrical cyclic four-electron transition state is predicted to be forbidden according to orbital symmetry theory.[28] This reaction has been shown to be dynamically concerted using computational methods (Scheme 4).[29] These results show formation of one C-C bond after 50 fs followed by the second C-C bond after 139 fs. There is no rotation along the double bond during cycloaddition.




**Scheme 4: Mechanism for the addition of dihalocarbene across an olefin**

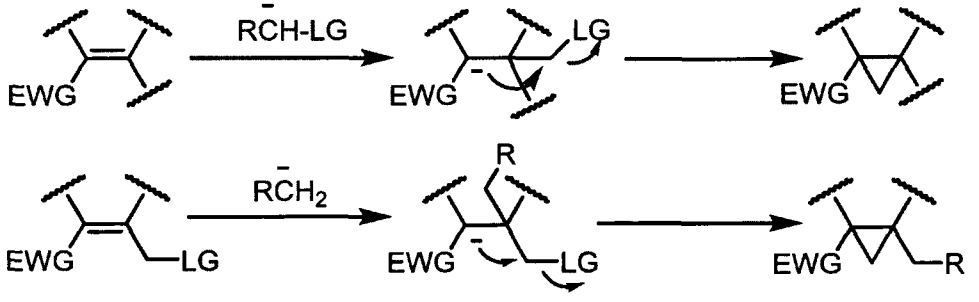
Transition metal carbenoid additions to olefins were popularized after H. E. Simmons and R. D. Smith described the first method to convert unactivated alkenes to cyclopropanes stereospecifically using $CH_2I_2$ and zinc-copper couple (Zn-Cu).[35] This transformation has proved to be a very general and powerful method for cyclopropane formation that it is named after its discoverers and is referred to as the Simmons-Smith reaction (or cyclopropanation).[30] A wide range of alkenes can be used: unactivated, electron-rich and electron-poor alkenes. However, electron-poor alkenes are electronically disfavoured as reaction partners and slower reaction rates are observed due to the electrophilic nature of the Zn carbenoid. In contrast, electron-rich alkenes undergo cyclopropanation at a faster rate, although highly substituted alkenes may be an exception to this rate of reaction trend due to increased steric hindrance. This cyclopropanation mechanism is stereospecific: the geometry of the olefin remains intact after the transformation (*ie.*, a disubstituted *Z*-alkene will give a 1,2-*cis* relationship in the corresponding cyclopropane). Several modifications have been developed to generate a reagent with higher activity. Popular modifications include contributions from Furukawa ($Et_2Zn/CH_2I_2$, higher yields and more reproducible),[31] Molander ($Sm/Hg/CH_2I_2$, chemoselective cyclopropanation of allylic alcohols in the presence of other olefins),[32] and Yamamoto ($i$-$Bu_3Al/CH_2I_2$, chemoselective cyclopropanation of unactivated alkenes in the presence of allylic alcohols).[33] The stereospecificity of the Simmons-Smith

reaction is rationalized by examining the mechanism, as the transformation is a concerted process proceeding via a three-centered "butterfly-type transition state" (Scheme 5).




**Scheme 5: Mechanism for the Furukawa modified Simmons-Smith reaction**

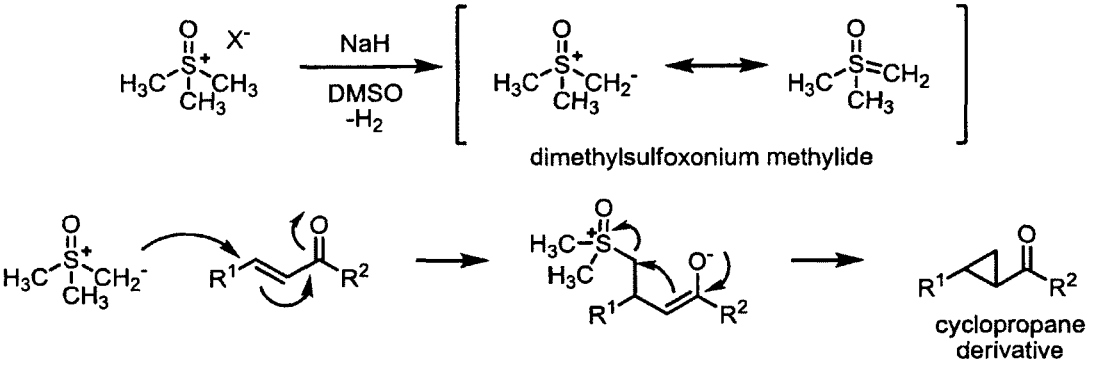
There are two main types of MIRC reactions used in the synthesis of cyclopropanes (Scheme 6). Both types include a conjugate addition event while they differ in the location of the incorporated leaving group: (a) in the Michael donor, or (b) the Michael acceptor. The former MIRC type being the more commonly used approach.




**Scheme 6: General methods for the synthesis of cyclopropanes via MIRC reactions**

The Corey-Chaykovsky cyclopropanation, named after the authors of the corresponding seminal publication, is a MIRC transformation where the Michael acceptor is typically, but not limited to, α,β-unsaturated carbonyl compounds and the leaving group is a sulfoxide or sulfide (Scheme 7). For the former, trimethylsulfoxonium halides

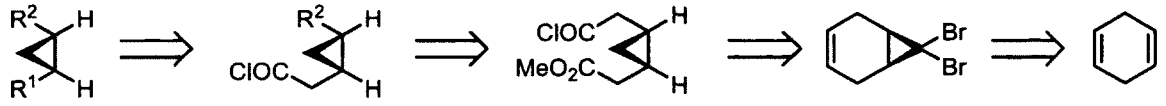
($Me_3S^+(O)X^-$), prepared by heating DMSO and methyl halide at reflux, are deprotonated with NaH in DMSO at room temperature or in DMSO/THF at 0 °C to generate a reactive species, dimethylsulfoxonium methylide (also known as the Corey ylide). Cyclopropanations using trimethylsulfonium halides or other counteranions ($Me_3S^+X^-$) typically require lower reaction temperature since many of these sulfonium salts decompose above 0 °C, while the corresponding sulfonium ylides may be too reactive even if sulfonium salts have practical stability above 0 °C.




**Scheme 7: Mechanism for the Corey-Chaykovsky cyclopropanation**

## 2.3 Selected Syntheses of Cyclopropane Fatty Acids

### 2.3.1 Racemic Chemical Syntheses of Dihydrosterculic Acid (1)

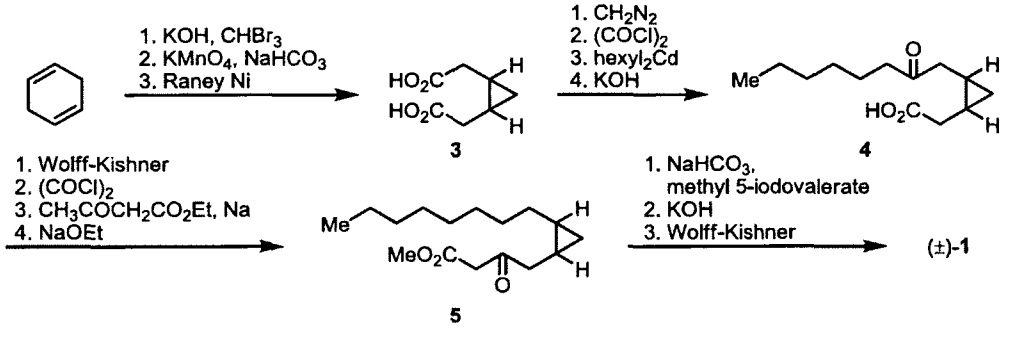



**Scheme 8: Hofmann retrosynthetic analysis of racemic dihydrosterculic acid (1)**

In 1959, Hofmann reported the landmark chemical synthesis of (±)-dihydrosterculic acid (**1**). His synthesis is impressive even today since it showcases important contributions from the synthetic community developed in the 1950's which are still used in modern organic synthesis. There are, however, still synthetic challenges that remain today. The concept of selective monofunctionalization (*ie.* monoesterification of an α,ω-diacid) is used in this synthesis whereas the modern method for tackling this problem is to simply separate the statistical mixture of products. Key strategies used in this synthesis include the sequential appendage of an alkyl chain by coupling an organocadmium reagent with an acid chloride: a transformation that has been scarce since the advent of olefination chemistry (Scheme 8). The cyclopropane was installed by addition of dibromocarbene to an olefin generating a now versatile dibromocyclopropane structure.

Overall, Hofmann's synthesis of (±)-**1** was achieved from 1,4-cyclohexadiene in 15 steps (Scheme 9).[8,34] The first step in the synthesis was the formation of the cyclopropane ring by addition of dibromocarbene. This was followed by oxidative cleavage of the remaining olefin and debromination to give cyclopropyl diacid **3**. The

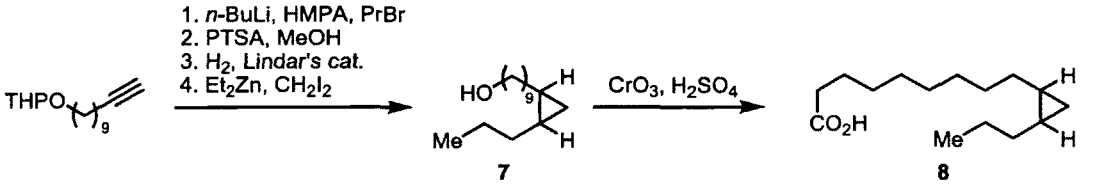
first alkyl side chain was installed by a rather tedious and stepwise protocol. Mono esterification of diacid **3** was performed upon exposure to diazomethane, conversion of the remaining carboxylic acid to the acid chloride and then to the hexyl ketone with dihexyl cadmium. This is followed by saponification to give keto acid **4**. Attachment of the remaining second side chain was performed by a slightly modified sequence to account for the highly oxidized terminus in the final product. The Wolff-Kishner reduction product of keto acid **4** was converted to its acid chloride then coupling with ethyl sodioacetoacetate and deacylation to afford β-ketoester **5**. A number of functioanlizations remained to give racemic dihydrosterculic acid in what was an elegent synthesis in natural product chemistry.




**Scheme 9: Hofmann racemic synthesis of dihydrosterculic acid (1)**

Within a year of the publication of Hofmann's synthesis of (±)-dihydrosterculic acid, Simmons and Smith discovered a new method at the time for the preparation of cyclopropanes upon treatment of an olefin with $CH_2I_2$ and a zinc-copper couple. They reported a much simplified synthesis of (±)-dihydrosterculic acid from methyl oleate in 51% yield in only two steps demonstrating an impressive rapid development accomplished at the time.[35]

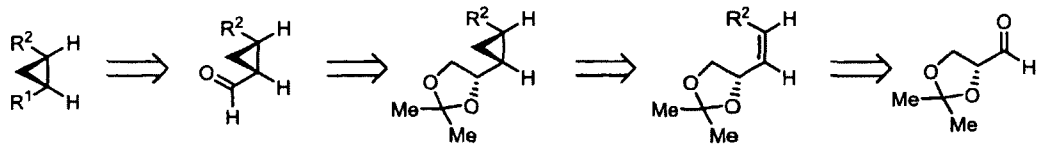
In 2005, De Voss studied cytochrome P450 using cyclopropyl containing fatty acids as mechanistic probes. [36] His synthesis of racemic *cis*- and *trans*- cyclopropane fatty acids demonstrates the simplicity of modern organic synthesis if stereoselectivity of cyclopropanation is not a concern (Scheme 10). Key strategy involves a stereoselective reduction of internal alkynes to *trans*- (using Li, $NH_3$) and *cis*- (using $H_2$, Lindlar's catalyst) olefins. His synthesis began with alkylation of THP-protected alcohol **6** followed by deprotection, semi-reduction and Simmons-Smith reaction to cyclopropyl alcohol **7**. Finally, Jones oxidation then gives racemic cyclopropane fatty acid **8**.




**Scheme 10: De Voss racemic synthesis of cyclopropane fatty acids**

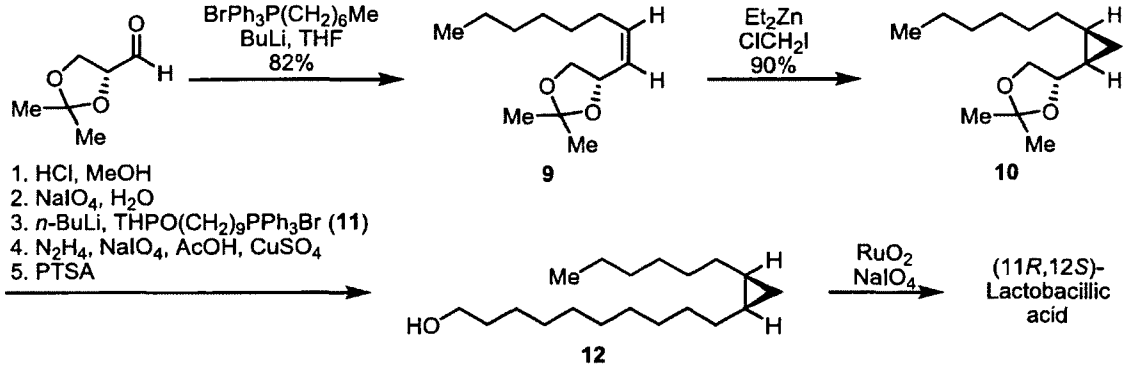
### 2.3.2 Baird Enantioselective Synthesis of (11*R*,12*S*)-Lactobacillic Acid

In 2003, Baird reported non-racemic syntheses of both enantiomers using two different strategies. [37] For the synthesis of the (11*R*,12*S*) stereoisomer, they chose to attach both alkyl chains by a Wittig olefination. Consequently, the selectivity of the first olefination establishes the required *cis*- geometry in the cyclopropane ring (Scheme 11). The key stereoselective transformation utilizes the directing ability of an oxygen atom in a Simmons-Smith reaction while the remainder of the synthesis involves several tedious manipulations.



**Scheme 11: Baird retrosynthetic analysis of (11*R*,12*S*)-lactobacillic acid**

The Baird synthesis begins with a Wittig olefination readily available 2,3-*O*-isopropylidene-D-glyceraldehyde (prepared in two steps from D-mannitol) and heptyltriphenylphosphonium bromide to give the desired *cis*- alkene **9** (Scheme 12). Enantioselective Simmons-Smith reaction of **9** gives cyclopropane **10** where the stereoselectivity is controlled by the directing effect of the allylic oxygen in the dioxolane ring while the absolute configuration was assigned upon comparison to known synthetic standards.



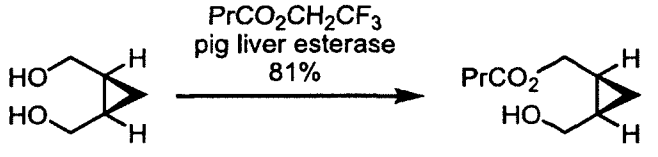

**Scheme 12: Baird enantioselective synthesis of (11*R*,12*S*)-lactobacillic acid**

Cleavage of the acetal with HCl and MeOH followed by oxidative cleavage of the resulting diol affords the corresponding cyclopropyl aldehyde. A similar strategy (to the first side chain) for appending the final side chain was used with the exception of a few protecting and reductive manipulations. Cyclopropyl aldehyde was subjected to Wittig olefination with phosphorane **11** as a mixture of stereoisomers followed by hydrazine

reduction of the alkene and THP deprotection with PTSA and MeOH. The resulting fatty alcohol **12** contains the correct number of carbons and was subjected to a ruthenium-catalyzed oxidation to afford (11*R*,12*S*)-lactobacillic acid in 2.2% yield in 8 steps from isopropylidene gluceraldehyde.

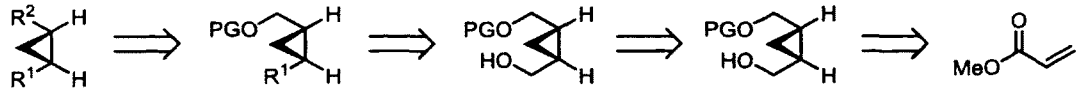
### 2.3.3 Baird Enantioselective Synthesis of (11*S*,12*R*)-Lactobacillic Acid

In the same publication as the previously described synthesis, Baird reported a synthesis of its enantiomer, (11*S*,12*R*)-lactobacillic acid. While not the most efficient synthesis to date, Baird showcases the application of a desymmetrization as the source of stereocontrol (Scheme 14). The cyclopropane ring was installed in the first step by a racemic MIRC reaction while their key strategy, similar to that of the Hofmann group, relies on a monofunctionalization exemplified by the enzymatic desymmetrization of cyclopropyl diols by pig liver esterase. (Scheme 13).[38] This strategy is a viable solution to a challenging problem in synthesis but is limited, however, to substrates compatible with enzymatic desymmetrization. Finally, the alkyl substituents are installed by a sequence of redox manipulations and Wittig olefinations to give the title compound.



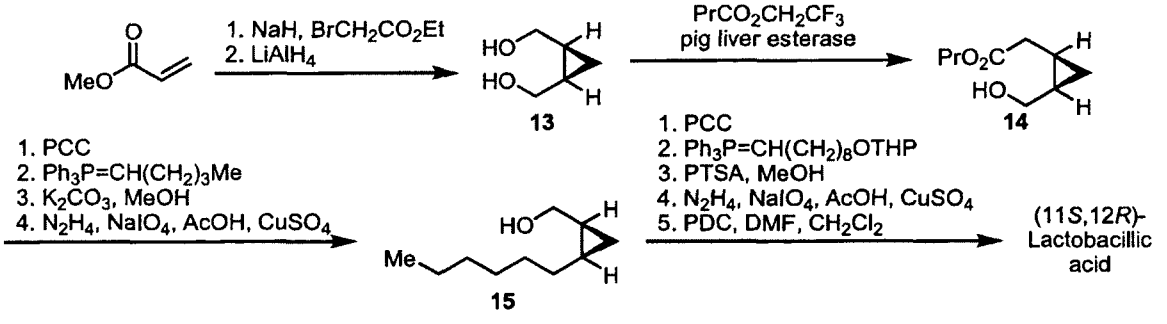

**13** **14**

**Scheme 13: Enzymatic desymmetrization of *cis*-cyclopropane 1,2-dimethanol (13)**



**Scheme 14: Baird retrosynthetic analysis for (11*S*,12*R*)-lactobacillic acid**

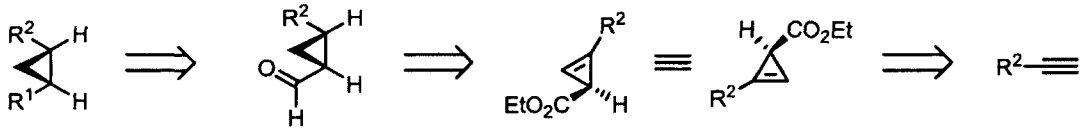
The Baird synthesis of (11*S*,12*R*)-lactobacillic acid begins with the preparation of cyclopropyl diol **13** from methyl acrylate (Scheme 15). Under exposure to pig liver esterase they obtained monoester **14**. The first side chain of the molecule was attached by a sequence that includes oxidation to the aldehyde, Wittig olefination, deprotection of the ester on the other side chain, and finally reduction of the olefin. The resulting alcohol **15** was converted to append the second side chain by a similar sequence as described for the first side chain. The only difference being that the end of the appended chain is protected as its THP ether. Simple deprotection and oxidation affords enantiomerically enriched lactobacillic acid. This route is not ideal for our enzymatic studies since stoichiometric amounts of chromium are needed. This synthesis was completed in 10 steps from diol **13** in 10.2% overall yield.



**Scheme 15: Baird enantioselective synthesis of (11*S*,12*R*)-lactobacillic acid**

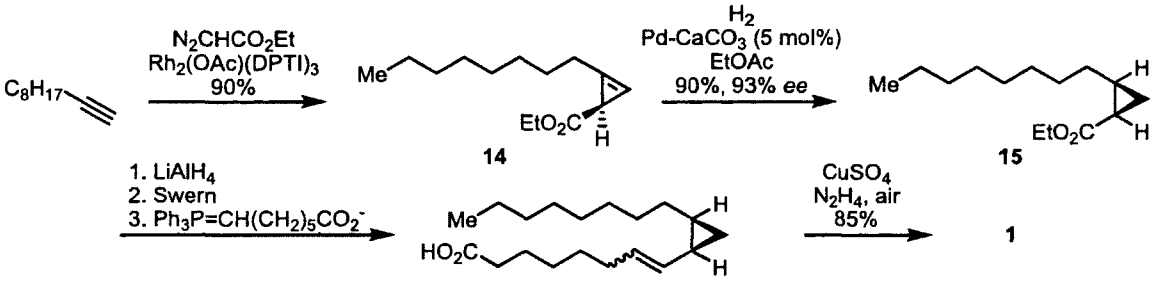
### 2.3.4 Corey Enantioselective Synthesis of (9*R*,10*S*)-Dihydrosterculic Acid (1)

In 2005, Corey reported a synthesis of naturally occurring (9*S*,10*R*)-dihydrosterculic acid.[39] The retrosynthetic analysis is shown below (Scheme 16) displaying a highly efficient strategy simplified by incorporating one alkyl chain ($R^2$) in the starting materials while incorporation the desired oxidation state of the acid terminus of $R^1$ upon attachment of the remaining alkyl chain (not shown).



**Scheme 16: Corey retrosynthetic analysis for (9*R*,10*S*)-dihydrosterculic acid**

The Corey synthesis is the shortest and highest yielding stereoselective synthesis of a cyclopropane fatty acid to date (Scheme 17). In his report, he developed a highly enantioselective cyclopropenation of terminal alkynes via rhodium-catalyzed decomposition of ethyl diazoacetate. This methodology, however, only defines the absolute stereochemistry of one carbon. The remaining stereocenter is set by a facially selective hydrogenation.



**Scheme 17: Corey enantioselective synthesis of (9*R*,10*S*)-dihydrosterculic acid (1)**

Corey's synthesis of (9*R*,10*S*)-dihydrosterculic acid (**1**) was achieved in 37% yield over six steps from 1-decyne. The synthesis begins with the key strategy, an impressive enantioselective [2+1] cycloaddition of ethyl diazoacetate to afford cyclopropene **14** in 95% yield and 93% *ee*. Stereoselective hydrogenation affords cyclopropyl ester **15** in 90% yield, giving the requisite *cis*- disubstituted cyclopropane geometry. This ester underwent redox manipulation to the corresponding aldehyde by: a) reduction of $CO_2Et$ to $CH_2OH$ using $LiAlH_4$ (78%); and Swern oxidation to CHO (95%). The second side chain ($R^1$) was appended in a similar sequence as Hofmann using a Wittig olefination with the ylide of 7-triphenylphosphine heptanoic acid bromide (72%, *Z*/*E* = 4:1), which was then reduced with hydrazine and $CuSO_4$ to give **1** in 85% yield (37% over six steps from 1-decyne).

# 3 Chapter: Results and Discussion

## 3.1 Project Goals

The ultimate goal of this project is the determination of cryptoregiochemistry and stereoselectivity for the $\Delta^9$ desaturation of dihydrosterculic acid (**1**). A requirement for this synthesis is for the regio- and sterospecific incorporation of deuterium atoms within dihydrosterculic acid. The figure below depicts a number of mechanistic probes we require for our mechanistic studies (Figure 6). First, we must develop a modular, stereoselective synthetic route to dihydrosterculic acid since all published syntheses contain insufficient stereoselectivity for deuterium incorporation or cyclopropanation at some point in the synthesis or require labeled reagents that would consume considerable synthetic effort to prepare.

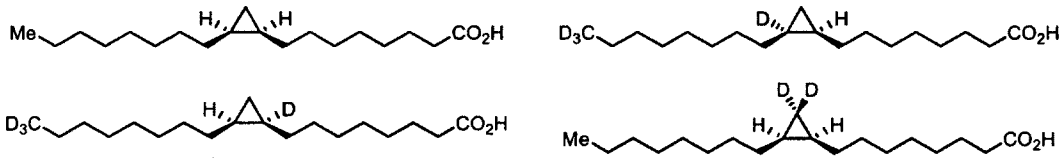


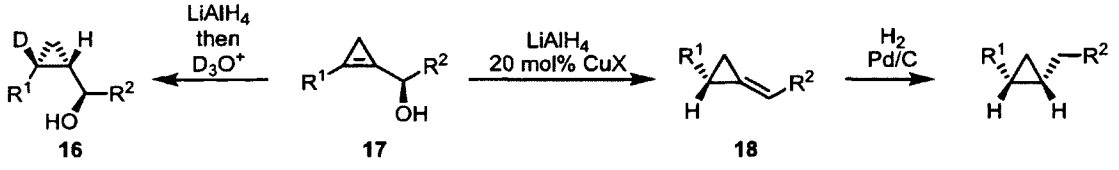

**Figure 6: Dihydrosterculic Acid (1) and Various Mechanistic Probes**

## 3.2 First Approach to Retrosynthetic Analysis and Synthetic Strategy Towards Dihydrosterculic Acid (1)

It was desired to develop a synthesis which minimizes protecting group manipulations and non-strategic bond redox and C-C bond formations, with an eye towards simplicity in the preparation of mechanistic probes for cyclopropane fatty acid desaturation.

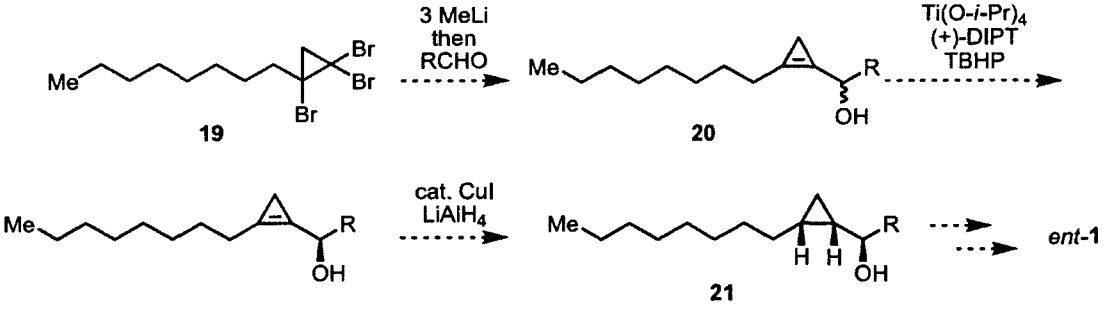
In our studies of developing a synthesis to dihydrosterculic acid, we devised a number of requirements to simplify our study. The synthesis must be highly diastereoselective, ideally stereospecific, in forming the *cis*-dialkylated cyclopropane motif. The synthesis must be short and allow for easy access to either enantiomer. The synthesis must also allow for modular incorporation of deuterium atoms for use as mechanistic probes for $\Delta^9$ desaturation.

Cyclopropene carbinols have recently received a great deal of attention from the synthetic community due to their ease of use as building blocks for natural products. These cyclopropene carbinols can be readily transformed by hydro- or carbometalation reactions on the strained internal double bond to form highly functionalized cyclopropanes in a stereoselective manner. [40] In 2006, Marek developed methodology for the stereoselective reduction of enantiomerically enriched cyclopropenyl carbinols (**17**) with $LiAlH_4$ in $Et_2O$ to cyclopropylcarbinols as single *cis* isomers (Scheme 18).[41] Alternatively, it was shown that a *syn* $S_N2'$ process occurred upon exposure of same cyclopropenyl carbinols with $LiAlH_4$ and catalytic CuI to afford enantiomerically pure alkylidene cyclopropanes (**18**). It was hypothesized that diastereoselectivity the arises from the minimization of 1,3-allylic strain of the substrate upon hydroxide directed copper hydride delivery completed by elimination. These systems undergo a facile, facially selective hydrogenation.




**Scheme 18: Marek's methodology for the diastereoselective formation of 1,2-*cis*-cyclopropanes**

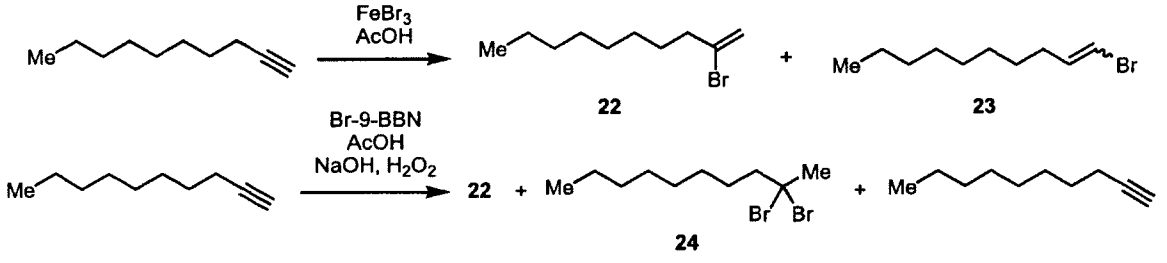
Our first proposed route using this notion is summarized below (Scheme 19). The synthesis would start with the conversion of a 1-decyne to corresponding 2-halo-1-alkene followed by cyclopropanation with dibromocarbene. The resulting tribromocyclopropane (**19**) was subjected to 3 equivalents of MeLi generating cyclopropenyllithium species and finally quenching with an aldehyde forming cyclopropene carbinol (**20**). Racemic **20** was resolved using the Sharpless kinetic resolution of allylic alcohols (cat. Ti(O-*i*-Pr)$_4$, (+)-DIPT, TBHP) which converts the undesired enantiomer to an epoxide.[42] Marek's methodologies could now be applied at this stage. Either the $S_N2'$ hydride delivery or the hydroxide directed copper hydride reduction could be used. Both methods give the required 1,2-*cis* relationship of the cyclopropane upon stereoselective hydrogenation but would also act as a point of divergence for accessing mechanistic probes. Upon formation of cyclopropane carbinol **21**, deoxygenation would be required followed by a few oxidative manipulations to give fatty acid *ent*-**1**.




**Scheme 19: Unsuccessful approach to the enantioselective synthesis of dihydrosterculic acid (1)**

Our synthesis began with the *syn* halohydrin addition formation to obtain 2-chloro-1-decene or 2-bromo-1-decene reported by Miranda.[43] However, in our hands addition across the alkene produced an inseparable mixture of regioisomers **22**, **23**

(Scheme 20). Cyclopropanation of this mixture with dibromocarbene[44] and subsequent formation of racemic cyclopropenyl carbinols proved unfruitful as insepearable mixtures and complicated NMR spectra were obtained. We then focused on utilizing stereospecific transformations to overcome the challenges of chromatographic separation. Another approach to vinyl bromide **22** was to perform a bromoboration/protodeboration sequence from 1-decyne.[45] However, difficulties were encountered with this method due to competitive dibromo-diboration affording an inseparable mixture of 1-decyne, vinyl bromide **22** and 2,2-dibromoalkane **24**. At the time of experimentation, Hoveyda reported a highly regioselective Ni-catalyzed formation of 2-halo-1-alkenes from terminal alkynes. [46] However, this methodology required the use of neat DIBAL-H, which was not readily available. Attempts at using commercially available DIBAL-H as a solution in toluene gave no conversion of starting material. No attempts at optimization were performed leading us to abandon this synthetic approach altogether.

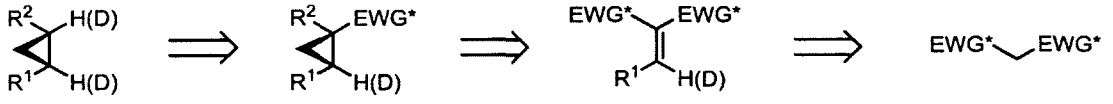



**Scheme 20: Approach to 2-halo-1-alkenes from terminal alkynes**

## 3.3 Successful Enantioselective Synthesis of Dihydrosterulic Acid (1)

### 3.3.1 Manthorpe Retrosynthetic Analysis

In our second approach to the synthesis of dihydrosterculic acid, we explored the use of chiral organosulfur compounds as the source of enantioselectivity, as well as, using C-S bond cleavage as a handle for regioselective alkylation (Scheme 21). The use of chiral sulfoxides (resresented as EWG* in Scheme 21) has been extensively explored.[47,48,49] To the best of our knowledge, the use of chiral 1,1-bis-sulfoxides have been applied once to the synthesis of natural products using a highly diastereoselective conjugate addition en route to (+)-*erythro*-roccellic acid.[50,51] Initial investigation of our proposed route was performed using nonanal as the electrophilic partner in the first step of the sequence. This would undoubtedly lead to *ent*-**1** but was used as a model for synthesis as an inexpensive, commercially available compound.

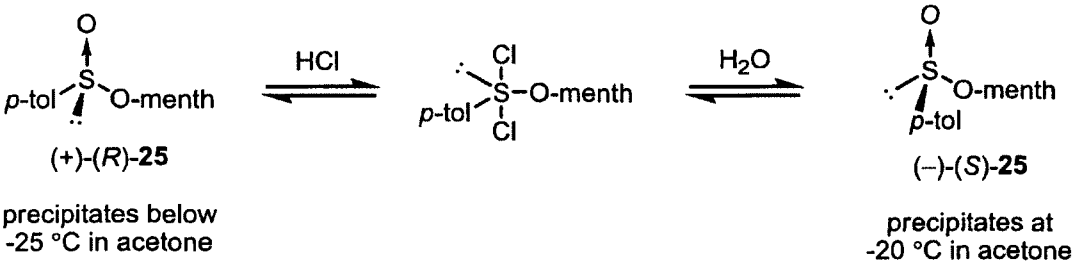



**Scheme 21: Manthorpe retrosynthetic analysis of dihydrosterculic acid (1)**

### 3.3.2 Preparation of $C_2$-Symmetrical Bis-Sulfoxide 26

Our initial method involved a three-step reaction sequence from commercially available *para*-tolueneselfinic acid hydrate (Scheme 23). [52] *para*-Toluenesulfinic acid hydrate requires cautious drying by azeotropic removal of water from toluene followed by removal of toluene. The subsequent step involves conversion of the dry sulfinate to the corresponding sulfinyl chloride via reaction with thionyl chloride. Toluene, a less hazardous alternative to benzene, cannot be used as the reaction solvent in this

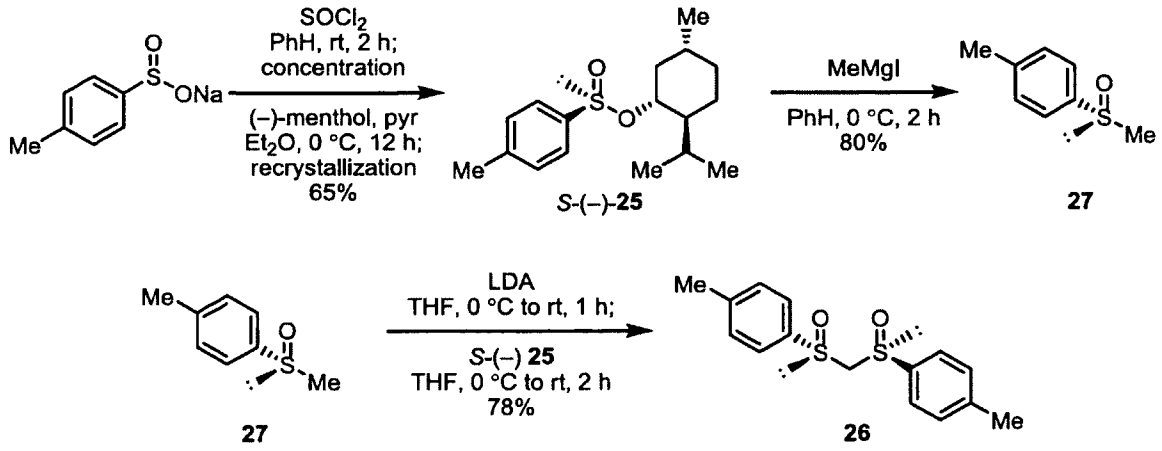
experiment since toluene gave the desired product in very low yield. Cautious addition of thionyl chloride to a benzene solution of dry *para*-toluenesulfinate over 30 minutes under a positive nitrogen atmosphere is also requied as it produces stoichiometric quantities of $SO_2$ gas upon generation of the sulfinyl chloride. Once the formation of the *p*-toluenesulfinyl chloride is complete, a solution of (–)-menthol in pyridine is added giving a mixture of diastereomeric menthyl sulfinate esters (**25**). Although this reaction is quite reproducible, the procedure is quite hazardous and labour intensive to carry out on large scale in a laboratory setting. It was observed that the desired diastereomeric sulfinate ester (–)-(*S*)-**25** selectively crystallizes in acetone at -20 °C but the undesired diastereomer (+)-(*R*)-**25** crystallizes at temperatures below -25 °C. Therefore, the use of a cryobath or an adequate temperature-controlled freezer is highly recommended to achieve accurate recrystallization. Epimerization of the mother liquor is required to increase yield initiated by the addition of small amounts of concentrated hydrochloric acid and stirring at room temperature (Scheme 22). After combination of all crystallized crops, two further crystallizations are required to increase purity by NMR and optical rotation.




**Scheme 22: Equilibrium between (–)-menthyl *p*-tolylsulfinate (25) and its diastereomer**

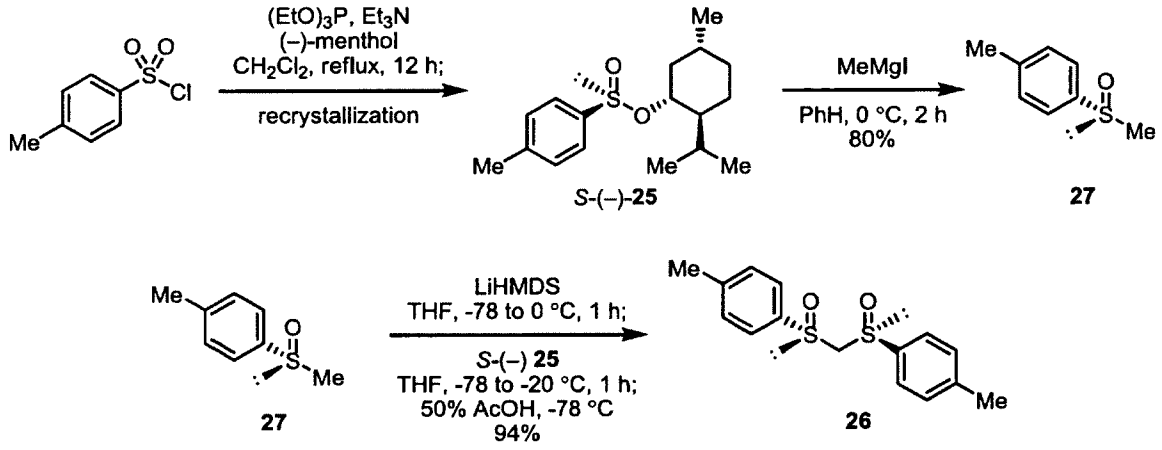
Although this procedure has been published in reputable academic journals, an alternative procedure was examined significantly improving safety measures and labour time of the experimentalist. We found the Sharpless procedure[53] to synthesize sulfinate ester **25** and the Reggelin procedure[54] to synthesize bis-sulfoxide **26** optimal (Scheme 24). There is no production of extremely hazardous materials such as gaseous $SO_2$. The procedure requires a simple reflux of TsCl, menthol, $Et_3N$ and $(MeO)_3P$ overnight. The recrystallization process required remains unchanged; however, a trituration of recovered material from THF is used to remove *p*-tolyl disulfone produced in the reaction mixture. (–)-(*S*)-**25** was subjected to methyl Grignard to afford enantiomerically enriched sulfoxide **27** in 72-80% yield and >95% *ee*. Repetition of the purification of this sulfoxide produced lower yields and required extensive labour time. Purification by flash column chromatography was preferred since there was no loss of product or optical activity.

Initial preparation of bis-sulfoxide **26** unnecessarily required 2 equivalents of sulfoxide **27**. Repetition of the experiment gave low yields while complicated purification. A simplified purification for **26** was discovered upon addition of $Et_2O$ to the crude oil. An optimized purification protocol was then used which consisted of precipitation of **26** and washing with $Et_2O$ to afford a white solid.




**Scheme 23: Preparation of ($S_S$,$S_S$)-bis-*p*-tolylsulfinylmethane (26) from *p*-tolylsulfinic acid sodium**

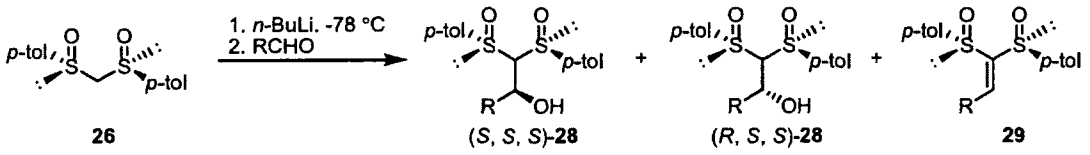
The second preparation of bis-sulfoxide **26** required only one equivalent of **27** and excess (typically 3-5 equivalents of LiHMDS). This protocol gave reproducibly high yields (80-94%) with using our improved purification procedure (See Experimental for details).




**Scheme 24: Preparation of ($S_S$,$S_S$)-*p*-tolyl-bis-sulfinylmethane (26) from tosyl chloride**

### 3.3.3 Preparation of Cyclopropyl Bis-Sulfoxide 33

In the laboratory of Malacria, a new synthesis of enantiopure 1,1-bis-*para*-tolyl-sulfoxides (**29**) was described in a two-step sequence.[55] The first reaction involves an alkylation of the lithium anion of bis-sulfoxide **26** with aldehydes resulting in a mixture of diastereomeric alcohols (**28**) and a trace amount of dehydrated product (**29**) (Scheme 25). The second reaction is a mild dehydration of the alcohols resulting from the previous reaction using morpho-CDI as the dehydration reagent.

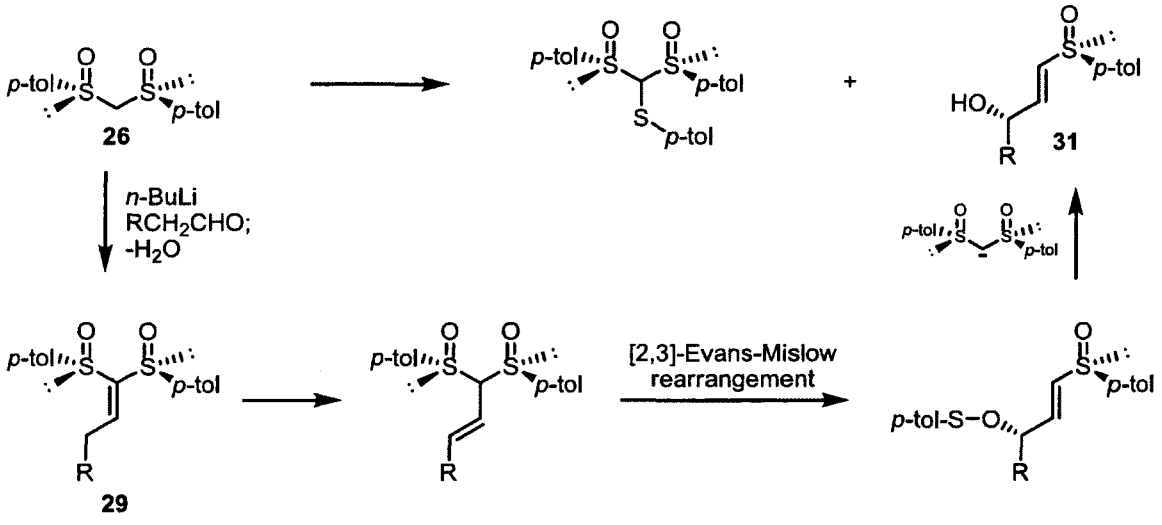



**26** (*S, S, S*)-**28** (*R, S, S*)-**28** **29**

**Scheme 25: Malacria's diastereoselective alkylation with 1,1-bis-sulfoxides and aldehydes**

The objective in the Malacria laboratories was to develop alternatives to Knoevenagel condensation of aldehydes and sulfoxides as the desired reaction afforded (*E*)-γ-hydroxyvinylsulfoxides,[56] and to examine the diastereoselectivity of the alkylation reaction. They added 1.1 equivalents of *n*-BuLi to **26** in THF at -40 °C to generate the corresponding lithium anion. After 1 h at that temperature, the mixture was cooled to -78 °C and 1.5 equivalents of aldehyde were added. They observed immediate alkylation but without complete consumption of starting materials. To overcome modest conversion, the reaction temperature was raised to -25 °C since above this temperature dehydration of the resulting bis-sulfinyl alcohols was observed. They speculate that the alkoxide formed after alkylation deprotonates **28** followed by a rapid elimination of LiOH. (Scheme 26) In the basic reaction conditions, isomerization of the alkylidene **29** to the allylic bis-

sulfoxide **30** followed by a [2,3]-Evans-Mislow rearrangement and S-O bond cleavage gives (*E*)-γ-hydroxyvinylsulfoxide **31**. This decomposition pathway was observed when isomerization of **29** occurs to give β,χ-unsaturated alkylidene bis-sulfoxides. Pentanal, *iso*-butyraldehyde, and acrolein were used as electrophiles but isomerization of **29** was not observed for *neo*-pentyl aldehyde or benzaldehyde since isomerization after dehydration is not possible. Their optimized conditions consisted of addition of 1.5 equivalents of aldehyde at -78 °C, stirring for 30 minutes at this temperature, followed by 1 hour at -40 °C, 1 hour at -25 °C and quenching with saturated $NH_4Cl$ at this temperature. This is typically followed by extraction with $Et_2O$ and chromatographic separation.




**Scheme 26: Decomposition pathway of 1,1-bis(p-tolylsulfinyl)-2-alcohols under basic conditions**

They also mention the necessity for HMPT as an additive to obtain appreciable conversion of benzaldehyde). In contrast to results of Solladie,[57] they observed good yields (70-82%), high diastereoselectivity (81:19-100:0) and formation of approximately

5% dehydrated adducts after chromatographic separation. Their rationale for the high degree of diastereoselectivity is depicted below (Figure 7). They speculate a lithium cation-chelated transition state in which the steric interactions of the aromatic substituent of bis-sulfoxide **26** and alkyl substituent in the aldehyde are minimized.

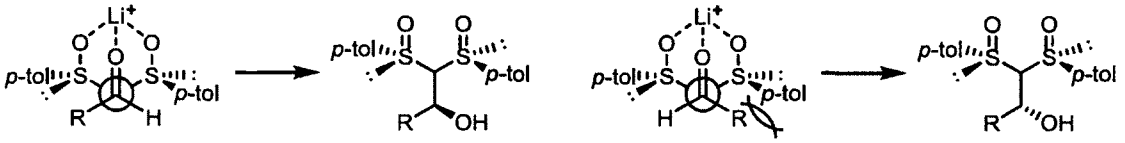



**Figure 7: Stereoselectivity model for the addition of bis(*p*-tolylsulfinyl)methyllithium to aldehydes**

Initial repetition of the protocol, using nonanal as the electrophile, proved to be a challenging task even though rigorous measures were taken. During these studies, routine operations such as overnight drying of **26** at 70 °C under high vacuum, use of distilled solvents, titration of *n*-BuLi prior to use, distillation of aldehydes, followed by immediate confirmation of their purity by $^1$H NMR and consumption were all performed with attention to detail. Unfortunately, complex mixtures of products were consistently obtained even after chromatography. The $^1$H NMR of the crude material contained a number of peaks in the carbonyl region characteristic of oligomerized linear aldehydes. Meanwhile, alkylations using freshly distilled *iso*-butyraldehyde and benzaldehyde (without HMPT as an additive) proceeded cleanly in high yield. In contrast to Malacria, chromatographic separation to remove unreacted aldehyde (for *iso*-butyraldehyde and benzaldehyde) did not produce any amounts of dehydrated adduct detecteable by NMR. Repetition of the conditions with >1.5 equivalents of *n*-BuLi unsurprisingly produced the corresponding (*E*)-γ-vinylhydroxysulfoxide **31** and thiolated bis-sulfoxide **32** but gave

simpler NMR spectra and insight into optimization. It became clear that the issue with this reaction is the production of dehydrated adduct. If dehydration was minimized in this alkylation, then formation of (*E*)-γ-vinylhydroxysulfoxides would also be minimized. It was realized that a reaction temperature of -25 °C (and even -40 °C!) was detrimental to these experiments. Allowing the reaction mixture to stir at -78 °C for 3 hours (the same total amount of time as reported in Malacria's conditions) still produced complex mixtures; however, the desired products were distinguishable by NMR. It was then hypothesized that an increased concentration of electrophile would increase the rate of alkylation and decreasing reaction time would minimize the formation of dehydration adduct. Routinely, 3-5 equivalents of freshly distilled nonanal and quenching the reaction mixture after 30 minutes at -78 °C resulted in 67% yield (83% brsm, 80:20 *dr*, determined by integration of the crude mixture by $^{1}$H NMR). These results were encouraging as they agreed well with the results for pentanal (67% yield, 82:18 *dr*) and could be considered an improvement since there was no mention of % conversion or recovery of unreacted **26** in the publication by Malacria. TLC analysis and chromatography attempts demonstrated that aldehyde oligomerization products and alcohol products were challenging to separate. Therefore, chromatography of the crude oil was routinely performed immediately following work up. It was not clear whether oligomerization was occurring during prolonged standing of the crude oil or during silica gel chromatography.

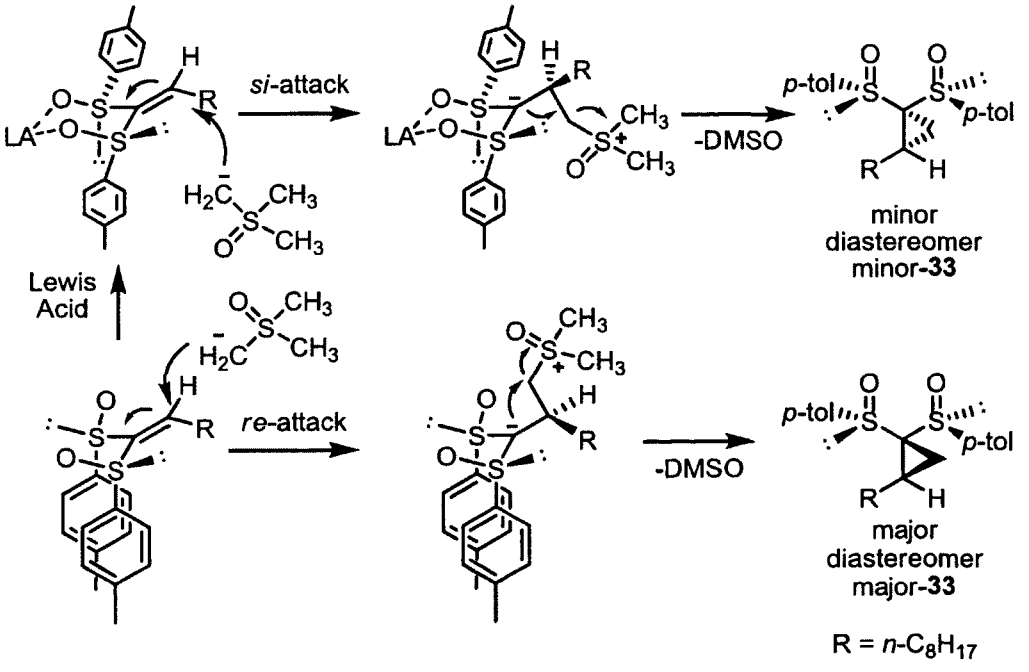
Upon optimization of the previous reaction, a mild, neutral dehydration was performed but provided inconsistent yield. It was speculated that this was a result of the variability in the previous reaction. The initial set of reaction conditions call for morpho-

CDI and catalytic $CuCl_2$ in MeCN at 70 °C for 3-5 hours. It was discovered that this reaction can be carried out at room temperature since formation of the morpholine-derived urea (insoluble in the reaction condition) was observed at this temperature after 15 minutes. The reported literature uses 2-3 equivalents of morphi-CDI. To save on experimental costs, 1.2 equivalents were routinely used while being stirred overnight with no noticeable depreciation of yield. The reaction mixture is then diluted in $CH_2Cl_2$ and filtered through a short pad of Celite® (to remove urea by-product) on top of a short pad on silica (to remove unreacted morpho-CDI). This simple procedure was the preferred method of semi-purification to afford a light blue-green coloured oil (presumably **29** complexed to $Cu^{2+}$) since the desired compound was found to be unstable to chromatography (silica gel and neutral alumina) and inaccessible by recrystallization (low as -80 °C; $CH_2Cl_2$, hexane, 1:1 $CH_2Cl_2$/hexane). It is important to note that a blue-green to green coloured oil was consistently obtained on 8 mmol scale in this reaction (yet colourless on approximately 1 mmol scale) and therefore may have affected the diastereoselectivity of the following reaction. The authors that demonstrated this method claimed recently[58] to have obtained a white solid for every product formed using this method. The fate of this copper impurity remains undetermined; however, a detailed procedure would be beneficial to ensure reproducibility.

In 2008, Marek described a diastereoselective Corey-Chaykovsky cyclopropanation of alkylidene 1,1-bis-sulfoxides. Diastereomeric ratios obtained range from 90:10-98:2 (92:8 dr for R = *n*-$C_{10}H_{21}$, the most similar substrate to our target) favouring *re*-attack of Corey's ylide as depicted in a stereoselectivity model (Scheme 27) based off a model proposed by Podlech and Klopper.[59] The diastereomeric mixture was

separable by chromatography while absolute configuration of the major diastereomer was determined by X-ray crystallographic analysis.

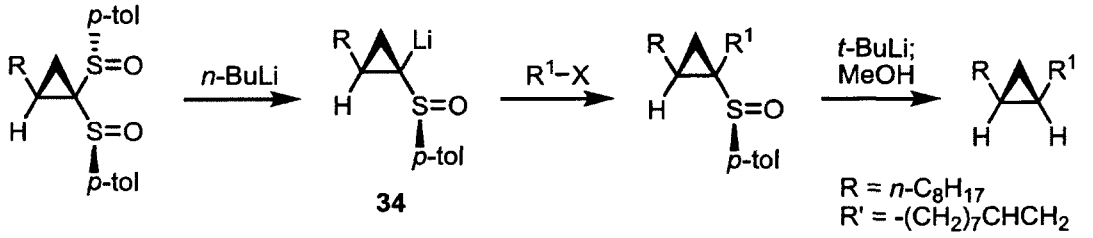
Initial repetition of the described protocol at 50 mg scale produced low yields and complex mixtures of unidentifiable products. All attempts at reproducing this reaction up to 250 mg of alkylidene **29** consistently resulted in these low yields (<20%) after chromatography. Many adjustments including using reagents and solvents with varying purity and source were performed on this scale in attempts to optimize yield without any success. Upon scaling the experiment to 1 g, an increase in yield (55-60%) and diastereoselectivity (88:12) were found comparable to literature precedent. The mixture of diastereomers **33** obtained in this reaction was separable on gram-scale only using PhMe and EtOAc as the solvent system.




**Scheme 27: Dual stereoselection model for Corey-Chaykovsky cyclopropanation of alkylidene 1,1-bis(sulfoxides)**

### 3.3.4 Preparation of Alkene 41 by Sequential C-S bond Cleavages

Marek and co-workers have developed a regioselective C-S bond cleavage / alkylation sequence en route to *cis*-substituted cyclopropanes (Scheme 28). It has been proposed that C-S bond cleavage is favoured to occur in a *cis*- relationship to the substituent R due to a release of steric interaction surrounding the cyclopropane ring. Nevertheless, this method gives us access to a pseudosymmetrical cyclopropane motif otherwise quite challenging to construct using asymmetric catalysis.




**Scheme 28: Marek's methodology for the preparation of diastereoselectively pure cyclopropanes**

We anticipated a number of challenges associated with this reaction such as the formation of a large number of side products with similar properties which could complicate chromatographic separation and NMR analysis. Marek noted the importance of using 3 equivalents of *n*-BuLi since the initial of C-S bond cleavage, butyl *p*-tolylsulfoxide (**35**), can be deprotonated by the desired nucleophilic partner **34**. Excess alkyllithium indeed generates a lithium anion of **35** producing a competitive alkylating agent in the reaction mixture. For this reason, 5 equivalents of electrophile are used to ensure complete alkylation. A number of compounds have been isolated from reaction mixture (Figure 8) such as alkylated sulfoxide **36** and **37**, diene **38**, and toluene. These products can be rationalized because **36** is more acidic than **35** leading to the formation of

dialkylated sulfoxide **37**. Meanwhile, diene **38** is a result of elimination of the alkyl iodide. Additionally, we speculate the existence of of non-aromatic sulfoxides **39** and **40** based on spectroscopic evidence resulting from displacement of aryllithium illustrates the complexity of this methodology. All sulfoxide-containing compounds were found to have similar $R_f$ values in a number of solvent mixtures complicating chromatography.

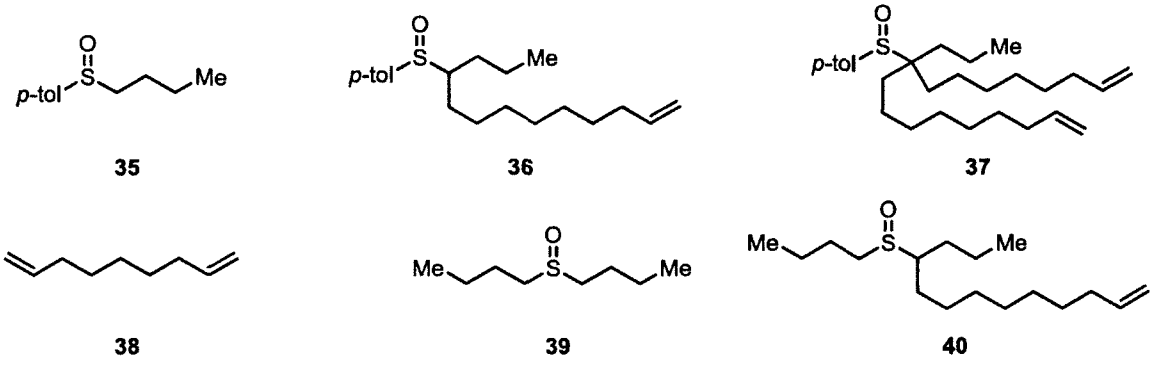



**Figure 8: Speculated side-products in Marek's regioselective C-S bond cleavage methodology**

At this point, we were uncertain of two issues: the regioselectivity of the reaction and the plausibility of clean purification. To overcome these challenges, exhaustive chromatographic separation and NMR analysis of all isolated and semi-purified compounds. The similarity of NMR spectra of by-products containing an *n*-butyl chain (derived from *n*-BuLi) and an *n*-octyl group proved too difficult for elucidation especially since it was clear that not one fraction of interest contained a single compound. Performing the experiment with the corresponding *iso*-propyl cyclopropane provided us with insight into the reaction. We observed a simplified NMR spectrum of the crude oil, as well as, semi-purified mixtures since the *iso*-propyl group was much more distinguishable than the *n*-octyl group by $^1$H NMR due to the characteristic splitting

pattern of the *iso*-propyl group. Finally, 2D NMR analysis of the major product and cleavage of its remaining C-S bond confirmed the *cis*-relationship in the cyclopropane ring. Successful purification of this compound was also used to determine the order of elution by chromatography. To our delight, purification of cyclopropyl sulfoxide **33** was achieved; however, multiple iterations were necessary to ensure high purity. With these insights in hand, yields of 72-75% were obtained compared to a 65% yield obtained by Marek and co-workers for similar compounds.

Cleavage of the remaining C-S bond was performed using *t*-BuLi and was found to produce higher yields when 3 equivalents of *t*-BuLi were used. Yields as high as 81% were obtained when typically yields of 50-60% were obtained with two equivalents of *t*-BuLi (compared to 80-82% obtained by the Marek and co-workers for similar substrates.)

### 3.3.5 Attempted Oxidative Cleavage of Alkene 41

With the fatty alkene (1*S*,2*R*)-1-(non-8-enyl)-2-octylcyclopropane (**41**) in hand, our remaining goal was to achieve a mild one-step oxidative cleavage to the carboxylic acid. While a one-step cleavage was ultimately possible, a number of multistep sequences were evaluated (Table 2). Attempts were first made to perform an $OsO_4$ catalyzed oxidative cleavage developed by Borhan using Oxone® as the oxidant.[60] Subjecting **41** to these conditions (Entry 1) gave no reaction due to low solubility while the reaction provided in high yields linear alkenes such as 1-dodecene and 1-octadecene (Entry 7). We then demonstrated that a similar alkene, octadecene, can be easily oxidized to the corresponding carboxylic acid (Entries 2 and 3) and hypothesized that the challenging step was the conversion of the intermediate diol to the aldehyde containing one less

carbon atom. A number of conditions were screened using a $C_{18}$ diol readily available in one-step in high yield (Entry 4). We ultimately abandoned this approach since our most promising conditions (Entries 5 and 6) proved unsuccessful.

**Table 2: Conditions screened for the oxidative cleavage of alkene 41**

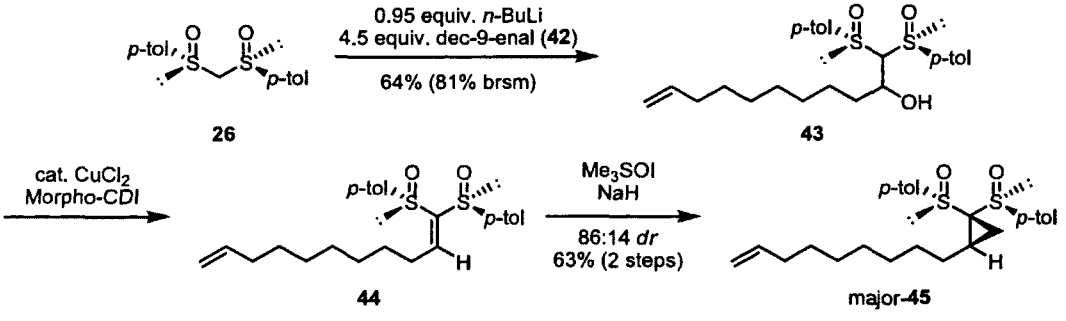
| Entry | Substrate | Conditions | Desired Product | % Yield | Comment |
|---|---|---|---|---|---|
| 1 | **41** | 1 mol% $K_2OsO_4.2H_2O$, Oxone®, DMF, rt | *ent*-**1** | - | Low solubility |
| 2 | octadecanal | PDC, DMF, rt | octadecanoic acid | 93 | - |
| 3 | octadecanal | Oxone®, DMF, *t*-BuOH | octadecanoic acid | 96 | - |
| 4 | 1-octadecene | 1 mol % $K_2OsO_4.2H_2O$, $K_3Fe(CN)_6$, $K_2CO_3$, *t*-BuOH, $H_2O$, rt | $C_{18}$ diol | 90 | - |
| 5 | *n*-$C_{18}$ diol | $NaIO_4$, $NaHCO_3$, $CH_2Cl_2$, $H_2O$ | octadecanal | - | Low solubility |
| 6 | *n*-$C_{18}$ diol | 5 equiv. $PhI(OAc)_2$, 0.01 M $CH_2Cl_2$, reflux | octadecanal | - | Low solubility |
| 7 | 1-octadecene | 1 mol% $K_2OsO_4.2H_2O$, Oxone®, DMF, *t*-BuOH rt | octadecanoic acid | 94 | - |
| 8 | **41** | 1 mol% $K_2OsO_4.2H_2O$, Oxone®, DMF, *t*-BuOH rt | *ent*-**1** | 32 | 63% brsm |
| 9 | **41** | *n*-$C_{16}H_{33}P(Bu)_3Br$, $KMnO_4$, $H_2O$, rt | *ent*-**1** | 84 | 5% oxidative chain shortening |
| 10 | **41** | $O_3$, NaOH, MeOH, $CH_2Cl_2$ (high dilution) | *ent*-**2** | 86 | - |

None of the oxidative conditions were without any drawbacks. High yields were obtained upon re-examination oxidative cleavage of octadecene with Borhan's conditions using *t*-BuOH as a co-solvent (Entry 7); however, subjection of **41** gave low conversions and yields. Dihydrosterculic acid (**1**) was obtained in 84% yield by a modified $KMnO_4$-mediated oxidative cleavage in aqueous media with a quaternary phosphonium salt

present as a phase-transfer catalyst.[61] Known overoxidation of products arising from further oxidative cleavage of the carboxylic acid in its enol form was deemed problematic. We anticipated these mixtures to be inseparable by chromatography leading to inaccurate optical rotation measurements. Ultimately, alternative methods such as ozonolysis were explored.

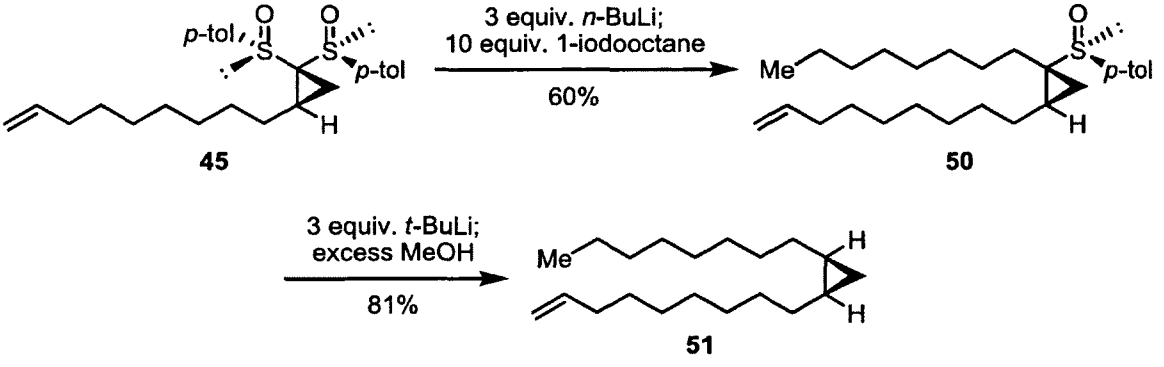
### 3.3.6 Successful Synthesis of (9*R*,10*S*)-Dihydrosterculic Acid (1)

We had sought to prepare the stereoisomer that naturally occurs in *Litchi chinsensis* once we had demonstrated that our synthetic route was viable on a model substrate. The synthesis of **1** begins with the $C_2$-symmetrical chiral auxiliary **26** and readily available 9-decen-1-al (**42**, from commercially available 9-decen-1-ol). We made cyclopropyl bis-sulfoxide 45 in a three step sequence previously described in the previous sub-sections (Scheme 29). Alkylation was achieved using 6 equivalents of **42** in 64% combined yield as a mixture of diastereomeric alcohols **43** and trace amounts of dehydrated adduct **44**. Upon removal of excess aldehyde, our mixture was subjected to a mild dehydration followed by a diastereoselective Corey-Chaykovsky cyclopropanation to give a separable mixture of **45** in 56% yield of major-**45** over 2 steps (86:14 *dr*).




**Scheme 29: Manthorpe enantioselective synthesis of cyclopropyl bis-sulfoxide 45**

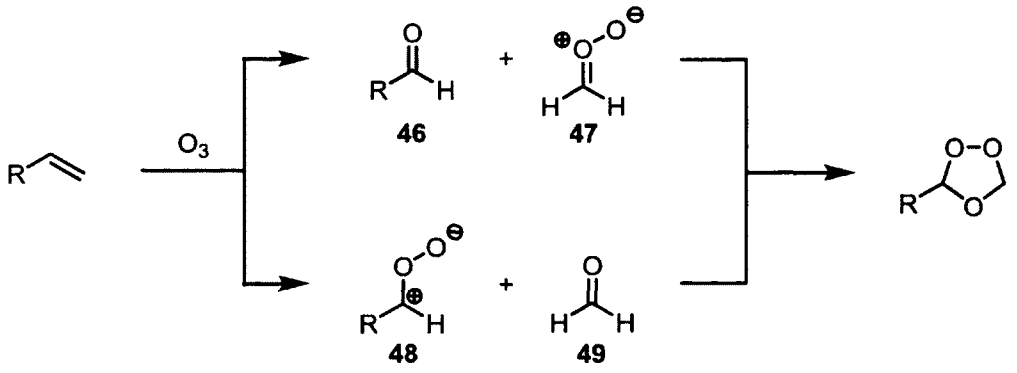
With cyclopropyl bis-sulfoxide **45** in hand, we obtained sulfoxide **46** in 73% yield following Marek's regioselective C-S bond cleavage/alkylation sequence using 10 equivalents of 1-iodooctane. The remaining cyclopropyl carbon-S bond was cleaved to alkene **47** in 84% yield.



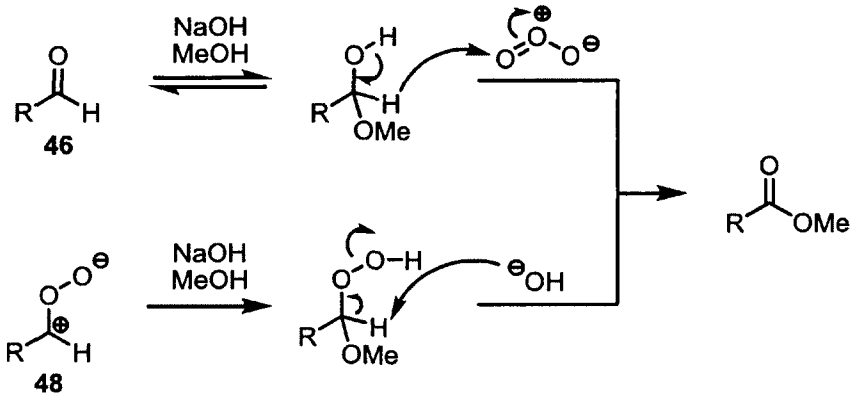

45 50 51

**Scheme 30: Synthesis of alkene 51 from cyclopropyl bis-sulfoxide 45**

For the completion of the synthesis, we performed an oxidative cleavage of the alkene to give the methyl ester, as we required a larger quantity of methyl ester **2** than acid **1** for the determination of optical rotation. In a typical ozonolysis, ozone and alkene undergo a series of 1,3-dipolar cycloadditions and reversions to generate a relatively stable 1,2,4-trioxalane. The intermediates of the cycloreversion event consist of aldehydes **46** and **49** and carbonyl oxides **47** and **48** (Scheme 31). In Marshall's conditions for ozonolytic cleavage, these intermediates are trapped as a hemiacetal and peroxyacetal, respectively, en route to a methyl ester (Scheme 32). For us, alkene **51** proceeded in high yield (92%) but a lower concentration of alkene in $CH_2Cl_2$ was needed to overcome low solubility.



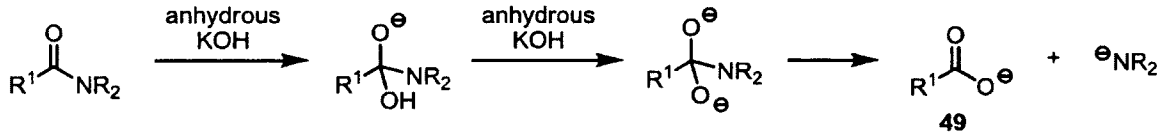

**Scheme 31: Formation of 1,2,4-trioxalanes via ozonolysis of alkenes**



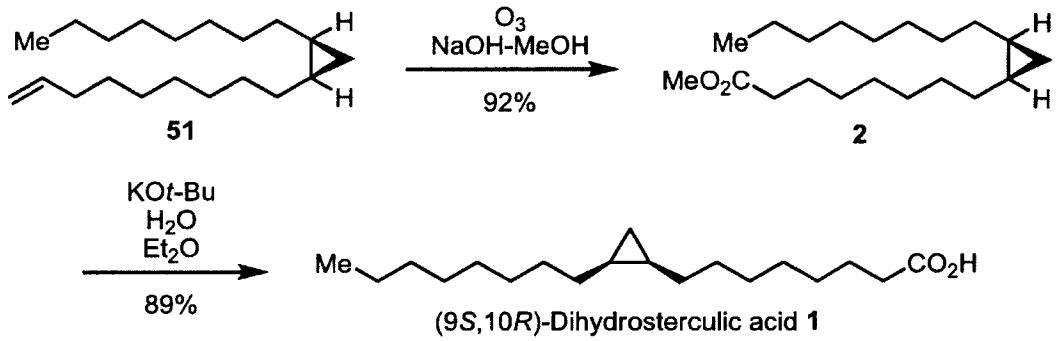

**Scheme 32: Mechanism for the formation of methyl esters via Marshall ozonolysis**

The final step in this synthesis is a hydrolysis of methyl dihydrosterculate (**2**). We anticipated this step might be challenging to obtain high yields and full conversion since reported hydrolyses of this compound have been low (51%[35] and 55%[38]). We turned our attention to conditions developed by Gassman for the hydrolysis of amides. In these conditions, typically 6 equivalents of KO*t*-Bu and two equivalents of $H_2O$ are used to generate 2 equivalents of anhydrous KOH. The second equivalent of KOH generates a highly reactive dianionic tetrahedral intermediate with collapses to form a carboxylate **49**

and potassium amide (Scheme 33). Gratifyingly, high yields of (9*R*,10*S*)-dihydrosterculic acid (**1**) was obtained using Gassman's conditions for the hydrolysis of **2** (Scheme 34).




**Scheme 33: Mechanism for the hydrolysis of amides using Gassman's conditions**




**Scheme 34: Completion of synthesis**

With enantioenriched methyl dihydrosterculate (**2**) in hand, we performed Tocanne's protocol for accurate determination of optical activity for long chain cyclopropane fatty esters. With this protocol we obtained optical activities with good agreement to compounds isolated from natural sources.

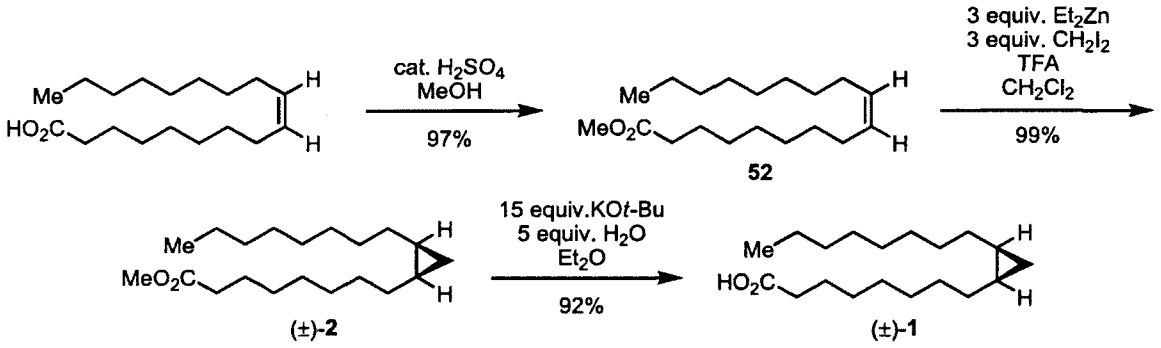
Exp. $[\alpha]^{D}_{22}$ = -13.9° (*c* = 0.467, $Et_2O$)
Lit. $[\alpha]^{D}_{21}$ = -14.8° (*c* = 0.9, $Et_2O$)[14]

Exp. $[\alpha]^{D}_{22}$ = +19.6° (*c* = 0.533, $Et_2O$)
Lit. $[\alpha]^{D}_{21}$ = +20.7° (*c* = 1, $Et_2O$)[14]

**Figure 9: Optical Activity of synthetic and naturally occuring 2 using Tocanne's protocol**

## 3.4 Synthesis of Racemic Dihydrosterculic Acid (1)

The synthesis begins with a Fischer esterification of oleic acid to give methyl oleate (**52**) in 97% yield. Cyclopropanation of the unactivated olefin was performed using a modified Simmons-Smith reaction to give (±)-**2** in 99% yield after chromatography. Finally, hydrolysis of (±)-**2** using Gassman's condition gave (±)-**1** in 92% yield on the first run as a model. We found that our conditions are of the highest yielding syntheses (88% over three steps) of racemic dihydrosterculic acid (**1**) to date.




**Scheme 35: An improved synthesis of racemic dihydrosterulic acid**

## 3.5 Summary

We report the first application of a diastereoselective Corey-Chaykovsky cyclopropanation using a $C_2$-symmetrical 1,1-bissulfoxide **26** in natural product synthesis with a synthesis of (9*R*,10*S*)-dihydrosterculic acid (**1**). This was achieved in 16.1% yield over eight steps from commercially available 9-decen-1-ol while featuring a regioselective C-S bond cleavage/ alkylation sequence to construct the cis relationship in the cyclopropane ring.

In these studies, we have improved the purification protocol for the preparation of **26** and have optimized subsequent alkylation chemistry of this auxiliary while emphasizing the difficulties encountered with the published literature. We also explored the non-ozonolytic oxidative cleavage of fatty terminal alkenes and described the challenges of optimizing this transformation. Finally, we have improved upon the current methods for hydrolysis of **2** and have applied this to the racemic and enantioselective syntheses of **1**.

Future research in this area includes the preparation of mechanistic probes using the route described herein and mechanistic studies of enzymatic $\Delta^9$ desaturation of **1**.

# 4 Chapter: Experimental

## 4.1 General Procedure

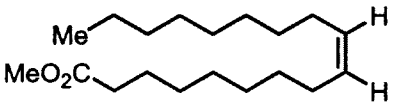
All reagents were reagent grade and purchased from Sigma-Aldrich and used as received. THF was distilled over $LiAlH_4$ prior to use. PhMe, PhH, $Et_2O$ and $CH_2Cl_2$ were distilled from $CaH_2$ prior to use. DMSO was distilled from and stored over sieves under $N_2$. All reactions involving air or moisture sensitive reagents of intermediates were performed under an inert atmosphere of $N_2$ in glassware that was flame dried or oven dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Heidolph® rotary evaporator at 40 °C (bath temperature). Thin layer chromatography was run on glass-backed Extra Hard Layer (60 Å) TLC plates purchased from Silicycle and visualized by fluorescence quenching under UV light and/or staining using $KMnO_4$. Chromatography was performed using forced flow (flash chromatography) on Silia-P Flash silica gel from Silicycle according to the method of Still,[62] unless otherwise noted.

IR spectra were recorded on a Varian 1000 Scimitar Series or an ABB Bomem MB Series spectrometer and were obtained neat on sodium chloride and reported as wavenumbers ($cm^{-1}$). $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance III 300 or Bruker AMX 400 MHz spectrometer and were obtained at the indicated field as solutions in $CDCl_3$ (stored over activated sieves) unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent (e.g., for $CDCl_3$, $\delta$ = 7.24 ppm and 77.0 ppm for $^1H$ and $^{13}C$ NMR, respectively) and are reported in parts per million (ppm, $\delta$) relative to TMS ($\delta$ = 0.00 ppm). Coupling constants ($J$) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet).

## 4.2 Synthesis of Racemic Dihydrosterculic Acid (1)

### 4.2.1 Racemic Methyl *cis*-Dihydrosterculate (2)

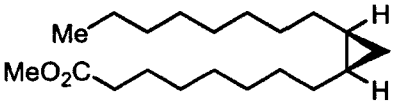
#### 4.2.1.1 Methyl Oleate (52)




A 1000 mL round-bottomed flask equipped with a reflux condenser was charged with a magnetic stir bar, oleic acid (15.00 g, 53.1 mmol, 1.0 equiv.), MeOH (150 mL) and a few drops of concentrated $H_2SO_4$. The reaction mixture was allowed to reflux for 12 hours and then cooled to room temperature. The resulting mixture was diluted with water and concentrated *in vacuo* to remove MeOH then diluted with EtOAc (250 mL). The combined organic layers were washed with $H_2O$ (3 x 100 mL) and saturated NaCl (1 x 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford **52** as a pale yellow oil (15.34 g, 97%) used without further purification.

(**52**): $R_f$ 0.66 (5% EtOAc in hexane; UV, $KMnO_4$). $^1$H NMR ($CDCl_3$, 400 MHz): δ 5.36 (m, 2H), 3.68 (s, 3H), 2.32 (t, $J$ = 7.2 Hz, 2H), 2.02 (m, 4H), 1.64 (quintet, $J$ = 7.2 Hz, 2H), 1.32-1.29 (m, 20H), 0.90 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 174.3, 130.0, 129.7, 51.4, 34.1, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.1, 27.2, 27.1, 25.0, 22.7. IR (NaCl plate, cm$^{-1}$): 3004, 2924, 2854, 1743, 1461, 1362, 1244, 1196, 1170, 1016. Spectroscopic data was in good agreement with data found in the literature.[63]

#### 4.2.1.2 Methyl (*Z*)-8-(2-octylcyclopropyl)octanoate (2)

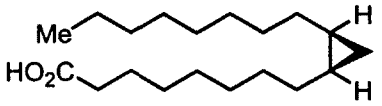



(±)

To a solution of $CH_2I_2$ (10.25 g, 38 mmol, 4.0 equiv.) in $CH_2Cl_2$ (57 mL, 1.0 M) stirred at 0 °C was added $Et_2Zn$ (19 mL, 19.0 mmol, 2.0 equiv., 1.0 M solution in hexane), and the reaction was stirred was 10 min. A solution of methyl oleate (**52**, 2.87 g, 9.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (19 mL) was added, stirred for 10 min, followed by addition of $CF_3CO_2H$ (1.08 g, 9.5 mmol, 1.0 equiv.) in $CH_2Cl_2$ (19 mL). The reaction was allowed to stir at 0 °C for 1 h. The resulting solution was quenched with cold, saturated $NH_4Cl$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were washed with saturated NaCl (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford yellow oil (3.21 g). Purification of the crude material by flash column chromatography gave (±)-**2** as a colourless oil (2.92 g, 99%).

(**2**): $R_f$ 0.70 (5% EtOAc in hexane; UV, $KMnO_4$). $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.69 (s, 3H), 2.32 (t, $J$ = 7.2 Hz, 2H), 1.64 (quintet, $J$ = 7.2 Hz, 2H), 1.39-1.14 (m, 24H), 0.90 (t, $J$ = 6.8 Hz, 3H), 0.67 (m, 2H), 0.57 (m, 1H), -0.31 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 174.3, 51.4, 34.1, 31.9, 30.2, 30.1, 29.6, 29.4, 29.3, 29.3, 29.1, 28.7, 28.6, 24.9, 22.7, 15.8, 15.7, 14.1, 10.9. IR (NaCl plate, cm$^{-1}$): 3058, 2925, 2854, 2360, 1743, 1458, 1363, 1248, 1198, 1169, 1020, 722. Spectroscopic data was in good agreement with data found in the literature.[16]

#### 4.2.1.3 Racemic Dihydrosterculic Acid (1)




(±)

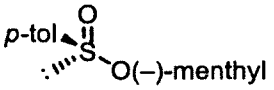
To a 25 mL round-bottomed flask charged with a magnetic stir bar, methyl dihydrosterculate ((±)-**2**, 100 mg, 0.32 mmol, 1.0 equiv.), KO*t*-Bu (532 mg, 4.74 mmol, 15 equiv.), THF (3 mL) was added 1 drop of distilled $H_2O$. This mixture was allowed to stir at room temperature. After 16 hours, the reaction mixture was quenched with saturated $NH_4Cl$ solution (3 mL) then concentrated *in vacuo* to remove THF. The resulting mixture was acidified to a pH of 1 (6 M HCl) then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude semi-solid. Purification by flash column chromatography (10% EtOAc in hexane) gave (±)-**1** as a colourless solid (87 mg, 92% yield, m.p. = 32-35 °C; Lit: m.p. = 34-37 °C).[35]

(**1**): $R_f$ 0.32 (10% EtOAc in hexane, $KMnO_4$). $^1$H NMR ($CDCl_3$, 400 MHz): δ 10.58 (broad, 1H), 2.37 (t, $J$ = 8 Hz, 2H), 1.54 (q, $J$ = 6.8 Hz, 2H), 1.39-1.24 (m, 24H), 0.90 (t, $J$ = 6.8 Hz, 3H), 0.67 (m, 2H), 0.59 (m, 1H), -0.31 (q, $J$ = 4.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 179.8, 34.0, 31.9, 30.2, 30.1, 29.6, 29.4, 29.3, 29.2, 29.1, 28.7, 28.6, 24.7, 22.7, 15.8, 15.7, 14.0, 10.9. IR (NaCl plate, $cm^{-1}$): 3058, 2989, 2925, 2675, 1711, 1465, 1413. Spectroscopic data was in good agreement with data found in the literature.[16]

## 4.3 Synthesis of $C_2$-symmetrical chiral auxiliary

### 4.3.1 (*S*,*S*)-Bis(*p*-tolylsulfinyl)methane (26)

#### 4.3.1.1 (1*R*,2*S*,5*R*)-(–)-Menthyl (*S*)-*p*-Toluenesulfinate (25)

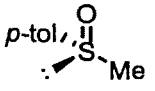



This protocol was adapted from the literature procedure reported by Sharpless.[53] Four 2000 mL round-bottomed flasks each equipped with a condenser and a magnetic stir bar were each charged with (–)-menthol (31.25 g, 0.20 mol, 1.0 equiv.), TsCl (45.76 g, 0.24 mol, 1.2 equiv.), $Et_3N$ (33.5 mL, 0.24 mol, 1.2 equiv.) and $CH_2Cl_2$ (1000 mL). $(MeO)_3P$ (35.5 mL, 0.30 mol, 1.5 equiv.) was added, and the reaction mixture was heated to reflux. After 12 h the reaction mixtures were allowed to cool to room temperature. The contents of two flasks were combined and washed with 1 M HCl (2 x 200 mL), saturated $NaHCO_3$ (200 mL) and saturated NaCl (2 x 200 mL). The contents of the remaining two flasks were combined and subjected to the same work-up procedure. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. This mixture was diluted in acetone, cooled to -20 °C and white solid was collected (four recrystallizations, 2 h at -20 °C for each crop). Concentrated HCl (five drops) was added to the remaining mother liquor in acetone and was stirred at room temperature for 15 min to epimerize the sulfinate ester. This mixture was cooled to -20 °C and a white solid was collected (eight crops). The combined white solid was diluted in THF, filtered, and concentrated *in vacuo* to remove *p*-tolyl disulfone to afford a white solid which was recrystallized from hot acetone to afford pure (–)-(*S*)-**25** as a white crystalline solid

(138.2 g, 58%, m.p.: 73-74 °C; Lit m.p. 73-74 °C).[52] This compound was routinely stored under nitrogen atmosphere at -20 °C if not used immediately.

(**25**): $R_f$ 0.32 (20% EtOAc in hexane; UV, $KMnO_4$). $[\alpha]^{22}_D$ = -198° (*c* = 2.0, acetone). [Lit.[52] $[\alpha]^{21}_D$ = -202°, (*c* = 2.0, acetone)]. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.60 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 4.14 (dt, *J* = 10.8, 4.8 Hz, 1H), 2.43 (s, 3H), 2.46-2.43 (m, 3H), 2.21 (m, 1H), 1.72-1.64 (m, 2H), 1.50 (m, 1H), 1.41 (m, 1H), 1.37-1.03 (m, 4H), 0.99-0.81 (m, 6H), 0.73 (d, *J* = 6.9 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 143.2, 142.4, 80.1, 47.9, 43.0, 34.03, 31.74, 25.2, 23.2, 22.1, 21.5, 20.9, 14.5. Spectroscopic data was in good agreement with data found in the literature.[52]

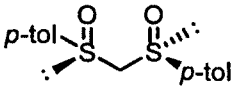
#### 4.3.1.2 (*R*)-Methyl *p*-tolyl Sulfoxide (27)




MeMgI (54.38 mL, 3.0 mol/L in $Et_2O$, 1.2 equiv.) was added dropwise to a stirring mixture of (–)-menthyl (*S*)-*p*-toluenesulfinate (**25**, 40.0 g, 136 mmol, 1 equiv.) in PhH (133 mL) at 0 °C and was allowed to stir at room temperature for 2 h followed by addition of saturated $NH_4Cl$ solution (100 mL). The organic layer was diluted with $Et_2O$ (100 mL), separated and washed with saturated sodium chloride solution (1 x 100 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to afford a colourless oil. The oil was allowed purified by flash column chromatography to give **27** colourless crystals (14.23 g, 72%, m.p. 105-106 °C; Lit: m.p. 105-107 °C).[52]

(**27**): $R_f$ 0.25 (20% EtOAc in hexane; UV). $[\alpha]^{22}_D$ = +144° (*c* = 2.0, acetone). [Lit.[52] $[\alpha]^{21}_D$ = +146° (*c* = 2.0, acetone)]. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz), 2.67 (s, 3H), 2.36 (s, 3H). Spectroscopic data obtained was in agreement with the data reported in the literature.[52]

#### 4.3.1.3 (*S*,*S*)-*p*-Tolyl-bis(*p*-tolylsulfinyl)methane (26)



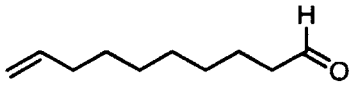

This protocol was adapter by the literature procedure reported by Reggelin.[54] *n*-Butyllithium (62.4 mL, 156 mmol, 3.3 equiv., 2.50 M in hexane, titrated prior to use.[64]) was added to a solution of HMDS (32.53 mL, 33 mmol, 3.3 equiv.) in THF (165 mL) at -78 °C. After addition, this mixture was warmed in an ice-water bath for 20 min to dissolve precipitated LiHMDS and then re-cooled to -78 °C. (*R*)-Methyl *p*-tolyl sulfoxide (**27**, 7.30 g, 47.3 mmol, 1.0 equiv., dissolved in 25 mL of THF) was added dropwise via cannula. After completion of addition, the mixtures was stirred at -20 °C for 30 min, then cooled to -78 °C. (1*R*,2*S*,5*R*)-(–)-Menthyl (*S*$_S$)-*p*-toluenesulfinate (**25**, 15.31 g, 52 mol, 1.1 equiv., dissolved in 40 mL of THF) was added dropwise via cannula and stirred for 1 h at -78 °C. At this time, 50% AcOH (40 mL) was added at -78 °C and the reaction mixture was concentrated *in vacuo* to remove THF and poured into saturated NaCl (75 mL) and EtOAc (75 mL). The aqueous was extracted with EtOAc (2 x 75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (150 mL until a pH of 8 was reached), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. This reaction mixture was purified by dilution in $Et_2O$ until a precipitate formed then an

additional 50 mL of $Et_2O$ was added. This mixture was filtered and the solid was rinsed with $Et_2O$ to afford **26** as a white solid (10.01 g, 73%, m.p. 128-130 °C, Lit. m.p. 129-131 °C).

(**26**): $R_f$ 0.32 (20% EtOAc in hexane; UV). $[\alpha]^{22}_D$ = +298.8 (*c* = 1.0, acetone). [Lit. $[\alpha]^{20}_D$ = +315, (*c* = 1.0, acetone)]. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, *J* = 8 Hz, 4H), 7.33 (d, *J* = 8 Hz, 4H), 3.99 (s, 2H), 2.42 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 142.5, 139.7, 130.4, 124.0, 84.9, 21.4. IR (NaCl plate, $cm^{-1}$): 3037, 2970, 2893, 2300, 1928, 1656, 1494, 1455, 1398, 1363, 1104, 1080, 1036, 913, 809, 711. Spectroscopic data was in good agreement with data found in the literature.[54]

### 4.3.2 (9*S*,10*R*)-Dihydrosterculic Acid (1)

#### 4.3.2.1 Dec-9-enal (42)

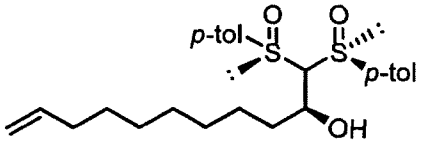



A 500 mL round-bottomed flask was equipped with a magnetic stir bar, $(COCl)_2$ (9.14 g, 72.0 mmol, 1.2 equiv.) and $CH_2Cl_2$ (150 mL) then was cooled to -78 °C under a $N_2$ atmosphere. To the resulting solution was added dropwise DMSO (10.65 mL, 150.0 mmol, 2.5 equiv.) in $CH_2Cl_2$ (50 mL) then stirred for 15 minutes. 9-Dec-en-1-ol (9.34 g, 60 mmol, 1.0 equiv.) in $CH_2Cl_2$ (100 mL) was added dropwise then was stirred for 20 min. To the resulting mixture was added $Et_3N$ (41.8 mL, 300 mmol, 5.0 equiv.) then was allowed to warmed to 0 °C over 2 h. The reaction mixture was diluted in $H_2O$ (100 mL). The organic layer was washed with 1 M HCl (3 x 100 mL) then saturated NaCl (100 mL).

The organic layer was dried over anhydrous $MgSO_4$, filtered then concentrated *in vacuo* to afford a yellow oil. The crude product was purified by flash column chromatography (20% EtOAc in hexane) to give **42** as a colourless oil (7.64 g, 83%).

(**42**): $R_f$ 0.25 (5% EtOAc in hexane, UV, $KMnO_4$). $^1H$ NMR ($CDCl_3$, 300 MHz): δ 9.78 (t, $J$ = 1.8 Hz, 1H), 5.81 (ddt, $J$ = 17.4, 10.2, 6.6 Hz, 1H), 4.97 (m, 2H), 2.43 (dt, $J$ = 1.8, 7.2 Hz, 2H), 2.05 (q, $J$ = 7.2 Hz, 2H), 1.65 (quintet, $J$ = 7.5 Hz, 2H), 1.42-1.28 (m, 6H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 203.0, 139.1, 114.2, 43.9, 33.7, 29.2, 29.1, 28.9, 28.7, 22.0. Spectroscopic data obtained was in good agreement with data found in the literature.[65]

#### 4.3.2.2 (*S*$_S$,*S*$_S$,2*S*)-1,1-Bis(*p*-tolylsulfinyl)undec-10-en-2-ol (major-43)

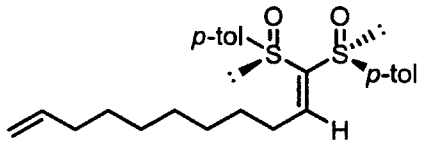



The protocol was adapted from the literature procedure reported by Malacria.[55] A 250 mL round-bottomed flask was charged with a magnetic stir bar, bis-sulfoxide **26** (2.50 g, 8.59 mol, 1.0 equiv.) and THF (36 mL) and was cooled to -78 °C. *n*-Butyllithium (3.44 mL, 8.59 mmol, 1.0 equiv., 2.50 M in hexane, titrated prior to use.[64]) was added dropwise at this temperature then the mixture was added to a -40 °C bath, stirred for 1 h, then re-cooled to -78 °C. Dec-9-enal (**42,** 6.00 g, 38.9 mmol, 4.5 equiv.) was added neat to the reaction mixture at -78 °C and stirred for 30 min followed by the addition of saturated $NH_4Cl$ solution (50 mL). This mixture was concentrated *in vacuo* to remove THF then

extracted with $CH_2Cl_2$ (2 x 50 mL). The combined organic layers were washed with saturated NaCl (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Unreacted bis-sulfoxide **26** was removed by tituration from $Et_2O$ (recovered 856 mg). The mother liquor was concentrated and semi-purified by flash column chromatography (20% EtOAc in hexane to remove unreacted aldehyde **39** then 100% EtOAc to afford a mixture of diastereomeric alcohols **43** and dehydration product **44** (2.45 g, 64% if pure **43**). This mixture was concentrate *in vacuo* used without further purification).

(**43**): $R_f$ 0.25 (20% EtOAc in hexane, UV, $KMnO_4$). $[\alpha]^{22}_D$ = +136.66 ($c$ = 0.48, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, $J$ = 8 Hz, 2H), 7.42 (d, $J$ = 8 Hz, 2H), 7.24 (d, $J$ = 8 Hz, 2H), 7.05 (d, $J$ = 8 Hz, 2H), 5.80 (ddt, $J$ = 17.4, 10.4, 6.6 Hz, 1H), 5.00 (ddd, $J$ = 17.2, 3.9, 1.6 Hz, 1H), 4.94 (ddd, $J$ = 10.0, 2.0, 1.2 Hz, 1H), 4.51 (m, 1H), 3.94 (d, $J$ = 2.0 Hz, 1H), 3.35 (d, $J$ = 0.8 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H), 2.02 (q, $J$ = 7.6 Hz, 2H), 1.86 (m, 1H), 1.70 (s, 1H), 1.41-1.09 (m, 10H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 142.2, 141.7, 139.9, 139.0, 138.5, 130.3, 130.3, 129.5, 124.6, 123.8, 114.2, 91.9, 67.0, 34.9, 33.7, 29.2, 28.9, 28.9, 28.8, 25.2, 21.5, 21.3. IR (NaCl plate, $cm^{-1}$): 3376, 3054, 2925, 2854, 1911, 1639, 1595, 1492, 1452, 1399, 1179, 1082, 1050, 909, 810, 732. Spectroscopic data was in good agreement with data found in the literature upon comparison to a structurally similar compound.[55]

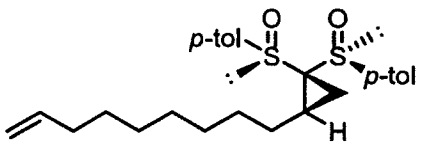
#### 4.3.2.3 ($S_S$,$S_S$)-1,1-Di-*p*-tolylsulfinyl-oct-1,10-diene (44)




This protocol was adapted from the literature procedure reported by Malacria.[55] A 250 mL round-bottomed flask was charged with the mixture of diastereomeric alcohols (**43**, 2.44 g, 5.46 mmol 1.0 equiv.), MeCN (100 mL), and Morpho-CDI (3.40 g, 8 mmol, 1.47 equiv.). To this solution, anhydrous $CuCl_2$ (107 mg, 0.8 mmol, 0.147 equiv.) was added and the mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted in $CH_2Cl_2$ and filtered through a sort pad of Celite® (to remove the urea by-product) and silica gel (to remove any excess Morpho-CDI), and concentration *in vacuo* to afford **44** as a yellow to blue-green oil (2.15 g, 92% yield if pure **44**). This oil was was used without further purification since it was unstable to silica gel flash chromatography.

(**44**): $R_f$ 0.22 (20% EtOAc, UV, $KMnO_4$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, $J$ = 8 Hz, 2H), 7.12 (m, 1H), 7.04-6.97 (m, 6H), 5.83 (ddt, $J$ = 6.8, 10.4, 17.2 Hz, 1H), 5.02 (ddd, $J$ = 17.0, 3.6, 2 Hz, 1H), 4.96 (ddd, $J$ = 10.4, 3.6, 2 Hz, 1H), 2.79 (m, 1H), 2.61 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.05 (m, 5H), 1.63-1.57 (m, 6H), 1.43-1.26 (m, 17H), 0.99 (m, 2H) . Spectroscopic data was in good agreement with data found in the literature upon comparison to a structurally similar compound.[55]

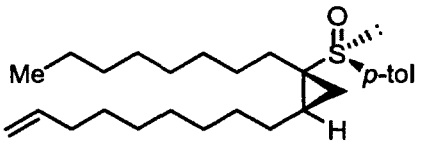
#### 4.3.2.4 ($S_S$,$S_S$,2)-1,1-Bis-p-tolylsulfinyl-2-dec-10-enylcyclopropane (major-45)




DMSO (50 mL) was cautiously added to a mixture of NaH (620 mg, 25.8 mmol, 5.14 equiv.) and $Me_3SOI$ (5.67 g, 25.8 mmol, 5.14 equiv.) (Warning! $H_2$ gas evolution!) and was stirred at room until mixture became homogeneous. To this solution was added alkylidene bis-sulfoxide (**44**, 2.15 g, 5.02 mmol, 1.0 equiv.) was stirred at room temperature for 12 h then quenched with saturated $NH_4Cl$ (50 mL). The mixture was extracted with $Et_2O$ (3 x 75 mL). The combined organic layers were washed with saturated NaCl (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (20% EtOAc in PhMe) to afford major-**45** as a colourless oil (658 mg, 54% yield over two steps).

**(major-45)**: $R_f$ 0.41 (20% EtOAc in PhMe, UV, $KMnO_4$). $[\alpha]^{22}_D$ = -113.30 (c = 0.233, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, J = 8 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 5.81 (m, J = 17.2, 10.4, 6.4 Hz, 1H), 5.02 (dd, J = 17.2, 1.6 Hz, 1H), 4.96 (dd, J = 10.4, 0.8 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H), 2.05 (q, J = 6.8 Hz, 2H), 1.80-1.62 (m, 6H), 1.40-1.25 (m, 9H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 143.14, 142.23, 139.11, 138.89, 138.43, 130.05, 129.80, 126.48, 125.19, 114.19, 62.94, 33.77, 29.62, 29.33, 29.01, 28.99, 28.88, 27.35, 25.01, 21.59, 21.45, 13.16. IR (NaCl plate, $cm^{-1}$): 3057, 2925, 2854, 1727, 1639, 1595, 1492, 1449, 1398, 1303, 1178, 1084, 1049, 907, 809, 725. Spectroscopic data was in good agreement with data found in the literature upon comparison to a structurally similar compound.[40]

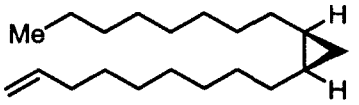
#### 4.3.2.5 ($S_S$,2)-1-Octyl-1-p-tolylsulfinyl-2-dec-10-enylcyclopropane (50)




This protocol was adapted from the literature procedure reported by Marek and co-workers.[40c] A solution of cyclopropyl bis-sulfoxide (major-**45**, 623 mg, 1.41 mmol, 1.0 equiv.) and THF (14.1 mL) was cooled to -78 °C. *n*-Butyllithium (1.69 mL, 3.0 equiv., 2.5 M in hexane, titrated prior to use.[64]) was added dropwise then stirred in a -40 °C bath for 1 h, then cooled to -78 °C. 1-Iodooctane (3.39 g, 14.1 mmol, 10.0 equiv.) was added to the reaction mixture, stirred at 0 °C for 3 h, and quenched with saturated $NH_4Cl$ solution (25 mL). Thi mixture was concentrated *in vacuo* to remove THF then extracted with $Et_2O$ (3 x 25 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (20% $Et_2O$ in hexane) to afford **50** as a colourless oil (352 mg, 60%).

**(50)**: $R_f$ 0.29 (20% $Et_2O$ in hexane). $[\alpha]^{22}_D$ = +54.21 (c = 0.2733, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, J = 8 Hz, 2H), 7.30 (d, J = 8, 2H), 5.82 (ddd, J = 17.2, 10.0, 6.8 Hz), 5.01 (ddd, J = 17.2, 3.6, 1.6 Hz), 4.98 (ddd , J = 10.0, 3.6, 1.6 Hz, 1H), 2.43 (s, 3H), 2.05 (q, J = 6.8 Hz, 2H), 1.65-1.55 (m, 3H), 1.43-1.24 (m, 25H), 0.91 (t, J = 6.8 Hz, 3H), 0.44 (t, J = 6.4 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 141.38, 139.77, 139.14, 129.47, 125.12, 114.15, 44.34, 33.78, 31.83, 29.75, 29.41, 29.37, 29.29, 29.25, 29.17, 29.01, 28.92, 28.29, 27.37, 26.15, 22.64, 21.41, 18.81, 14.68, 14.08. IR (NaCl, $cm^{-1}$): 2925, 2854, 2360, 1640, 1492, 1464. Spectroscopic data was in good agreement with data found in the literature upon comparison to a structurally similar compound.[40]

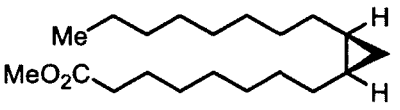
#### 4.3.2.6 (1*S*,2*R*)-1-(Non-8-enyl)-2-Octylcyclopropane (51)




This protocol was adapted from the literature procedure reported by Marek and co-workers.[40c] A 100 mL round-bottomed flask was charged with a magnetic stir bar, sulfoxide (**50**, 152 mg, 0.37 mmol, 1.0 equiv.), PhMe (7.3 mL) and was cooled to -78 °C. *t*-Butyllithium (1.09 mL, 109 mmol, 3.0 equiv. 1.0 M in pentane) was added dropwise to the mixture then was stirred for 10 min. To the resulting mixture was added MeOH (1 mL) at -78 °C, then stirred at 0 °C for 1 h. The reaction was quenched with saturated $NH_4Cl$ (10 mL) and was extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to afford a crude oil. This oil was purified by flash column chromatography (100% hexanes) to afford **51** as a colourless oil (79 mg, 81%).

(**51**): $R_f$ 0.95 (hexane, UV, $KMnO_4$). $[\alpha]^{22}_D$ = +2.545 (c = 0.3933, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 5.84 (ddt, J = 17.2, 10.0, 6.8 MHz, 1H), 5.01 (ddd, J = 17.2, 3.2, 2.0 Hz), 4.95 (ddd, J = 10.0, 3.2, 2.0 Hz, 1H), 2.06 (q, J = 6.8 Hz, 2H), 1.40-1.15 (m, 26H), 0.91 (t, J = 6.4 Hz, 3H), 0.67 (m, 2H), 0.58 (m, 1H), -0.31 (q, J = 5.2 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 139.26, 114.06, 33.82, 31.93, 30.22, 30.19, 29.69, 29.61, 29.54, 29.36, 29.16, 28.96, 28.72, 28.71, 22.69, 15.78, 14.10, 10.92. IR (state, $cm^{-1}$): 3059, 2924, 2854, 1641, 1465, 1377, 991, 909, 721. Spectroscopic data was in good agreement with data found in the literature upon comparison to a structurally similar compound.[40]

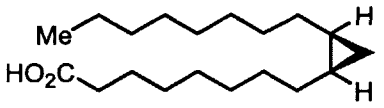
#### 4.3.2.7 Methyl 8-((1*S*,2*R*)-2-Octylcyclopropyl)Octanoate (2)




A 100 mL three-necked round-bottomed flask was equipped with an $O_3$ inlet, a glass adapter fixed with Tygon® tubing, and a glass stopper and charged with a magnetic stir bar, olefin (**51**, 75 mg, 0.27 mmol, 1.0 equiv.), NaOH (0.324 g, 8.08 mmol, 30.0 equiv.), MeOH (3 mL) and $CH_2Cl_2$ (10 mL) then the mixture was cooled to -78 °C. To the resulting mixture was bubbled $O_3$ until the reaction mixture turned a light blue colour (5 h). At this time, the reaction mixture was bubbled with $N_2$ for 10 min to remove excess $O_3$ then diluted with $H_2O$ and $Et_2O$ and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with $E_2O$ (2 x 25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a crude oil. Purification of flash column chromatography (10% $Et_2O$ in hexane) gave **2** a colourless oil (71 mg, 92% yield).

**(2):** $R_f$ 0.71 (5% EtOAc in hexane, UV, $KMnO_4$). $[\alpha]^{22}_D$ = +1.745 (c = 0.5733, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 300 MHz): δ 3.68 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 1.66-1.62 (m, 2H), 1.39-1.20 (m, 24H), 0.90 (t, J = 6.6 Hz), 0.68-0.64 (m, 2H), 0.61-0.54 (m, 1H), -0.32 (q, J = 4.8 Hz). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 174.33, 51.41, 34.13, 30.21, 30.12, 29.68, 29.44, 29.35, 29.30, 29.17, 28.72, 28.67, 24.97, 22.69, 15.77, 15.74, 14.10, 10.92. IR (NaCl plate, $cm^{-1}$): 3058, 2925, 2854, 1744, 1458. Spectroscopic data was in good agreement with data found in the literature.[14]

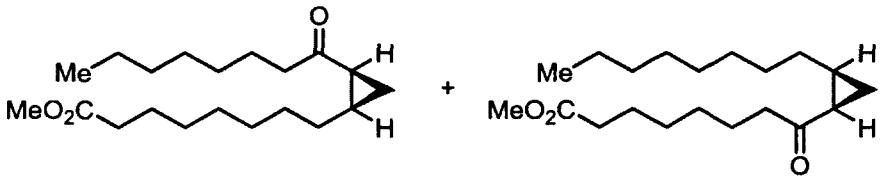
#### 4.3.2.8 (9*S*,10*R*)-Dihydrosterculic Acid (1)




To a 25 mL round-bottomed flask charged with methyl oleate (**2**, 43 mg, 0.14 mmol, 1.0 equiv.), THF (2 mL), KO*t*-Bu (229 mg, 2.1 mmol, 15 equiv.) and added one drop of $H_2O$ at room temperature. This mixture was allowed to stir for 18 hours then was quenched with saturated $NH_4Cl$ solution, acidified to a pH of 1, and extracted with hexanes (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a crude solid. This was purified by flash column chromatography to afford **1** as a white solid. (37 mg, 89% yield, m.p. 32-33 °C, Lit. m.p. 34-37 °C.)[35]

**(1)**: $R_f$ 0.3 (10% EtOAc in hexane, UV, $KMnO_4$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.37 (t, J = 7.6 Hz, 2H), 1.67 (quintet, J = 6.8 Hz, 2H), 1.39-1.15 (m, 24H), 0.90 (t, J = 6.8 Hz, 3H), 0.68-0.65 (m, 2H), 0.61-0.55 (m, 1H), -0.31 (q, J = 5.2 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 179.89, 34.02, 31.93, 30.21, 30.12, 29.68, 29.41, 29.35, 29.28, 29.07, 28.72, 28.66, 24.69, 22.69, 15.78, 15.73, 14.09, 10.92. Spectroscopic data was in good agreement with data found in the literature.[14]

### 4.3.2.9 Oxidation of Methyl (9*S*,10*R*)-Dihydrosterculate (2)




This protocol was adapter by the literature procedure reported by Buist.[14] A solution of $CrO_3$ (124 mg, 1.25 mmol) in glacial acetic acid (2.8 mL) containing 3% water was added to a solution of methyl dihydrosterculate (**2**, 58 mg) in $CCl_4$ (0.5 mL). This mixture was allowed to stir for 96 h at rt followed by addition of MeOH. The reaction mixture was diluted with hexane (10 mL), sequentially washed with ice-cold $H_2O$ (10 mL), saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give a crude oil. This oil was purified by flash column chromatography (1:10 $Et_2O$:hexane) to afford recovered starting material (14 mg), the 11-keto derivative (7 mg, 12% yield) and the 8-keto derivative **52** (8 mg, 13% yield).

**Methyl (*Z*)-8-(2-octylcyclopropyl)-8-oxooctanoate (53):** $R_f$ 0.16 (10% $Et_2O$ in hexane, UV, $KMnO_4$). $[\alpha]^{22}_D$ = -13.9 (c = 0.467, $Et_2O$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.65 (s, 3H), 2.54 (t, J = 7.4 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 2.01 (m, 1H), 1.62 (m, 4H), 1.52-1.14 (m, 19H), 0.88 (t, J = 6.8 Hz, 3H). Spectroscopic data was in good agreement with the data found in the literature.[16]

**Methyl (*Z*)-8-(2-octanoylcyclopropyl)octanoate (54):** $R_f$ 0.19 (10% $Et_2O$ in hexane, UV, $KMnO_4$). $[\alpha]^{22}_D$ = +19.6 (c = 0.533, $Et_2O$). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.66 (s, 3H), 2.54 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 2.03-1.99 (m, 1H), 1.63-1.61 (m, 4H), 1.52-1.14 (m, 19H), 0.88 (t, J = 6.8 Hz, 3H). Spectroscopic data was in good agreement with the data found in the literature.[14]

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