STUDIES ON TOTAL SYNTHESIS OF BIOACTIVE NATURAL PRODUCTS CHAETOMELLIC ACID A, 1,7(*Z*)-NONADECADIENE-2,3-DICARBOXYLIC ACID, 2-(*β*-CARBOXYETHYL)-3-OCTYLMALEIC ANHYDRIDE, 2-CARBOXYMETHYL-3-HEXYLMALEIC ANHYDRIDE, NOSTOCLIDE I, SARKOMYCIN, HOMOSARKOMYCIN, SECOCRISPIOLIDE, MITOMYCIN K AND MITOMYCIN C

THESIS
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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Studies on Total Synthesis of Bioactive Natural Products Chaetomellic acid A, 1,7(Z)-Nonadecadiene-2,3-dicarboxylic acid, 2-(β-Carboxyethyl)-3-octylmaleic anhydride, 2-Carboxymethyl-3-hexylmaleic anhydride, Nostoclide I, Sarkomycin, Homosarkomycin, Secocrispiolide, Mitomycin K and Mitomycin C***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Anirban Kar*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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Title of the Thesis: "***Studies on Total Synthesis of Bioactive Natural Products Chaetomellic acid A, 1,7(Z)-Nonadecadiene-2,3-dicarboxylic acid, 2-(β-Carboxyethyl)-3-octylmaleic anhydride, 2-Carboxymethyl-3-hexylmaleic anhydride, Nostoclide I, Sarkomycin, Homosarkomycin, Secocrispiolide, Mitomycin K and Mitomycin C***"
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Abstract

The present dissertation is divided into three chapters. The first chapter reports a concise account on the S_N2' Grignard coupling reactions. The second chapter describes in detail our contribution towards the synthesis of rasfernesyl-protein transferase inhibitor chaetomellic acid A, 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid, 2-(*β*-carboxyethyl)-3-octylmaleic anhydride, 2-carboxymethyl-3-hexylmaleic anhydride, cytotoxic nostoclide I, anitumor sarkomycin, maculalactones A-C and antibiotic rubrolides (Figure 1) as well as our studies on NBS induced *Z*- to *E*-alkene isomerization and benzylic bromination of aromatic amines using molecular bromine. This chapter also describes our studies on synthesis of bioactive natural products secocrispiolide, mitomycin K and mitomycin C. The third chapter presents spectra of some important compounds synthesized.

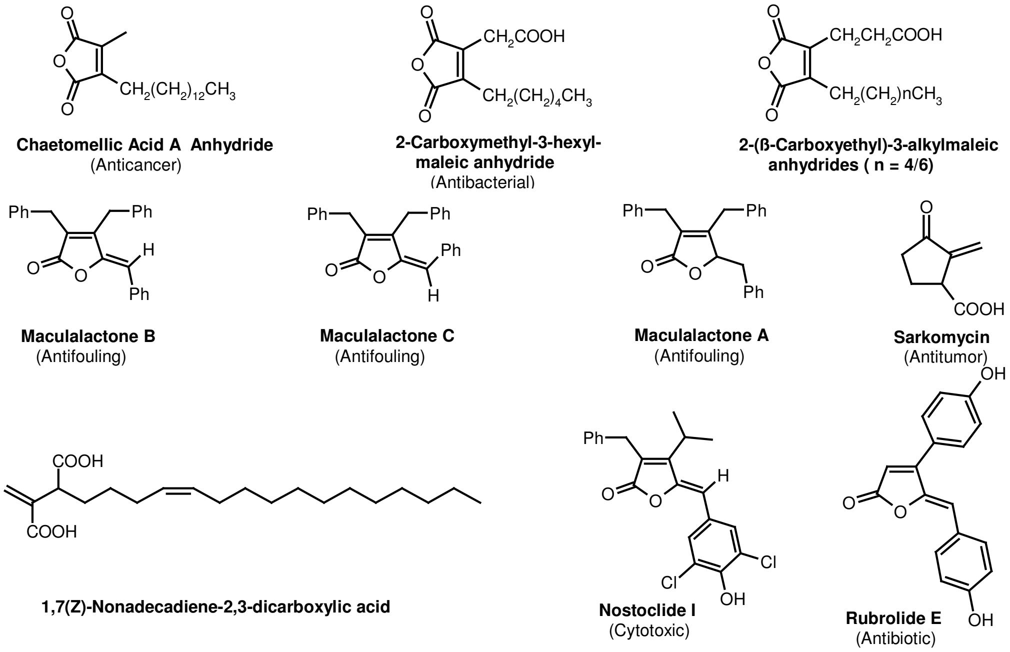


Figure 1: Natural products synthesized

CHAPTER ONE: S_N2' Grignard Coupling Reactions in Organic Synthesis

The great value of the Grignard reaction to the synthetic chemist is its generality as a building block for an impressive range of structures and functional groups. Starting from the discovery of this reaction, in less than 100 years the chemical literature contains tens of thousands of references of this reaction. This chapter portrays a concise account on S_N2' Grignard coupling reactions, factors affecting the product distribution and their applications in synthetic organic chemistry.

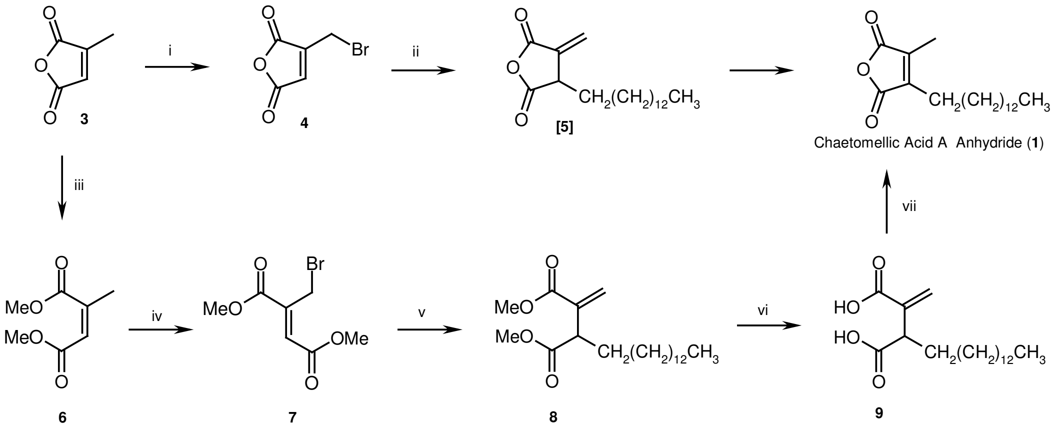
CHAPTER TWO: Synthesis of Natural and Unnatural Disubstituted Maleic Anhydrides and Bioactive Natural Products

This chapter is divided into four sections. The first section presents a facile synthesis of naturally occurring chaetomellic acid A and 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid and also studies on NBS induced *Z*- to *E*-alkene isomerization. The second section describes efficient syntheses of natural products 2-(β-carboxyethyl)-3-octylmaleic anhydride, 2-carboxymethyl-3-hexylmaleic anhydride, maculalactones A-C and nostoclide I. The third section summarizes an efficient synthesis of sarkomycin and rubrolide analogues, while the fourth section describes a study on benzylic bromination of aromatic amines using molecular bromine and also some studies on synthesis of bioactive natural products secocrispiolide, mitomycin K and mitomycin C.

Section A: I. A Facile Synthesis of Chaetomellic acid A

Chaetomellic acid A has been recently isolated from *Chaetomella acutiseta* and its dianionic form is a potent and highly specific inhibitor of rasfernesyl-protein transferase. Although nine total syntheses are reported in literature including three from our group, new practical synthetic approaches towards this compound is a challenging task for the organic chemist.

This section describes a facile synthesis of chaetomellic acid A (**1**) via S_N2' Grignard coupling reaction of tetradecylmagnesium bromide with dimethyl bromomethylfumarate (**7**) followed by hydrolysis of the diester to diacid accompanied by ring closure and simultaneous exocyclic to endocyclic carbon-carbon double bond isomerization with 38% overall yield in 5-steps (Scheme 1).

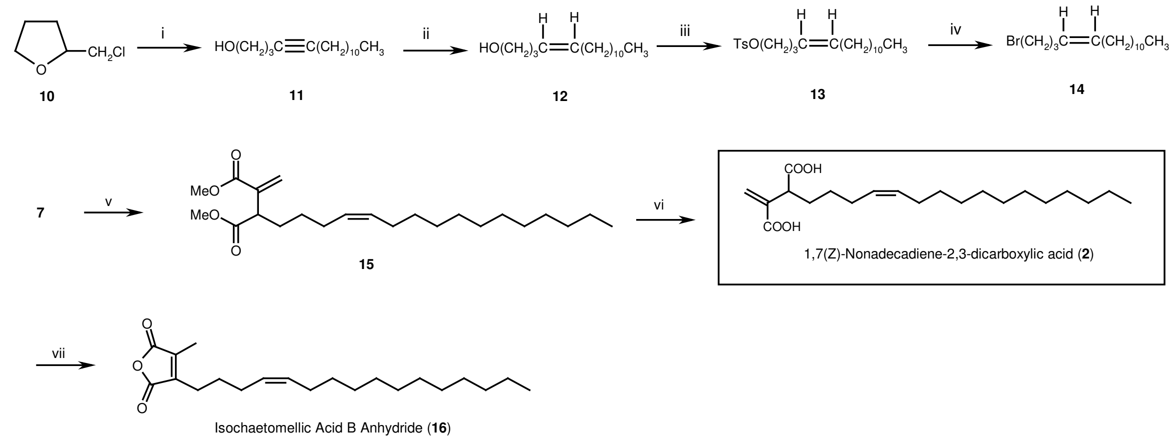


Scheme 1. *Reagents, conditions and yields*: (i) NBS, DBP, CCl_4, reflux, 8 h (55%); (ii) $C_{14}H_{29}MgBr$, Et_2O, rt, 8 h (8-10%); (iii) CH_3OH, H^+/H_2SO_4, reflux, 12 h (75%); (iv) NBS, AIBN, CCl_4, reflux, 12 h (85%); (v) $C_{14}H_{29}MgBr$, Et_2O, HMPA, rt, 8 h (60%); (vi) AcOH + HCl (7:3), reflux, 2 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

Section A: II. An Efficient Synthesis of 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic acid

This novel dicarboxylic acid (**2**) was isolated from cultures of a white-rot fungus *Ceriporiopsis subvermispora*. The compound has one chiral centre but the absolute configuration has not yet been established. The structure was confirmed by ^{1}H NMR, ^{1}H-^{1}H-COSY, ^{13}C NMR, HMQC and HMBC NMR and GC-MS data of its dimethyl ester.

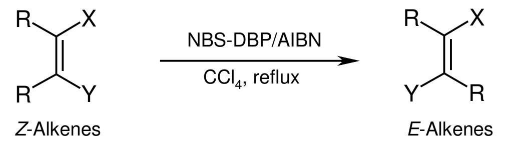
This section describes the first total synthesis of this novel dicarboxylic acid (**2**) via a chemoselective S_N2' Grignard coupling reaction with **7** and hydrolysis of the diester to obtain diacid **2** (Scheme 2). The desired (*Z*)-hexadeca-4-enyl bromide (**14**) was prepared from tetrahydrofurfuryl chloride (**10**) in four steps with 57% overall yield. The diacid **2** in refluxing acetic anhydride furnished isochaetomellic acid B anhydride (**16**) in ~100% yield.



Scheme 2. *Reagents, conditions and yields*: (i) $LiNH_2/NH_3$, $C_{11}H_{23}Br$, – 78 °C to – 33 °C to rt, 4 h (80%); (ii) H_2, Lindlar Pd, quinoline, hexane, rt, 30 min (99%); (iii) *p*-TsCl, TEA, DMAP, CH_2Cl_2, rt, 6 h (86%); (iv) LiBr, $NaHCO_3$, acetone, rt, 15 h (85%); (v) $CH_3(CH_2)_{10}CH{=}CH(CH_2)_3MgBr$, Et_2O, HMPA, rt, 8 h (62%); (vi) LiOH, THF + H_2O (2:1), rt, 18 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

Section A: III. *N*-Bromosuccinimide-Dibenzoyl Peroxide/Azobisisobutyronitrile: A Reagent for *Z*- to *E*-Alkene Isomerization

This section describes studies on the NBS-DBP/AIBN induced *Z*- to *E*-carbon-carbon double bond isomerization of olefins having variety of substituents (Scheme 3).



R = H, CO_2H, CO_2Me; X/Y = H, Me, Alkyl, CH_2Br, $CHBr_2$, Ph, Aryl, CO_2Me, CONHAr

Scheme 3

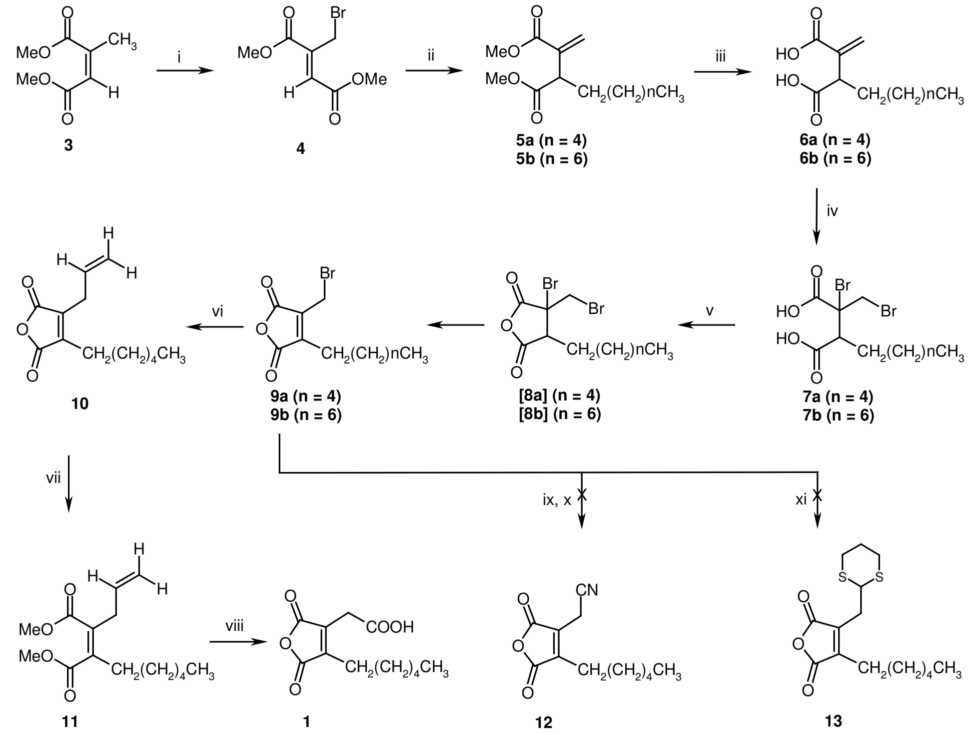
Section A: IV. Experimental

This section presents the detailed experimental procedures including tabulated spectral and analytical data for compounds synthesized in Section A.

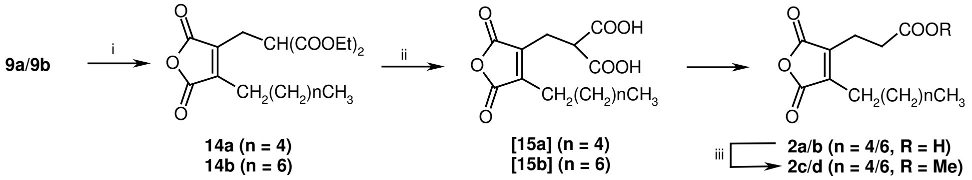
Section B: I. A Facile Access to Natural and Unnatural Disubstituted Maleic Anhydrides

During the past decade several structurally interesting compounds with dialkylsubstituted maleic anhydride moieties have been isolated as bioactive natural products and synthesized in view of their promising bioactivities. The 2-carboxymethyl-3-hexylmaleic anhydride (**1**) has been isolated as a novel metabolite from the *Aspergillus* FH-X-213 from an apple. In 1994, Soda *et al* reported the biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacica* A-1419, to produce two new maleic anhydride derivatives 2-(β-carboxyethyl)-3-hexylmaleic anhydride (**2a**) and 2-(β-carboxyethyl)-3-octylmaleic anhydride (**2b**). Recently Baldwin *et al* have reported the first synthesis of these novel natural products using versatile copper-mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate.

This section describes a facile new route to these natural products via the potential building blocks 2-bromomethyl-3-alkylmaleic anhydrides **9a/b**. These compounds **9a/b** were synthesized starting from dimethyl citraconate (**3**) via NBS-bromination, S_N2' Grignard coupling reactions, hydrolysis, molecular bromine addition and dehydrative ring closure reaction pathway with 49-51% overall yield in 5-steps. Chemoselective allylic substitution of bromoatom in **9a** with Grignard reagents gave the unsymmetrical maleic anhydride **10** in 55% yield. The naturally occurring 2-carboxymethyl-3-hexylmaleic anhydride (**1**) was synthesized from **10** via esterification, ozonolysis and oxidation route. The synthesis of two naturally occurring 2-(β-carboxyethyl)-3-alkylmaleic anhydrides **2a/b** have been completed via a chemoselective diethylmalonate coupling reaction followed by acid induced hydrolysis (Scheme 4 & 5).



Scheme 4. *Reagents, conditions and yields:* (i) NBS (1.5 equiv.), AIBN, CCl_4, reflux, 12 h (85%); (ii) $CH_3(CH_2)_nCH_2MgBr$ (1.5 equiv., n = 4/6), Et_2O, HMPA, – 20 ºC, 0.5 h (64-65%); (iii) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h (90-92%); (iv) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (v) Ac_2O, reflux, 1.5 h (~100%); (vi) C_2H_3MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, – 5 to 0 ºC (55%); (vii) CH_2N_2, Et_2O, 0 ºC, 3 h (95%); (viii) O_3, $(CH_3)_2CO$, – 78 ºC, 3 min then $Na_2Cr_2O_7.H_2O$, H_2SO_4, H_2O, Et_2O, 0 ºC, 3 h then 1 M aq. NaOH then 1 M aq. HCl, (42%); (ix) NaCN (1.1 equiv.), MeOH, rt, 2 h (0%); (x) CuCN (5 equiv.), MeOH, reflux, 8 h (0%); (xi) 1,3-dithiane (1.1 equiv.), *n*-BuLi (1.2 equiv.), THF, HMPA, 6 h (0%).

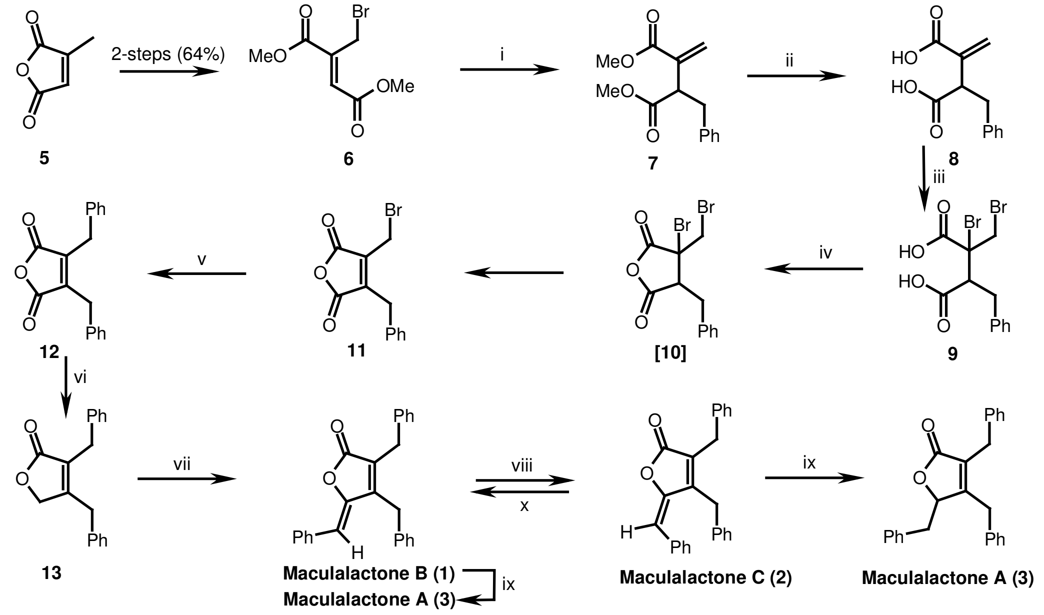


Scheme 5. *Reagents, conditions and yields*: (i) (a) Diethyl malonate (1.1 equiv.), NaH (1.1 equiv.), C_6H_6, rt, 8 h, (b) H^+/HCl (72-74%); (ii) AcOH + HCl (1:1), reflux, 12 h (95-96%); (iii) CH_2N_2, Et_2O, 0 ºC, 3 h (95%).

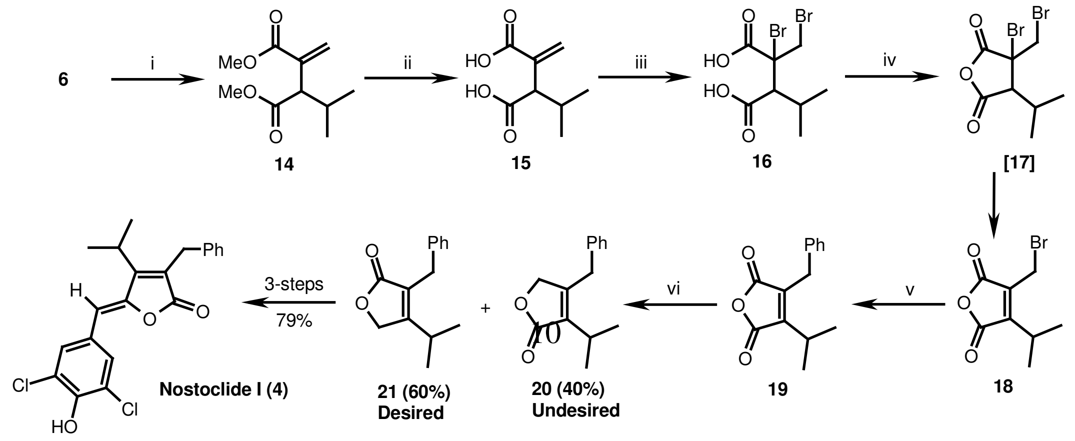
Section B: II. Synthesis of Naturally Occurring Bioactive Butyrolactones: Maculalactones A-C and Nostoclide I

Maculalactones A-C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity. The natural (+)-maculalactone A has been assigned *S*-configuration. Till date only one synthesis of these butyrolactones **1**-**3** has been reported in the literature. Nostoclide I (**4**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and possesses cytotoxic activity. Till date two syntheses of **4** are known in the literature.

This section describes a simple multistep (9 to 10 steps) synthesis of naturally occurring butyrolactones maculalactone A (**3**), maculalactone B (**1**) maculalactone C (**2**) and nostoclide I (**4**) starting from citraconic anhydride (**5)** with good overall yields via dibenzylmaleic anhydride (**12**) and benzylisopropylmaleic anhydride (**19**). The two anhydrides **12** and **19** were prepared by S_N2' coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**6**), LiOH-induced hydrolysis of esters to acids, bromination of carbon-carbon double bond, in situ dehydration followed by dehydrobromination and chemoselective allylic substitution of bromoatom in disubstituted anhydrides **11** and **18** with appropriate Grignard reagents. The $NaBH_4$ reduction of these



Scheme 6. *Reagents, conditions and yields:* (i) $PhCH_2MgBr$ (1.5 equiv.), THF, HMPA, – 20 ºC, 0.5 h (70%); (ii) (a) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) C_6H_5MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, – 5 to 0 ºC (45%); (vi) $NaBH_4$ (2.5 equiv.), THF, 0 ºC, 2 h (91%); (vii) Piperidine (0.7 equiv.), PhCHO (1 equiv.), MeOH, rt, 16 h (77%); (viii) $CHCl_3$, rt, 8 days (50%); (ix) H_2, Pd/C, EtOAc, 12 h (75%); (x) Δ, 200 ºC, 3 h (100%).



anhydrides **12** and **19** furnished the desired lactones **13** and **21** respectively. The lactone **13** on Knoevenagel condensation with benzaldehyde furnished maculalactone B (**1**), which on carbon-carbon double bond isomerization gave maculalactone C (**2**), while **1** on selective catalytic hydrogenation gave maculalactone A (**3**) (Scheme 6 & 7). The conversion of lactone **21** to nostoclide I (**4**) is known in the literature.

Scheme 7. *Reagents, conditions and yields:* (i) C_3H_7MgBr (1.5 equiv.), THF, HMPA, – 20 °C, 0.5 h (79%); (ii) (a) LiOH (10 equiv.), THF + H_2O (3:1), rt, 18 h, (b) H^+/HCl (91%); (iii) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) C_6H_5MgBr (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, – 5 to 0 °C (43%); (vi) $NaBH_4$ (2.5 equiv.), THF, 0 °C, 4 h (70%).

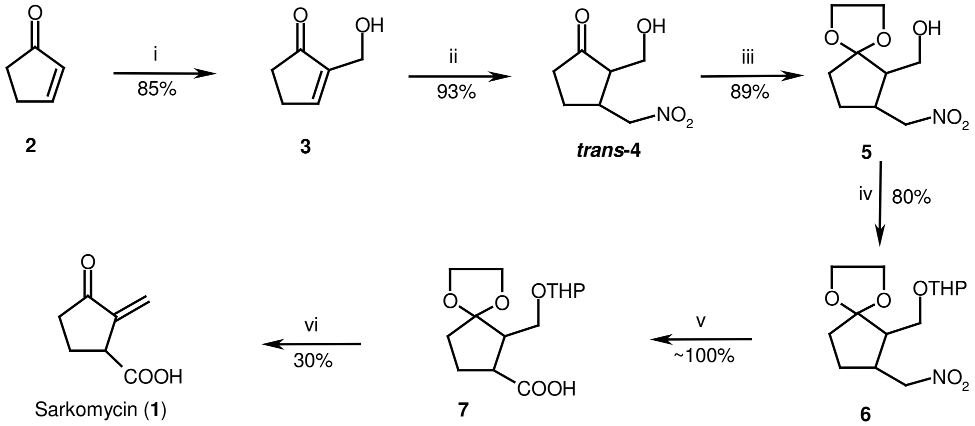
Section B: III. Experimental

This section presents the detailed experimental procedures including tabulated spectral and analytical data for compounds synthesized in Section B.

Section C: I. A Simple Synthesis of (±)-Sarkomycin

The α-methylene ketone and lactone functionalities are found to be present in a great number of compounds having anticancer properties. Simplest of those, sarkomycin (**1**), was produced by a strain of the soil microorganism *Streptomyces erythromegenes* and reported to show powerful inhibitory effect on Ehrlich ascites tumors in mice. Since its isolation in 1953 by Umezawa *et al*, several elegant synthetic routes to this rather unstable natural product, its corresponding esters and analogues have been reported in view of their promising biological activity.

This section describes a facile 6-step route to (±)-sarkomycin (**1**) with 17% overall yield via Michael addition of nitromethane to 2-hydroxymethyl-2-cyclopentenone (**3**), Oxone induced oxidative Nef reaction and acid catalyzed dehydration pathway (Scheme 8). Similarly cyclohexenone will provide an easy access to homosarkomycin.

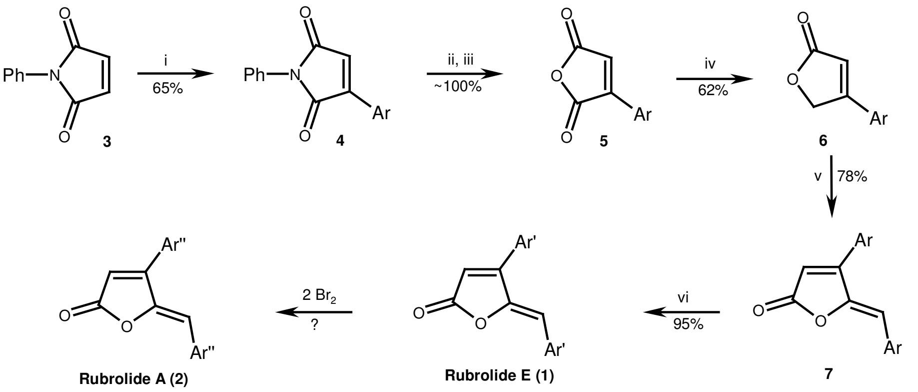


Scheme 8. *Reagents, conditions and yields*: (i) Aq. formaldehyde, imidazole (cat.), THF, rt, 17 days (85%); (ii) Nitromethane, Triton B (cat.), 65 ºC, 5 h (93%); (iii) Ethylene glycol, *p*-TSA (cat.), benzene, reflux, 12 h (89%); (iv) Dihydropyran, PPTS (cat.), CH_2Cl_2 rt, 5 h (80%); (v) (a) MeOH, 0.5 N Na_2HPO_4, 1N NaOH, Oxone, rt, 2 h, (b) H^+/HCl (~ 100%); (vi) 0.5 N HCl, rt, 10 h (30%).

Section C: II. An Efficient Synthesis of Rubrolide E and Analogues

Rubrolides are a family of biologically active marine ascidian (tunicate) metabolites which have been isolated from *Ritterella rubra* and *Synoicum blochmanni*. Rubrolides A-H are potent antibiotics and show moderate but selective inhibition of protein phosphatases 1 and 2A. On the other hand, rubrolides K, M, L and I show significant cytotoxicity against P-388 suspension culture of mouse lymphoid neoplasm, the monolayer cultures of human lung carcinoma (A-549), human colon carcinoma (HT-29) and human melanoma (MEL-28). Till date only one synthesis of each rubrolide A, D, M and N and two syntheses of rubrolide C and E are known in the literature.

This section describes an efficient synthesis of rubrolide E (**1**) starting from *N*-phenylmaleimide (**3**) via Meerwein coupling with *p*-anisyldiazonium chloride, hydrolysis to diacid, dehydrative ring closure to anhydride, regioselective reduction to lactone, Knoevenagel condensation with anisaldehyde followed by demethylation pathway with 24% overall yield in 6-steps. The selective tetrabromination of rubrolide E (**1**) to get rubrolide A (**2**) is in progress (Scheme 9).



Ar = *p*-anisyl; Ar' = *p*-hydroxyphenyl; Ar'' = 3,5-dibromo-4-hydroxyphenyl

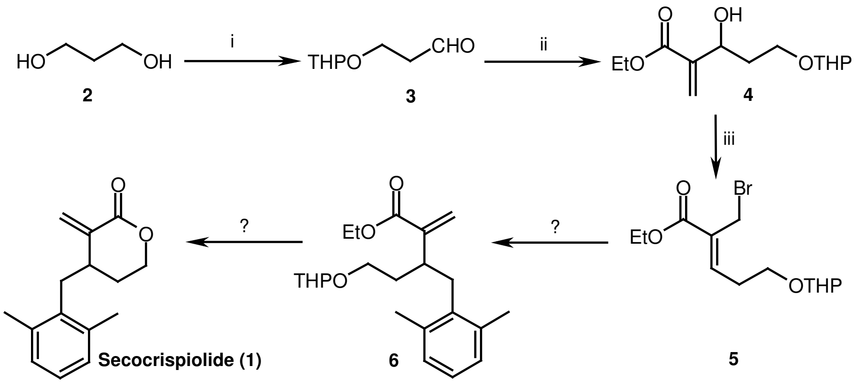
Scheme 9. *Reagents, conditions and yields*: (i) *p*-Anisyldiazonium chloride, $CuCl_2$, *p*H 3, aq. acetone 35 ºC, 24 h (65%); (ii) (a) aq. KOH, methanol, reflux, 4 h, (b) H^+/HCl; (iii) Ac_2O, reflux, 3 h (~100% over the two steps); (iv) $NaBH_4$ (2.5 equiv.), THF, 0 ºC, 2 h (62%); (v) Piperidine (0.7 equiv.), *p*-anisaldehyde (1 equiv.), MeOH, rt, 16 h (78%); (vi) BBr_3, CH_2Cl_2, -78 ºC to rt, 24 h (95%).

Section C: III. Experimental

This section presents the detailed experimental procedures including tabulated spectral and analytical data for compounds synthesized in Section C.

Section D: I. Synthetic Studies on Secocrispiolide

Secocrispiolide (**1**) was isolated from *Pulicaria crispa* in 1979. Till date only one synthesis of this novel natural product is known. This section describes the synthetic studies on secocrispiolide (**1**) by chemoselective S_N2' Grignard coupling with bromoester **5**. 1,3-Dihydroxy propane on monoprotection followed by PCC oxidation yielded the desired aldehyde **3** which was then subjected to Baylis-Hillman reaction with ethyl acrylate to give



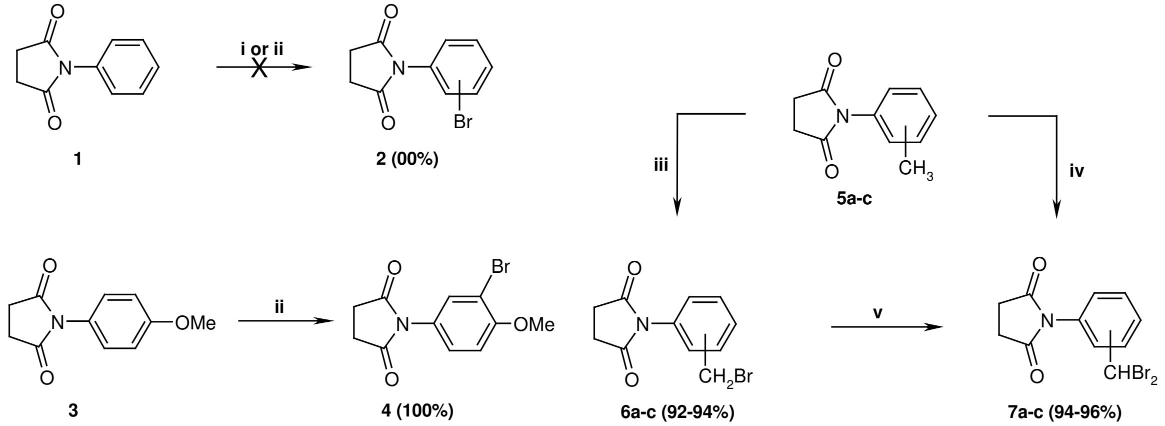
Scheme 10. *Reagents and conditions*: (i) (a) DHP (0.5 eqiv.), conc. HCl (few drops), 3 h, (45%), (b) PCC (3 equiv.), anhydrous NaOAc (10 mol%), DCM, rt, 6 h (85%); (ii) Ethyl acrylate (6 equiv.), DABCO (10 mol%), rt, 7 days (86%); (iii) NBS (1equiv.), Me_2S (1 equiv.), DCM, rt, 24 h (95%).

the ester **4** in 86% yield. The ester **5** was treated with NBS and Me_2S complex to yield the desired bromoester **5** in 96% yield (Scheme 10). We are now in search of a suitable condition for the S_N2' Grignard coupling of 2,6-dimethylbenzylmagnesium bromide with bromoester **5** to get the protected intermediate **6**, which upon deprotection will provide secocrispiolide (**1**).

Section D: II. Synthetic Studies on Benzylic Mono- and *gem*-Dibromination of Primary Aromatic Amine Derivatives Using Molecular Bromine

There is no direct method to obtain aniline derivatives, wherein the electrophilic substitutions are directed by secondary activating group on the phenyl ring and also for benzylic halogenations on aniline derivatives. During the studies for the synthesis of structurally interesting and biologically important heterocycles and bioactive natural products, we noticed that the lone pair of electrons on nitrogen atom in *N*-aryl cyclic imides has no influence on the aryl ring and it is fully in conjugation with two imide carbonyls. We reasoned and planned to take advantage of this useful observation to add a new concept in the chemistry of primary aromatic amines.

Scheme 11a **Scheme 11b**



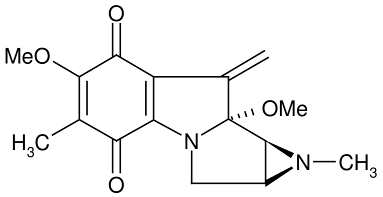
a: -ortho b: -meta c: -para

Reagents, conditions and yields: (i) Br_2 (1.25 mmol), CCl_4, reflux, 24 h; (ii) Br_2 (1.25 mmol), AcOH, rt, 6 h (aqueous workup); (iii) Br_2 (1.25 mmol), CCl_4, rt, 4 h; (iv) Br_2 (2.50 mmol), CCl_4, reflux, 8 h; (v) Br_2 (1.25 mmol), CCl_4, reflux, 8 h.

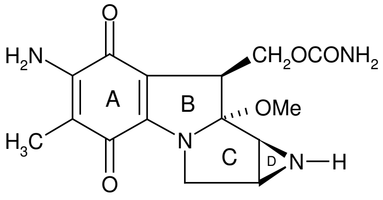
This section describes a systematic study on benzylic mono- and *gem*-dibromination of primary aromatic amine derivatives using molecular bromine (Scheme 11a & 11b). The reactions of *N*-(*o*/*m*/*p*-tolyl)succinimides (**5a-c**) with 1.25 equivalents of molecular bromine in CCl_4 at room temperature furnished the corresponding benzylic mono brominated products **6a-c** in 92-94% yields, while with 2.50 equivalents of molecular bromine in refluxing CCl_4, furnished *gem*-dibromo products **7a-c** in 94-96% yields. It is also possible to obtain the nuclear bromination in these *N*-protected primary aromatic amines at an alternate site by using suitably substituted aniline derivatives. Thus the reaction of **3** with 1.25 equivalents of molecular bromine in acetic acid gave the desired mono brominated product **4** in nearly 100% yield.

Section D: III. Synthetic Studies on Mitomycin K and C

Mitomycins are famous for their structural novelty and antitumor activity. They were first isolated in 1956 from *Streptomyces caespitosur* by Hata and co-workers in Japan. In 1962, they were also isolated from *Streptomyces veticillatus* and characterized[6] in United States of America. The absolute configuration of mitomycin A, mitomycin C, mitomycin K and porfiromycin have been formulated from X-ray crystallographic data. The emergence of mitomycin C as a clinically useful anticancer chemotherapeutic resource promotes continuing research in this field. However, in spite of the enormous amount of synthetic activity the mitomycins have inspired, the only successful total synthesis of naturally occurring mitomycins were those described by Kishi et al. and Fukuyama et al. In addition, the total synthesis of a related natural product mitomycin K, have been reported by Danishefsky et al. and Jimenez et al.



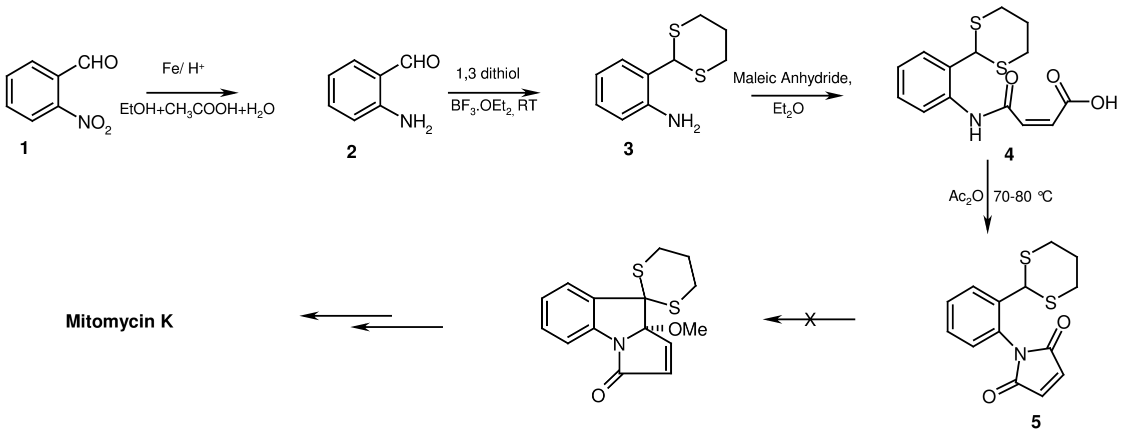
Mytomycin K



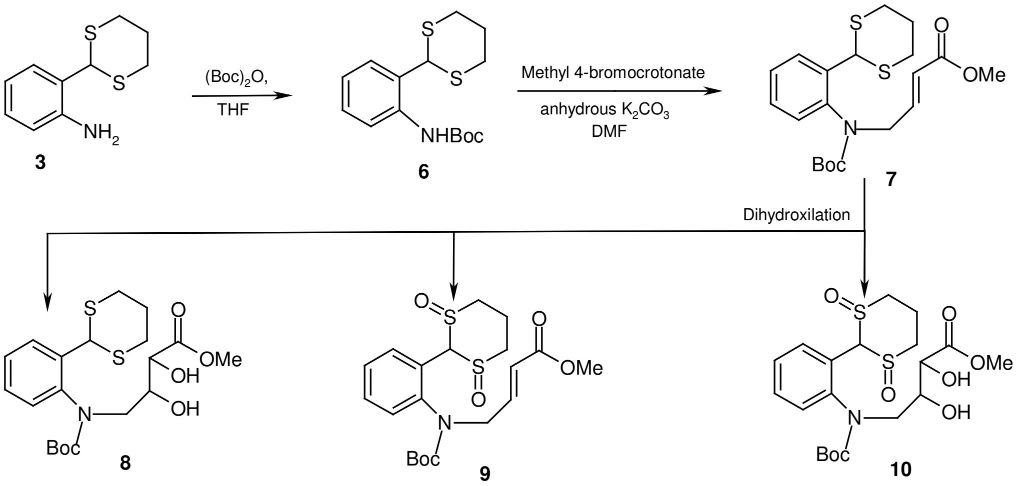
Mytomycin C

This section demonstrates studies on the synthesis of mitomycin core structure via reactivity Umpolung. To check the reactivity, we have first synthesized the suitable intermediate imide **5** starting from *o*-nitrobenzaldehyde (Scheme 12). All our attempts to ring close dithianylmaleimide with an introduction of an angular oxygen functionality to complete the synthesis of mitomycin K and C skeleton met with failure.

We then to changed our synthetic approach. Our modified synthetic approach involved *N*-allylation of a suitably substituted monoprotected aniline **6** with methyl 4-bromo crotonate followed by intramolecular condensation to get the eight-member precursor of mitomycins. The *N*-Boc dithianylaniline **6** on reaction with methyl 4-bromocrotonate gave the corresponding *N*-allylated product **7** in 68% yield. Unfortunately all our attempts for dihydroxylation of **7** gave a complex mixture of all possible dihydroxylated and sulfur oxidised products. We could separate our desired product **8** but the yield was only 5-10% (Scheme 13).

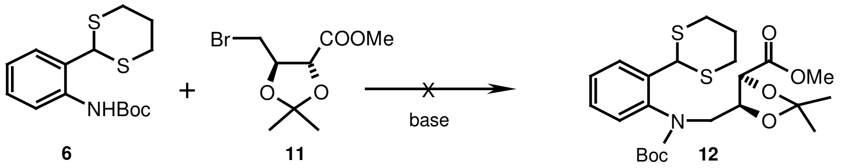


Scheme 12



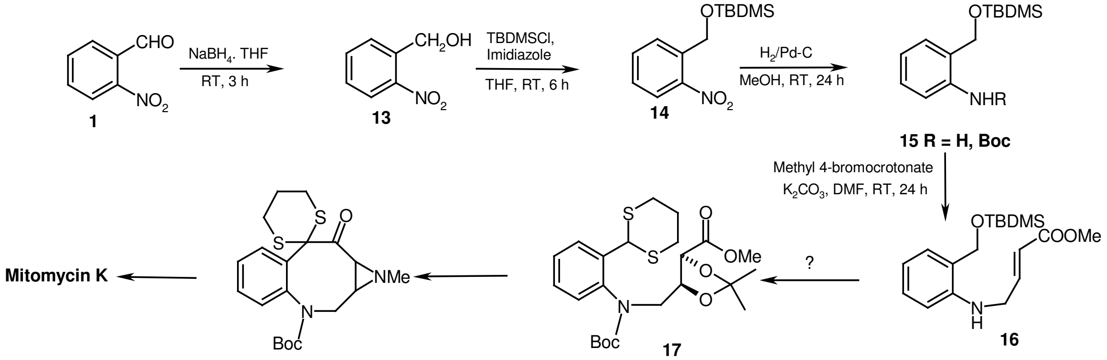
Scheme 13

An alternate chiral pool strategy was planned to circumvent the above problem posed by sulfur atom's oxidation. We prepared the precursor **11** starting from L-ascorbic acid using known literature procedure (Scheme 14). All our attempts for the *N*-alkylation of **6** with the bromo ester **11** met with failure.



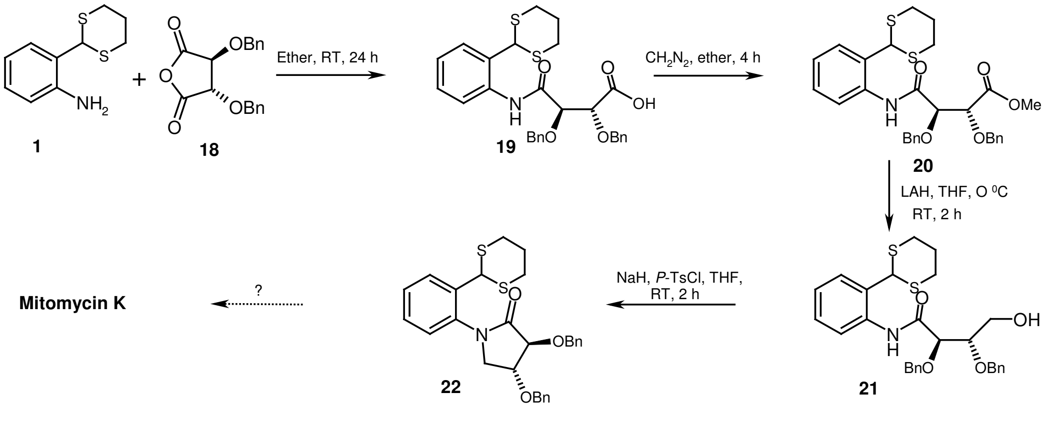
Scheme 14

We reasoned that insertion of dithiane-functionality after *N*-allylation and dihydroxylation might solve this problem. So we synthesized the intermediate **16** starting from *ortho*-nitrobenzaldehyde and conversion of **16** to **18** is in progress (Scheme 15).



Scheme 15

Very recently, starting from dithianylaniline and dibenzyltartaric anhydride we have synthesized the necessary building block **22** in four steps with high overall yield and further studies on introduction of labile angular oxygen function via intramolecular reactivity umpolung are in progress (Scheme 16).



Scheme 16

Section D: III. Experimental

This section presents the detailed experimental procedures including tabulated spectral and analytical data for compounds synthesized in Section D.

CHAPTER THREE: Spectral Data

This chapter presents spectra of some important compounds synthesized.

Note: Compound numbers in the abstract are different from those in the thesis.

CONTENTS

Chapter One: **S_N2' Grignard Coupling Reactions in Organic Synthesis**

Chapter Two: **Synthesis of Natural and Unnatural Disubstituted Maleic Anhydrides and Bioactive Natural Products**

2.1 **Section A**

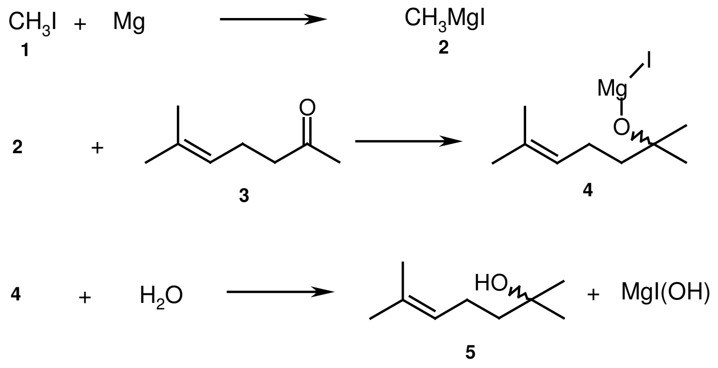
I. [2.1A] **A Facile Synthesis of Chaetomellic acid A**

II. [2.1B] **An Efficient Synthesis of 1,7(Z)-Nonadecadiene-2,3-dicarboxylic acid**

III. [2.1C] *N-Bromosuccinimide-Dibenzoyl Peroxide/Azobisisobutyro nitrile: A Reagent for Z- to E-Alkene Isomerization*

1.1 Introduction

Grignard reaction was first observed by Barbier in later part of nineteenth century as he reported that a mixture of methyl iodide, a ketone and magnesium metal in diethylether produced a tertiary alcohol.[1] Based on this unusual observation, one of his students, Victor Grignard made a detailed study to establish the mechanistic pathway of Barbier's observation in three distinct steps[2] (Scheme 1).



Scheme 1

The great value of this observation is the recognition that, this sequence was quite general and can be useful to prepare a wide variety of new compounds. On the basis of this futuristic observation and the work done by Grignard to improve many aspects of this reaction, he was recognized with the Nobel Prize in chemistry in 1912 at the age of 39. Ever since then, there has been a constant rise in the popularity of Grignard reactions as a versatile tool of the community of organic chemists for synthesis with generation of variety of new carbon-carbon bonds.

Amongst the many types of applications of Grignard reactions, nucleophilic substitution has attracted lots of attention over the past few years. Basically, nucleophilic substitution reaction follows either S_N1 or S_N2 mechanistic pathway in solution or in gas phase involving electron pair mechanisms.

Typically, for an S_N1 reaction, the mechanism invokes a first order process, with formation of a free carbocation, thereby leading to racemization of the chiral centre in a secondary leaving group (Figure 1, Equation 1).

In the S_N2 substitution, the reaction invokes a second order process, with inversion of configuration at the chiral centre in a secondary leaving group (Figure 1, Equation 2). In

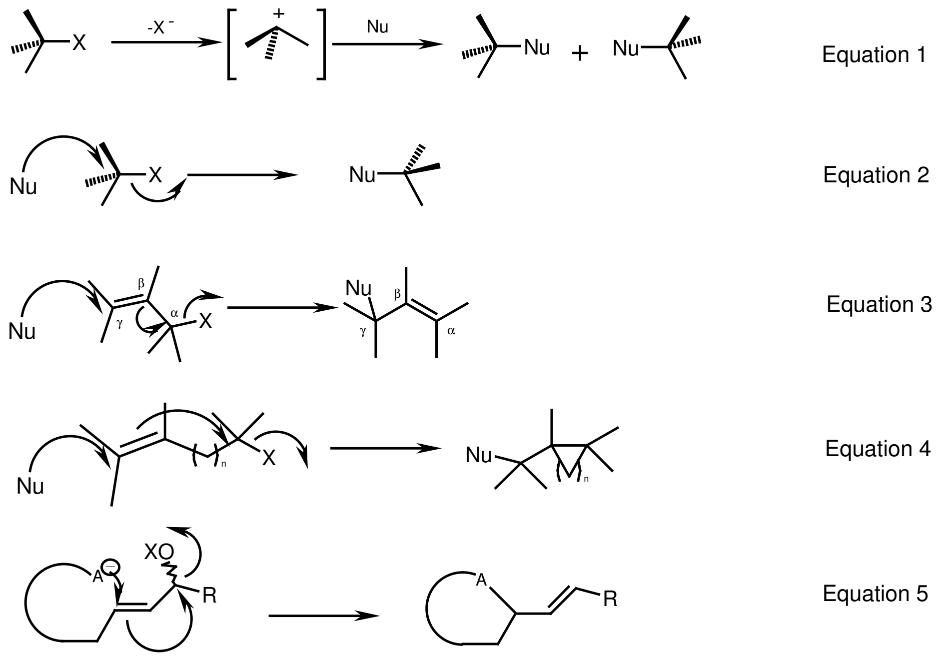


Figure 1 Intermolecular and Intramolecular Nucleophilic Substitution Reactions

allylic and propargylic compounds the S_N2' nucleophilic substitution takes place with a migration of the carbon-carbon double bond (Figure 1, Equation 3). The mechanism is a second order allylic rearrangement and occurs at the γ-position when the α-position is sterically more crowded. The stereochemistry of the S_N2' substitution is rather complex, but in acyclic systems the reaction is stereospecific and the nucleophile enters *syn* to the leaving group. A frontier orbital analysis has been proposed to rationalize this process.[3,4] Nevertheless, *anti*-reactions are possible, depending upon the nature of the nucleophile and the leaving group.

In a manner similar to the allylic and propargylic examples, other systems, in the presence of a double bond, also undergo a nucleophilic substitution through an S_N2' pathway, but with formation of a ring owing to double bond migration (Figure 1, Equation 4). Occasionally intramolecular reactions can take place, usually favoring S_N' mechanism as against an S_N process (Figure 1, Equation 5).

Over the past few decades, studies on controlling the chemo-, regio- and stereoselectivities of allylic substitution reactions have been well documented in the literature and S_N2' Grignard coupling reaction has emerged as a very powerful tool in selective carbon-carbon bond formation.[5-7] Several catalysts including copper[8-10] have found their way to increase the γ-selectivity in S_N2' reactions. In the recent past more attention has been paid to introduce enantioselectivity in allylic substitution reactions. Figadere and Franck have given a very practical and important account on several aspects of S_N2' Grignard coupling reactions covering the literature up to the end of 1994. This chapter portrays a concise account on recent developments of S_N2' Grignard coupling reactions starting from early 1995 to early 2005 and their application towards the synthesis of natural products. We have tried our best to assemble the essence of the literature to systematically present the information here, but no pretension of completeness is claimed.

1.2 S_N2' Grignard Coupling Reactions with Allylic Substrates

Allylic substrates with a good leaving group can undergo S_N2' coupling reaction with an array of nucleophiles. Feasibility of the reaction depends greatly upon the nature of the leaving group, polarity of the double bond, nature of the nucleophile and reaction conditions. S_N2' Grignard coupling reactions with allylic substrates are found to be one of the most widely used transformations to generate carbon-carbon bonds with variety of substituents. Synthetic utility of S_N2' Grignard coupling reactions with allylic substrates is therefore continuously sought after by organic chemists and in this section we have discussed the recent literature employing a substrate-based classification of the same.

1.2.1 Allyl Halides

Most of the mechanistic studies to establish the reaction course of Grignard reagents with allylic substrates are based on allylic halides. Alexakis et al. reported that Grignard reagents could undergo enantioselective copper catalyzed S_N2' substitution on achiral allylic chlorides. Their work demonstrates a detailed study on effective γ-coupling reaction of a Grignard reagent with both aromatic and aliphatic substituted allylic chlorides in presence of CuTC (copper thiophene 2-carboxilate) as a catalyst and a chiral phosphoramidite ligand. They have shown that phosphorus ligands derived from tetraaryl-1,3-dioxolone-4,5-dimethanol (taddol) were highly effective chiral reagents in the reaction with cinnamyl chloride (γ/α = 94/6, 73% *ee*),[11] whereas second generation phosphoramidite ligands (Figure 2) improved this result,[12] with a wider scope of applicability (Table 1-3).

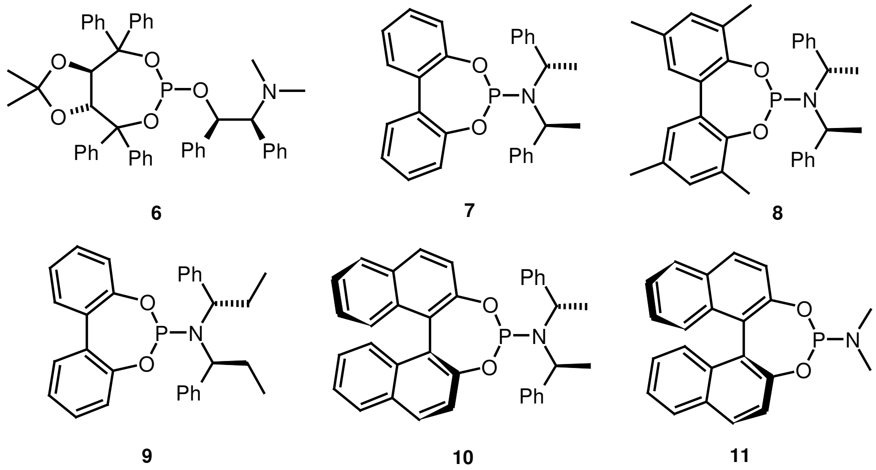
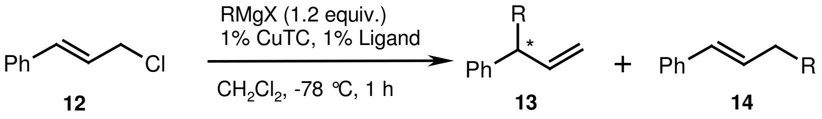


Figure 2 Chiral Ligands Used for Asymmetric S_N2' Grignard Coupling Reactions with Allyl Halides

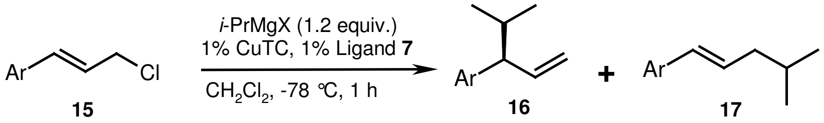
Table 1 Asymmetric S_N2' Reactions of Cinnamyl Chloride with Various Grignard Reagents



Entry	Ligand	Grignard Reagent	% Conversion[a]	13/14	% ee (*R*/*S*)
1	**6**	EtMgBr	100 (97)	96/04	82 (***R***)
2	**7**		100 (96)	92/08	79 (***S***)
3	**6**	MeMgBr	95	31/69	61 (***R***)
4	**7**		83	12/88	62 (***S***)
5	**6**	*n*-PrMgBr	100 (96)	80/20	75 (***R***)
6	**7**		100	59/41	69 (***S***)
7	**6**	3-Butenyl-MgBr	100	91/09	61 (***R***)
8	**7**		100 (94)	71/29	48 (***S***)
9	**6**	4-Pentenyl-MgBr	100	90/10	72 (***R***)
10	**7**		100 (92)	73/27	64 (***S***)
11	**6**	*i*-PrMgBr	100	88/12	46 (***R***)
12	**7**		100 (98)	90/10	83 (***S***)

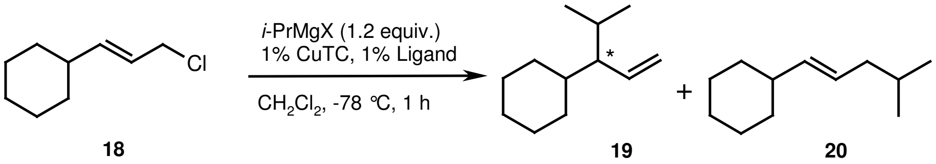
[a] In parentheses: isolated % yield of the mixture of regioisomers.

Table 2 Asymmetric S_N2' Reactions of Various Cinnamyl Chlorides with *i*-PrMgBr in Presence of Ligand **5**



Entry	Ar	% Yield	16/17	% ee
1	2-Naphthyl	97	92/08	85
2	4-Cl-C_6H_4	92	87/13	79
3	3,4-DiCl-C_6H_3	93	89/11	80
4	4-Me-C_6H_4	93	91/09	83
5	4-MeO-C_6H_4	98	90/10	77
6	3-MeO-C_6H_4	98	91/09	86
7	3,5-CH_2O_2-C_6H_3	96	92/08	82

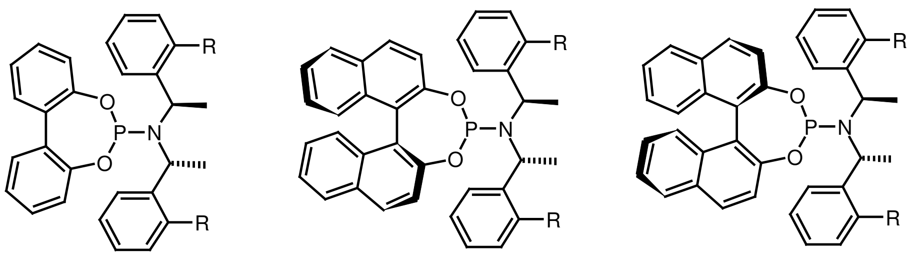
Table 3 Asymmetric S_N2' Reactions of (3-Chloropropenyl)cyclohexane with *i*-PrMgBr



Entry	Ligand	Cu Salt	% Conversion	19/20	% ee (***R***/***S***)
1	**6**	CuCN	100	96/04	2 (***R***)
2	**6**	CuTC	100	83/17	13 (***R***)
3	**7**	CuCN	100	99/01	51 (***S***)
4	**7**	CuTC	100	99/01	68 (***S***)
5	**8**	CuTC	100	18/82	18 (***S***)
6	**8**	CuTC	100	98/02	68 (***S***)
7	**10**	CuCN	100	99/01	49 (***R***)
8	**10**	CuTC	100	99/01	74 (***R***)
9	**10′**[a]	CuTC	100	97/03	63 (***S***)
10	**11**	CuTC	100	96/04	12 (***R***)

[a] **10′** is the (S_a, *SS*) diastereomer of ligand **10**.

In early 2004 Alexakis and coworkers introduced their improved third generation phosphoramidite ligands (Figure 3) for the same application with increase in stereo selectivity (*ee* values up to 96% in most of the cases). The reaction conditions were also compatible with one pot Ru-catalyzed metathesis procedure to generate higher order carbocycles (Table 4).[13] After completion of the allylic substitution process, addition of 5% Grubbs catalyst to the same reaction mixture smoothly afforded the ring closed products **27** in good yield with high enantioselctivity.



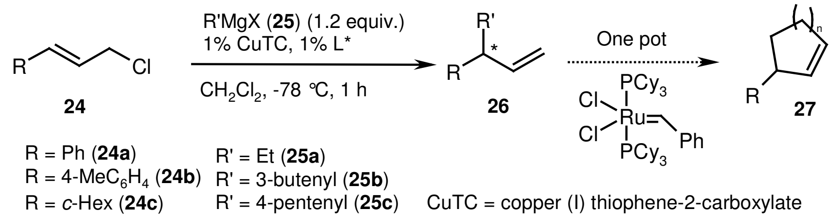
21a R = H
21b R = OMe

22a R = H
22b R = OMe

23a R = H
23b R = OMe

Figure 3 Chiral Ligands Used for S_N2' Asymmetric Allylic Substitutions with Grignard Reagents

Table 4 S_N2' Enantioselective Cu-catalyzed Allylic Substitutions with Grignard Reagents

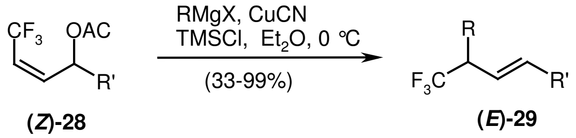


Entry	R	R′	L*	% Conv. of 24[a]	γ/α	% *ee* (26)	% Yield (27)	% *ee* (27)
1	**24a**	**25a**	**21a**	99	91/09	79 (***S***)	-	-
2	**24a**	**25a**	**22a**	99	72/28	77 (***S***)	-	-
3	**24a**	**25a**	**23a**	99	79/21	55 (***S***)	-	-
4	**24a**	**25a**	**21b**	99	98/02	74 (***R***)	-	-
5	**24a**	**25a**	**22b**	99	73/27	46 (***S***)	-	-
6	**24a**	**25a**	**23b**	(86)	99/01	96 (***R***)	-	-
7	**24a**	**25b**	**23b**	(83)	96/04	92 (***R***)	77	92 (***R***)
8	**24a**	**25c**	**23b**	(81)	91/09	96 (***R***)	69	96 (***R***)
9	**24b**	**25a**	**23b**	(85)	99/01	96 (***R***)	-	-
10	**24b**	**25b**	**23b**	(83)	97/03	93 (***R***)	79	93 (***R***)
11	**24b**	**25c**	**23b**	(86)	91/09	94 (***R***)	72	94 (***R***)
12	**24c**	**25a**	**23b**	(82)	99/01	91 (-)	-	-

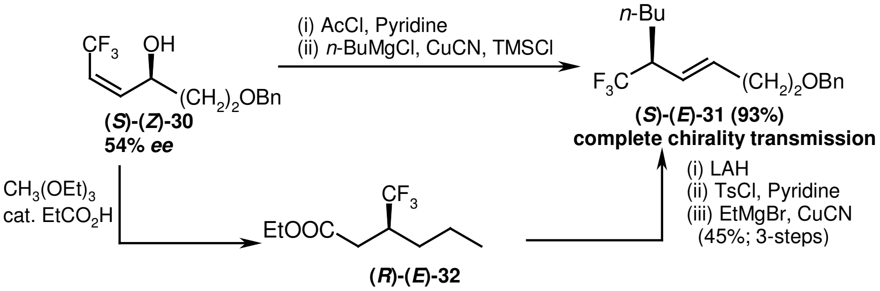
[a] In parentheses: isolated yield of the mixture of regioisomers.

1.2.2 Allyl acetates

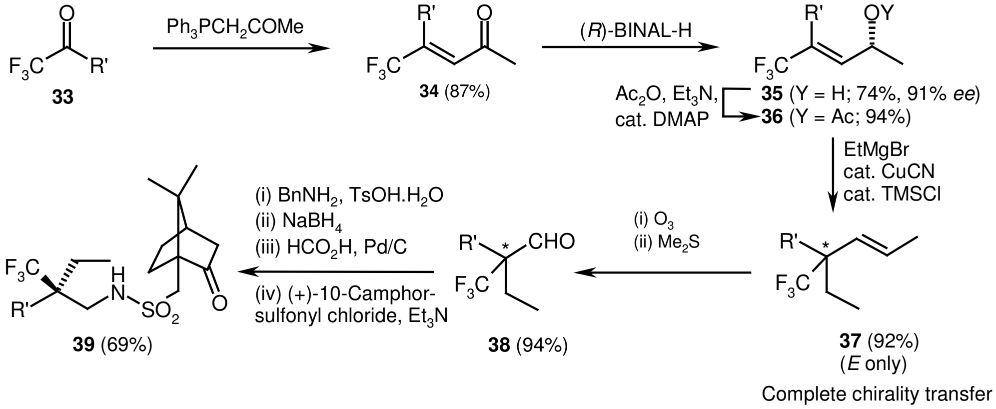
Yamazaki et al. reported that γ-trifluromethylated allylic acetates **28** react quite smoothly with various Grignard reagents to yield respectively a high percentage of S_N2' substitution products **29** (E:Z = upto 99:01) in presence of catalytic amount of CuCN and TMSCl (Scheme 2), without any trace of the corresponding S_N2 products, the reason being the electron withdrawing effect of a -CF_3 group.[14] They have also established the *anti*-S_N2' mechanism of the Grignard substitution on the basis of the results obtained with (*S*)-allylic acetate (Scheme 3).



Scheme 2



Scheme 3

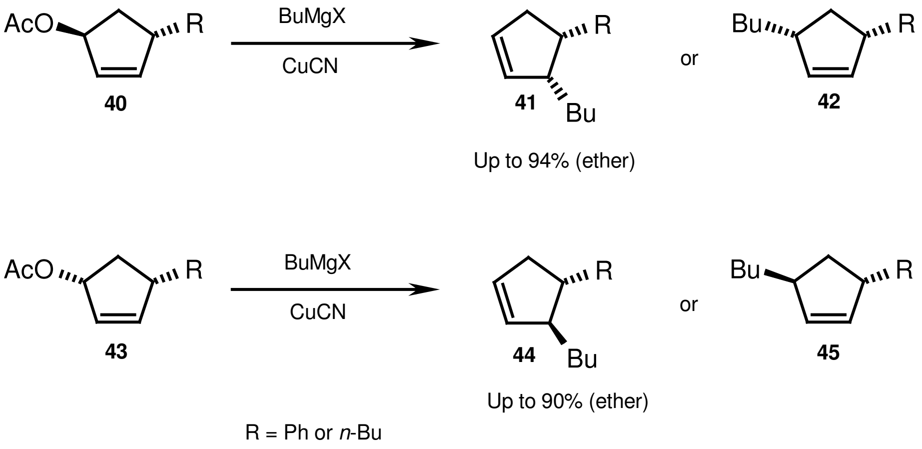


Scheme 4

In another communication Yamazaki and coworkers have also described that Cu(I)-catalyzed S_N2' Grignard coupling reaction with -CF_3 containing secondary allylic acetates

36, which can serve as a useful tool for the generation of optically active quaternary carbon centres (Scheme 4).[15]

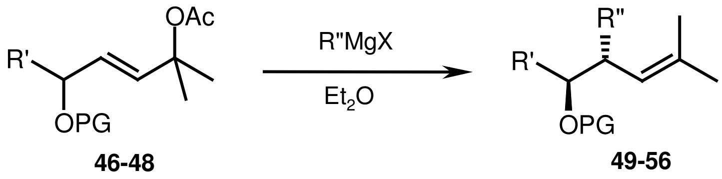
Kobayashi et al. reported alkylation of 4-substituted 1-acetoxy-2-cyclopentenones with copper regents derived from *n*-BuMgX (X= Cl, Br) and CuCN in 2:1 ratios in THF and Et_2O.[16] *cis*-1,4-Isomers **42a**,**b** (a, R = Ph; b, R = *n*-Bu) were produced regioselectively from the corresponding *trans*-acetates **40a**,**b** with the reagent BuMgCl and CuCN (2:1) in THF, while the BuMgBr-based reagent with 2:1 and 1:1 ratios in Et_2O furnished the corresponding *cis* 3,4-isomers **41a**,**b**. Similar results were obtained with *cis*-acetates **43a**,**b** (a, R = Ph; b, R = *n*-Bu) (Scheme 5). The regioselectivity in reactions of both the substrates is very much solvent dependent. S_N2' substitution product predominates in ether whereas use of THF as solvent majorly provides S_N2 coupled product irrespective of the reagents used.



Scheme 5

Chong et al. have shown that S_N2' substitution of δ-substituted allylic acetates with Grignard reagents and copper catalysts proceed with high diastereoselectivities.[17a] The presence of benzyloxy, methoxymethoxy, and *tert*-butyldimethylsilyloxy groups in starting materials favor the *anti*-isomer with very high selectivity (*anti*:*syn* = 99:01) (Table 5). The presence of hydroxyl group reverses the selectivity and the *syn*-isomer is favored with *anti*:*syn* ratio 01:99 (Table 6). The *anti*-selectivity observed with δ-alkoxy substituents may be rationalized using Felkin-Anh/Cram argument as noted by Nakamura,[17b] whereas the *syn*-selectivity observed with a hydroxyl group suggests that the reagent coordinates with the substrate, delivering the alkyl group from the same face.

Table 5 Copper Cyanide Catalyzed S_N2' Reactions of Grignard Reagents with δ-Alkoxysubstituted Allyl Acetates[a]

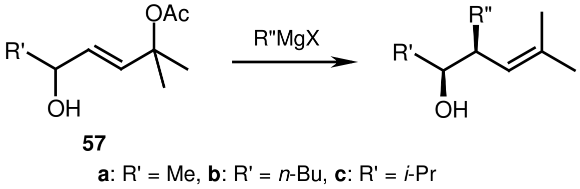


46: PG = Bn, **47**: PG = TBS, **48**: PG = MOM
a: R' = Me, **b**: R' = *n*-Bu, **c**: R' = *i*-Pr

Entry	Acetate	R″	Product	% Yield	Diasteriomeric Ratio
1	**46a**	*n*-Bu	**49a**	72	86:14
2	**46a**	*i*-Pr	**50a**	70	74:26
3	**46a**	*t*-Bu	**51a**	73	83:17
4[b]	**46a**	Ph	**52a**	64	79:21
5	**46b**	*n*-Bu	**49b**	89	90:10
6	**46b**	*i*-Pr	**50b**	85	79:21
7	**46b**	*t*-Bu	**51b**	89	87:13
8	**46b**	Ph	**52b**	68	88:12
9	**46c**	*n*-Bu	**49c**	80	98.5:1.5
10	**46c**	*i*-Pr	**50c**	76	98.5:1.5
11	**46c**	*t*-Bu	**51c**	94	99:01
12	**46c**	Ph	**52c**	75	99:01
13	**46c**	Me	**53c**	77	98:02
14	**46c**	Et	**54c**	84	99:01
15	**47b**	*n*-Bu	**55b**	89	80:20
16	**47c**	*n*-Bu	**55c**	81	95:05
17	**48b**	*n*-Bu	**56b**	85	83:17
18	**48c**	*n*-Bu	**56c**	88	98:02

[a] Reactions were carried out using 2.0 equiv. of R″MgX with 10 mol% CuCN in ether. [b] 50 mol% CuCN was used.

Table 6 Copper Cyanide Catalyzed S_N2' Reactions of Grignard Reagents with δ-Hydroxysubstituted Allyl Acetates[a]



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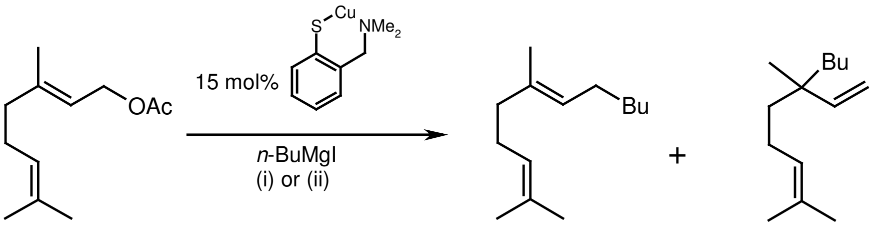
a: R' = Me, **b**: R' = *n*-Bu, **c**: R' = *i*-Pr

Entry	Acetate	R″	Product	% Yield	Diasteriomeric Ratio
1	**57a**	*n*-Bu	**58a**	69	89:01
2[b]	**57a**	*n*-Bu	**58a**	76	80:20
3	**57a**	*i*-Pr	**59a**	71	79:21
4	**57a**	*t*-Bu	**60a**	79	97:03
5	**57b**	*n*-Bu	**58b**	84	93:07
6[b]	**57b**	*n*-Bu	**58b**	68	86:14
7	**57b**	*i*-Pr	**59b**	68	86:14
8	**57b**	*t*-Bu	**60b**	83	99:01
9	**57c**	*n*-Bu	**58c**	79	88:12
10	**57c**	*i*-Pr	**59c**	68	56:44
11	**57c**	*t*-Bu	**60c**	83	94:06

[a] Reactions were carried out using 2.5 equiv. of R″MgX with 50 mol% CuCN in CH_2Cl_2. [b] Reactions in Et_2O using 10 mol% CuCN.

In early 1995 Bäckvall and coworkers established that the regioselectivity of the reaction between geranyl acetate and *n*-BuMgI catalyzed by an achiral arenethiolatocopper (I) complex can be tuned to either α- or γ-substitution by variation in reaction conditions (Scheme 6).[18]

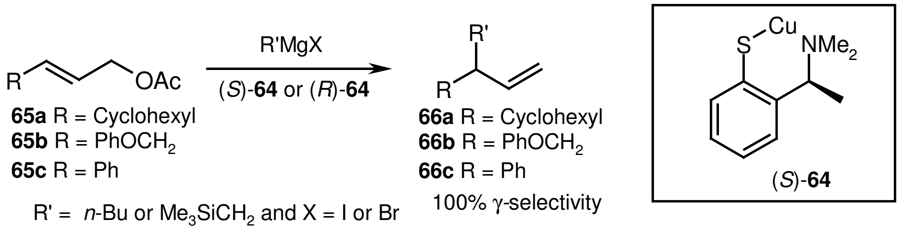


61 **62** (α-product) **63** (γ-product)

(i) Et_2O, 0 °C, 120 min addition time of *n*-BuMgI, γ–product (100%)
(ii) THF, -30 °C, 5 min addition time of *n*-BuMgI, α-product (100%)

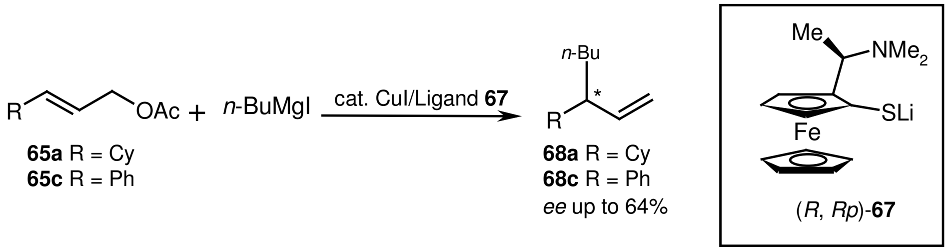
Scheme 6

Upon using chiral copper arenethiolates as catalyst, reaction of *n*-BuMgCl with allyl acetate gave the γ-substitution product with 45% *ee* (Scheme 7).[19,20] The use of copper arenethiolates prepared in situ from the corresponding arenethiols has also been studied and similar results were obtained when preformed arenethilates were used. Use of *n*-BuMgBr and Me_3SiCH_2MgI as Grignard reagents increased the enantiomeric excess up to 50 and 53% respectively.[19]



Scheme 7

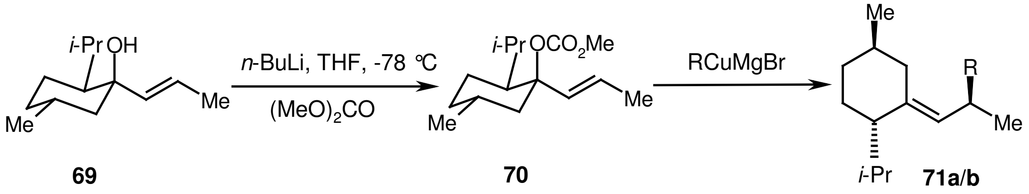
Bäckvall and coworkers have also introduced the application of ferrocenyl thiolates as ligands in copper catalyzed asymmetric substitution reaction of allyl acetates with Grignard reagents.[21] The catalyst formed from lithium thiolate **67** gave the *γ*-product in high selectivity (88% yield, α:γ = up to 98:02) and with up to 64% *ee* (Scheme 8). Neutral thioether ligands gave essentially racemic product in the copper catalyzed reaction of **65a** with *n*-BuMgI, which shows the importance of anionic coordination to copper by sulfur.



Scheme 8

1.2.3 Allyl Carbonates

Spino et al. reported highly *anti*-selective S_N2' addition of copper catalyzed Grignard reagents to allyl carbonates.[22] The method, which uses menthone as a chiral auxiliary, is a useful alternative to the alkylation of chiral enolates giving rise to very high diastereoselectivity (Scheme 9).

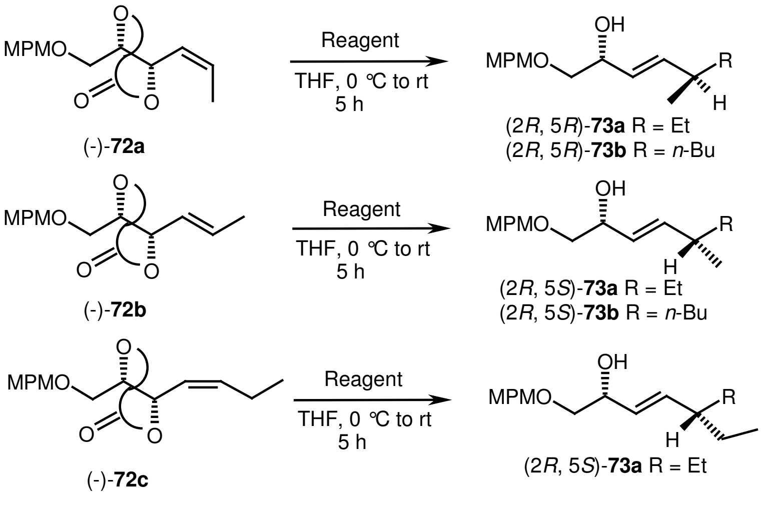


(*R*)-**71a**; R = $H_2C{=}CH(CH_2)_2$ (73% yield, 99% *de*)
(R)-**71b**; R = (Cyclohexyl)$_2$ (91% yield, 99% *de*)

Scheme 9

Allylic cyclic carbonates **72a-c** are also good substrates for excellent regio- and diastereoselective allylation to form optically active (*E*)-allylic alcohols **73a-b** using Grignard reagents in the presence of NiCl$_2$(dppe) as catalyst (Table 7).[23] In almost all cases the obtained diastereoselectivity was excellent (>99%).

Table 7 Nickel Catalyzed S$_N$2′ Grignard Addition to Cyclic Allylic Carbonates

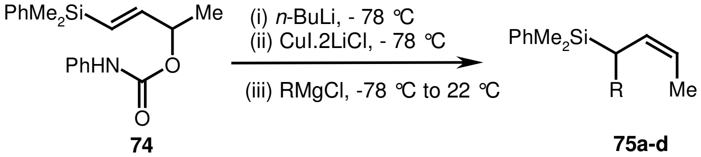


Entry	Substrate	Reagent	Product	% Yield
1	**72a**	EtMgBr (4 equiv.), NiCl$_2$(dppe) (5 mol%)	(2*R*, 5*R*)-**73a**	79
2	**72a**	*n*-BuMgCl (4 equiv.), NiCl$_2$(dppe) (5 mol%)	(2*R*, 5*R*)-**73b**	60
3	**72b**	EtMgBr (4 equiv.), NiCl$_2$(dppe) (5 mol%)	(2*R*, 5*S*)-**73a**	80
4	**72b**	*n*-BuMgCl (4 equiv.), NiCl$_2$(dppe) (5 mol%)	(2*R*, 5*S*)-**73b**	58
5	**72c**	MeMgCl (4 equiv.), NiCl$_2$(dppe) (5 mol%)	(2*R*, 5*S*)-**73a**	70

1.2.4 Allyl carbamates

Woerpel and coworkers reported that the use of (trimethylsilyl)magnesium chloride as nucleophile in copper mediated allylic substitution reaction of allyl carbamates afforded S_N2' coupled product in good yield, with high γ-selectivity and high (*Z*)-selectivity (*E*:*Z* = 06:94) (Table 8).[24]

Table 8 Copper Catalyzed S_N2' Grignard Reactions with Allyl Carbamates



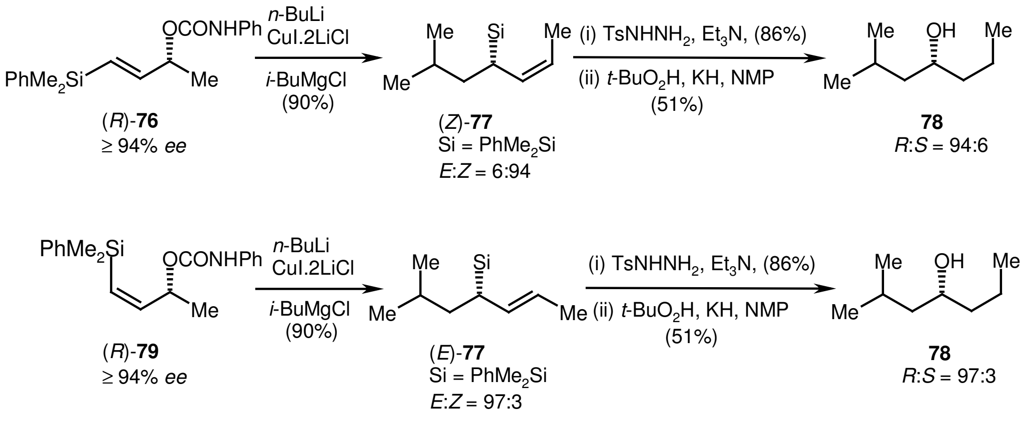
74

75a-d

Entry	Product	R	*E*:*Z*	% Yield	γ/α
1	**75a**	Me	38:62	72	93:07
2	**75b**	*i*-Bu	06:94	90	95:05
3[a]	**75c**	$PhMe_2SiCH_2$	04:96	68	99:01
4	**75d**	*i*-Pr	13:87	71	99:01

[a] The reaction was performed at 0-22 °C using CuI as catalyst.

The same group also prepared both (*Z*)- and (*E*)-allylic silanes with high stereoselectivity via the copper-mediated S_N2' substitution of allylic carbamates by organometallic reagents. The reaction of alkylmagnesium reagents with (*E*)-allylic carbamate **76** provided (*Z*)-allylic silane **77**, whereas alkylmagnesium reagents react with (*Z*)-allylic carbamate **79** to afford (*E*)-allylic silane **77**.



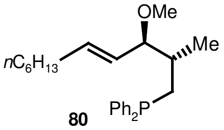
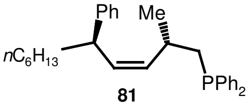
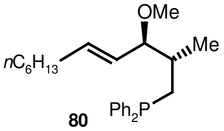
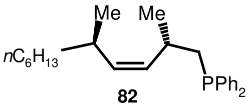
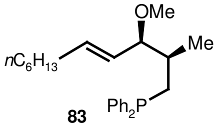
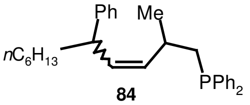
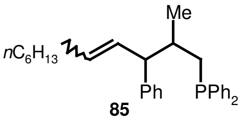
Scheme 10

This method also allows readily available nonracemic allylic carbamates to be converted to chiral (*Z*)- and (*E*)-allylic silanes with high stereoselectivity (Scheme 10).[25] This observed stereochemistry can be explained by considering *syn*-attack . The reaction of alkylmagnesium reagents with allylic carbamates occurs likely by transmetallation of the Grignard reagent to copper, followed by an oxidative addition of copper to form a carbamate complex promoting the *syn*-delivery of the alkyl group.

1.2.5 Allyl Ethers

Nickel found its way to catalyze addition of alkyl Grignard reagents to allylic ethers in a very highly regio- and stereoselective way.[26] As shown in Table 9 upon alkylation with PhMgBr and 5 mol% of $(Ph_3P)_2NiCl_2$ allylic ether **80** was converted to **81** in high yield and with excellent control of regio-, diastereoselectivity and olefin geometry. Nickel catalyzed alkylation of **80** with MeMgBr is known to proceed with 98% regio-, diastereoselectivity and olefin geometry to afford **82** (75%). Allylic ether **83** undergoes alkylation at a rate superior to that of **80**, indicating that diminishing of selectivity is probably not due to the inefficient P-Ni association in the former case.

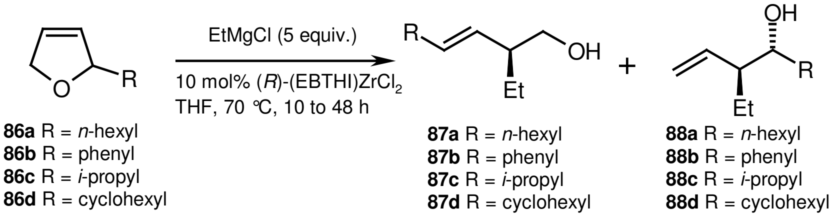
Table 9 Effect of Local Chirality on Efficiency and Selectivity of Ni-catalyzed Alkylation

Substrate	Grignard Reagent	Product	Regioselectivity	*cis*:*trans*	*ds* [a]	% Yield (h)
 **80**	PhMgBr	 **81**	99:01	49:01	10:01	85 (6)
 **80**	MeMgBr	 **82**	99:01	49:01	49:01	75 (12)
 **83**	PhMgBr	 **84**  **85**	1:1		1:1	85 (3)

[a] Diasteriomeric ratio.

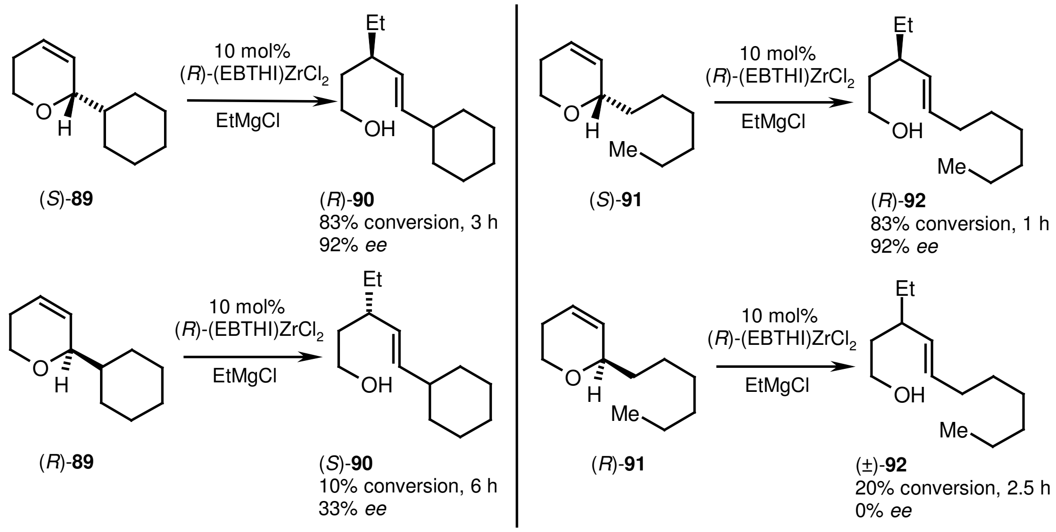
Reaction course of 2-substituted furans are totally different. Treatment of the 2-substituted furan with 5 equiv of EtMgCl and 10 mol% (*R*)-(EBTHI)ZrCl$_2$ in THF at 70 °C afforded both the primary and secondary alcohols arising from two enantiomers of the substrate in high diastereoselectivity and olefin geometry-selelectivity (Table 10).[27]

Table 10 Zirconocene-catalyzed Kinetic Resolution of Dihydrofurans



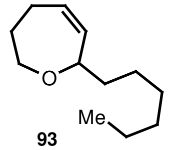
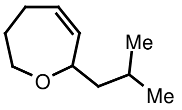
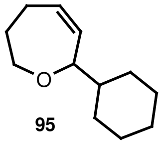
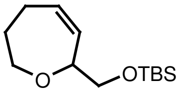
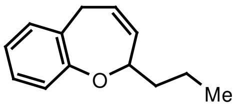
Substrate	% Yield (87)	% *ee* (87)	% Yield (88)	% *ee* (88)	*anti*:*syn* (88)
86a	48	98	48	98	95:05
86b	49	96	49	95	95:05
86c	31	98	33	98	95:05
86d	23	95	26	99	99:01

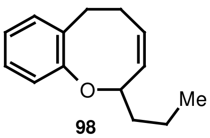
Some of the isomers of racemic cyclic allylic ethers are known to react sluggishly with a Grignard reagent. This sluggishness could be attributed to effective kinetic resolution of cyclic allylic ethers (Scheme 11). Hoveyda and coworkers reported an asymmetric zirconium-catalyzed kinetic resolution of 2-substituted cyclic ethers. As illustrated in Table 11, when racemic unsaturated seven-membered ethers **93**, **94** & **96** (entries 1, 2 and 4) were treated with 10 mol% of (*R*)-(EBTHI)Zr-binol and 5 equiv of EtMgCl in THF, at 60% (±3%) conversion the unreacted starting material is recovered with outstanding levels of enantiomeric purity (>96% *ee*). The entries in Table 12 give a proof that Zr-catalyzed kinetic resolution of 2-substituted dihydropyrans are sensitive to the steric bulk of the pedant alkyl group,[28] with bulkier alkyl groups tending to decrease the enantioselectivity.



Scheme 11

Table 11 Zirconocene-catalyzed Kinetic Resolution of 2-Substituted Medium Ring Ethers[a]

Entry	Substrate	Time	% Conversion	Unreacted Subs. Config., (% *ee*)
1	 **93**	40 min	58	***R*** (99)
2	 **94**	30 min	58	***R*** (99)
3	 **95**	90 min	60	***R*** (70)
4	 **96**	100 min	63	***R*** (96)
5	 **97**	8 h	60	***R*** (60)

6	 **98**	11 h	63	*R* (79)

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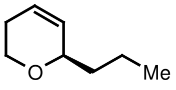
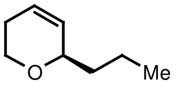
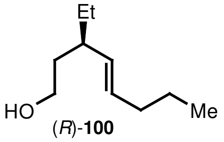
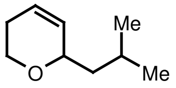
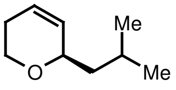
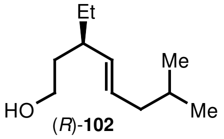
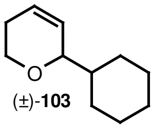
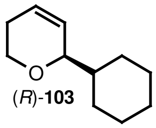
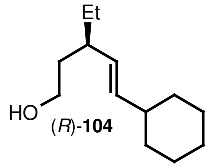
[a] Conditions: 10 mol% of (*R*)-(EBTHI)Zr-binol, 5.0 equiv. of EtMgCl, THF, 70 °C.

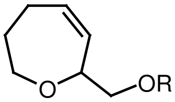
Table 12 Zirconocene-catalyzed Kinetic Resolutions and Enantioselective Allylic Substitution of Unsaturated Pyrans[a]

Substrate	Recovered Substrate	*% ee*	Product	*% ee*
 (*R*)-**99**	 (*R*)-**99**	>99	 (*R*)-**100**	94
 (±)-**101**	 (*R*)-**101**	96	 (*R*)-**102**	87
 (±)-**103**	 (*R*)-**103**	78	 (*R*)-**104**	74

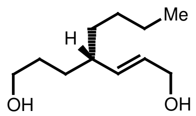
[a] Conditions as reported for Table 11, except that (*R*)-(EBTHI)$ZrCl_2$ was used as precatalyst. All data obtained at 60% (±2%) conversion; mass recovery >90% in all cases.

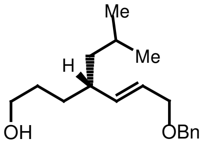
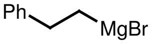
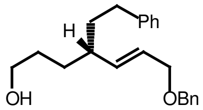
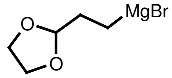
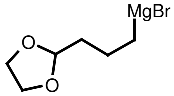
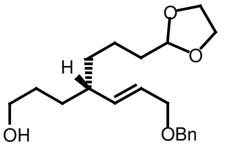
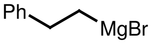
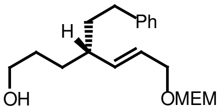
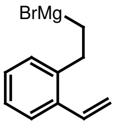
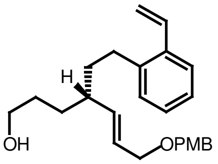
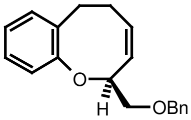
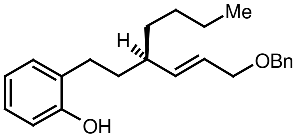
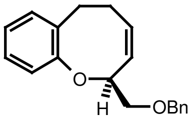
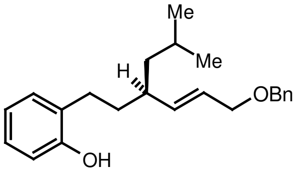
In continuation of this work, Hoveyda and coworkers reported an efficient stereoselective heteroatom-assisted allylic alkylation of cyclic ethers with Grignard reagents. These processes proceed readily at ambient temperature with high yield and enantioselectivity (Table 13).[29]

Table 13 S_N2' Reactions of Grignard Reagents with Cyclic Allylic Ethers[a]



R = H (**105a**); R = Bn (**105b**); R = MEM (**105c**); R = PMB (**105d**)

Entry	Substrate	Grignard Reagent	Product	% yield (*% ee*)
1	(*S*)-**105a** R = H	*n*-BuMgCl	 (*S*)-**106**	93 (96)

2	(*S*)-**105b** R = Bn	*i*-BuMgBr	 (*S*)-**107**	87 (96)
3	(*S*)-**105b** R = Bn	 **108**	 (*R*)-**109**	88 (96)
4	(*S*)-**105b** R = Bn	 **110**	No reaction[b]	-
5	(*S*)-**105b** R = Bn	 **111**	 (*S*)-**112**	89 (96)
6	(*S*)-**105c** R = MEM	 **108**	 (*S*)-**113**	78 (96)
7	(*S*)-**105d** R = PMB	 **114**	 (*S*)-**115**	99 (99)
8	 (*R*)-**116**	*n*-BuMgCl	 (*R*)-**117**	67 (96)
9	 (*R*)-**116**	*i*-BuMgCl	 (*R*)-**118**	71 (96)

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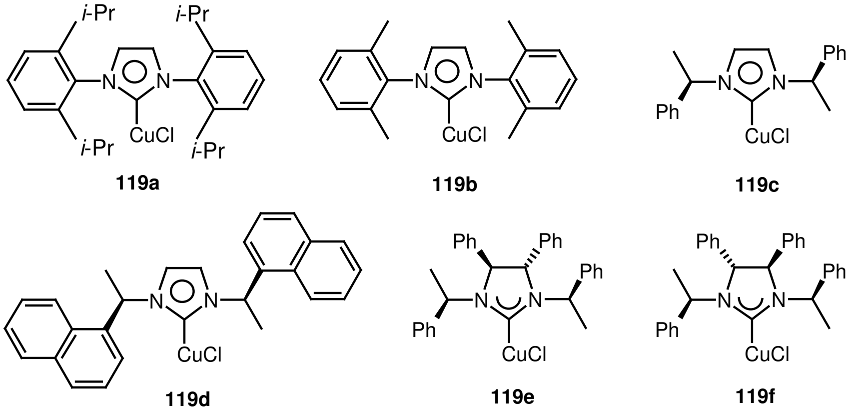
[a] Conditions: 5 equiv. of Grignard reagent, 22 °C, THF, 12-24 h. [b] Probably, the intramolecular Mg-O chelation preempts association of the metal with the Lewis basic alkoxy group and/or the C-C π cloud, a factor that may be critical to success of the olefin alkylation.

Okamoto and coworkers reported that the reaction of allylic compounds with alkyl Grignard reagents in the presence of a catalytic amount of copper *N*-heterocyclic carbene (NHC) complexes (Figure 4) proceed predominantly in an S_N2' reaction pathway to give γ-

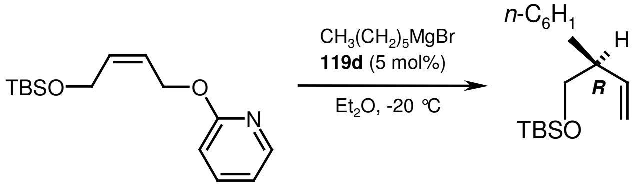
substituted products in excellent yields.[30] The method was applied to asymmetric synthesis by using optically active NHC ligands. Best results were obtained with the compound (*Z*)-**120** and ligand **119d** with γ/α-selectivity of 98/02 and up to 70% *ee* (Scheme 12).



119a **119b** **119c**

119d **119e** **119f**

Figure 4 Ligands Used for Asymmetric S_N2' Reactions of Allyl Substrates



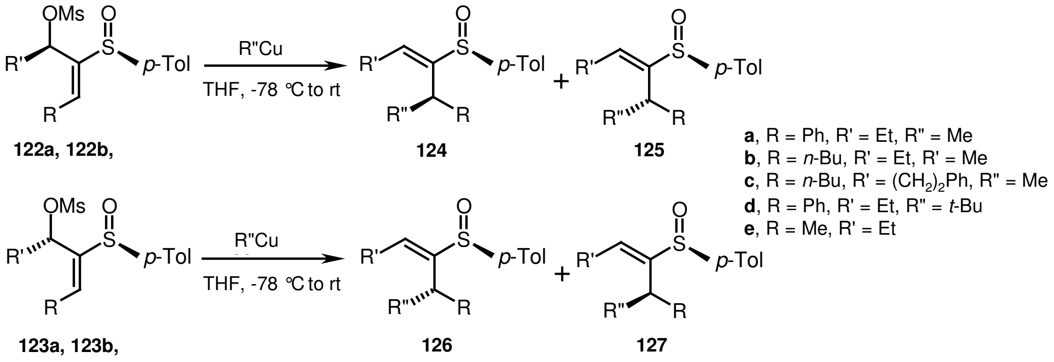
(*Z*)-**120** **121**

Scheme 12

1.2.6 Allyl Silylethers

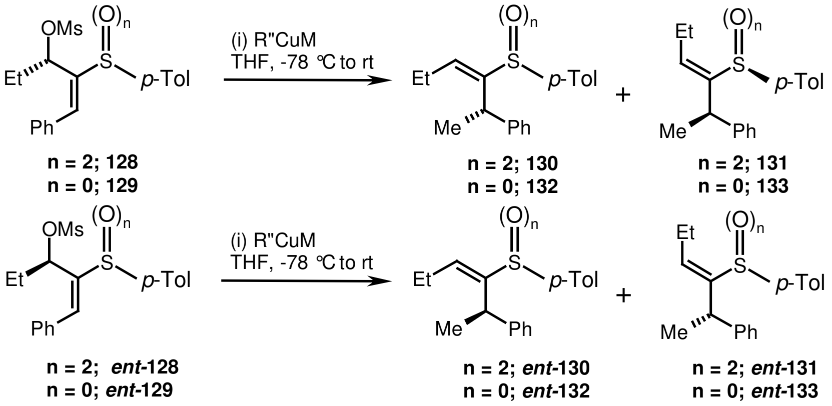
Allylic silyl ethers are reported to be very efficient substrates towards chirality transfer by S_N2' displacement with Grignard reagents. Marino et al. established a new methodology to effect the regio- and stereocontrolled S_N2' substitution of allylic mesyloxy vinyl sulfoxides, sulfides and sulfones. The stereochemical outcome of these processes is primarily controlled by the configuration of the allylic mesylate, with sulfides and sulfoxides (Table 14), displaying very similar results. The related sulfones allow for a reversal of stereochemistry at the newly created centre from a starting material of the same absolute configuration as the allylic alcohol (Table 15).[31]

Table 14 Copper Catalyzed S$_N$2′ Grignard Reactions with Allylic Sulfinyl Mesylates



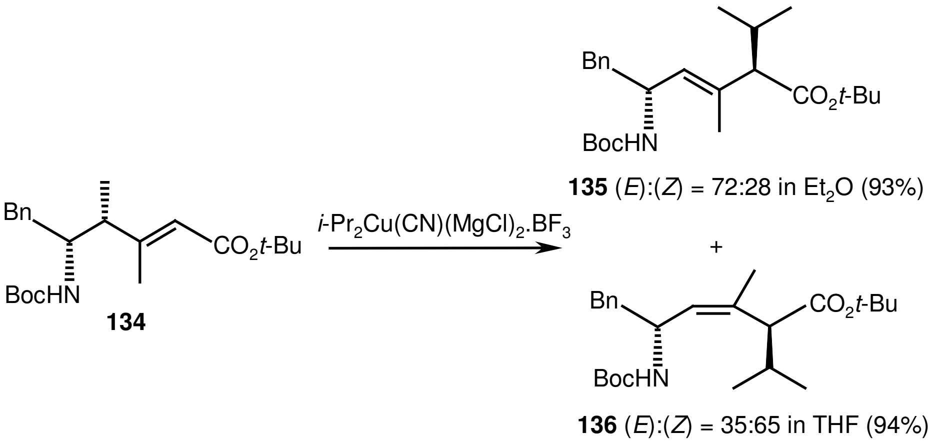
Entry	Substrate	R″CuM	Product Ratio	% Yield
1	**122b**	Me_2CuMgBr	**124b**:**125b** = 36:64	52
3	**123a**	MeCuCNMgBr	**126a**:**127a** = 06:94	80
3	**123a**	*t*-BuCuCNMgCl	**126d**:**127d** = 06:94	71
4	**123b**	MeCuCNMgBr	**126b**:**127b** = 37:63	80
5	**123b**	Me_2CuMgBr	**126b**:**127b** = 00:100	50
6	**123e**	*n*-BuCuCNMgCl	**124b**:**125b** = 00:100	43

Table 15 Copper Catalyzed S$_N$2′ Grignard Reactions with Allylic Sulfonyl and Sulfenyl Mesylates



Entry	Substrate	R″CuM	Product	Ratio	% Yield
1	**128**	MeCuCNMgBr	**130**:**131**	83:17	74
2	**128**	$Me_2CuCN(MgBr)_2$	**130**:**131**	91:09	76
3	***ent*-128**	$Me_2CuCN(MgBr)_2$	***ent*-130**: ***ent*-131**	93:07	81
4	**129**	MeCuCNMgBr	**132**:**133**	06:94	58
5	***ent*-129**	MeCuCNMgBr	***ent*-132**: ***ent*-133**	06:94	61

In early 2002, Fujii and coworkers reported that α-alkylation of γ-mesyloxy-β-methyl-α,β-unsaturated esters with organocyanocuprate-BF_3 complexes derived from isopropylmagnesium chloride in diethyl ether or tetrahydrofuran preferentially afforded the *ψ*[(*E*)-CH=CMe]- or *ψ*[(*Z*)-CH=CMe]-isosteres, respectively via *anti*-S_N2' mechanism (Scheme 13).[32] The ratio of the products is assumed to be determined by the population of two different conformers in the transition state, which is in turn very much solvent dependent. These isosteres can afford valuable tools for restriction of peptide bonds to *trans*- and *cis*-conformations, respectively. They may be vital for the evaluation of effects of *N*-methylamino acids on conformation of peptides.

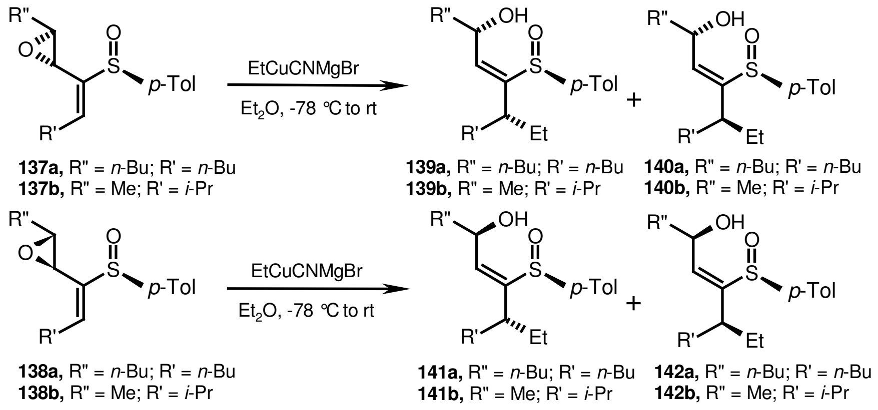


Scheme 13

1.2.7 Allyl Epoxides

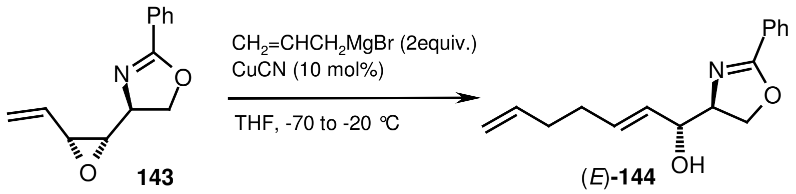
The S_N2' cleavage of allylic epoxides by organomatallic additions, including Grignard reagents is a well-established and useful method to obtain allylic alcohols. Marino et al. showed that acyclic epoxyvinyl sulfoxides **137a**,**b** and **138a**,**b** undergo high regio- and stereoselective S_N2' displacements with Grignard reagent based organocuprates to give α'-alkylated, γ-oxygenated (*Z*)-α,β-unsaturated sulfoxides in moderate to good yields and with good to excellent diastereoselectivities (Table 16).[33]

Table 16 Copper Catalyzed S_N2' Grignard Reactions with Epoxyvinyl Sulfoxides



Entry	Substrate	R″	R′	*Syn*-S_N2'	*Anti*-S_N2'	% Yield
1	**137a**	*n*-Bu	*n*-Bu	**139a** (27)	**140a** (73)	56
2	**138a**	*n*-Bu	*n*-Bu	**142a** (5)	**141a** (95)	64
3	**137b**	Me	*i*-Pr	**139b** (25)	**140b** (75)	30
4	**138b**	Me	*i*-Pr	**142b** (0)	**141b** (100)	50

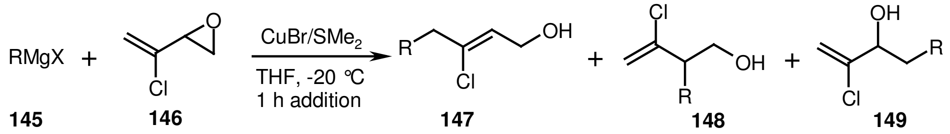
As a part of the work towards the synthesis of sphingadienine-type glucocerebrosides Murakami et al. reported that S_N2' ring opening of vinyl epoxide **143** by allylmagnesium bromide in presence of CuCN afforded (*E*)-allylic alcohol **144** with 68% yield (Scheme 14).[34]

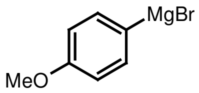
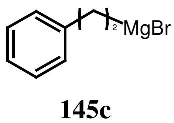
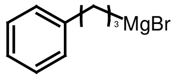
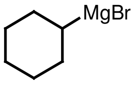
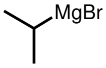
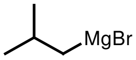
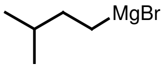
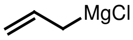
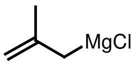
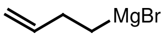
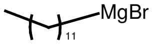


Scheme 14

(Z)-3-Chloroallylic epoxide (**146**) is known to react with phenylmagnesium bromide (**145a**) in presence of copper (I) bromide/dimethyl sulfide as catalyst to give (Z)-3-chloroalkene (**147a**, R = Ph) as major product (**147a**:**148a** = 54.1:1, R = Ph). Other Grignard reagents were also efficiently used in this reaction (Table 17) and in these additions, the products corresponding to **148** and **149** were observed at most as minor products (3%, combined).[35]

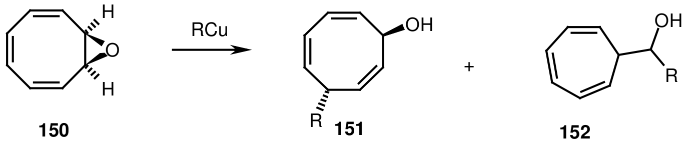
Table 17 S_N2' Grignard Coupling Reactions with 2-Chloro-3,4-epoxy-1-butene



Entry	Grignard Reagent	Product	% Yield	*Z*:*E* ratio
1	 **145b**	**147b**	89	11.1:1.0
2	 **145c**	**147c**	82	16.3:1.0
3	 **145d**	**147d**	77	20.1:1.0
4	 **145e**	**147e**	74	23.5:1.0
5	 **145f**	**147f**	76	22.1:1.0
6	 **145g**	**147g**	78	18.0:1.0
7	 **145h**	**147h**	80	15.2:1.0
8	 **145i**	**147i**	72	7.0:1.0
9	 **145j**	**147j**	74	6.5:1.0
10	 **145k**	**147k**	87	13.9:1.0
11	 **145l**	**147l**	77	14.5:1.0

Pineschi and coworkers reported the alkylative S_N2' ring opening of 1,3,5,7-cyclooctatetraene monoepoxide (COT-monoepoxide) **150** with very low occurrence of ring-contraction-isomerization product.[36] The CuCN-catalyzed addition of MeMgBr (3.0 equiv.) afforded as the main reaction product *trans*-cyclooctratrienol **151a** (62%), derived from epoxide alkylation in the allylic position (Table 18, Entry 1). The same product was selectively obtained when organocuprates such as MeCuCN(MgBr) and $Me_2CuCN(MgBr)_2$ were used. The CuCN-catalyzed addition of EtMgBr afforded **151b** (75%) with only a marginal isomerization pathway product (6% of **152b**). The phenyl and vinyl cuprates gave a relatively complex reaction mixture of products from which it was possible to isolate the cyclooctatrienols **151c** (40%) and **151d** (8%) respectively (entries 5 and 6, Table 18).

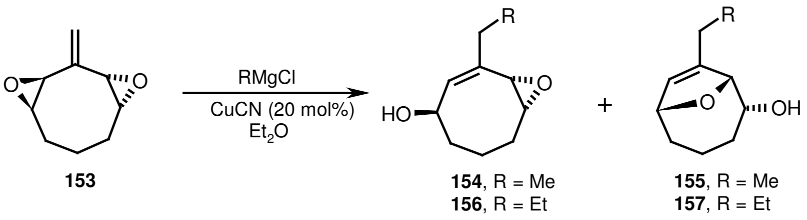
Table 18 S_N2' Addition of Grignard Reagents to COT-monoepoxide **150**



a, R = Me; b, R = Et; c, R = Ph; d, R = vinyl

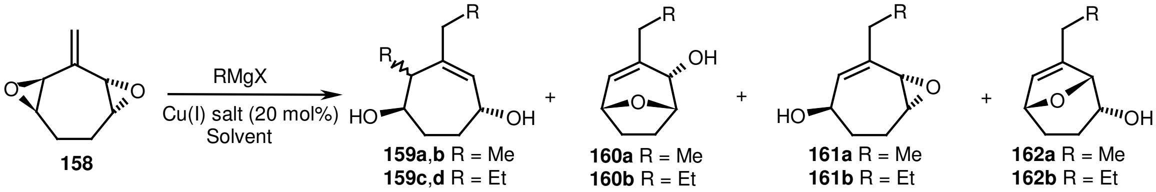
Entry	Reagents and Reaction Conditions	151/152 ratio
1	MeMgBr/cat. CuCN, Et_2O, 2.5 h, 0 °C	62/38
2	MeCuCN(MgBr), THF, 1.5 h, 0 °C	98/02
3	$Me_2CuCN(MgBr)_2$, THF, 1.5 h, 0 °C	82/18
4	EtMgBr/cat. CuCN, Et_2O, 2 h, 0 °C	94/06
5	PhCuCN(MgBr), THF, 24 h, 0 °C	96/04
6	(vinyl)CuCN(MgBr), THF, 24 h, 0 °C	95/05

Pineschi and coworkers also undertook a detailed study of copper catalyzed addition of Grignard reagents to vinyl diepoxides.[37] The copper catalyzed addition of MeMgCl to *trans*-vinyl diepoxide **153a** occurred smoothly in ether to afford a 62:38 mixture of the allylic epoxy alcohol **154** and the oxabicyclic compound **155**, whereas reaction with EtMgCl proceeded in a similar way, affording a 72:28 mixture of **156** and **157** (Scheme 15). The behavior of homologue **158** was very different. Upon treating with threefold excess of the Grignard reagent, the diol adducts of type **159** were always obtained as an approximately equimolar and inseparable mixture of diastereoisomers and were accompanied by variable amounts of alcohol **160-162a/162b**, depending on the type of RMgX and the reaction conditions used (Table 19).



Scheme 15

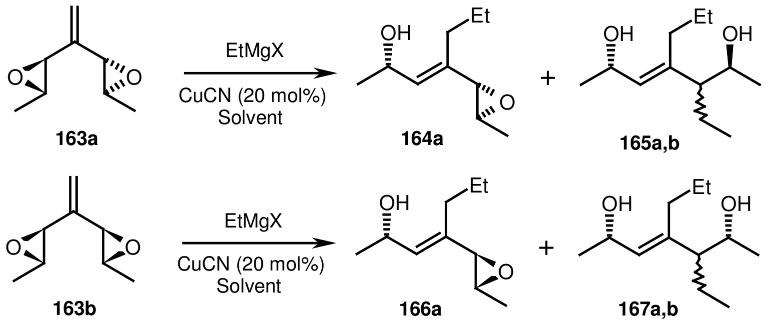
Table 19 Copper(I)-catalyzed Addition of Grignard Reagents to Vinyl Diepoxide **158**



Entry	RMgX	Solvent	Copper Salt	% Conv.	Product Distribution
1	MeMgBr	Et_2O	CuCN	98	**159a,b** (75%), **160a** (17%) **161a** (1%), **162a** (7%)
2	MeMgCl	Et_2O	CuCN	95	**159a,b** (49%), **160a** (21%) **161a** (25%), **162a** (5%)
3	MeMgBr (1.2 equiv.)	Et_2O	CuCN	76	**159a,b** (59%), **160a** (35%) **161a** (4%), **162a** (6%)
4	MeMgCl (1.2 equiv.)	Et_2O	CuCN	82	**159a,b** (20%), **160a** (20%) **161a** (50%), **162a** (10%)
5	MeMgCl	THF	CuCN	98	**159a,b** (86%), **160a** (10%) **161a** (1%), **162a** (4%)
6	MeMgBr	THF	CuCN	98	**159a,b** (81%), **160a** (14%) **161a** (1%), **162a** (4%)
7	MeMgCl	THF	CuBr-Me_2S	95	**159a,b** (80%), **160a** (16%) **161a** (1%), **162a** (3%)
8	EtMgBr	THF	CuCN	98	**159c,d** (88%), **160b** (8%) **161b** (1%), **162b** (4%)
9	EtMgBr	THF	CuBr-Me_2S	95	**159c,d** (76%), **160b** (17%) **161b** (1%), **162b** (6%)

Similar control over reactivity, depending on the reagents and solvent used for the reaction, was also observed in the acyclic series of vinyl diepoxide of type **163** (Table 20).

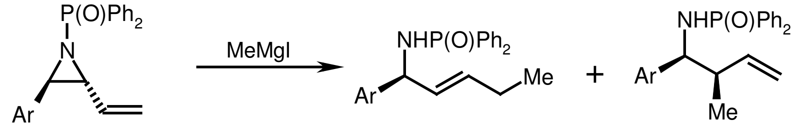
Table 20 S_N2' Copper(I)-catalyzed Addition of Grignard Reagents to Vinyl Diepoxide **163**



Entry	Substrate	EtMgX	Solvent	% Conv.	Product Distribution
1	**163a**	EtMgCl	Et_2O	92	**164a** (58%), **165a**,**b** (42%)
2	**163b**	EtMgCl	Et_2O	95	**166a** (57%), **167a**,**b** (43%)
3	**163a**	EtMgBr	THF	95	**164a** (3%), **165a**,**b** (97%)
4	**163b**	EtMgBr	THF	95	**166a** (ca. 5%), **167a**,**b** (ca. 95%)

1.2.8 Allyl Aziridines

Allylic aziridines are potential precursors of substituted allylic amines. In early 1996, Sweeney et al. reported that the S_N2' ring opening reaction of activated *N*-diphenylphosphonyl allylic aziridines **168** with methylmagensium iodide gave a 80:20 mixture of γ:α-alkylated products with moderate yields (42-43%) (Scheme 16).[38]



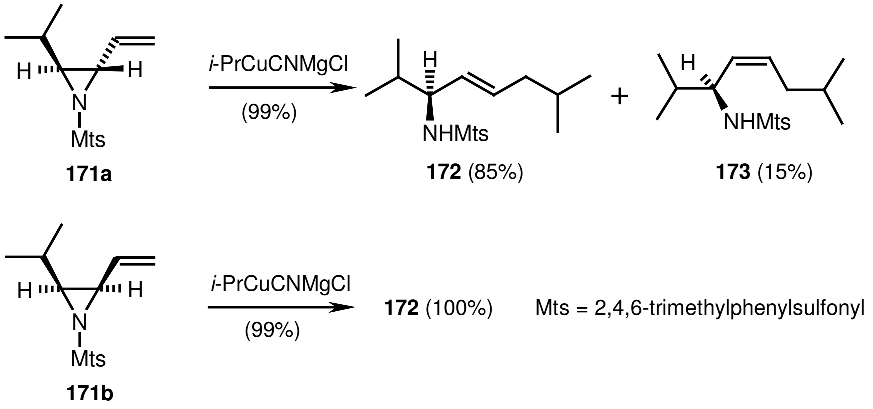
168a, Ar = Ph
168b, Ar = 4-Br-C_6H_4

169a, Ar = Ph (80%)
169b, Ar = 4-Br-C_6H_4 (80%)

170a, Ar = Ph (20%)
170b, Ar = 4-Br-C_6H_4 (20%)

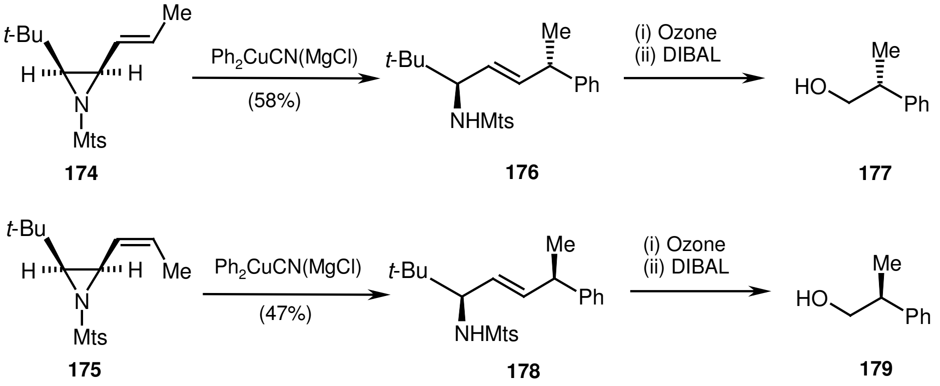
Scheme 16

In the following year Ibuka and coworkers reported that on treatment with copper catalyzed Grignard reagents, *N*-activated 2,3-*cis*-3-alkyl-2-vinylaziridine **171b** produced exclusively (*E*)-allyl amines in high yields (99%), presumably via an *anti*-S_N2' reaction pathway. On the other hand, under identical conditions, *N*-activated 2,3-*trans*-alkyl-2-vinylaziridine **171a** gave an 85:15 mixture of (*E*)- and (*Z*)-allyl amines (combined yield, 99%) (Scheme 17).[39]



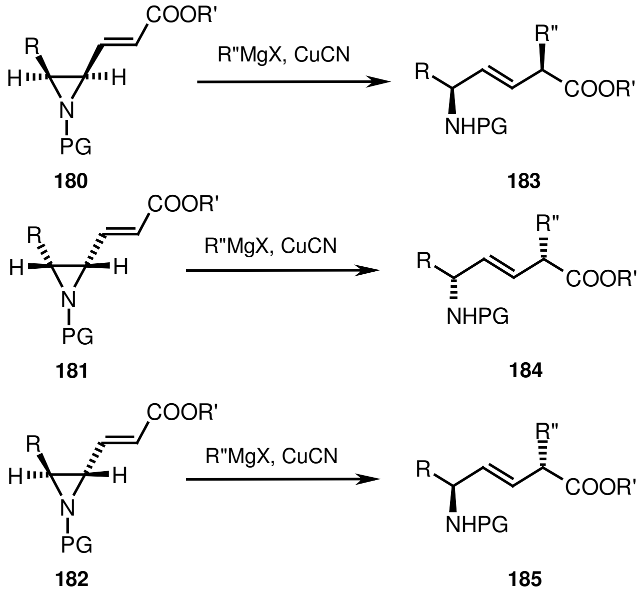
Scheme 17

The reaction of (*E*)-aziridine **174** with a higher order diphenylcyanocuprate, $Ph_2CuCN(MgCl)_2$, provided exclusively *anti*-S_N2'-substitution product **176**. The absolute configuration at the phenylated carbon centre was established by conversion of **176** into the known (*R*)-2-phenylpropan-1-ol **177** through a two-step sequence of reactions as illustrated in Scheme 18. In a similar manner, the isomeric (*Z*)-propenylaziridine **175** was converted into (*S*)-2-phenylpropan-1-ol **179** via the *anti*-S_N2' intermediate **178** establishing the stereochemical course of the reaction to be *anti*-S_N2' type of addition (Scheme 18).[40]



Scheme 18

This methodology was extensively used to prepare (*E*)-alkene dipeptide isosteres.[41-43] Copper catalyzed *anti*-S$_{N}$2′addition of Grignard reagent to aziridines bearing an α,β-unsaturated ester of the type **180-182** gave (*E*)-alkene dipeptide isosteres **183-185** in very good yield (ranging from 75-99% depending upon the aziridine and Grignard reagent) and with high regioselectivity (Scheme 19). Herein the attack of incoming neucleophile at the α-carbon in an α,β-unsaturated system with the ring opening of aziridine moiety is noteworthy.



R, R' = alkyl or aryl
PG = Ts or Mts

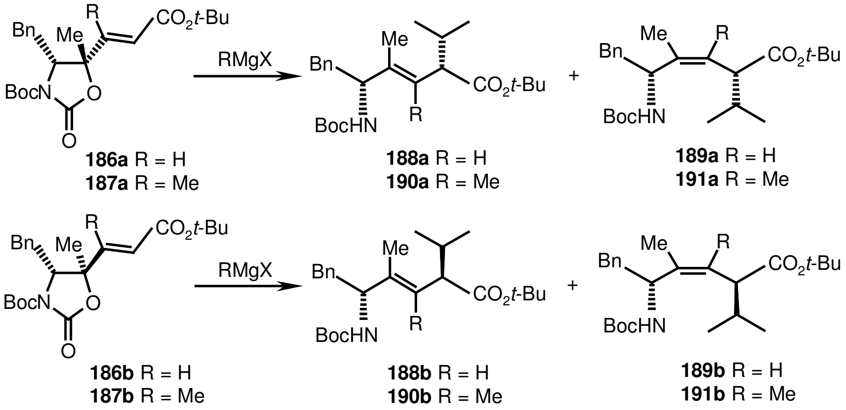
Ts = *p*-tolylsulfonyl
Mts = 2,4,6-trimethylphenylsulfonyl

Scheme 19

1.2.9 Allyl Oxazolidinones

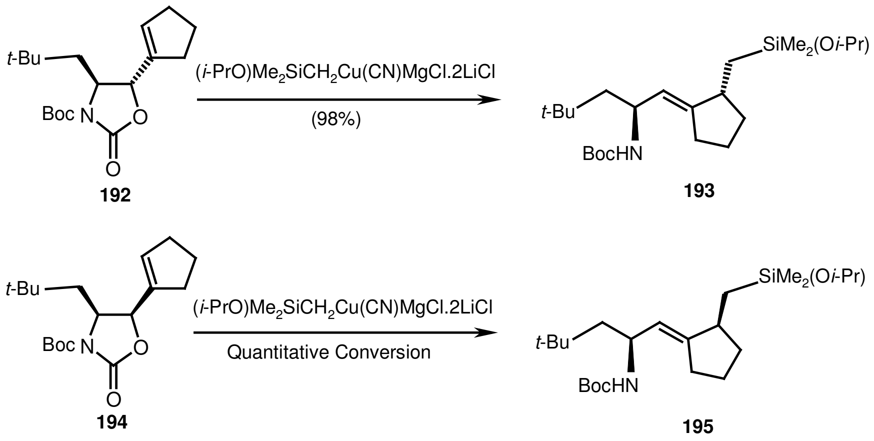
Allylic oxazolidinones can act as suitable substrates for S$_{N}$2′ Grignard addition via an addition and in situ decarboxylation to design variety of allyl amines. Fujii and coworkers reported that copper catalyzed *anti*-S$_{N}$2′ addition of Grignard reagents to β-(oxazolidin-2-on-5yl)-α,β-unsaturated esters **186a**,**b** and **187a**,**b** afforded (*E*)-allylic amines as major product (Table 21).[44]

Table 21 Alkylation of β-(Oxazolidin-2-on-5yl)-α,β-unsaturated Esters **186a**,**b** and **187a**,**b** with Grignard Reagents



Entry	Substrate	Reagent and Reaction Conditions	% Yield	Product Ratio
1	**186a**	*i*-PrCu(CN)MgCl.BF$_3$.2LiCl (4 equiv.), -78 °C, 30 min	95	**188a**:**189a** = 100:0
2	**186a**	*i*-PrCu(CN)(MgCl)$_2$.BF$_3$.2LiCl (4 equiv.), -78 °C, 30 min	95	**188a**:**189a** = 100:0
3	**186b**	*i*-PrCu(CN)MgCl.BF$_3$.2LiCl (4.2 equiv.), -78 °C, 30 min	99	**188b**:**189b** = 68:32
4	**186b**	*i*-PrCu(CN)(MgCl)$_2$.BF$_3$.2LiCl (4.2 equiv.), -78 °C, 30 min	85	**188b**:**189b** = 79:21
5	**187a**	*i*-PrCu(CN)(MgCl)$_2$.BF$_3$.2LiCl (4 equiv.), -78 °C, 30 min, then 0 °C, 3 h	48	**190a**:**191a** = 76:24
6	**187a**	*i*-PrCu(CN)(MgCl)$_2$.BF$_3$.2LiCl (6 equiv.), -78 °C, 30 min, then 0 °C, 3 h	73	**190a**:**191a** = 75:25
7	**187a**	*i*-PrCu(CN)(MgCl)$_3$.BF$_3$.2LiCl (4 equiv.), -78 °C, 30 min, then 0 °C, 3 h	77	**190a**:**191a** = 68:32
8	**187b**	*i*-PrCu(CN)(MgCl)$_2$.BF$_3$.2LiCl (4 equiv.), -78 °C, 30 min, then 0 °C, 3 h	95	**190b**:**191b** = 79:21

In the same year, Fujii and coworkers also reported the use of this methodology to synthesize (*E*)-alkene *trans*-xaa-pro dipeptide mimetics. Oxazolidinone **192**, when reacted with (*i*-Pro)Me$_2$SiCH$_2$Cu(CN)MgCl.2LiCl in THF at -78 °C for 30 min, with additional stirring for 3 h at 0 °C, proceeded quantitatively with ring opening and decarboxylation to give exclusively *anti*-S$_N$2′ product **193**, whereas reaction of **194** proceeded quantitavely to afford alkylated product **195** (Scheme 20).[45] In these cyclic systems, unlike acyclic allylic carbamates, the corresponding nitrogen lacks the ability to undergo complexation due to the presence of an *N*-Boc group. Therefore, reactive intermediates account for the organocopper mediated *anti*-S_N2' reactions.



Scheme 20

1.2.10 Allyl Thioethers

Reactivity of allylic thioethers was found to be completely different as compared to that of allylic ethers primarily because of the better leaving group ability of the thioethers. Calo et al. reported that enantioselective cross coupling reaction of Grignard reagent in presence of CuBr with optically active allylic thioethers **196-202** (Figure 5) in diethyl ether produced high yield of γ-substituted products (α:γ = 99%) (Figure 6) with moderate to high enantioselectivity (Table 22).[46]

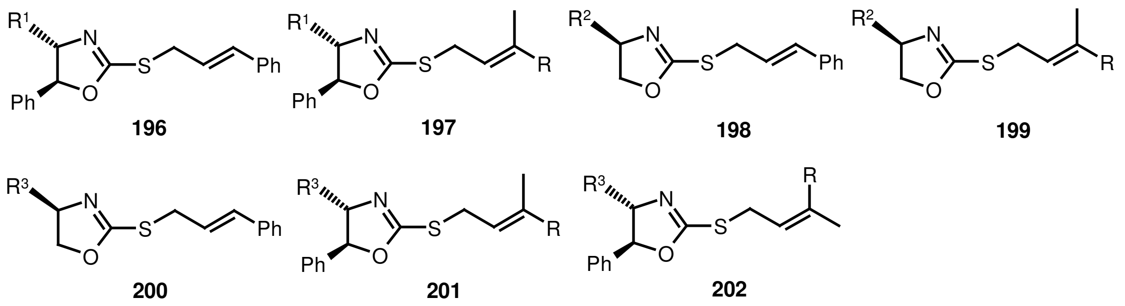
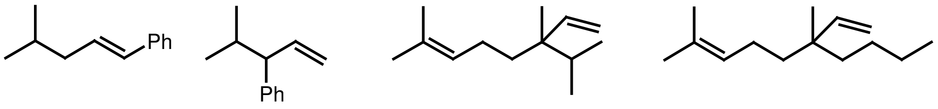


Figure 5 Substrates Used for Regioselective Cross-coupling Reactions with Grignard Reagents



203 204 205 206

Figure 6 Products Formed from Regioselective Cross-coupling Reactions with Grignard Reagents

The regioselectivity depends on the solvent as well as the CuBr:allylic sulfide ratio. The change of CuBr:Grignard reagent ratio to 0.2:1.5 in the reaction of **200** with *i*-PrMgBr in THF gave prefentially **203**; when the reaction was performed by adding the Grignard reagent dropwise to the substrate and CuBr at –30 °C over 15 min with CuBr:substrate:organomagnesium ratio 4:1:1.5, excellent γ-selectivity (>99%) was observed. The regio- and enantioselectivity of these reactions is related to the coordination exerted by the heterocyclic nitrogen towards the organocopper species.

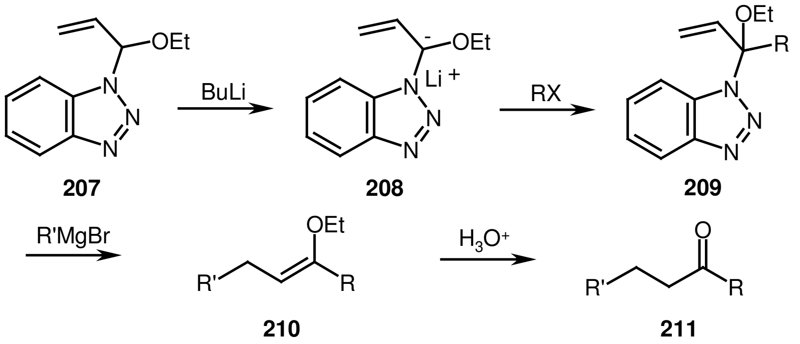
Table 22 Enantioselective Cross-coupling Reactions of Grignard Reagents with allylic thioethers **196-202** in Diethyl Ether [a]

Entry	**Substrate**	**RMgBr**	**Product**	**% Yield**	**% *ee* (*R*/*S*)**
1	**196**	*i*-Pr	**204**	78	58 (***S***)
2	**197**	*i*-Pr	**205**	-	73 (nd)
3	**198**	*i*-Pr	**204**	80	78 (***R***)
4	**199**	*i*-Pr	**205**	83	98 (nd)
5	**200**	*i*-Pr	**204**	82	50 (***S***)
6	**201**	*i*-Pr	**205**	74	83 (nd)
7	**201**	*n*-Bu	**206**	-	67 (nd)
8	**202**	*i*-Pr	**205**	78	77 (nd)

ndNot determined.

1.2.11 Allyl Benzotriazoles

Katritzky et al. reported that α-(benzotriazolyl)allylic ethers of the type **209** can react in S_N2' fashion with certain Grignard reagents to give enol ethers **210**, which can be directly hydrolyzed to corresponding ketones **211** in moderate to good yields (3-steps, 31-81%) (Scheme 21). The same methodology can be used for the convenient preparation of 1,4-diketones, γ-hydroxyalkyl ketones and α-hydroxyalkyl ketone.[47] This elegant method has potential widespread applicability to generate a diverse range of 1,4-diketones with variety of substituents.



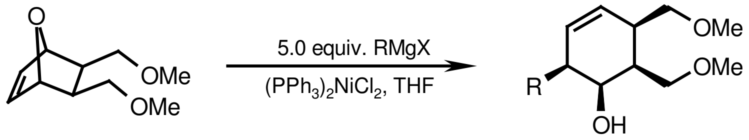
210a R = *n*-$C_{12}H_{25}$, R' = *n*-C_4H_9; **211a** R = Et, R' = *p*-$CH_3C_6H_4$
211b R = *n*-Bu, R' = *p*-$CH_3C_6H_4$; **211c** R = 3-MeBu, R' = *p*-$CH_3C_6H_4$
211d R = 3-MeBu, R' = Ph; **211e** R = *n*-C_6H_{17}, R' = *p*-$CH_3C_6H_4$
211f R = 3-MeBu, R' = *i*-Pr; **211g** R = *i*-Pr, R' = Ph
211h R = *i*-Pr, R' = 3-MeBu; **211i** R = Cyclohexyl, R' = Ph

Scheme 21

1.2.12 Oxabicyclic Alkenes

Oxabicyclic compounds are known to undergo ring opening reactions with Organomagnesium reagents leading to synthetically valuable six and seven membered ring systems. Lautens et al. reported that a catalytic amount of $(PPh_3)_2NiCl_2$ can promote the reaction of [2.2.1]-oxabicyclic alkene **212** with 5.0 equiv of MeMgBr after 23 h in THF to afford ring opened product **213** in 70% yield as a single isomer (Table 23, Entry 1).[48] Similar results were also obtained in the coupling reaction of **212** with PhMgBr and $PhCH_2MgCl$, although the latter occurs in low yield (Table 23, Entry 2 and 3). The reaction was highly regioselective, forming a product equivalent to clean S_N2' attack, and highly stereoselective in which the nucleophile attacks on the same side of the ring as the bridging oxygen (*syn*-attack).

Table 23 $(PPh_3)_2NiCl_2$-catalyzed S_N2' Ring Opening Reactions of Oxabicyclic Alkene **212** with Grignard Reagents



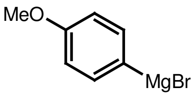
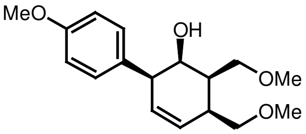
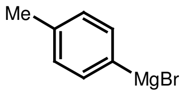
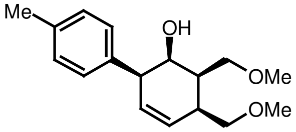
212

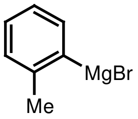
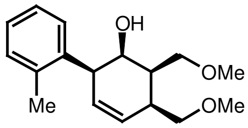
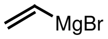
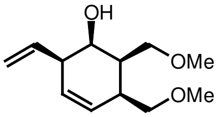
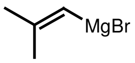
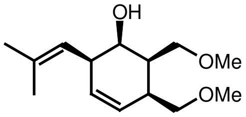
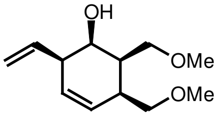
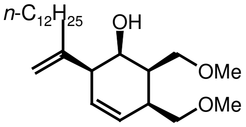
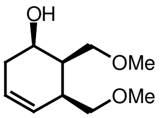
213 R = Me
214 R = Ph
215 R = $PhCH_2$

Entry	RMgX	Catalyst (mol%)	Time	Temp.	Product	% Yield
1	MeMgBr	2.6	23 h	rt	**213**	70
2	PhMgBr	2.5	5 h	rt	**214**	67
3	$PhCH_2MgBr$	6.0	3 h	reflux	**215**	18

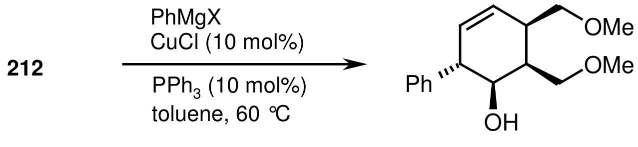
In 2000 Nakamura and coworkers also reported iron-catalyzed *syn*-ring opening of compound **212** with PhMgBr in THF at room temperature exclusively affording **214** in 62% yield.[49] Two years later Nakamura and coworkers reported a detailed study of ring-opening reactions of **212** with 2.0 equiv of various Grignard reagents in presence of $FeCl_3$ (5 mol%) and TMEDA (3 equiv) in THF (Table 24).[50]

Table 24 Iron-catalyzed S_N2' Ring Opening Reactions of Oxabicyclic Alkene **212** with Grignard Reagents

Entry	RMgX	Temp.	Time	Product (% Yield)
1		25 °C	3 h	 **216** (69%)
2		25 °C	5 h	 **217** (72%)

3		65 °C	1 h	 **218** (75%)
4		65 °C	13 h	 **219** (41%)
5		65 °C	5 h	 **220** (40%)
6	EtMgBr	25 °C	1 h	 **219** (24%)
7	*n*-$C_{14}H_{29}$MgBr	25 °C	1 h	 **221** (54%)
8	*i*-PrMgBr	25 °C	1 h	 **222** (92%)

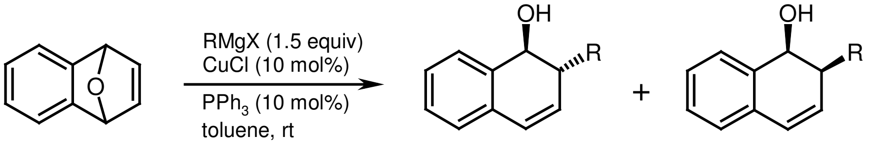
Carretero and coworkers also described that, unlike nickel or iron, copper catalyzed ring opening reactions show predominant preference for *anti*-attack.[51] The reaction of **212** in copper catalyzed condition gave *anti*-ring opened product **223** (Scheme 22), whereas the ring-opening of benzo-substituted oxabicyclic alkene **224** with a variety of Grignard reagents is known to occur with very high regioselectivity and *anti*-stereoselectivity in the presence of substoichiometric amounts of CuCl and PPh_3 (Table 25). In the copper catalyzed reaction, the stereochemical outcome can be explained by a copper catalyzed S_N2' attack in which the in situ formed organocuprate reacts with the alkene *anti* with respect to the leaving group (*endo*-attack). The resulting π-allylic copper would then undergo a reductive elimination to give the observed ring opened product **223**.



223

Scheme 22

Table 25 Cu-catalyzed S_N2' Grignard Ring Openings of Oxabenzonorbornadiene **224** with Grignard Reagents



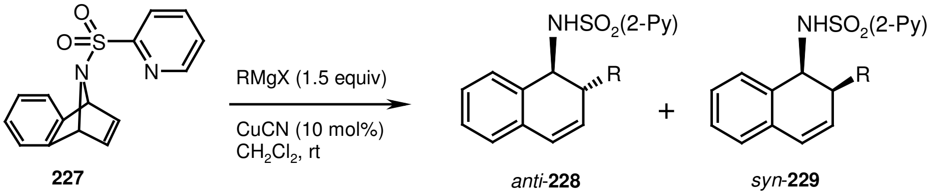
224 *anti*-**225** *syn*-**226**

Entry	RMgX	Time (h)	Product	*anti*/*syn*	% Yield
1	MeMgBr	6	**225a**	98:02	92
2	EtMgBr	0.3	**225b**	97:03	76
3	EtMgBr	0.3	**225b**	95:05	83
4	*i*-BuMgBr	3	**225c**	98:02	89
5	*n*-$C_{10}H_{21}$MgCl	4	**225d**	90:10	66
6	CyclohexylMgCl	2	**225e**	98:02	51
7	CyclohexylMgCl	1	**225e**	98:02	64
8	BnMgBr	12	**225f**	98:02	47
9	PhMgBr	2	**225g**	98:02	90
10	PhMgBr	4	**225g**	98:02	84
11	*p*-OMe-C_6H_4MgBr	12	**225h**	98:02	92
12	*p*-F-C_6H_4MgBr	1.5	**225i**	98:02	94

1.2.13 Azabicyclic Alkenes

Alike oxabicyclic alkenes, the corresponding azabicyclic alkenes are also known to undergo S_N2' ring-opening reactions with Grignard reagents. Carretero et al. reported that copper catalyzed ring-opening reactions of *N*-activated azabicyclic alkene **227** proceed smoothly to the corresponding 1-aminodihydronaphthalenes in good to excellent chemical yields and very high *anti*-selectivity (Table 26).[52]

Table 26 Cu-catalyzed S_N2' Ring Opening of Azabenzonorbornadiene **227** with Grignard Reagents

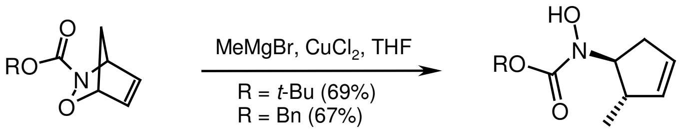


Entry	RMgX	Time (min)	Product	*anti*/*syn*	% Yield
1	MeMgBr	120	**228a**	98:02	89
2	$TMSCH_2MgBr$	95	**228b**	93:07	73
3[a]	EtMgCl	20	**228c**	98:02	65
4	$PhCH_2MgCl$	20	**228d**	98:02	53
5[a]	*n*-$C_{10}H_{21}MgCl$	20	**228e**	85:15	74
6	PhMgBr	15	**228f**	98:02	93
7	*p*-Me-C_6H_4MgCl	10	**228g**	98:02	91
8	*p*-OMe-C_6H_4MgCl	10	**228h**	98:02	98
9	*p*-F-C_6H_4MgCl	20	**228i**	98:02	92
10	3,5-[Bis(CF_3)]C_6H_4MgBr	15	**228j**	98:02	97
11	1-NaphthylMgBr	30	**228k**	98:02	91
12	MesitylMgBr	480	**228l**	98:02	87
13	2-ThienylMgBr	120	**228m**	98:02	88

[a] CuCl was used instead of CuCN.

1.2.14 Oxa-azabicyclic Alkenes

Certain oxa-azabicyclic alkenes also undergo ring-opening reactions with a wide variety of nucleophiles. Miller and coworkers reported S_N2' ring-opening reactions of *N*-Boc cycloadduct **230** and *N*-Cbz cycloadduct **231** with methylmagnesium bromide in presence of 10 mol% of $CuCl_2$ to give *anti*-1,2-products **232** and **233** respectively (Scheme 23).[53]



230, R = *t*-Bu
231, R = Bn

232, R = *t*-Bu
233, R = Bn

Scheme 23

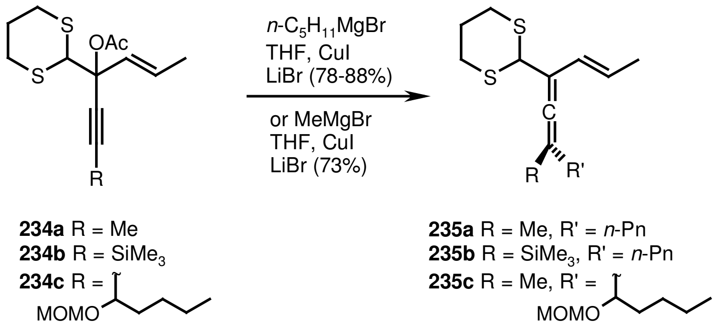
In summary, we have presented a concise account of S_N2' coupling reactions of Grignard reagents with allylic substrates with or without metal catalysis. Some of the reactions, especially reactions of allylic epoxides, aziridines and ring opening reactions of oxa- and azabicyblic alkenes have application potential in organic synthesis as the regio- and stereoslelectivities observed in these reactions are well defined. However, by fixing the reaction parameters, it is possible to perform all these reactions in a highly chemo-, regio- and stereoselective fashion. We foresee that many more such applications of S_N2' Grignard coupling reactions will be reported in the near future.

1.3 S_N2' Grignard Coupling Reactions with Propargylic Substrates

Propargylic substrates are known to undergo very smooth S_N2' coupling reactions to produce mainly allenic derivatives. Allenes in general and 2,3-allenol derivatives in particular are versatile building blocks for advanced organic synthesis. Generation of allenes in stereoselective manner thus became a fascinating field in organic chemistry during the past decade. The easy transfer of chirality residing in propargylic substrates to the formed allenic products by the reaction of Grignard reagents has been well documented in the recent literature. Herein, we present a concise summary of these reactions classified based on the substrates.

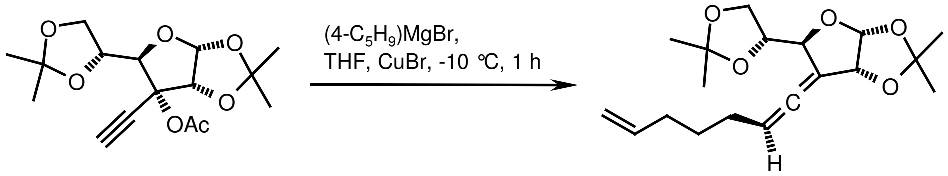
1.3.1 Propargyl Acetates

Propargyl acetate has been used by Spino et al. to prepare vinyl allenes, which in turn can undergo smooth cycloaddition rections.[54] Thus propargyl acetate **234** when reacted with dialkylcuprate under strictly defined conditions led to vinylallenes **235**. The presence of more reactive propargyl acetate, reduces the formation of byproducts from addition to the double bond (Scheme 24). They have used these vinyl allenes for intermolecular [4+2]-cycloaddition to prepare six membered cyclic compounds having tetrasubstituted *exo*-cyclic double bonds.



Scheme 24

As a part of their synthetic studies towards the construction of the tricyclic framework of the natural product emunicin, Gurjar and coworkers recently reported a highly diastereoselective S_N2' addition of pentenylmagnesium bromide to propargyl acetate **236** giving the allene **237** in good yield (Scheme 25).[55]

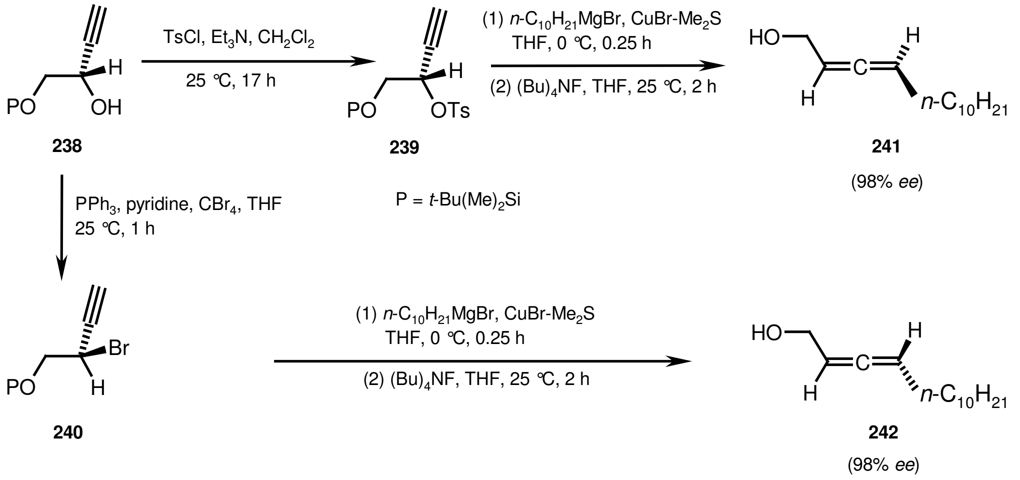


236 **237**

Scheme 25

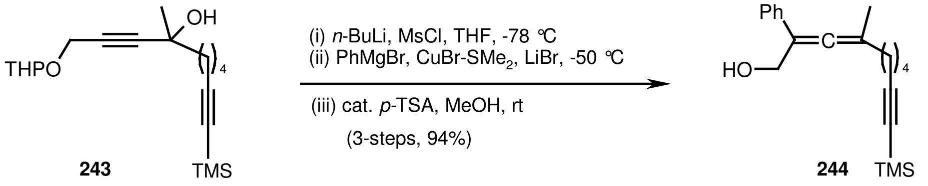
1.3.2 Propargyl Silylethers

Optically active allenes can be obtained from optically active propargyl derivatives in high enantiomeric purity. As a part of their synthetic studies towards Lipoxygenase inhibitors, Marnett and coworkers prepared both the dextro- and levorotatory allenes **241** & **242** in good yield and with high enantiomeric purity by the copper catalyzed reaction of decylmagnesium bromide with parent proprgyl tosylate and propargyl bromide (Scheme 26).[56] They have further used these optically active allenes to synthesize (carboxyalkyl)benzyl allenyl ethers and tested them as inhibitors of 12-lipoxygenase (12-LO) from porcine leukocute cytosol.



Scheme 26

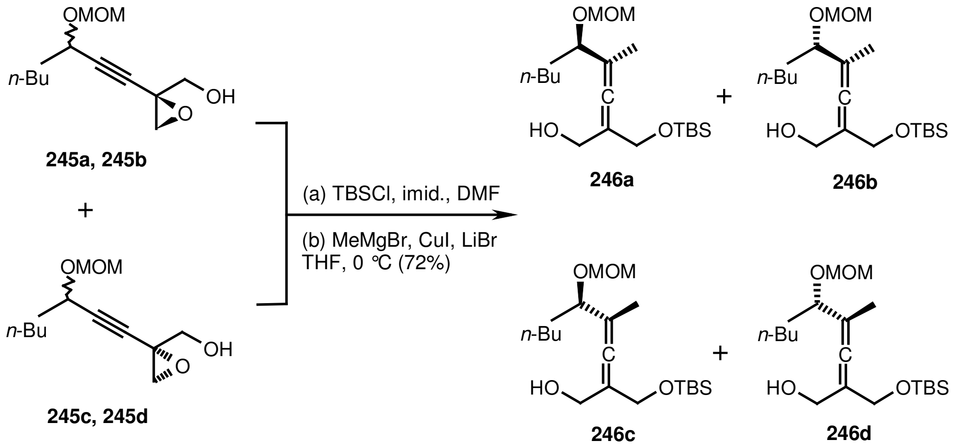
Malcria and coworkers also reported synthesis of allenic alcohol **244** by the use of copper catalyzed S_N2' displacement of propargyl mesylate in very good yield (Scheme 27).[57] They have used this allenic alcohol **244** for diastereoselective construction of 11-aryl steroid skeleton.



Scheme 27

1.3.3 Propargyl Epoxides

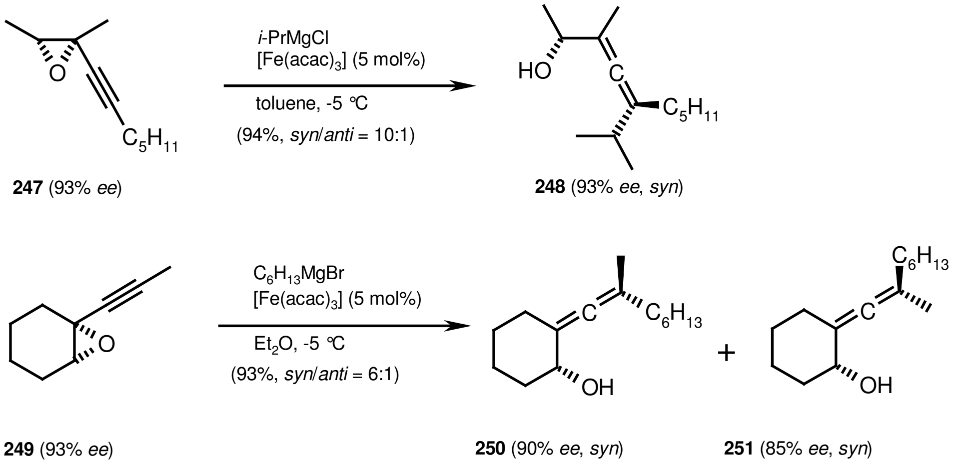
Propargyl epoxides are known to undergo S_N2' addition to give 2,3-allenols. Spino et al reported that the highly *anti*-selective addition of methylmagnesium bromide to propargyl epoxides **245** in presence of copper catalyst yielded the diastereomeric allenic alcohols **246** in a 1:1 ratio each possessing 54% *ee* (Scheme 28).[58]



Ratios: **245a**:**245b**, **245c**:**245d**, **246a**:**246b**, and **246c**:**246d** = 1:1
245a+**245b**:**245c**+**245d** and **246a**+**246b**:**246c**+**246d** = 4:1

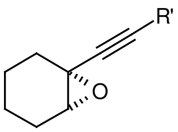
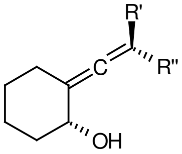
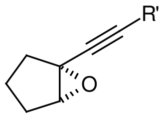
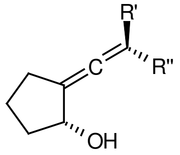
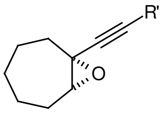
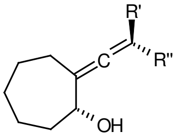
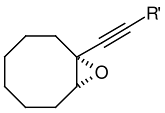
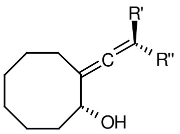
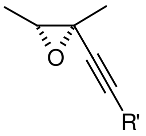
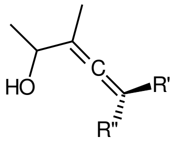
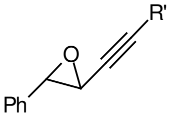
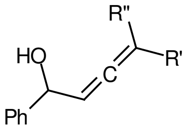
Scheme 28

Fürstner et al. reported iron catalyzed S_N2' Grignard addition of propargyl epoxide, where the central chirality of epoxides was transferred to the axial chirality of the resulting 2,3-allenols with high fidelity (Scheme 29).[59] Moreover, propargyl epoxides with terminal or nonterminal alkynes units react with similar ease (Table 27). The present consistent reactivity trend has been interpreted in terms of a directed delivery of the nucleophile to the alkyne, which occurs only after the catalyst and/or the Grignard reagent is coordinated to the oxygen atom of the substrate.

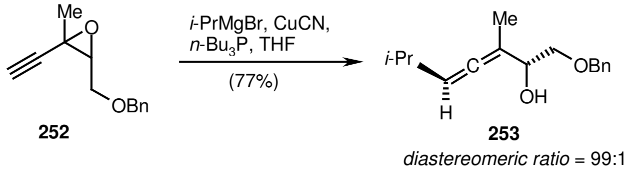


Scheme 29

Table 27 Synthesis of 2,3-Allenols from Iron Catalyzed S_N2' Grignard Reactions with Propargyl Epoxide

Entry	Substrate	R′	R″MgX	Solv.	Major Product	*syn*: *anti*	% Yield
1		H	$C_6H_{13}MgBr$	toluene		78:22	72
2		H	PhMgBr	toluene		75:25	83
3		H	MeMgBr	toluene		55:45	71
4		Me	$C_6H_{13}MgBr$	Et_2O		86:14	93
5		Me	$C_6H_{13}MgBr$	Et_2O		78:22	75
6		Me	$C_6H_{13}MgBr$	Et_2O		50:50	54
7		Me	*i*-PrMgCl	Et_2O		84:16	79
8		Me	*i*-PrMgCl	toluene		90:10	70
9		Me	PhMgBr	Et_2O		66:34	98
10		Ph	MeMgBr	Et_2O		65:35	69
11		CH_2OH	$C_6H_{13}MgBr$	Et_2O		92:08	65
12		Me	$C_6H_{13}MgBr$	toluene		80:20	73
13		Me	$C_6H_{13}MgBr$	toluene		88:12	80
14		Me	*i*-PrMgCl	toluene		84:16	79
15		Me	$C_6H_{13}MgBr$	toluene		92:08	62
16		Me	$C_6H_{13}MgBr$	Et_2O		75:25	90
17		Me	*i*-PrMgCl	toluene		86:14	75
18		Me	*i*-PrMgCl	Et_2O		60:40	89
19		C_5H_{11}	*i*-PrMgCl	toluene		91:09	94
20		C_5H_{11}	*i*-PrMgCl	Et_2O		75:05	64
21		C_5H_{11}	EtMgBr	toluene		82:18	55

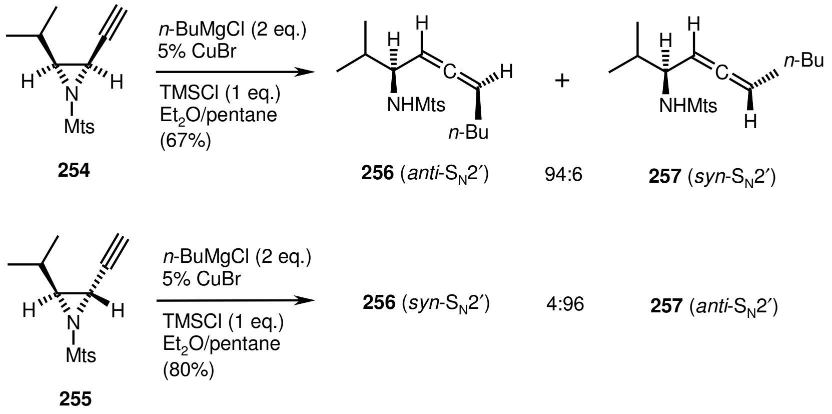
Recently Krause et al. reported a convenient method for preparation of diastereomerically pure 2,3-allenol **253** from the corresponding propargyl epoxide **252** using *anti*-selective copper catalyzed Grignard addition, which can be useful for generation of 3-pyrrolines (Scheme 30).[60]



Scheme 30

1.3.4 Propargyl Aziridines

Propargylic aziridines are known to undergo smooth S_N2' Grignard coupling reactions to give amino allenes. Ibuka and coworkers reported the synthesis of chiral *N*-protected aminoallenes from 3-alkyl-2-ethynylaziridines via copper catalyzed Grignard addition. The reaction of two aziridines **254** and **255** with *n*-BuMgCl yielded in each case a mixture of two S_N2' products, favoring the product formed by the nucleophilic attack *anti* to the leaving aziridine moiety in both the cases (Scheme 31).[61]

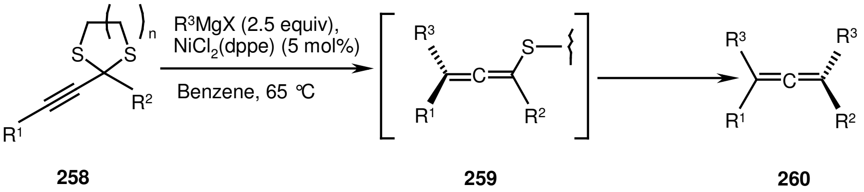


Scheme 31

1.3.5 Propargyl Dithioacetals

Propargyl dithioacetals **258** can also undergo S_N2' addition reactions with Grignard reagents to give the allenic products following a second coupling of the formed intermediate allenyl thioether **259** with the same Grignard reagent as described by Luh and coworkers (Table 28).[62] This method will be practically useful for the generation of tetrasubstituted allenes.

Table 28 Ni-catalyzed Grignard Cross Coupling Reactions of Dithioacetals **258**

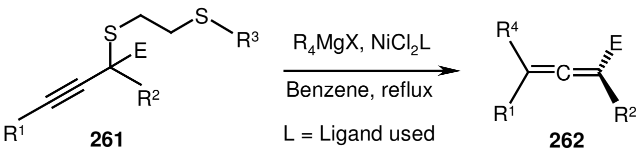


Entry	Substrate	n	R^1	R^2	R^3	Product (% Yield)
1	**258a**	2	Ph	H	Me	**260a** (88)
2	**258b**	1	Ph	Me	Me	**260b** (90)
3	**258c**	1	Ph	Ph	Me	**260c** (79)
4	**258d**	1	Bu	Me	Me_3SiCH_2	**260d** (90)
5	**258b**	1	Ph	Me	Me_3SiCH_2	**260e** (92)
6	**258e**	1	Me_3Si	Me	Me_3SiCH_2	**260f** (95)
7	**258f**	1	PhC≡C	Me	Me	**260g** (78)
8	**258b**	1	Ph	Me	Ph	**260h** (56)
9	**258c**	1	Ph	Ph	Et	**260i** (55)
10	**258c**	1	Ph	Ph	Bu	**260j** (57)

1.3.6 Propargyl Thioethers

Carbon and sulfur have similar electronegativities, rendering the carbon-sulfur bond ambiphilic. Accordingly, the carbon end of a thioether linkage can serve either as an electrophilic centre or as a carbanionic leaving group. Luh and coworkers also described that propargylic thioethers react with Grignard reagents in presence of Ni catalyst to yield substituted allene derivatives (Table 29).[63] Employing this method, di-, tri, as well as tetrasubstituted allenes can be synthesized conveniently.

Table 29 Ni-catalyzed Grignard Cross Coupling Reactions of Thioethers **261**



Entry	Subs.	R^1	R^2	E	R^3	R^4	L	Product (% Yield)
1	**261a**	Ph	Me	Me	*t*-Bu	$TMSCH_2$	dppe	**262a** (72)
2	**261b**	Ph	Me	$H_2C{=}CHCH_2$	*t*-Bu	*n*-Bu	dppe	**262b** (62)
3	**261c**	Ph	Ph	Bu	*n*-Bu	Ph	dppe	**262c** (67)

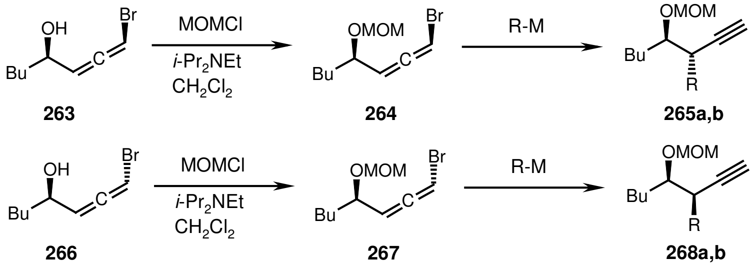
In summary, S_N2' Grignard coupling reactions of propargylic substrates provide an easy access to allene derivatives. Propargylic epoxide and aziridines are the best suited substrate for effecting chirality transfer to produce nonracemic hydroxy and aza allenes, which have wide spread applicability in the field of organic chemistry. In most of the cases the reagent attacks *anti* to the leaving group, therefore it is easy to predict the product stereochemistry.

1.4 S_N2' Grignard Coupling Reactions with Bromoallenes

It is well known that the application of acetylene chemistry is one of the key tools of modern organic chemists. The acetylenic moiety provides a convenient unit, which may be converted into a variety of functionalities, and optically active alkynyl compounds are employed as versatile building blocks for the design and construction of more complex chiral molecules. One of the easiest ways to generate an acetylene moiety is the S_N2' coupling reaction of bromoallenes.

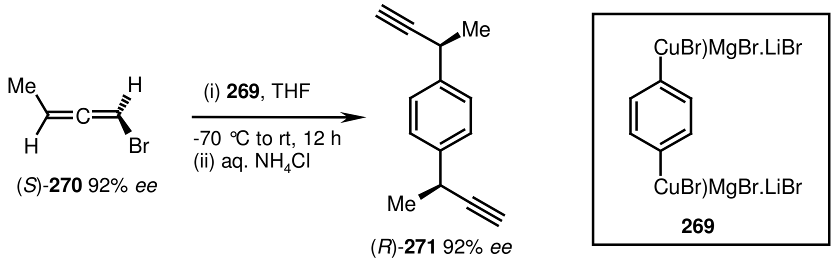
Bromoallenols derived from propargylic epoxides can be transferred in a stereospecific fashion and into 1,2-disubstituted homopropargylic protected alcohols with Grignard reagents with or with out copper salt (Table 30).[64] Apparently, the presence of the heteroatoms in the α-position of the allenyl moiety not only directs the substitution reaction in the *anti*-S_N2' way, but also considerably enhances the reaction rate of Grignard reagents.

Table 30 Protected Homopropargylic Alcohols from Protected Bromoallenols **264** and **267**



Entry	Substrate	R-M	Product	% Yield
1	**264**	*i*-PrMgBr/CuBr (5%)	**265a**	85
2	**264**	*i*-Pr / MgBr$_2$/Me$_2$S	**265a**	42
3	**264**	*i*-PrMgBr	**265a**	90
4	**264**	AllylMgBr/ CuBr (5%)	**265b**	53
5	**267**	*i*-PrMgBr	**268a**	83

Recently, Caporusso et al. reported selective synthesis of 1,4-bis(2-propynyl)benzenes starting from the corresponding bromoallenes by the reaction with organbis(heterocuprates) generated from di-Grignard reagents. The high 1,3-*anti*-stereoselectivity of the coupling process allows for obtaining enantiomerically enriched α,ω-diyne **271** from optically active allenic substrate **270** (Scheme 32).[65]



Scheme 32

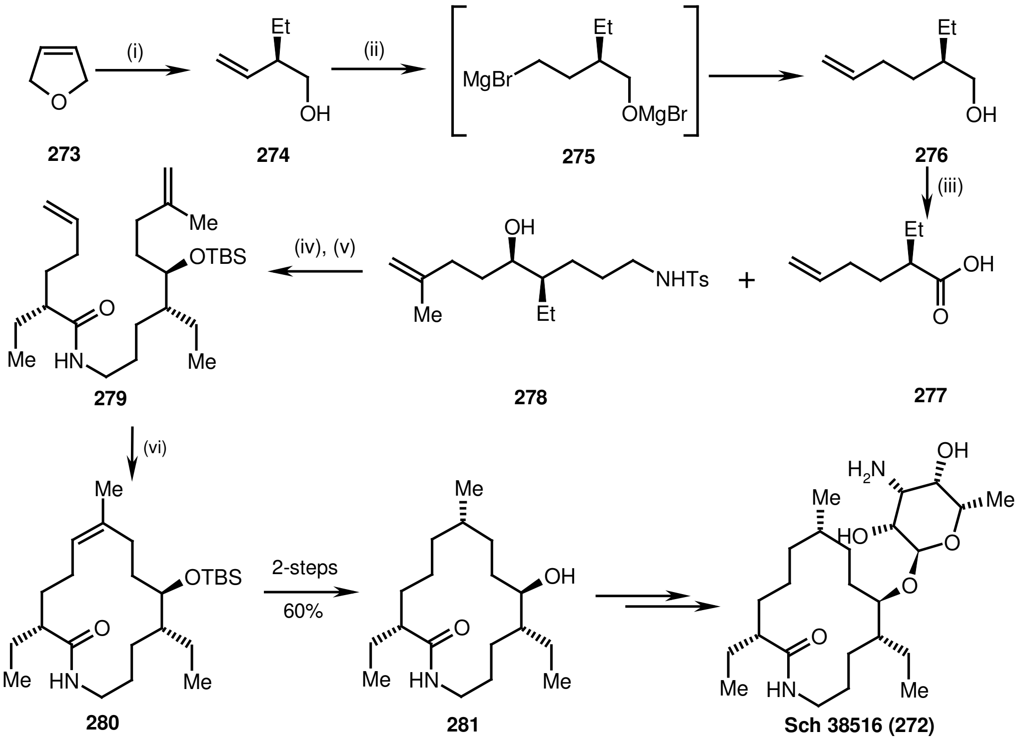
In summary, S_N2' cross coupling reactions of Grignard reagents with bromoallenes are the most convenient methods for the synthesis of chiral 1-alkynes. The raction proceeds in general, in high 1,3-*anti* stereoselective pathway. The regiochemical outcome of this reaction greatly depends on steric interactions, an increase in the bulk of the incoming nucleophile generally favoring the formation of alkyne derivatives, rather than the simple S_N2 coupled product.

1.5 S_N2' Grignard Coupling Reactions in Natural/Unnatural Product Synthesis

The vast developments in the area of S_N2' Grignard coupling reactions during the last 100 years span have been reflected through the appearance of number of publications on synthesis of natural and unnatural products, employing it as one of the key reactions. Although several aspects of S_N2' Grignard coupling reactions are well proved today, it is still a challenging task to introduce these reactions to design rather complex target molecules. This section describes some important applications of S_N2' Grignard coupling reactions in natural and unnatural product synthesis.

1.5.1 Synthesis Sch 38516 Aglycon

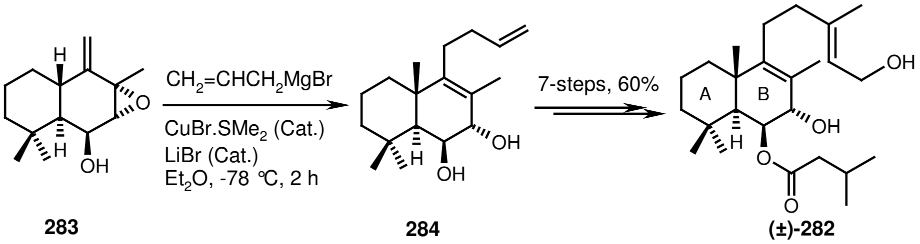
Sch 38516 (**272**), an antifungal agent, was discovered by researchers at Schering-Plough and is active against influenza A virus.[66] Hoveyda and coworkers reported an efficient enantioselective synthesis of the aglycon part of **272** by coupling of carboxylic acid **277** and amine **278**, followed by ring closing metathesis of the formed diene **279**. The carboxylic acid **277** was synthesized through asymmetric S_N2' alkylation of dihydropyran **273** (Scheme 33).[67]



Scheme 33 *Reagents, conditions and yields*: (i) EtMgBr (0.8 equiv.), (*S*)-[EBTHI]-Zr-BINOL (0.4 mol%), THF, 70 turnovers; (ii) *n*-PrMgBr (3 equiv.), Cp_2TiCl_2, THF; then CH_2CHBr (4 equiv.), $(Ph_3)_2NiCl_2$ (2-steps, 72%); (iii) $[n\text{-}CH_3(CH_2)_2]_4NRuO_4$, MeCN, NMO (3 equiv.) (65%); (iv) DCC (1 equiv.), *N*-methylmorpholine (3 equiv.), HOBT (1.2 equiv.), 22 °C, 12 h (60%); (v) TBSOTf (3 equiv.), 2,6-lutidine (4 equiv.), CH_2Cl_2, 0 °C (90%); (vi) $Mo(CHCMe_2Ph)[N(2,6\text{-}\{i\text{-}Pr\}2C_6H_3)(OCMe\{CF_3\}_2)]_2$ (25 mol%), C_6H_6, 50 °C (60%).

1.5.2 Synthesis of 6-β-Isovaleroxylabda-8,13-diene-7α,15-diol

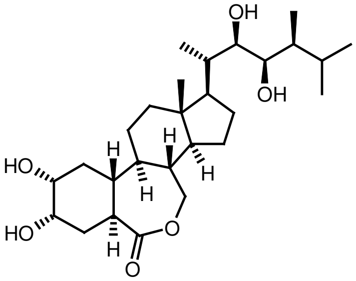
6-β-Isovaleroxylabda-8,13-diene-7α,15-diol (**282**), a diterpene diol isolated from the marine pulmonate limpet *Trimusculus recticulants*, exhibits potent repellent activity against predatory starfish.[68] Ohfune and coworkers reported the synthesis of this marine natural product by the stereocontrolled construction of the B-ring of (±)-**282** via S_N2' alkylative epoxide cleavage followed by standard organic transformations (Scheme 34).[69]



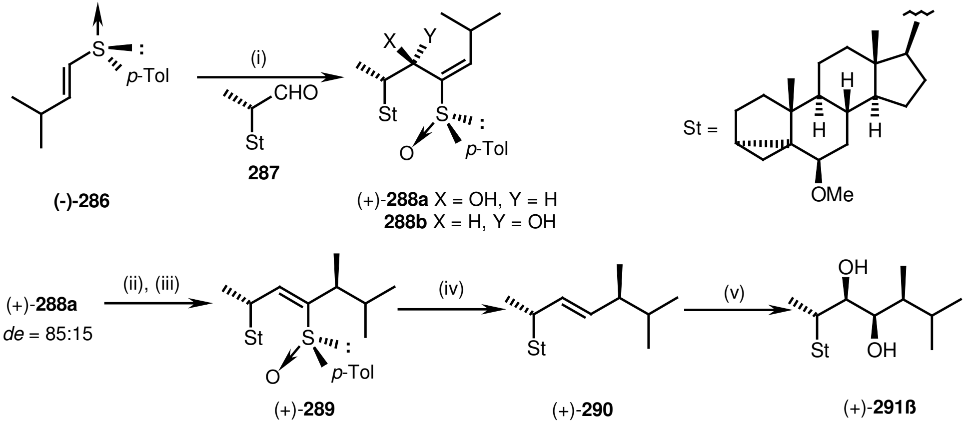
Scheme 34

1.5.3 Formal Synthesis of Brassinolide

Plant growth regulator brassinolide (**285**) was isolated from bee-collected pollen of *Brassica Napus* L. by USDA scientists in 1979.[70] Marino et al. reported highly stereocontrolled formal synthesis of brassinolide via chiral sulfoxide directed S_N2'



Brassinolide (285)

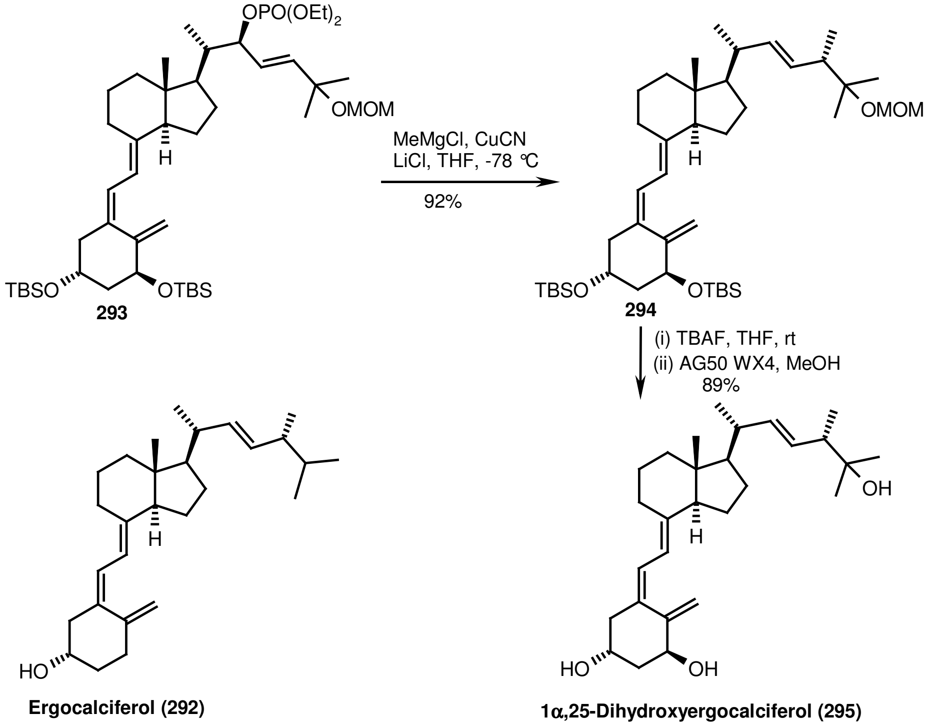


Scheme 35 *Reagents, conditions and yields*: (i) LDA, THF, -78 °C, **287** (75%); (ii) Ms_2O, Pyridine (93%); (iii) MeCuCNMgBr, THF, 0 °C to rt (71%); (iv) (a) *t*-BuLi, THF, -78 °C; (b) MeOH (95%); (v) 10 mol% $K_2OsO_2(OH)_4$, 40 mol% $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $Me_2SO_2NH_2$, *t*-BuOH/H_2O (1:1), rt, 30 h (70%).

reactions.[71] Copper mediated S_N2' displacement of nonracemic mesyalate by Grignard reagent gave them the corresponding allylic sulfoxide **289**, which on removal of sulfinyl group and asymmetric dihydroxilation gave rise to the (22*R*, 23*R*, 24*S*)-diol (+)-**291**β, a known precursor of brassinolide with complete stereoselectivity (Scheme 35). Similar results were also obtained with (+)-**286**.

1.5.4 Synthesis of 1α, 25-Dihydroxyvitamin D₂ (1α,25-Dihydroxyergocalciferol)

The non-natural vitamin D_2 (**292**, ergocalciferol) was administered to humans and domestic animals on the assumption that its metabolism and biological activity parallel that of vitamin D. There is now strong evidence that vitamin D_2 also undergoes a double hydroxylation to produce 1α,25-dihydroxyvitamin D_2 (**295**) and it induces cell-differentiation and inhibits the proliferation of a number of tumor cell lines, including leukemic cells.[72] Mouriño and coworkers reported an efficient approach involving S_N2'

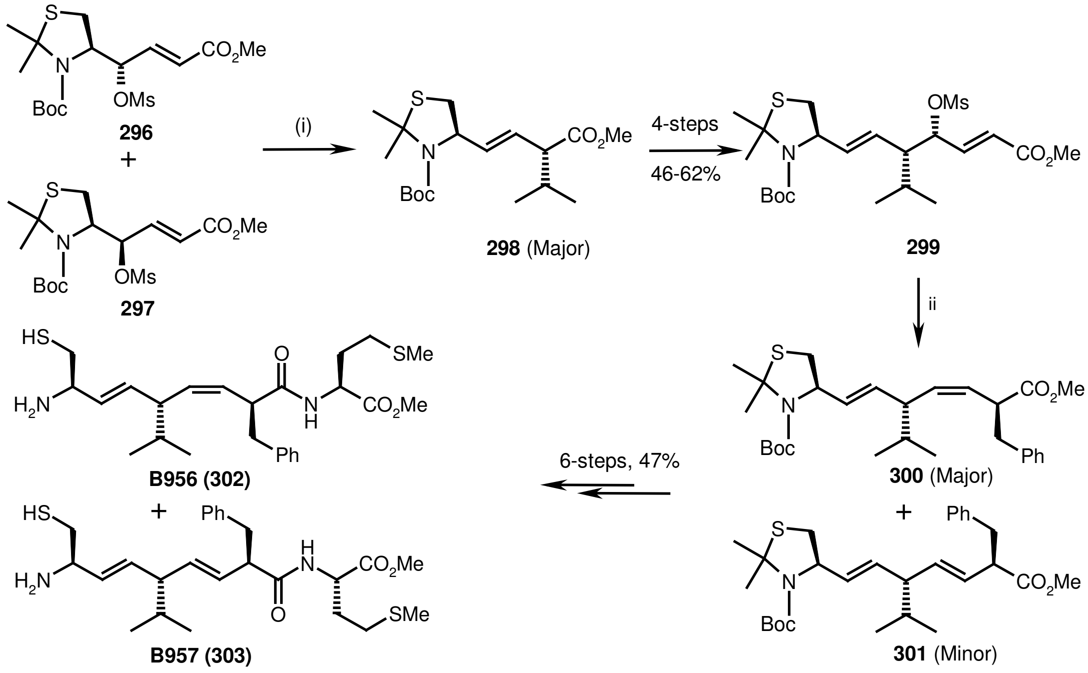


Scheme 36

anti-displacement of the phosphate group of **293** by organocuprate generated from MeMgCl, CuCN and LiCl, without affecting the labile vitamin D triene system, to give after deprotection, 1α,25-dihydroxyvitamin D_2 (**295**) (Scheme 36).[73]

1.5.5 Synthesis of Bis-olefinic CVFM Mimetics B956 and B957

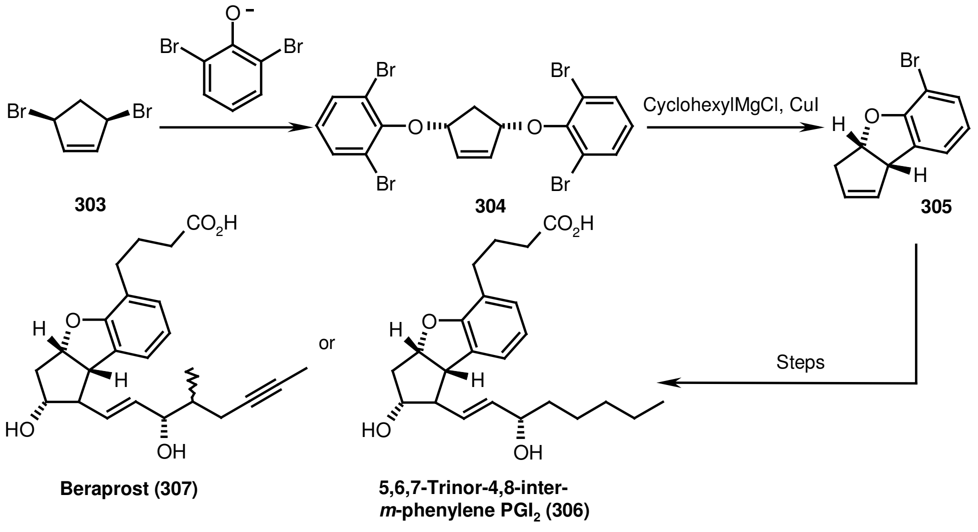
Lewis and coworkers reported an efficient synthetic route for bis-olefin mimetics of the prototype farnesyl transferase tetrapeptide inhibitor, CVFM, such as B956 (**302**) and B957 (**303**). Generation of both the double bonds in these syntheses are based on S_N2' displacement of allylic mesylates using copper catalyzed Grignard reactions as key steps (Scheme 37).[74] The second unusual S_N2' coupling reaction furnished the (*Z*)-isomer **300** as a major product.



Scheme 37 *Reagents, conditions and yields*: (i) CuCN, *i*-PrMgCl, THF, $BF_3.OEt_2$, 0 °C; **296** + **297**, -78 °C (~94%); (ii) CuCN, BnMgCl, THF, -20 °C to rt; **299**, -78 °C (89%).

1.5.6 Synthesis of 5,6,7-Trinor-4,8-inter-*m*-phenylene PGI_2 and Beraprost

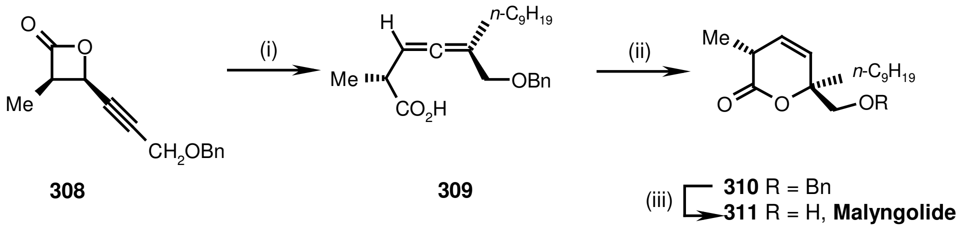
Since the discovery of prostacyclin (PGI_2), much attention has been paid to synthesis of its analogues to improve its chemical stability and to separate its multiple biological activities.[75] Nagase and coworkers reported regio- and stereoselective synthesis of 5,6,7-Trinor-4,8-inter-*m*-phenylene PGI_2 and Beraprost via an intramolecular coupling reaction of phenyl ether **303** (Scheme 38).[76]



Scheme 38

1.5.7 Synthesis of (-)-Malyngolide

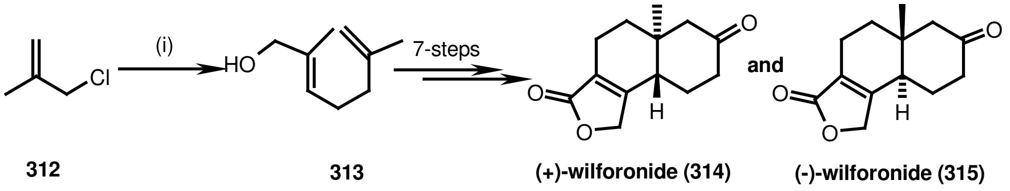
Alkene substituted β-lactones are known to react with different copper catalyzed Grignard reagents to give β-allenic carboxylic acids.[77] Nelson et al. utilized this S_N2' ring opening reaction to produce a concise, fully stereocontrolled synthesis of naturally occurring (-)-malyngolide[78] in three steps with 64% overall yield starting from lactone **308** (Scheme 39).[77]



Scheme 39 *Reagents, conditions and yields*: (i) *n*-$C_9H_{19}MgBr$, 10 mol% CuBr, THF, -78 °C (92%); (ii) 10 mol% $AgNO_3$, 5 mol% *i*-Pr_2Net, 80 °C, CH_3CN (80%); (iii) H_2, Pd-C (87%).

1.5.8 Synthesis of Wilforonide

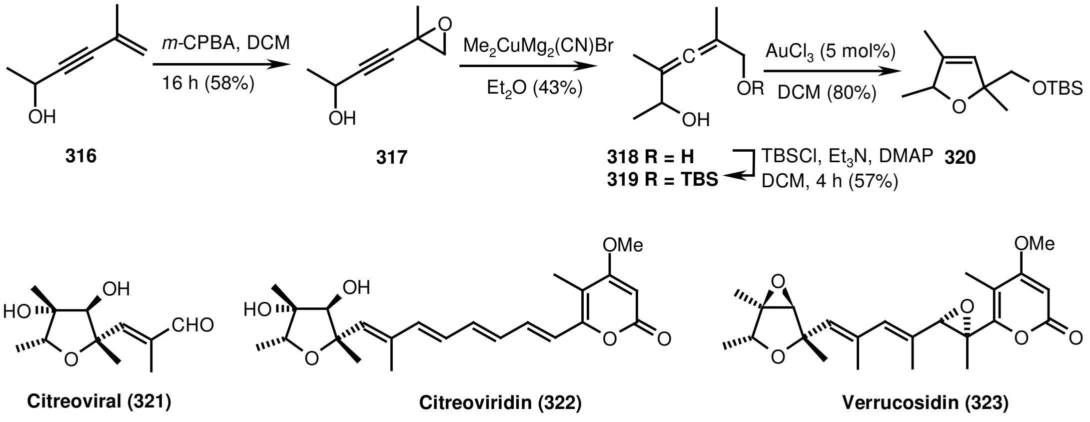
Wilforonide, a terpenoid isolated from the Chinese medicinal herb *Triperygium wilfordii* Hook F (Lei Gong Teng),[79] was found to have significant anti-inflammatory activity. It was also effective in inhibiting T-cell proliferation and cytokine release. Yang and coworkers reported enantioselective syntheses both (+)-wilforonide and (-)-wilforonide using the allylic alcohol **313** in 7-steps with 3% and 9% overall yields respectively (Scheme 40).[80] The allylic alcohol **313** was prepared in 97% yield (*E*/*Z* = 13:01) by reacting the Grignard reagent of 3-chloro-2-methyl-1-propene with 2-methyl-2-vinyloxirane in the presence of CuI.



Scheme 40 *Reagents, conditions and yields*: (i) Mg, THF, 0 to 25 °C, 15 h; CuI, 2-methyl-2-vinyloxirane, -20 °C, 1 h (97%, *E*/*Z* ratio = 13:1).

1.5.9 Formal Synthesis of Citreoviral

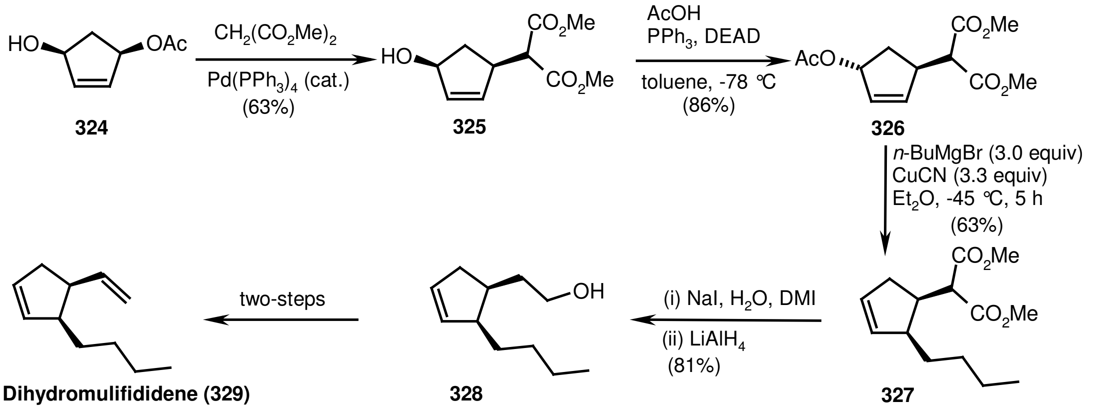
Citreoviral (**321**), the functionalized aldehyde, is a key intermediate in the synthesis of two structurally related antiparasitic mytotoxins, citreoviridin (**322**)[81a] and verrucosidin (**323**).[81b] Citreoviridin in particular, isolated from *Penicillium citreoviride*, has gained further interest as a potent neurotoxin due to its highly specific inhibition of mitochondrial F_1, F_0-ATPase causing cardiac Beriberi disease.[81c] Krause et al. reported a short and concise synthesis of 2,5-dihydrofuran **320**, a versatile precursor for *rac*-citreoviral (**321**) via copper catalyzed Grignard addition to propargylic epoxide followed by gold-catalyzed cyclization strategy (Scheme 41).[82]



Scheme 41

1.5.10 Synthesis of Dihydromultifidene

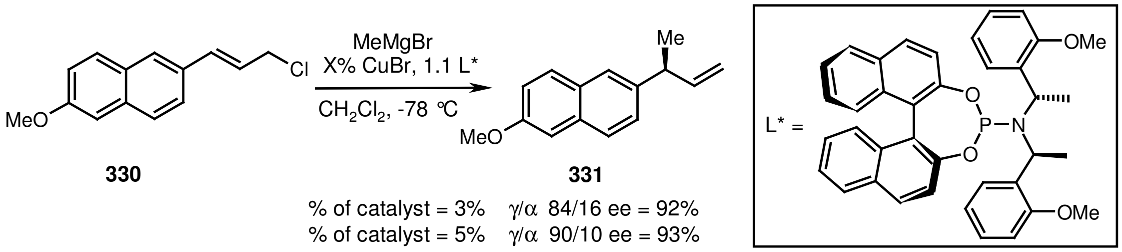
Dihydromultifidene (**329**) is a pheromone of the brown algae *Dictyopteris acrostichoides*.[83] Kobayashi et al. reported an enantioselective synthesis of this natural product **329** using copper catalyzed S_N2' displacement of allylic acetate **326** by Grignard reagent (Scheme 42).[16]



Scheme 42

1.5.11 Formal Synthesis of (+)-Naproxen

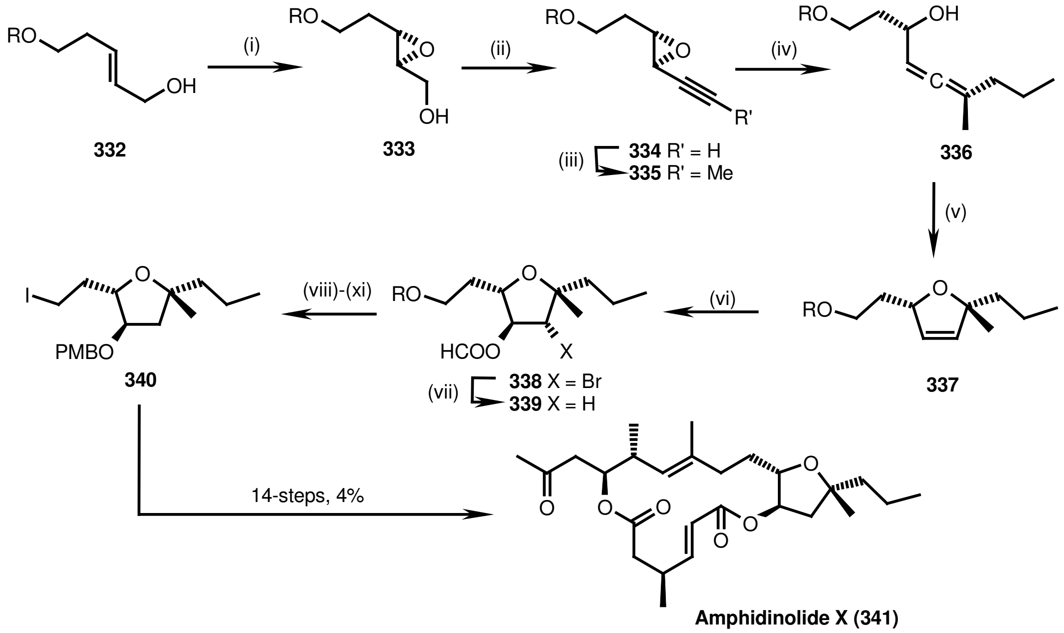
(+)-Naproxen is a well known nonsteroidal anti-inflammatory drug.[84] Alexakis and coworkers reported the synthesis of the direct precursor **330** via copper catalyzed allylic substitution with very high regio- and enantioselectivity (Scheme 43).[85]



Scheme 43

1.5.12 Synthesis of Amphidinolide X

Amphidinolide X is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than two hydroxyacid entities.[86] This natural product also possesses promising cytotoxicity against murine lymphoma and human epidermoid carcinoma. Fürstner and coworkers reported the total synthesis of amphidinolide X using iron catalyzed *syn*-S_N2' ring opening of propargylic epoxide as the key step (Scheme 44).[87]



Scheme 44 *Reagents, conditions and yields*: (i) $Ti(Oi\text{-}Pr)_4$ cat., L-(+)-DET, *t*-BuOOH, MS 4 Å, CH_2Cl_2 (97%, *ee* = 83%); (ii) (a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (b) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH (67%); (iii) LiHMDS, MeOTf, THF (95%); (iv) PrMgCl, $Fe(acac)_3$ cat., toluene (62%, *syn*:*anti* = 8:1); (v) $AgNO_3$, $CaCO_3$, aqueous acetone (90%); (vi) NBS, DMF/H_2O (15/1) (65%); (vii) AIBN, $(TMS)_3SiH$, toluene; (viii) $NaHCO_3$, MeOH, (2-steps, 90%); (ix) $PMBOC(=NH)CCl_3$, PPTS, CH_2Cl_2/C_6H_{12} (76%); (x) TBAF, THF (97%); (xi) I_2, PPh_3, imidazole, MeCN/Et_2O (92%).

Recently we have synthesized chaetomellic acid A,[88] 1,7(Z)-nonadecadiene-2,3-dicarboxylic acid,[88] 2-carboxymethyl-3-hexylmaleic anhydride,[89] 2-(ß-carboxyethyl)-3-alkylmaleic anhydrides,[89] Maculalactones A-C[90] and Nostoclide I[90] using S_N2' coupling reaction of appropriate Grignard reagents with dimethyl bromomethylfumarate as one of the key steps and these results will be discussed in chapter two, as a part of this dissertation.

In summary, we have described how the S_N2' Grignard coupling reactions can serve as a powerful tool in designing complex target molecules. All the syntheses discussed here, describe very exciting and novel chemistry, each having it's own advantage. The present S_N2' Grignard coupling reaction strategy has provided an easy access to a diverse range of bioactive natural products with different origins. Since most of these S_N2' coupling reactions discussed here effect bond formation stereoselectively and many of these processes are not feasible without a metal catalyst, the ability of chemists to execute multistep synthesis schemes will now be significantly more sophisticated.

1.6 Summary

In this chapter, we have provided a concise account on S_N2' Grignard coupling reactions, factors affecting the product distribution and their applications in synthetic organic chemistry. The great value of the Grignard reaction to the synthetic organic chemist is its generality as a building block for an impressive range of structures and functional groups. Over the last ten years, there has been a massive improvement in this area in terms of controlling the chemo-, regio- and stereoslecetivity. There has been extensive use of several metal catalysts including copper, nickel, iron and palladium for better regioselectivity. Amongst them copper has emerged as the most versatile catalyst in terms of regio- and stereoselectivity. Several chiral complexes have also been introduced as catalyst to impart high order of chirality in the case of racemic substrates. Asymmetric induction in S_N2' Grignard coupling reactions through chirality residing in nonracemic substrates has also been investigated extensively in the past decade.

Most of the studies in this field are directed towards allylic substrates. Allylic substrates are known to undergo S_N2' displacement to form variety of alkenes, allylic alcohols and allylic amines, whereas propargylic substrates are best known for generation of a wide range of substituted allenes. We have presented a brief account on S_N2' Grignard coupling reactions with allylic and propargylic substrates, describing the reaction course substrate wise by providing 31 schemes and 30 tables. In the past decade, S_N2' Grignard coupling reactions have found several applications in synthesis of natural products and their unnatural analogs. The importance of S_N2' Grignard coupling reaction in natural and unnatural product synthesis has been reviewed in the last section with the help of 12 brief schemes. All the information collected and presented here has been well supported by providing 99 recent references from various monographs and international journals.

The chemistry of S_N2' Grignard coupling reactions is highly important and attractive from both basic and applied point of view. After little more than 100 years of the path-breaking discovery of Grignard reagent, the area and application of this reagent has become very large. Yet we feel that there is scope to introduce more novelty to this highly challenging field. Especially in the case of stereoselective transformations, there is a continuous search of catalysts and ligands that can provide a better solution for achieving both the γ-selectivity as well as stereoselectivity in one shot. The continuously increasing stream of publications on this subject permits the hope that even in the foreseeable future there should be a clear understanding of the product formation in S_N2' Grignard coupling reactions, which in turn will increase the feasibility of the application of this important reaction in organic synthesis. Therefore, studies towards Grignard coupling reactions in general and of S_N2' Grignard coupling reactions should provide a bright fascinating field for further investigations.

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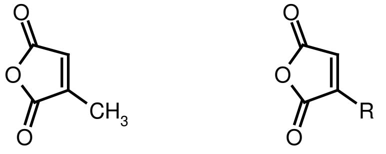
2.1A Section A: I. A Facile Synthesis of Chaetomellic acid A

2.1A.1 Background

Maleic anhydride (2,5-furandione) was prepared for the first time two centuries ago and became commercially available a century later by the catalytic oxidation of benzene using vanadium pentoxide.[1] Being a multifunctional entity, it finds applications in nearly every field of both laboratory and industrial chemistry. A lot of interest has been centered in the use of maleic anhydride as a building block in organic synthesis, because of its versatility. It is a versatile synthon wherein all the sites are amenable for a variety of reactions and possesses exceptional selectivity in reactions towards several nucleophiles. The vast array of nucleophilic reactions undergone by maleic anhydrides confer a high synthetic potential on them.[2] In the past century, several symmetrically and unsymmetrically substituted maleic anhydride derivatives have been prepared, the simplest of them being methylmaleic anhydride or citraconic anhydride (**1**). Although the utilities of methylmaleic anhydride (**1**) have been well proved in laboratory as well as in industrial practice,[3] only three synthetic approaches towards methylmaleic anhydride are known in the literature: (i) starting from citric acid by double dehydrative decarboxylation and isomerization,[4] (ii) from ethyl acetoacetate via cyanohydrin formation followed by dehydrative cyclization[5] and (iii) by the gas phase oxidation of isoprene.[6] Only a few approaches are known for the synthesis of alkylmaleic anhydrides **2** in the literature. The first approach involves the conjugate addition of organocuprates to dimethyl acetylenedicarboxylate as a key reaction.[7] Recently, two synthetic approaches have been reported for compound **2** by palladium-catalyzed dicarbonylation of terminal acetylenes.[8,9]

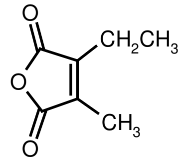


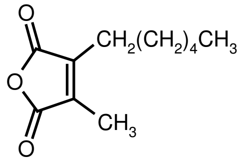
1

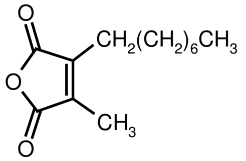
2 R = alkyl

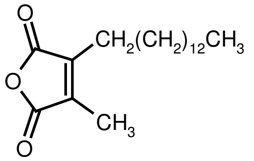
Figure 2. Monoalkyl substituted maleic anhydrides

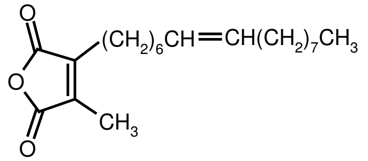
Another simplest and most widely used derivative of dialkylsubstituted maleic anhydride is dimethylmaleic anhydride (DMMA). More than 20 synthetic approaches to dimethylmaleic anhydride using a variety of strategies are known in literature.[10] The list of approaches to dimethylmaleic anhydride with an overall yield of greater than 60% includes (i) oxidation of but-2-ene in the presence of a metal catalyst with 68% yield[11] (ii) self condensation of ethyl α-bromopropionates with 67% yield[12] (iii) oxidation of but-2-yne in 2-steps with 63% overall yield[13] (iv) one-pot approach employing maleic anhydride and 2-aminopyridine with 75% yield[14] and (v) an elegant approach using Wittig reaction of methylmaleimide-TPP adduct with paraformaldehyde.[10] Other approaches give poor to moderate (13-57%) overall yield of dimethylmaleic anhydride.

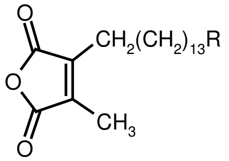

2-Ethyl-3-methylmaleic anhydride (**3**) (flavouring agent)[15]

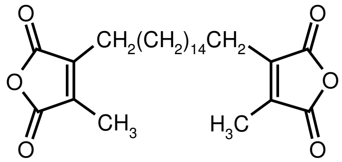

2-Hexyl-3-methylmaleic anhydride (**4**) (flavouring agent)[16]

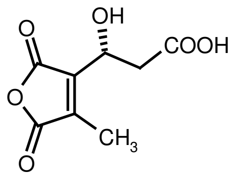

2-Octyl-3-methylmaleic anhydride (**5**) (flavouring agent)[17]

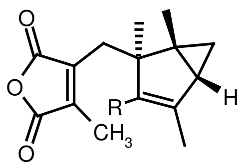

Chaetomellic acid A anhydride (**6**) (ras farnesyl-protein transferase inhibitor)[18]

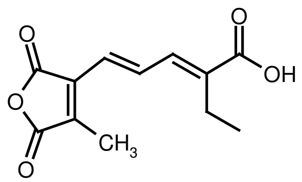

Chaetomellic acid B anhydride (**7**) (ras farnesyl-protein transferase inhibitor)[18]

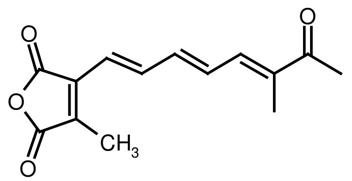

Aspergillus acid A (**8**) [R = $(CH_2)_3OAc$][19]
Aspergillus acid B (**9**) [R = $COCH_3$][19]
(S)-Aspergillus acid C (**10**) [R = $CH(OH)CH_3$][19]
(S)-Aspergillus acid D (**11**) [R = $CH(OAC)CH_3$][19]
(activity unknown)


Tyromycin A (**12**) (aminopeptidase inhibitor, potential cytostatic activity)[20]


Maleic anhydride segment of tautomycin (**13a**) (antifungal, antibiotic)[21]


Lindenanolide E (R = CHO) (**14**) (HIV-1 integrase inhibitor)[22]


Telfairic anhydride (**15**) (activity unknown)[23]


Graphenone (**16**) (activity unknown)[24]

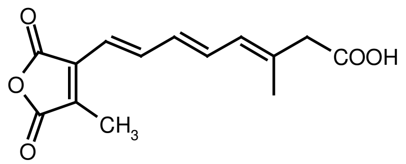

Itaconitin (**17**) (activity unknown)[25]

Figure 3. Naturally occurring dialkylsubstituted maleic anhydrides

Recently, several structurally interesting and biologically important dialkylsubstituted maleic anhydrides have been isolated as bioactive natural products and some of them are listed in Figure 3. The structural features of these molecules reveal that they might have been designed in nature by the combination of pyruvic acid and the respective long chain carboxylic acids. These target molecules received immediate attention from several elegant schools of synthetic organic chemistry for the synthesis of the natural product itself and also of its analogues for structure activity relationship studies.

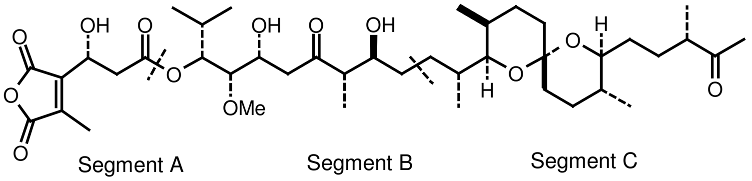
2-Ethyl-3-methylmaleic anhydride (**3**)[15] was isolated from *Paederia foetida L.*(from volatile oil) *Sambucus nigra L.* (fruit) whereas 2-hexyl-3-methylmaleic anhydride (**4**)[16] and 2-octyl-3-methylmaleic anhydride (**5**)[17] were isolated from *Agropyrum repens* (Rhizome) and *Pseudomonas cepacia* A-1419 respectively. To the best of our knowledge no synthesis of these natural product has been reported in the literature.

Assante *et al*, in 1979, isolated four new secondary metabolites aspergillus acids A-D produced by the mould *Aspergillus wentii* when grown on yeast-glucose medium[19] and these natural products were also established to be derivatives of citraconic anhydride with remotely functionalized long hydrocarbon chains (Figure 3). Very recently a facile first synthesis of these naturally occurring remotely functionalized secondary mould metabolite anhydrides **8-11** has been described from our group starting from *N-p*-tolyl citraconimide using Wittig reaction as the key step in 3-6 steps with 20-65% overall yields.[26]

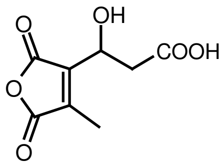
Tyromycin A (**12**) has been recently isolated from mycelial cultures of basidomycete *Tyromyces lacteus* (Fr.) Murr,[20] and its structure was established as 1,16-bis-(4-methyl-2,5-dioxo-3-furyl)hexadecane by using spectral and analytical techniques and by transformation into the corresponding tetramethyl ester and diimide derivatives.[20] Tyromycin A (**12**) is the first bioactive natural product with two citraconic anhydride units, which suggests a biosynthesis by condensation of an activated eicosanedioic acid with two molecules of oxaloacetate. Till date only two syntheses of tyromycin A are reported. The first synthesis involves the well-known decarboxylative Barton-radical coupling reaction.[27]

The second synthesis of tyromycin A was reported from our laboratory employing a one-pot double Wittig reaction involving methylmaleimide-TPP adduct and aliphatic dialdehyde as a key step.[28]

Isono and co-workers[21] reported the isolation of tautomycin (**18**) from a strain of *Streptomyces spiroverticillatus* as a new antibiotic with strong antifungal activity against *Sclerotinia sclerotiorum*. The same group elucidated the structure of tautomycin on the basis of chemical degradation and spectroscopic evidence.[21] 2D INADEQUATE spectroscopy of tautomycin labeled with [1,2-^{13}C] acetate permitted the complete assignment of ^{13}C and ^{1}H signals and established the total structure. The broad retrosynthetic analysis of tautomycin afforded segment A, B, and C as shown in structure **18**. Segment A of tautomycin is a highly oxygenated molecule with three carboxylic groups and one hydroxy group. According to Chamberlin *et al*[29] the greatest challenge in the synthesis of tautomycin lies in the construction of the simple looking 2,3-disubstituted maleic anhydride segment A **13**. To date, five multi-step synthesis of segment A **13**,[29-33] including the most recent synthesis developed in our laboratory,[33] have been accomplished using various elegant strategies. The synthesis reported from our laboratory looks simple but provides a racemic mixture of **13b**.



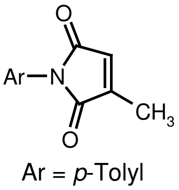
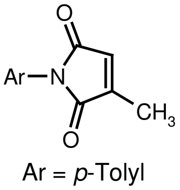
Tautomycin (18)

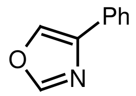
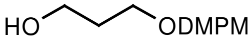
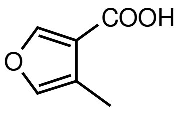


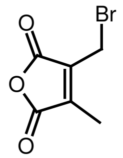
13b

A new methylmaleic anhydride metabolite has been isolated in 1996 by Edward and his co-workers[23] from the culture medium of the fungus *Xylaria telfairii* Berk and was named as telfairic anhydride (**15**). Two other structurally similar natural products, graphenone (**16**)[24] and itaconitin (**17**)[25] have been isolated from the cultures of spore derived mycobionts of the lichens *Graphis scripta* and from the species *Aspergillus itaconicus* and *Aspergillus gorakhpurensis* respectively. A biological role for such a structure does not appear to have been established yet. Very recently, lindenanolide E (**14**)[22] has been isolated from the species *Lindera chunii* Merr with HIV-1 integrase inhibiting activity. Till date, no synthesis has been reported for telfairic anhydride (**15**), graphenone (**16**), itaconitin (**17**) and lindenanolide E (**14**). Chemistry involved in syntheses of aspergillus acids A-D (**8-11)**, Tyromycin A (**12**) and segment A of tautomycin (**13a & 13b)** has been tabulated in Table 1.

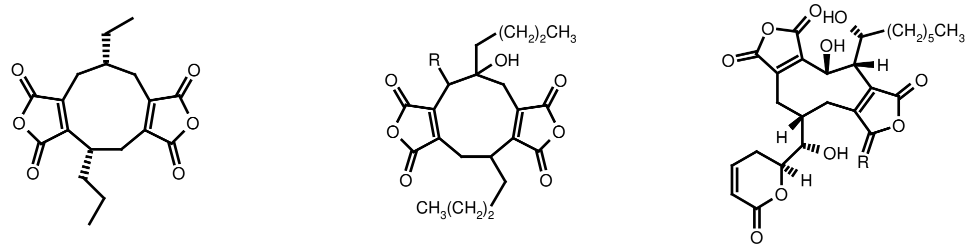
Table 1 **Reported Syntheses of aspergillus acids A-D** (8-11)**, Tyromycin A** (12) **and segment A of tautomycin** (13a **&** 13b)

No.	Starting Material	Reagents and Conditions	Product	Overall Yield	Ref.
1	 *N-p*-Tolyl methylmaleimide	(i) Ph$_3$P, AcOH, CHC(CH$_2$)$_{13}$CHO or H$_3$CCOOCH$_2$(CH$_2$)$_{14}$CH$_2$CHO reflux, 24 h; (ii) Et$_3$N, THF, reflux, 48 h; (iii) KOH (30% aq.), THF-MeOH (1:2), reflux, 12 h; (iv) 6 M H$_2$SO$_4$ /AcOH (1:2), reflux, 8 h; (v) (a) aq. NaOH/THF, 50 °C, 2 h, (b) NaBH$_4$, 0 °C to rt, 2 h, (c) H$^+$/HCl; (vi) Ac$_2$O, Py, rt, 24 h, (vii) Amano PS, vinyl acetate, hexane-benzene (2:1), 40-43 °C, 72 h; (viii) (a) K$_2$CO$_3$, MeOH, 0 °C to rt, 2 h, (b) H$^+$/HCl.	**8-11**	54% for **8** (5-steps); 65% for **9** (3-steps); 53% for **10** (4-steps); 48% for **11** (5-steps, 72% *ee*) 23% for (+)-**10** (5-steps, 70% *ee*); 20% for (-)-10 (6-steps, 72% *ee*)	26
2	HOOCCH$_2$(CH$_2$)$_{14}$CH$_2$COOH 1,18-octadecanedioic acid	(i) (a) 2,2' dithiobis(pyridine *N*-oxide), PPh$_3$, DCM, 30 min, (b) hν, citraconic anhydride, 10-15 °C, 30 min.	**12**	74%	27
3	 *N-p*-Tolyl methylmaleimide	(i) (a) TPP, AcOH, 1,18-octadecanedial, reflux, 10 h, (b) △, 140-150 °C, 30 min; (ii) (a) KOH, H$_2$O, THF, CH$_3$OH, reflux, 2 h, (b) H$^+$/HCl.	**12**	71%	28

3	 4-Phenyloxazole	(i) Ethyl tetrolate, C_6H_6, 190 °C, sealed tube; (ii) DIBAL, −78 °C; (iii) MnO_2; (iv) Chiral *N*-acetyloxazolidinone, *n*-Bu_2BOTf, Et_3N, DCM, −78 to 0 °C; (v) Raney nickel (W-4) acetone-phosphate buffer (9:1); (vi) $^tBuMe_2SiOTf$, $^iPr_2Net$; (vii) O_2, $h\nu$, rose Bengal, $^iPr_2NEt$, DCM, 0 °C; (viii) PCC, MS 4Å, DCM, rt; (ix) $LiOH/H_2O$; (x) (a) CH_2N_2, Et_2O, (b) HF-Py.	(*S*)- Isomer **13a**	18%	30
4	 Monoprotected 1,3-propane diol	(i) (a) DMSO, SO_3.pyridine, DCM, 0 °C, (b) $Ph_3P{=}CHCOO^tBu$, DCM, 25 °C; (iii) AD-mix-β, $MeSO_2NH_2$, ^tBuOH-H_2O, 0 °C; (iii) DDQ, pyridine, MS 4Å, DCM, 5 °C; (iv) DMP, pyridine, DCM, 25 °C; (v) $(EtO)_2P(O)CH(Me)COOEt$, ^tBuOK, THF, −60 °C to −20 °C; (vi) (a) PPTS, methanol, 25 °C, (b) DEIPSCl, imidazole, DCM, 3 to 25 °C, (c) AcOH, THF-H_2O, 0 to 25 °C; (vii) DMP, DCM, 25 °C; (viii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^tBuOH, H_2O, 25 °C.	(*S*)- Isomer **13a**	83%	31
5	 4-Methyl-3-furan carboxylic acid	(i) CH_3ONHCH_3.HCl, DEPC, Et_3N, DMF, 0 °C to rt; (ii) CH_3COOCH_3, LDA, THF, −78 to 0 °C then HCl, 0 °C to rt; (iii) H_2, 100 atm., cat. (*S*)-(BINAP)Ru(II), CH_3OH, 28 °C; (iv) DEIPSCl, imidazole, DCM, 0 °C to rt; (v) (a) LiOH, THF-H_2O (6:1), rt, (b) BnOH, DCC, DMAP, THF, rt; (vi) (a) O_2, $h\nu$, rose bengal, $^iPr_2NEt$, DCM, 0 °C, (b) PCC, MS 4Å, DCM, rt.	(*S*)- Isomer **13a**	31%	32

6	$\mathrm{BnOOC{-}C{\equiv}C{-}COOBn}$ Dibenzyl acetylene dicarboxylate	(i) MeCuLiCN, Et$_2$O, −78 °C, then 3-pentenoyl chloride, −78 to 0 °C; (ii) (a) (−)-DIP chloride, THF, -20 °C, 3 days, (b) TESCl, TEA, DCM, 0 °C; (iii) O$_3$, DCM, −78 °C then PPh$_3$, −78 °C to rt; (iv) NaClO$_2$, 2-methyl-2-butene, ^{t}BuOH/H$_2$O, 0 °C.	(*S*)-Isomer **13a**	78%	29
7	 (Bromomethyl)methylmaleic anhydride	(i) (a) Diethyl malonate, NaH, C$_6$H$_6$, rt, 8 h, (b) H$^+$/HCl; (ii) con. HCl, reflux, 12 h; (iii) NBS, benzoyl peroxide, CHCl$_3$, reflux, 24 h; (iii) (a) 1N aq. KOH, rt, 3 h, (b) H$^+$/HCl; (v) CH$_2$N$_2$, Et$_2$O, 0 °C, 3 h.	(±)-Segment A **13b**	44%	33

A more complex dialkylsubstituted class of maleic anhydrides known in the literature is the nonadride class of natural products. Natural products in this small structural class possess a nine membered ring as the core unit.[34] A few of them are listed in Figure 4.



Byssoclamic Acid (**19**)

Scytalidin (**20**) R = H
Castaneolide (**21**) R = OH

Rubratoxin A (**22**) R = H, OH
Rubratoxin B (**23**) R = O

(+)-CP-225,917 (phomoidride A, **24**)

(-)-CP-263,114 (phomoidride B, **25**)

Figure 4. Naturally occurring complex dialkylsubstituted maleic anhydrides

Byssochlamic acid (**19**)[35] was isolated from ascomycete *Byssochlamys fulva* and both scytalidin (**20**) and castaneolide (**21**) were isolated[36] from *Macrophoma castaneicola*. Biological activity of these natural products has yet to be established. Hepatotoxic rubratoxin A (**22**) and rubratoxin B (**23**) have been isolated[37] from the species *Penicillium rubrum* and the latest examples of this structural family, phomoidrides A (**24**) and B (**25**) (CP-225,917 and CP-263,114), have been isolated by a research group at Pfizer from an unidentified fungus which also produces zaragozic acid.[38] These nonadrides attracted the attention of the researchers due to their powerful inhibition of Ras farnesyl protein transferase.[38] CP molecules exemplify architectures of unprecedented molecular connectivities and complexities and possess intriguing biological activity.

The intriguing structural features and promising biological activity of the nonadrides inspired several synthetic chemists to embark on a journey toward the total synthesis of the natural products falling in this rather unique league. Much of the attention, not surprisingly, has been captured by the phomoidrides, which with their fascinating yet complex structures and potential activity prove to be an alluring yet challenging target. Amongst the other nonadrides, only byssochlamic acid and phomoidrides have been successfully synthesized while not much attention has been focused on the other members of the nonadride family. Only two synthesis of byssochlamic acid are known in the literature[39] whereas the Herculean efforts of the synthetic community toward the total syntheses of phomoidrides A and B have culminated in four completed total syntheses and at least 18 advanced synthetic approaches have been developed in recent years. Recently, the chemistry of phomoidrides A and B has been reviewed by John L. Wood and coworkers.[40]

With this knowledge of rich chemistry of maleic anhydride derivatives in mind we planned the synthesis of chaetomellic acid A anhydride (2-tetradecyl-3-methylmaleic anhydride). The dicarboxylic acids chaetomellic acid A (**26**) and chaetomellic acid B (**27**) were isolated from fermentation extract of the coleomycete *Chaetomella acutiseta* (Figure 5), by a group of scientists[18] at Merck, USA in 1993. The structural assignment of chaetomellic anhydride A (**6**) and chaetomellic anhydride B (**7**) has been done on the basis of analytical and spectral data. The position and geometry of the double bond in chaetomellic acid B was established by MS analysis of monoepoxide (prepared by reacting **7** with *meta-*

chloroperbenzoic acid in dichloromethane). The biogenesis of these compounds[18] may be occurring through an aldol condensation of palmitate or *cis*-oleate with pyruvate followed by dehydration pathway.

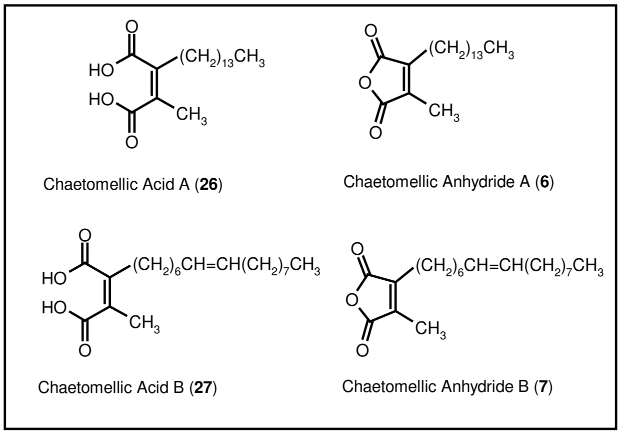
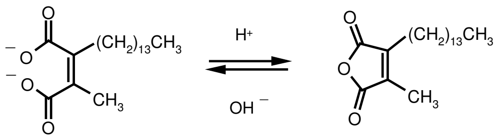


Figure 5



28

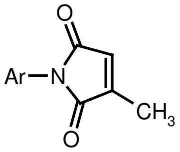
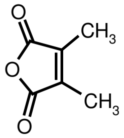
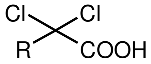
6

Figure 6

Chaetomellic acid A and B have been identified as potent inhibitors of Ras farnesyl-protein transferase[18,41] (FPTase), an enzyme catalyzing a post-translational modification of Ras. Mutated form of Ras oncogens found in about 25% of the human tumors[42] and believed to play a key role in their growth. Molecular modeling studies reveal that these acids structurally resemble FPP. Analyses of the substrate requirements for FPTase have shown that the enzyme binds with selective isoprenoid pyrophosphates and CaaX tetrapeptides.[43] Potential peptide inhibitors [eg. CVLS (IC_{50} = 2 μM), CVIM (IC_{50} = 0.1 μM), CVFM (IC_{50} = 0.02 μM)] can be designed from the substrate. However, peptides are not desired compounds to be considered as therapeutic agents due to their rapid metabolism *in-vivo* and hence, there has been an increased interest towards non-peptide inhibitors. During screening of the natural products, two novel dicarboxylic acids chaetomellic acid A (**26**) and chaetomellic acid B (**27**) were isolated and identified[18] as potent FPTase inhibitors with IC_{50} value 55 and 185 nM respectively. These acids were characterized as alkyl *cis*-dicarboxylates and appear to mimic FPP at the active site of enzyme. Molecular modeling studies reveal that these acids structurally resemble FPP. These classes of natural products have propensity to cyclize as shown in Figure 6 and all members of this family were isolated in the anhydride form. However, they actually exhibit their FPTase inhibitory activity in the dianionic form as shown above in compound **28**. Chaetomellic acid A (**26**) is 3 times more potent than chaetomellic acid B (**27**) and became the main attraction of synthetic efforts because of its potent FPTase inhibitory activity for the treatment of cancer. Recently, the dianion of chaetomellic acid A (**28**) has found application in characterizing the FPP (fernesyl diphospahte) bonding site in rubber transferase.[44] After its isolation in 1993, the past eleven years have seen ten syntheses[45-54] of **6** and two synthesis[47,51] of **7** being accomplished including four from our group. The chemistry of all nine syntheses of **6** and two of **7** is summarized in Table 2.

Table 2 Reported syntheses of chaetomellic anhydride A (**6**) and chaetomellic anhydride B (**7**)

No.	**Starting Compound**	**Reagents and Conditions**	**Product**	**Overall Yield**	**Ref.**
1	$CH_3(CH_2)_{14}COOMe$ Methyl palmitate	(i) Methyl pyruvate, LDA, THF, −78 °C to −10 °C; (ii) 2,6-Di-^{t}butyl-4-methyl pyridine, *p*-tolunesulphonic anhydride, pyridine, DCM; (iii) DBU, toluene, reflux; (iv) (a) NaOH-CH_3OH-THF-H_2O; (b) 4N HCl.	**6**	18%	45
2	$CH_3(CH_2)_{12}CH_2Br$ Tetradecyl bromide	(i) $CoCl_2$, $dmgH_2$, pyridine, $NaBH_4$, NaOH, CH_3OH; (ii) PhSSPh, *hv*; (iii) *m*-CPBA, pH 7.4 phosphate buffer, DCM.	**6**	64%	46
3	$MeOOCCH_2COOMe$ Dimethyl malonate	(i) NaH, $C_{14}H_{29}Br$ or $C_{16}H_{29}Br$, THF-DMF, reflux, 1.5 h; (ii) $BrCH(CH_3)COOMe$, NaH, THF-DMF, reflux, 1.5 h; (iii) (a) ethanolic KOH, (b) H^+/H_2O, reflux; (iv) *N*-methylmorpholine, methylchloroformate; (v) Et_3N, TMSOTf, C_6H_6, reflux, 2 h; (vi) Br_2, Bu_4NBr.	**6 or 7**	83% for **6** & 80% for **7**	47
4	$MeOOC{-}{\equiv}{-}COOMe$ Dimethyl acetylenedicarboxylate	(i) (a) $C_{14}H_{29}Cu(Me_2S)MgBr$; (b) MeI, THF-HMPA, (c) aq. NH_4Cl; (ii) (a) $LiOH/H_2O$, (b) H^+/HCl.	**6**	78%	48
5	$CH_3(CH_2)_{12}CH(Br)COCl$ 2-Bromopalmitoyl chloride	(i) 2-Amino pyridine, Et_3N, Et_2O, rt; (ii) ^{t}BuOH, reflux; (iii) maleic anhydride, NaOAc, reflux.	**6**	62%	49

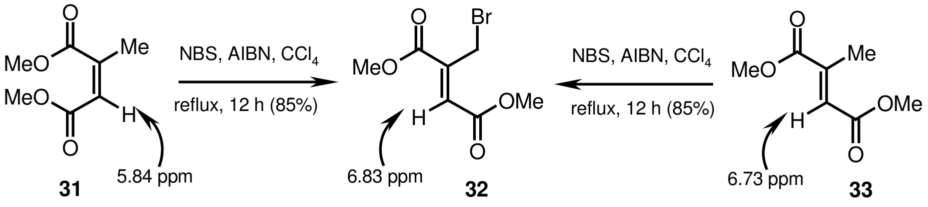
6	 Ar = *p*-Tolyl *N*-*p*-Tolyl methylmaleimide	(i) (a) PPh_3, AcOH, reflux, 2 h, (b) $CH_3(CH_2)_{12}CHO$, reflux, 18 h; (c) Δ, 140-150 °C, 0.5 h; (ii) (a) $KOH/H_2O/CH_3OH/THF$, reflux, 2 h, (b) H^+/HCl..	**6**	89%	50
7	RCOOH R = $C_{14}H_{29}$ Pentadecanoic acid R = $C_{16}H_{31}$ (*Z*)-8-Heptadecanoic acid	(i) (a) DCC, 2-mercaptopyridine *N*-oxide, DCM, 2 h, (b) citraconic anhydride, *hv* (500 W), 10-15 °C, 0.5 h.	**6 or 7**	70% for **6** & 60% for **7**	51
8	 Dimethylmaleic anhydride	(i) NBS, DBP, CCl_4, reflux, 10 h; (ii) $CH_3(CH_2)_{13}MgX$, Et_2O/THF, HMPA, CuI, −5 to 0 °C.	**6**	36%	52
9	 R = $CH_2(CH_2)_{12}CH_3$ 2,2-dichloropalmitic acid	(i) (a) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (b) 4, pyridine, 23 °C, 1 h (89%); (ii) CuCl/TMEDA, MeCN-CH_2Cl_2, 60 °C, 20 h (99%); (iii) (a) Na, MeOH-Et_2O, 25 °C, 20 h, (b) H^+/H_2O (89%); (iv) (a) KOH, MeOH-THF, reflux, 2 h, (b) H^+/H_2O (70%).	**6**	55%	53

Studies of structure-activity relationship and pharmacological tests have stimulated the development of chemical synthesis for the production of larger quantities of chaetomellic anhydride A (**6**) than that available from natural sources. It is quite evident that novel chemistry has been reported in all above approaches towards the synthesis of 6 and each synthesis having its own advantages. Yet newer and better synthetic approach towards this compound is a challenging task for the organic chemist as evidenced by the high price of 6, which is sold by ICN or Calbio Chem at ca 18000/g.[53] Recently we have demonstrated a chemoselective Grignard coupling reaction with an intact preservation of cyclic anhydride moiety.[52] We have studied several Michael type addition reactions to carbon-carbon double bond in maleic anhydrides and their derivatives and they are potential starting materials for the synthesis of natural products[33,55] and heterocycles.[56] On the basis of these studies, we felt that chaetomellic anhydride A (**6**) can be synthesized via chemoselective S_N2' carbon-

carbon coupling reaction of an appropriate Grignard reagent with suitable substrate like bromomethylmaleic anhydride (**29**) or dimethyl bromomethylfumarate (**32**) and our results are summarized in the following part (Scheme 2).[54]

2.1A.2 Present Work: Results and Discussion

Reaction of citraconic anhydride (**1**) with NBS/benzoyl peroxide in carbon tetrachloride under reflux followed by Kugelrohr distillation of the obtained oily product gave bromomethylmaleic anhydride (**29**)[57] in 55% yield with 98% purity (by ^{1}H NMR). The freshly distilled anhydride **29** was used immediately, as **29** starts undergoing slow decomposition after 24 hours. The reactions of Grignard reagent tertadecylmagnesium bromide with the highly reactive monosubstituted bromoanhydride **29** in presence/absence of HMPA with/without copper catalyst were not selective and yielded only 8-10% of the desired product chaetomellic acid A anhydride (**6**). We did several experiments to control the reactivity of anhydride **29**, but all our attempts met with failure. To obtain the selectivity, we planned for preparation of a relatively less reactive starting material dimethyl bromomethylfumarate (**32**). The reaction of citraconic anhydride (**1**) with methanol/H_2SO_4 under reflux gave the desired diester **31** in 75% yield.[58] The diester **31** on treatment with NBS/AIBN in refluxing carbon tetrachloride underwent smooth allylic bromination to yield bromodiester (**32**) in 85% yield.[59] The high difference in vinylic proton signal in product **32** and starting material **31** (vinylic proton signal appears at 6.83 and 5.84 for **32** and **31** respectively) forced us to investigate whether an in situ isomerization accompanied the allylic bromination. The process isomerization of (*Z*)-isomer to (*E*)-isomer along with allylic bromination was confirmed by obtaining the same product **32** from the corresponding dimethyl methylfumarate (**33**) under the same set of reaction conditions (Scheme 1). (vinylic proton signal appeared at 6.83 and 6.79 ppm, when the ^{1}H NMR of **32** was recorded in $CDCl_3$ and CCl_4 respectively for compounds obtained from both the starting materials). In Section 2.1C we have described in detail the NBS-DBP/AIBN induced *Z*- to *E*- carbon-carbon double bond isomerization with several types of olefins having a variety of substituents.



Scheme 1

The unsymmetrical bromodiester **32** has five alternate sites available for nucleophilic reactions, viz (i) two ester carbonyls for 1,2-additions (ii) two sites for Michael addition and (iii) allylic bromo atom for nucleophilic substitution reaction (Figure 7). The freshly prepared Grignard reagent from tetradecyl bromide, in the presence of HMPA reacted in a highly chemo- and regioselective S_N2' fashion with bromodiester **32**, that is, Michael addition followed by elimination of allylic bromo atom to give the net S_N2' product **34** in 60% yield.[59] The diester **34** on refluxing with glacial acetic acid and concentrated HCl (7:3) mixture gave the dicarboxylic acid **35** in 98% yield, which in refluxing acetic anhydride furnished the desired bioactive natural product chaetomellic acid A anhydride

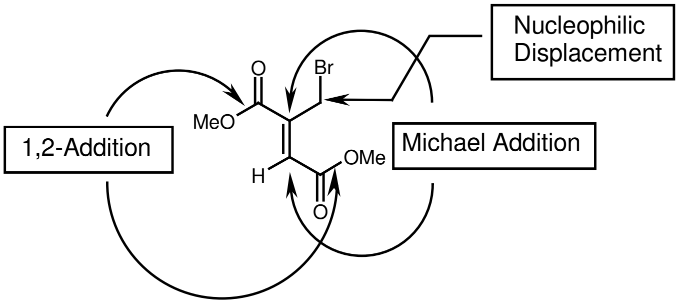
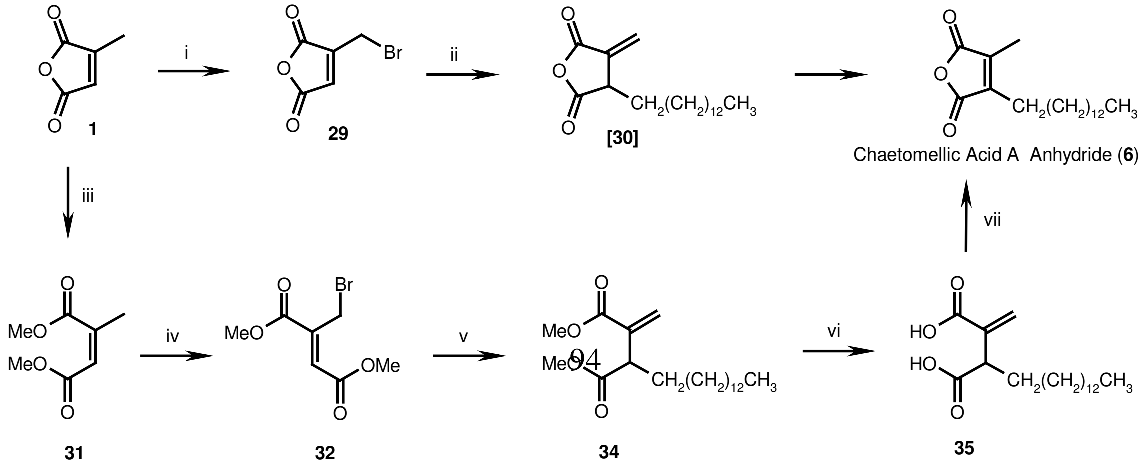


Figure 7



(**6**) in nearly 100% yield (Scheme 2).[54] In this reaction both the formation of intermediate cyclic anhydride **30** and *gem*-dialkyl substituted exocyclic to tetrasubstituted endocyclic

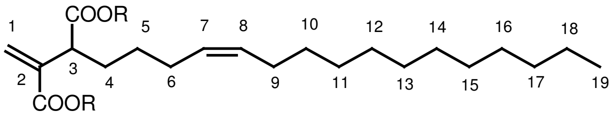
Scheme 2 *Reagents, conditions and yields*: (i) NBS, DBP, CCl_4, reflux, 8 h (55%); (ii) $C_{14}H_{29}MgBr$, Et_2O, rt, 8 h (8-10%); (iii) CH_3OH, H^+/H_2SO_4, reflux, 12 h (75%); (iv) NBS, AIBN, CCl_4, reflux, 12 h (85%); (v) $C_{14}H_{29}MgBr$, Et_2O, HMPA, rt, 8 h (60%); (vi) AcOH + HCl (7:3), reflux, 2 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

carbon-carbon double bond migration took place in one pot. The analytical and spectral data obtained for **6** were in complete agreement with the reported data.[18] In the present five-step synthesis, the natural product chaetomellic acid A anhydride (**6**) was obtained with 38% overall yield.

2.1B Section A: II. An Efficient Synthesis of 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic Acid

2.1B.1 Background

Very recently group of researchers from the Kyoto University in Japan isolated[60] a novel compound 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (NDA, **36**, Figure 8) from cultures of a white-rot fungus *Ceriporiopsis subvermispora* as its diester **37**. The structural assignment of NDA, **37** was done on the basis of ^{1}H NMR, ^{1}H-^{1}H-COSY, ^{13}C NMR, HMQC and HMBC NMR and GC-MS data of the corresponding dimethyl ester **37**. It was found to be an itaconic acid derivative, linking a hydrophobic hexadecenyl group at the C-3 position of the core structural unit.[60] This novel natural product has been classified as a special group of fungal metabolite, which has amphiphilic properties due to its hydrophilic itaconate moiety and hydrophobic aliphatic chain. The configuration of the double bond was determined by coupling constant of the olefinic protons (H-7, H-8), measured by spin decoupling of the methylene protons vicinal to the double bond. The value of $^{3}J_{\text{H-7, H-8}}$ = 11.5 Hz indicated that the configuration is *cis*. Although this novel natural product has one chiral centre its absolute configuration and biological role are yet to be established.



R = H; 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic acid (**36**)
R = Me (**37**)

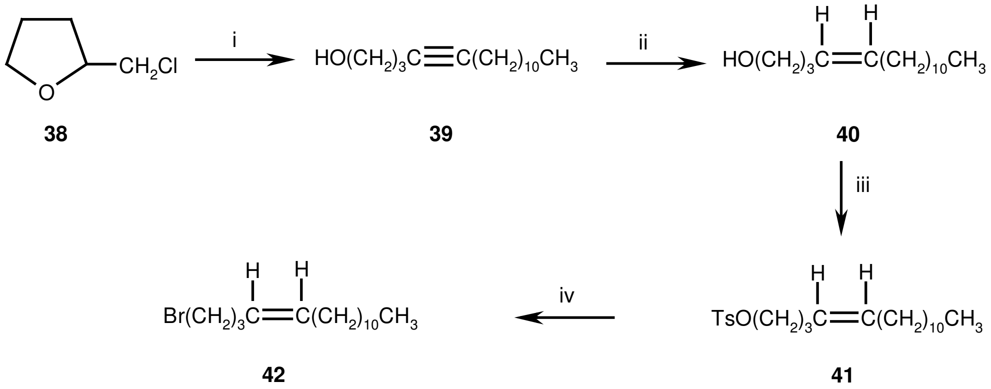
Figure 8

Since chaetomellic acids are active in their dianionic form, we felt that synthesis of itaconic acid analogue **36** will be of interest and useful for biological evaluation studies.

Compounds containing such exo-type or exocyclic carbon-carbon double bonds are generally synthesized by using Wittig reactions,[28,61] coupling reactions involving reduction of carbon-carbon triple bonds[62] and S_N2' coupling reactions[63] of appropriate substrates and nucleophiles. We planned for the first synthesis of this natural product using S_N2' coupling reaction as a key step (Scheme 4).[54]

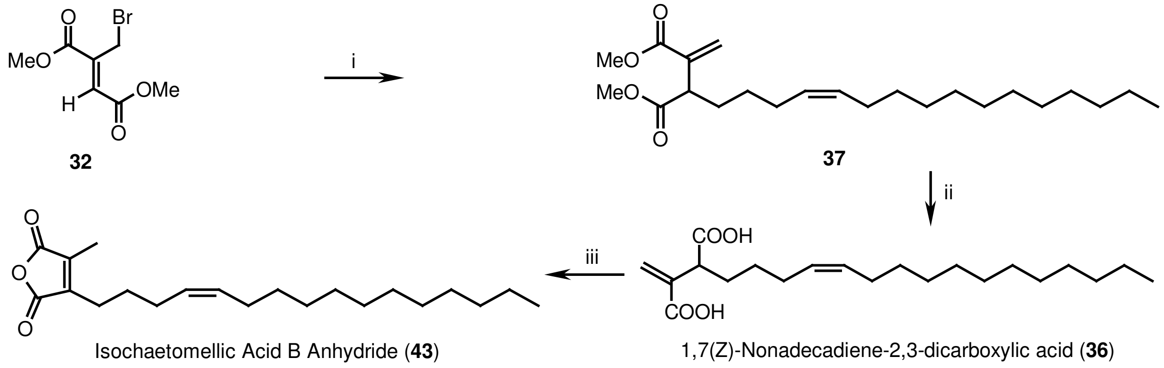
2.1B.2 Present Work: Results and Discussion

On successful completion of synthesis of chaetomellic acid using dimethyl bromomethylfumarate (**32**), we planned for the first synthesis of recently isolated novel dicarboxylic acid **36**. The alkenyllbromide required for generation of Grignard reagent was prepared from tetrahydrofurfuryl chloride (**38**). The reaction of tetrahydrofurfuryl chloride (**38**) with $LiNH_2/NH_3$, followed by treatment with undecyl bromide gave the acetylene derivative **39** in 80% yield.[64] Catalytic hydrogenation of **39** with Lindlar catalyst gave the *cis* olefin **40** in 97% yield. Conversion of **40** to corresponding tosylate **41** (86%) followed by displacement of –OTs using LiBr in acetone at room temperature gave the required (*Z*)-hexadeca-4-enyl bromide (**42**) in 85% yield. The overall yield of **42** in four steps was 57% (Scheme 3).[54]



Scheme 3 *Reagents, conditions and yields*: (i) $LiNH_2/NH_3$, $C_{11}H_{23}Br$, – 78 °C to – 33 °C to rt, 4 h (80%); (ii) H_2, Lindlar Pd, quinoline, hexane, rt, 30 min (99%); (iii) *p*-TsCl, TEA, DMAP, CH_2Cl_2, rt, 6 h (86%); (iv) LiBr, $NaHCO_3$, acetone, rt, 15 h (85%).

The bromide **42** (high molecular weight) was purified by column chromatography, and the residual water was removed by azeotropic distillation with benzene, as it was required in highly pure form for generation of the Grignard reagent. To maintain the ~100% *cis*-geometry we avoided the purification of halide **42** by distillation under vacuo. Our initial attempt to generate Grignard reagent from bromide **42** in sodium-dried ether met with failure, but finally we could smoothly convert it to the corresponding Grignard reagent, when the reaction was carried out in LAH-dried ether. The freshly prepared Grignard reagent from **42** in presence of HMPA, chemo- and regioselectively coupled with bromodiester **32** to yield S_N2' product **37** with 62% yield. The two singlet peaks at $\delta = 5.76$ and 6.37 in ^1H NMR spectra of compound **37** directly confirm the presence of an *exo*-methylene group. The diester **37** on LiOH induced hydrolysis followed by acidification gave the desired novel natural product 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**36**) in 98% yield (Scheme 4).[54] The analytical and spectral data obtained for the corresponding dimethyl ester **37** were in complete agreement with reported data.[60] The dicarboxylic acid **36** in refluxing acetic anhydride gave isochaetomellic acid B anhydride **43** in quantitative yield. In the present first four-step synthesis, the natural product 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**36**) was obtained with 39% overall yield.

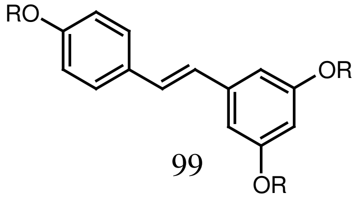


Scheme 4 *Reagents, conditions and yields*: (i) $CH_3(CH_2)_{10}CH=CH(CH_2)_3MgBr$, Et_2O, HMPA, rt, 8 h (62%); (ii) LiOH, THF + H_2O (2:1), rt, 18 h (98%); (iii) Ac_2O, reflux, 2 h (~100%).

2.1C Section A: III. *N*-Bromosuccinimide-Dibenzoyl Peroxide/ Azobis-isobutyronitrile: A Reagent for *Z*- to *E*-Alkene Isomerization

2.1C.1 Background

The generation of carbon-carbon double bonds in geometrically pure form is one of the most important reactions in synthetic organic chemistry[65] and many elegant methods are known in the literature for achieving the same.[66] However, in many of the reactions, such as Wittig reaction or alkene metathesis, mixtures of *Z*- and *E*-alkenes are also formed[66,67] and radical[68] or photochemical[69] reactions have been used to transform the *Z*-isomers to the corresponding *E*-isomers. Photochemical methods for these isomerizations, with or without sensitization, are often not satisfactory as the reactions are very slow and give rise to undesired product. More methods involving catalysis by diaryl disulfide,[68b,c] iodine,[69a] R_3SnH-Et_3B (R = Ph or *n*-Bu)[68d] and some other examples are reported in the literature. Amongst them the former two got widespread applicability over a range of substrates. Isomerization of (*Z*)-stilbene to the *E*-isomer and dimethyl maleate to dimethyl fumarate are usually catalyzed by bromine via the reversible addition of a bromine radical to the double bond.[70] Recently Spencer et al. have demonstrated[71] a facile palladium(II)-catalyzed isomerization of *Z*-arylalkenes to *E*-arylalkenes, and have used this methodology in the synthesis of trimethoxy resveratrol[72] (Figure 9) to demonstrate its synthetic potential. The high biological importance of resveratrol prompted them to synthesize it as a single geometrical isomer and they achieved it by first synthesizing it via Wittig reaction in 92% yield (1:1 mixture of *Z*- and *E*-isomers) followed by isomerization of the obtained mixture to *E*-isomer in 94% yield.



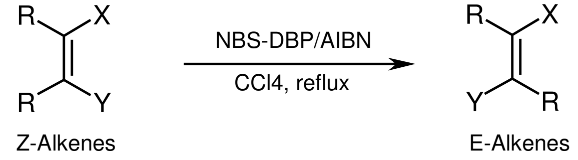
R = Me; Trimethoxy resveratrol (**44**)
R = H; Resveratrol (**45**)

Figure 9

The provision of a new method for isomerization of *Z*-olefins to *E*-olefins is a task of current interest and in this context; we herein present our studies on an easy access to several types of geometrically pure *E*-olefins using *N*-bromosuccinimide-dibenzoyl peroxide/azobisisobutyronitrile (NBS-DBP/AIBN) as a reagent for *Z* to *E* isomerization.

2.1C.2 Present Work: Results and Discussion

In our on going studies on the synthesis of recently isolated bioactive natural products, we carried out the reaction of dimethyl methylmaleate (**31**) with NBS-AIBN and obtained dimethyl bromomethylfumarate (**32**) in 85% yield. Both allylic bromination and isomerization of the carbon-carbon double bond took place in one-pot via an in situ addition-elimination of the bromine radical, which was further confirmed by obtaining the same product from dimethyl methylfumarate[54] (**35**) (Table 3, Entry 3). On the basis of this observation,[73] we prepared a systematic plan to study the NBS-DBP/AIBN induced *Z*- to *E*- carbon-carbon double bond isomerization with several types of olefins having a variety of substituents.[75] The results are presented in Scheme 5 and Table 3. Maleic acid (**46**), on treatment with NBS-DBP in refluxing acetic acid, gave fumaric acid (**47**) in 90% yield, while dimethyl maleate (**48**), on treatment with NBS-AIBN in refluxing CCl_4 gave dimethyl fumarate (**49**) in 98% yield (Entries 1 and 2). The process of carbon-carbon double bond isomerization was found to be slow in tetrasubstituted dimethyl dimethylmaleate (**50**) using 1.1 equivalents of NBS while the use of 2.5 equivalent of NBS gave a 1:1 mixture of dimethyl dibromomethylmaleate (**51**) and dimethyl dibromomethylfumarate (**52**) in 96% yield (Entry 4). Interestingly, dimethyl methoxymaleate (**53**), on treatment with NBS-DBP in refluxing CCl_4, did not show any

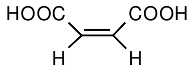
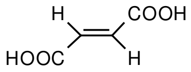
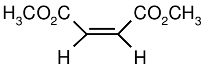
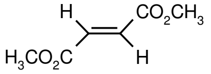
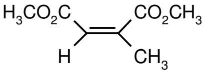
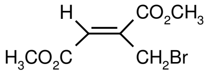
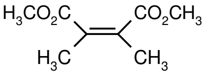
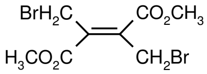
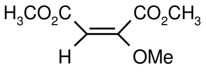
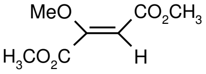
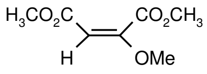
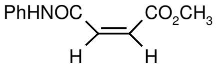
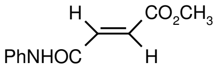
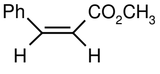
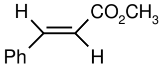
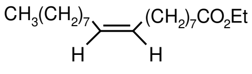
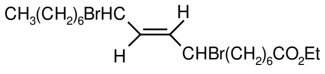
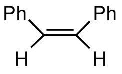
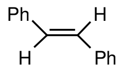


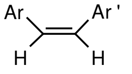
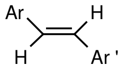
R = H, CO_2H, CO_2Me; X/Y = H, Me, Alkyl, CH_2Br, $CHBr_2$, Ph, Aryl, CO_2Me, CONHAr

Scheme 5

reaction. On the contrary, the corresponding dimethyl methoxyfumarate (**54**) underwent very smooth carbon-carbon double bond isomerization to yield dimethyl methoxymaleate (**53**) in 92% yield, revealing that the *E*-isomer is thermodynamically more stable than the *Z*-isomer, probably due to the presence of the extended conjugation involving the lone pairs of electrons on oxygen atom in the -OMe group of the *E*-isomer (Entries 5 and 6). Methyl maleanilate (**55**) and methyl *Z*-cinnamate (**57**) under similar reaction conditions gave the corresponding *E*-products in 90% and 96% yields respectively (Entries 7 and 8). As expected, methyl *Z*-oleate (**59**) on treatment with NBS-DBP in refluxing CCl_4 gave the methyl *E*-dibromooleate (**60**) in 95% yield, while under the same set of reaction conditions

Table 3 NBS-DBP/AIBN Induced Carbon-Carbon Double Bond Isomerizations

Sr. No.	Starting Material[a]	Reaction Conditions	Product	% Yield
1	 **46**	NBS (2.0 eqv.), DBP, AcOH, reflux, 6 h	 **47**	90
2	 **48**	NBS (1.1 eqv.), AIBN, CCl_4, reflux, 1 h	 **49**	98
3	 **31**	NBS (1.5 eqv.), AIBN, CCl_4, reflux, 12 h	 **32**	85
4	 **50**	NBS (2.5 eqv.), DBP, CCl_4, reflux, 2 h	 **52**	46[b]
5	 **53**	NBS (2.0 eqv.), DBP, CCl_4, reflux, 8 h	No Reaction	0
6	 **54**	NBS (2.0 eqv.), DBP, AcOH, reflux, 8 h	 **53**	92
7	 **55**	NBS (4.0 eqv.), DBP, CCl_4, reflux, 10 h	 **56**	90
8	 **57**	NBS (1.1 eqv.), AIBN, CCl_4, reflux, 2 h	 **58**	96
9	 **59**	NBS (2.5 eqv.), DBP, CCl_4, reflux, 4 h	 **60**	95
10	 **61**	NBS (2.0 eqv.), DBP, CCl_4, reflux, 3 h	 **62**	~ 100

11	 **63**	NBS (1.1 eqv.), DBP, CCl_4, reflux, 2 h	 **44**	60[c]

[a] The *Z*-alkenes and geometric mixtures of alkenes were prepared by using known literature procedures.[70,75] [b] 50% Dimethyl dibromomethylmaleate (**51**) was also formed. [c] 10-15% Mixture of ring brominated products was also obtained. Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl.

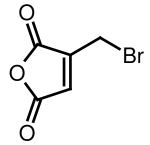
Z-stilbene (**61**) was transformed into *E*-stilbene (**62**) in ~100% yield (Entries 9 and 10). *Z*-Trimethoxystilbene (**63**), on treatment with NBS (1.1 equiv.) and DBP (catalytic) in refluxing CCl_4 gave the trimethoxy derivative of bioactive resveratrol (**44**)[72] in 60% yield and due to the mesomeric effect of the –OMe groups, we also observed 10-15% formation of mixtures of ring brominated *E*-trimethoxystilbene derivatives (Entry 11). As indicated in Table 3, we could isomerize different types of olefins with a variety of substituent patterns from *Z*- to *E*- forms using NBS-DBP/AIBN and the present method is simple and efficient.

In summary, in this section we have demonstrated the synthesis of bioactive natural product chaetomellic acid A anhydride (**6**) and 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**36**) with good overall yields using S_N2' Grignard coupling reaction as a key step. In the above mentioned coupling reaction with **32**, the chemo- and regioselective attack of the Grignard reagents on vinylic carbon in absence of copper catalyst is interesting and useful. It was also possible to couple the above Grignard reagents under similar reaction conditions without using HMPA to obtain **33** with 48 to 50% yields. Such type of migration of trisubstituted to *gem*-disubstituted carbon-carbon double bond with the loss of conjugation with one of the ester carbonyl is note-worthy. The present studies also provide a useful general approach for the synthesis of compounds containing such exo-type or exocyclic carbon-carbon double bonds[76] for structure activity relationship studies. We have also demonstrated that the reagent NBS-DBP brings about both allylic bromination and *Z*- to *E*- carbon-carbon double bond isomerization. The *Z*-alkenes without allylic hydrogens in pure form or mixtures of geometric isomers can be easily transformed into the corresponding *E*-alkenes using NBS-DBP/AIBN in quantitative yields. The present studies also provide a useful caution mark to the chemists attempting allylic bromination of *Z*-alkenes.

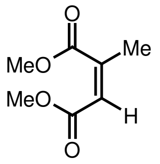
2.1D Section A: IV. Experimental Section

Commercially available citraconic anhydride, methyl fumaric acid, undecyl bromide, tetradecyl bromide, magnesium turnings, HMPA, tertrahydrofurfuryl chloride, lithium ribbon, Lindlar catalyst, quinoline, *p*-toluenesulfonyl chloride, DMAP, lithium bromide, acetic anhydride, *N*-bromosuccinimide, dibenzoyl peroxide, azobisisobutronitrile, maleic acid, dimethyl maleate and ethyl *Z*-oleate were used. The *Z*-alkenes and geometric mixtures of alkenes were prepared by using known literature procedures.[30a,71,77]

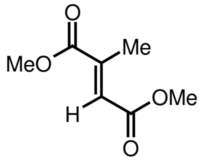
3-Bromomethyl-2,5-furandione (29). A mixture of citraconic anhydride (**1**) (4.48 g, 40 mmol), *N*-bromosuccinimide (14.24 g, 80 mmol) and catalytic amount of dibenzoyl peroxide (200 mg, 0.83 mmol) in carbon tetrachloride (300 mL) was gently refluxed for 4 h in a 500 mL round bottom flask. The reaction mixture was allowed to cool at room temperature, a second portion of dibenzoyl peroxide (200 mg, 0.83 mmol) was added and again the refluxing was continued 4 h longer. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL x 2); the combined organic layer was washed with water (100 mL x 2) and brine (100 mL) and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick yellow oil, which on silica gel column chromatographic purification using petroleum ether/ethyl acetate (8:2) gave crude product (5.80 g) which was further purified by distillation using Kugelrohr apparatus. The first fraction (1.21 g) was a mixture of **1** and **29** while a second fraction obtained at 120-125 °C (2 mm) was the anhydride **29**: 4.19 g (55% yield, 98% purity by ^{1}H NMR).

 **29** **$C_5H_3BrO_3$** (191)	Thick oil. **IR** (Neat): ν_{max} 1846, 1774, 1645 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 200 MHz): δ 4.26 (s, 2H), 6.96 (s, 1H). **^{13}C NMR** (CDCl$_3$, 50 MHz): δ 18.3, 131.6, 147.9, 162.3, 163.1. **MS** (*m/e*): 192, 190, 111, 79, 67.

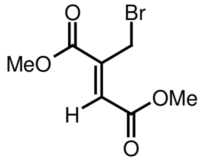
Dimethyl methylmaleate (31). A solution of citraconic anhydride (**1**) (4.48 g, 40 mmol) in methanol (40 mL) and H_2SO_4 (0.5 mL) mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with water (20 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether/ethyl acetate (9:1) as eluent furnished pure diester **31**: 4.74 g (75% yield).

 **31** **$C_7H_{10}O_4$** (158)	Thick oil. **IR** (Neat): ν_{max} 1736, 1726, 1655 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.04 (bs, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 5.84 (bs, 1H).

Dimethyl methylfumarate (33). Repetition of above experimental procedure with methylfumaric acid (5.20 g, 40 mmol) yielded the dimethyl methylfumarate (**33**) in same yield.

 **33** **$C_7H_{10}O_4$** (158)	Thick oil. **IR** (Neat): ν_{max} 1734, 1724, 1645 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.24 (d, J = 2 Hz, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 6.73 (q, J = 2 Hz, 1H).

Dimethyl bromomethylfumarate (32). A mixture of **31** (4.74 g, 30 mmol), *N*-bromosuccinimide (8.00 g, 45 mmol) and catalytic amount of AIBN (200 mg, 1.22 mmol) in carbon tetrachloride (150 mL) was gently refluxed for 12 h in a 250 mL round bottom flask. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL x 2); the combined organic layer was washed with water (50 mL x 2), brine (50 mL) and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick yellow oil, which was purified by chromatography on silica gel column using petroleum ether/ethyl acetate (9:1) to give the desired bromo diester **32**: 6.05 g (85% yield).

 **32** **$C_7H_9BrO_4$** (237)	Thick oil. **IR** (Neat): ν_{max} 1730, 1726, 1643 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H), 3.88 (s, 3H), 4.72 (s, 2H), 6.83 (s, 1H). **^{1}H NMR** (CCl_4, 200 MHz): δ 3.87 (s, 3H), 3.93 (s, 3H), 4.70 (s, 2H), 6.79 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 22.1, 51.7, 52.5, 127.9, 142.4, 164.5, 164.7. **MS** (*m/e*): 238, 236, 206, 204, 179, 177, 125, 98, 68, 59. **Anal. Calcd for $C_7H_9BrO_4$**: C, 35.47; H, 3.83. Found: C, 35.59; H, 3.72.

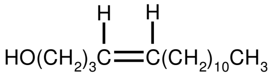
Dimethyl methylfumarate (**33**) (4.74 g, 30 mmol) with same set of reaction conditions furnished **32** in 86% yield.

4-Hexadecyn-1-ol (39). Lithium (1.05 g, 150 mmol) in presence of ferric nitrate (50 mg) was dissolved in freshly distilled ammonia (250 mL) at – 78 °C (disappearance of blue color). To this freshly prepared lithium amide solution was added tetrahydrofurfuryl chloride (**38**) (6.03 g, 50 mmol) during 10 minutes time and the reaction mixture was stirred for 3 h at –33 °C. After all the tetrahydrofurfuryl chloride (**38**) was consumed (by TLC), *n*-undecyl bromide (11.75 g, 50 mmol) in THF (10 mL) was added drop wise to the stirred and cooled reaction mixture at – 33 °C. It was then stirred for additional 0.5 h and allowed to reach room temperature. The residue was treated with saturated ammonium chloride solution and extracted with ether (50 mL x 5); the combined organic layer was washed with water (50 mL x 2) and brine (50 mL) and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick oil, which was purified by chromatography on silica gel column using petroleum ether/ethyl acetate (8:2) to give pure **39**: 9.53 g (80% yield).

	Thick oil. **IR** ($CHCl_3$): ν_{max} 3423, 2400, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.87 (t, *J* = 8 Hz, 3H), 1.25 (bs, 16H), 1.43 (quintet, *J* = 6 Hz, 2H), 1.73 (quintet, *J* = 8

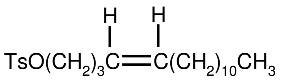
$HO(CH_2)_3C{\equiv}C(CH_2)_{10}CH_3$ **39** **$C_{16}H_{30}O$** (238)	Hz, 2H), 1.89 (bs, 1H), 2.05-2.20 (m, 2H), 2.20- 2.35 (m, 2H), 3.74 (t, *J* = 6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 14.0, 15.4, 18.7, 22.6, 28.9-29.6 (7-carbons), 31.6, 31.9, 61.9, 79.2, 81.0. **MS** (*m/e*): 238, 226, 209, 184, 153, 111, 97, 83, 67, 55. **Anal. Calcd for $C_{16}H_{30}O$**: C, 80.61; H, 12.68. Found: C, 80.57; H, 12.70.

4(*Z*)-Hexadecen-1-ol (40). To a solution of **39** (9.52 g, 40 mmol) in hexane (150 mL) were added Lindlar palladium catalyst (800 mg) and quinoline (2 mL). The reaction mixture was vigorously stirred at room temperature under slightly positive pressure until hydrogen absorption ceased (0.5 h). The mixture was filtered, and filtrate was concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (8:2) to give **40**: 9.51 g (99% yield).

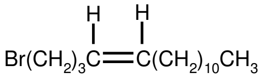
 $HO(CH_2)_3\overset{H}{C}{=}\overset{H}{C}(CH_2)_{10}CH_3$ **40** **$C_{16}H_{32}O$** (240)	Thick oil. **IR** (Neat): ν_{max} 3354, 1465 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.26 (bs, 18H), 1.51 (bs, 1H), 1.64 (quintet, *J* = 8 Hz, 2H), 2.04 (quintet, *J* = 6 Hz, 2H), 2.14 (quintet, *J* = 6 Hz, 2H), 3.67 (t, *J* = 6 Hz, 2H), 5.30-5.50 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.9, 22.6, 23.6, 27.2, 29.3-29.6 (7-carbons), 31.9, 32.7, 62.5, 128.8, 130.7. **MS** (*m/e*): 240, 222, 194, 152, 109, 96, 82, 68, 55. **Anal. Calcd for $C_{16}H_{32}O$**: C, 79.93; H, 13.41. Found: C, 79.91; H, 13.44.

4(*Z*)-Hexadecen-1-tosylate (41). *p*-Toluenesulfonyl chloride (11.47 g, 60 mmol) was added to a solution of **40** (7.20 g, 30 mmol), anhydrous triethyl amine (9.09 g, 90 mmol) and DMAP (75 mg) in anhydrous dichloromethane (150 mL) with stirring and ice cooling. Stirring was continued for 6 h at room temperature. The reaction mixture was then poured into ice water and extracted with dichloromethane (50 mL x 3). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9:1) to give **41**: 10.13 g (86% yield).

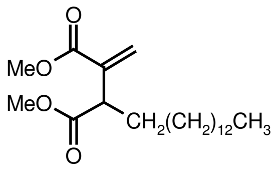
	Thick oil. **IR** (Neat): ν_{max} 1598, 1465, 1365, 1176 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.26 (bs, 18H), 1.69 (quintet, *J* = 8 Hz, 2H), 1.95 (quintet, *J* = 8 Hz, 2H), 2.06 (quintet, *J* = 8 Hz, 2H), 2.45 (s, 3H), 4.03 (t, *J* = 6 Hz, 2H), 5.15-5.45 (m, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.79

 $\mathrm{TsO(CH_2)_3\overset{H}{C}{=}\overset{H}{C}(CH_2)_{10}CH_3}$ **41** **$C_{23}H_{38}O_3S$** (394)	(d, *J* = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.9, 21.4, 22.5, 22.9, 27.0, 28.8-29.5 (8-carbons), 31.8, 69.9, 127.2, 127.7, 129.6, 131.5, 133.5, 144.4. **MS** (*m/e*): 222, 194, 173, 155, 124, 109, 91, 68. **Anal. Calcd for $C_{23}H_{38}O_3S$**: C, 70.00; H, 9.71. Found: C, 70.03; H, 9.67.

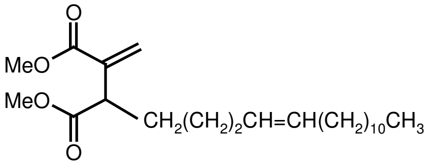
4(*Z*)-Hexadecen-1-bromide (42). To a solution of **41** (9.85 g, 25 mmol) in dry acetone (150 mL) were added $NaHCO_3$ (21.0 g, 250 mmol) and anhydrous lithium bromide (15.23 g, 175 mmol). The reaction mixture was stirred for 15 h at room temperature, then diluted with ether (100 mL) and filtered through Celite. The organic solution was concentrated in vacuo, and the residue was diluted with ether (75 mL). The ether layer was washed with water (20 mL), 5% $Na_2S_2O_3$ solution (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether to give **42**: 6.44 g (85% yield).

 $\mathrm{Br(CH_2)_3\overset{H}{C}{=}\overset{H}{C}(CH_2)_{10}CH_3}$ **42** **$C_{16}H_{31}Br$** (303)	Thick oil. **IR** (Neat): ν_{max} 1465, 1224 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.26 (bs, 18H), 1.91 (quintet, *J* = 8 Hz, 2H), 2.05 (quintet, *J* = 6 Hz, 2H), 2.20 (quintet, *J* = 6 Hz, 2H), 3.41 (t, *J* = 8 Hz, 2H), 5.20-5.55 (m, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 14.1, 22.7, 25.7, 27.3, 29.3-29.7 (7-carbons), 31.9, 32.7, 33.2, 127.3, 131.8. **MS** (*m/e*): 304, 302, 205, 181, 164, 162, 150, 148, 137, 111, 97, 83, 69. **Anal. Calcd for $C_{16}H_{31}Br$**: C, 63.36; H, 10.30. Found: C, 63.39; H, 10.27.

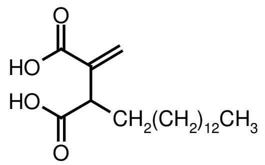
Dimethyl 1-heptadecen-2,3-dicarboxylate (34). A fresh solution of *n*-tetradecylmagnesium bromide in ether was prepared as follows. A solution of *n*-tetradecyl bromide (2.49 g, 9 mmol) in LAH-dried ether (10 mL) was added at room temperature to magnesium turnings (648 mg, 27 mmol) in ether (10 mL) under argon with constant stirring in three equal portions at an interval of 10 minutes. The reaction mixture was further stirred at room temperature for 4 h. TLC of the reaction mixture in *n*-pentane showed quantitative conversion of the halide in to the Grignard reagent. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (2.69 g, 15 mmol) and **32** (711 mg, 3 mmol) in anhydrous ether (15 mL) at room temperature. The reaction mixture was further stirred at room temperature for 8 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (20 mL) and ether (10 mL). The reaction mixture was extracted with ether (20 mL x 3), the combined ethereal extracts were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **34**: 637 mg (60% yield).

 **34** **$C_{21}H_{38}O_4$** (354)	Thick oil. **IR** (Neat): ν_{max} 1738, 1728, 1630 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.86 (t, J = 6 Hz, 3H), 1.24 (bs, 24H), 1.50-2.00 (m, 2H), 3.49 (t, J = 8 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 5.74 (s, 1H), 6.35 (s, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 14.0, 22.6, 27.4, 29.2-29.5 (9-carbons), 31.3, 31.8, 46.5, 51.8, 51.9, 126.3, 138.6, 166.6, 173.6. **Anal. Calcd for $C_{21}H_{38}O_4$**: C, 71.14; H, 10.80. Found: C, 71.10; H, 10.73.

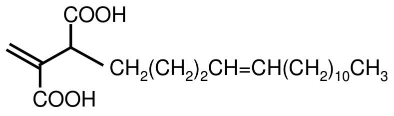
Dimethyl 1,7(*Z*)-nonadecadiene-2,3-dicarboxylate (37). Repetition of above procedure using (*Z*)-hexadeca-4-enyl magnesium bromide [prepared from **42** (2.73 g, 9 mmol) and magnesium (648 mg, 27 mmol)] and **32** (711 mg, 3 mmol) gave the corresponding diester **37**: 707 mg (62% yield).

 **37** **$C_{23}H_{40}O_4$** (380)	Thick oil. **IR** (Neat): ν_{max} 1740, 1726, 1630, 1458, 1437 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.35 (quintet, J = 6 Hz, 2H), 1.66 (m, 1H), 1.80-2.15 (m, 5H), 3.51 (t, J = 8 Hz, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 5.34 (m, 2H), 5.76 (s, 1H), 6.37 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 14.0, 22.6, 26.8, 27.2, 27.5, 29.3, 29.6 (6-carbons), 30.8, 31.9, 46.4, 51.9, 52.0, 126.6, 128.8, 130.6, 138.4, 166.6, 173.6. **MS** (*m/e*) 380, 348, 320, 289, 261, 236, 193, 158, 140, 126, 107, 93, 79, 67. **Anal. Calcd for $C_{23}H_{40}O_4$**: C, 72.59; H, 10.59. Found: C, 72.67; H, 10.53.

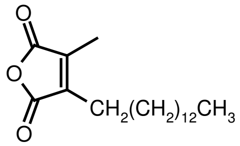
1-Heptadecen-2,3-dicarboxylic acid (35). Concentrated hydrochloric acid (3 mL) was added to a solution of **34** (531 mg, 1.50 mmol) in acetic acid (7 mL) and the reaction mixture was refluxed for 2 h. The reaction mixture was then cooled, concentrated in vacuo, and the residue was diluted with ethyl acetate (30 mL). The ethyl acetate layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **35**: 479 mg (98% yield).

 **35** **$C_{19}H_{34}O_4$** (326)	**Mp**: 98-99 °C (benzene). **IR** (Nujol): ν_{max} 1703, 1693, 1628 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 8 Hz, 3H), 1.26 (bs, 24H), 1.60-1.85 (m, 1H), 1.85-2.10 (m, 1H), 3.40 (t, J = 8 Hz, 1H), 5.84 (s, 1H), 6.55 (s, 1H), 7.35-8.30 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 14.0, 22.6, 27.4, 29.3-29.6 (9-carbons), 30.7, 31.9, 46.6, 129.4, 137.7, 171.6, 179.3. **Anal. Calcd for $C_{19}H_{34}O_4$**: C, 69.90; H, 10.50. Found: C, 69.93; H, 10.37.

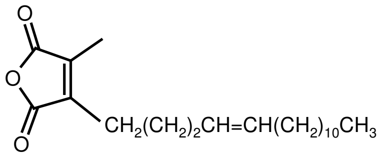
1,7(Z)-nonadecadiene-2,3-dicarboxylic acid (36). Aqueous lithium hydroxide solution (230 mg in 2 mL water) was added to a solution of **37** (570 mg, 1.50 mmol) in tetrahydrofuran (4 mL) and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then concentrated in vacuo, and the residue was diluted with ethyl acetate (50 mL) and acidified to pH 2 with 2 N hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (10 mL x3). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **36**: 520 mg (98% yield).

 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic Acid **(36)** **$C_{21}H_{36}O_4$** (352)	Thick oil. **IR** (Neat): ν_{max} 2683, 1713, 1699, 1628 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.40 (quintet, J = 6 Hz, 2H), 1.65-1.85 (m, 1H), 1.85-2.20 (m, 5H), 3.43 (t, J = 8 Hz, 1H), 5.36 (m, 2H), 5.85 (s, 1H), 6.55 (s, 1H), 8.72 (bs, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 14.0, 22.6, 26.8, 27.3, 27.5, 29.2, 29.3-29.7 (6-carbons), 29.8, 31.9, 46.8, 128.7, 129.6, 130.8, 137.5, 171.5, 179.2. **MS** (*m/e*): 352, 334, 316, 306, 295, 277, 261, 239, 221, 193, 179, 151, 126, 112, 97, 81, 67. **Anal. Calcd for $C_{21}H_{36}O_4$**: C, 71.55; H, 10.29. Found: C, 71.47; H, 10.37.

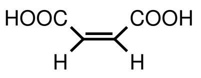
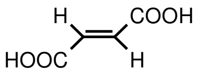
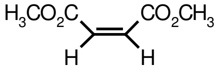
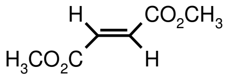
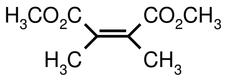
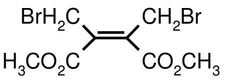
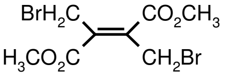
2-Tetradecyl-3-methylmaleic anhydride (Chaetomellic acid A anhydride, 6). A solution of **34** (326 mg, 1 mmol) in acetic anhydride (5 mL) was refluxed for 2 h and the reaction mixture was allowed to reach room temperature, concentrated under vacuo at 50 °C and diluted with ethyl acetate (20 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **6**: 308 mg (~100% yield).

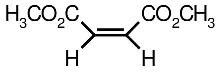
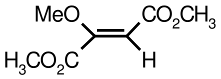
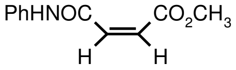
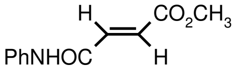
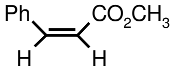
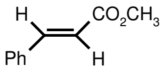
 Chaetomellic Acid A Anhydride **(6)** **$C_{19}H_{32}O_3$** (308)	Thick oil. **IR** (Neat): ν_{max} 1770, 1680 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 7 Hz, 3H), 1.15-1.45 (bs, 22H), 1.46-1.69 (m, 2H), 2.07 (s, 3H), 2.45 (t, J = 7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 9.6, 14.3, 22.9, 24.6, 27.7, 29.0-31.0 (9-carbons), 32.1, 140.6, 144.9, 166.0, 166.4. **MS** (*m/e*) 308, 290, 191, 150, 126, 91, 81, 69. **Anal. Calcd for $C_{19}H_{32}O_3$**: C, 73.98; H, 10.46. Found: C, 73.73; H, 10.39.

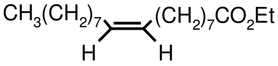
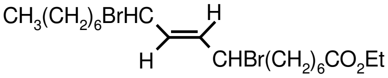
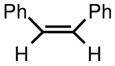
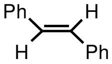
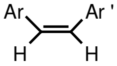
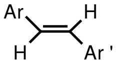
(Z)-2-Hexadeca-4-enyl-3-methylmaleic anhydride (Isochaetomellic acid B anhydride, 43). It was prepared similarly from **36** (352 mg, 1 mmol) and acetic anhydride (5 mL) as described above to obtain the corresponding anhydride **43**: 333 mg (~100% yield).

 Isochaetomellic Acid B Anhydride **(43)** **$C_{21}H_{34}O_3$** (334)	Thick oil. **IR** (Neat): ν_{max} 1767, 1740, 1460, 1271 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.65 (quintet, J = 8 Hz, 2H), 1.90-2.25 (m, 4H), 2.08 (s, 3H), 2.47 (t, J = 8 Hz, 2H), 5.20-5.55 (m, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 9.4, 14.0, 22.6, 26.9, 27.3, 27.5, 29.3, 29.5 (6-carbons), 29.6, 31.9, 127.7, 131.8, 140.5, 144.5, 165.8, 166.2. **MS** (*m/e*): 334, 289, 278, 266, 223, 205, 165, 149, 126, 97, 83, 69, 57. **Anal. Calcd for $C_{21}H_{34}O_3$**: C, 75.41; H, 10.25. Found: C, 75.35; H, 10.33.

General Procedure for the isomerization of *Z*-alkenes to *E*-alkenes. A mixture of *Z*-alkene, *N*-bromosuccinimide and catalytic amount of DBP/AIBN (10 mol %) in carbon tetrachloride (5-10 mL per mmol of substrate) was gently refluxed (see Table 1). The mixture was allowed to cool to room temperature and then filtered. The residue was washed with CCl_4 and the combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as an eluent to obtain the desired *E*-alkene.

 Maleic acid (**46**) **$C_4H_4O_4$** (116)	**Mp**: 143 °C. **IR** (Nujol): ν_{max} 2700-2500, 1707, 1636, 1587, 1568, 1460, 1435, 1263, 1221, 862, 608 cm^{-1}. **^{1}H NMR** (Acetone-d_6, 200 MHz): δ 6.43 (s, 2H), 9.60 (bs, 2H).
 Fumaric acid (**47**) **$C_4H_4O_4$** (116)	**Mp**: 298-300 °C (sublimes). **IR** (Nujol): ν_{max} 2700-2500, 1703, 1462, 1377, 1277, 928, 721, 644 cm^{-1}. **^{1}H NMR** (Acetone-d_6, 200 MHz): δ 6.80 (s, 2H), 9.89 (bs, 2H).
 Dimethyl maleate (**48**) **$C_6H_8O_4$** (144)	Thick oil. **IR** (Neat): ν_{max} 1734, 1645, 1439, 1391, 1223, 1165, 1007, 864, 822 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.74 (s, 6H), 6.23 (s, 2H).
 Dimethyl fumarate(**49**) **$C_6H_8O_4$** (144)	**Mp**: 100–101 °C. **IR** (Nujol): ν_{max} 1726, 1645, 1439, 1310, 1215, 1161, 1034, 980, 758, 669 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.82 (s, 6H), 6.88 (s, 2H).
 Dimethyl dimethylmaleate (**50**) **$C_8H_{12}O_4$** (172)	Thick oil. **IR** (Neat): ν_{max} 1724, 1649, 1437, 1271, 1198, 1167, 1101, 932, 762 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.96 (s, 6H), 3.77 (s, 6H).
 Dimethyl dibromomethylmaleate (**51**) **$C_8H_{10}BrO_2$** (330)	Thick oil. **IR** (Neat): ν_{max} 1728, 1634, 1435, 1321, 1277, 1217, 1155, 1074, 957 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.85 (s, 6H), 4.25 (s, 4H).
	Thick oil. **IR** (Neat): ν_{max} 1726, 1628, 1435, 1269, 1217, 1161, 1103, 1007, 847, 785 cm^{-1}.

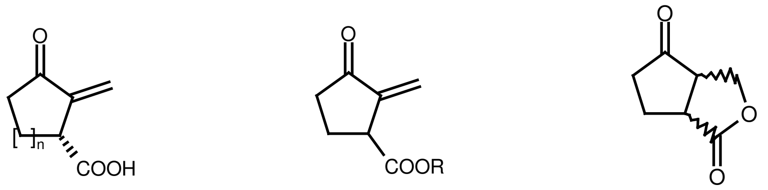
Dimethyl dibromomethylfumarate (**52**) **$C_8H_{10}BrO_2$** (330)	**^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.92 (s, 6H), 4.50 (s, 4H).
 Dimethyl methoxymaleate (**53**) **$C_7H_{10}O_5$** (174)	Thick oil. **IR** ($CHCl_3$): ν_{max} 1753, 1720, 1630, 1439, 1371 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.71 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 5.21 (s, 1H).
 Dimethyl methoxyfumarate (**54**) **$C_7H_{10}O_5$** (174)	Thick oil. **IR** ($CHCl_3$): ν_{max} 1745, 1726, 1641, 1437, 1269 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.75 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.18 (s, 1H).
 Methyl maleanilate (**55**) **$C_{11}H_{11}O_3N$** (205)	**Mp**: 76-77 °C. **IR** (Nujol): ν_{max} 3252, 1732, 1668, 1632, 1597 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.85 (s, 3H), 6.22 (d, J = 12 Hz, 1H), 6.45 (d, J = 12 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 7.35 (t, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 10.85 (bs, 1H).
 Methyl fumaranilate (**56**) **$C_{11}H_{11}O_3N$** (205)	**Mp**: 164-165 °C. **IR** ($CHCl_3$): ν_{max} 3325, 1717, 1684, 1659 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H), 6.85-7.65 (m, 7H), 7.90-8.20 (m, 1H).
 Methyl (Z)-cinnamate (**57**) **$C_{10}H_{10}O_2$** (162)	Thick oil. **IR** (Neat): ν_{max} 1724, 1628, 1271, 1200, 1169 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.73 (s, 3H), 5.98 (d, J = 12 Hz, 1H), 6.98 (d, J = 12 Hz, 1H), 7.20-7.70 (m, 5H).
 Methyl (E)-cinnamate (**58**) **$C_{10}H_{10}O_2$** (162)	**Mp**: 36-38 °C. **IR** ($CHCl_3$): ν_{max} 1717, 1638, 1281, 1204, 1173 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.82 (s, 3H), 6.46 (d, J = 16 Hz, 1H), 7.30-7.60 (m, 5H), 7.71 (d, J = 16 Hz, 1H).

 Ethyl-9-(*Z*)-octadecenoate (**59**) **$C_{20}H_{38}O_2$** (310)	Thick oil. **IR** (Neat): $\nu_{\max}$ 1740, 1464, 1373, 1180, 1036, 723 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.86 (t, *J* = 6 Hz, 3H), 1.27 (bs, 25H), 1.60 (m, 2H), 2.00 (m, 2H), 2.27 (t, *J* = 8 Hz, 2H), 4.11 (q, *J* = 8 Hz, 2H), 5.33 (t, *J* = 6 Hz, 2H).
 Ethyl-9-(*E*)-8,11-dibromooctadecenoate (**60**) **$C_{20}H_{36}Br_2O_2$** (468)	Thick oil. **IR** (Neat): $\nu_{\max}$ 1730, 1462, 1373, 1180, 1034, 962 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.26 (m, 21H), 1.50-2.00 (m, 4H), 2.29 (t, *J* = 8 Hz, 2H), 4.13 (q, *J* = 8 Hz, 2H), 4.40-4.90 (m, 2H), 5.70-6.00 (m, 2H).
 *Z*-Stilbene (**61**) **$C_{14}H_{12}$** (180)	Thick oil. **IR** (Neat): $\nu_{\max}$ 1601, 1493, 1447, 924, 779, 698 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 6.60 (s, 2H), 7.05-7.35 (m, 10H).
 *E*-Stilbene (**62**) **$C_{14}H_{12}$** (180)	**Mp**: 122-123 °C. **IR** ($CHCl_3$): $\nu_{\max}$ 1599, 1495, 1452, 1217, 962, 762, 692 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 7.12 (s, 2H), 7.15-7.60 (m, 10H).
 *Z*-4-Methoxy-3′,5′-dimethoxystilbene (**63**) Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl **$C_{17}H_{18}O_3$** (270)	Thick oil. **IR** (Neat): $\nu_{\max}$ 1600, 1591, 1510, 1250, 1155 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.69 (s, 6H), 3.80 (s, 3H), 6.30-6.40 (m, 1H), 6.44-6.51 (m, 2H), 6.46 (d, *J* = 12 Hz, 1H), 6.56 (d, *J* = 12 Hz, 1H), 6.80 (d, *J* = 10 Hz, 2H), 7.25 (d, *J* = 10 Hz, 2H).
 *E*-4-Methoxy-3′,5′-dimethoxystilbene (**44**) Ar = 3,5-dimethoxyphenyl; Ar ′ = *p*-methoxyphenyl **$C_{17}H_{18}O_3$** (270)	**Mp**: 78 °C. **IR** ($CHCl_3$): $\nu_{\max}$ 1612, 1589, 1510, 1252, 756 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 9H), 6.32-6.44 (m, 1H), 6.60-6.70 (m, 2H), 6.86-6.94 (d, *J* = 16 Hz, 1H), 6.88-6.92 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 16 Hz, 1H), 7.46 (d, *J* = 8 Hz, 2H).

3.1A Section C: I. A Simple Synthesis of (±)-Sarkomycin

2.1A.1 Background

α-Methylene ketone and lactone functionalities are found to be present in a great number of compounds having anticancer properties. Simplest of those, sarkomycin (**134**), was produced by a strain of the soil microorganism *Streotomyces erythromegenes*[114] and reported to show powerful inhibitory effect on Ehrlich ascites tumors in mice.[115] Sarkomycin (**134**) selectively inhibits DNA synthesis and it has been suggested that the site of the inhibition is DNA polymerase, probably at the sulfhydryl group.[116] Structural determination studies[117] revealed that sarkomycin (**134**) possesses a single asymmetric centre, which was assigned as *S* configuration and later revised by Hill to *R* configuration by chemical transformation studies.[118] After initial isolation and structure determination it attracted considerable attention and was used in clinical trials in Japan[119] and the USA.[120] Further pharmacological studies[116,121] led to the marketing in Japan of a preparation containing this substrate as an antitumor drug by Banyu Pharmaceutical Co., Ltd., Tokyo.[122a] In spite of initial reports of positive action, it was concluded that the compound is not active against solid tumors. Nevertheless, though the structure of sarkomycin is very



n = 1, Sarkomycin (**134**)
n = 2, Homosarkomycin (**135**)
n = 3, Bishomosarkomycin (**136**)

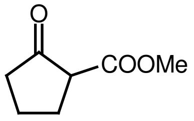
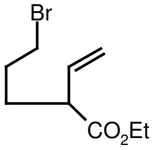
R = H, (±)-Sarkomycin (**134a**)
R = Me, **134b**
R = Et. **134c**

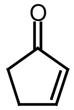
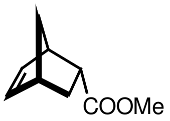
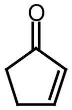
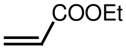
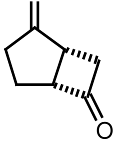
Cyclosarkomycin (**137**)

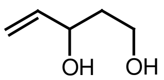
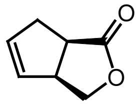
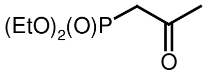
Figure 12

simple, it's total synthesis faces great difficulties. This is due to the fact that sarkomycin itself, as well as a large number of its derivatives present a high chemical instability, being very sensitive to both acids and bases, undergoing dimerization and polymerization easily. This makes them very much unstable inclusively towards cold storage. Since its isolation in 1953 by Umezawa *et al*, several elegant synthetic routes to this rather unstable natural product,[122] corresponding esters[123] and its more stable precursor cyclosarkomycin[122b,k-m] have been reported in view of their promising biological activity (Figure 12). Recently Amri and coworkers have reported the synthesis of sarkomycin analogues, homosarkomycin ethyl ester and bishomosarkomycin ethyl ester (Figure 12), using cyclic β-ketophosphonate as a key intermediate.[124] The chemistry involved in some of the recent and efficient syntheses has been tabulated in Table 6.

Table 6 A Few Recent Synthetic Approaches Towards Sarkomycin

No.	Starting Compound	Reagents and Conditions	Product	Overall Yield	Ref.
1	 2-(Carbomethoxy)-cyclopentanone	(i) NaH, *p*-TolSO$_2$SMe; (ii) Ethylene glycol, *p*-TSA, benzene; (iii) (a) NaIO$_4$, MeOH, then rt, 24 h, (b) CaCO$_3$, toluene, 110 °C; (iv) CH$_3$NO$_2$, tertamethylguanidine, rt, 3 days; (v) (a) LiAlH$_4$, AlCl$_3$, Et$_2$O, 0 °C, 30 min, (b) Dihydropyran, PPTS (cat.), CH$_2$Cl$_2$ rt, 4 h; (vi) (a) 1 N NaOH, aq. MgSO$_4$, KMnO$_4$, rt, 5 h, (b) H$^+$/HCl; (vii) 0.5 N HCl, rt, 10 h.	**134a**	5%	122g
2	 5-Bromo-2-vinyl-pentanoic acid ethyl ester	(i) NaI, Me$_2$CO, rt; (ii) AgNO$_3$, Et$_2$O, rt; (iii) *p*-Chlorophenylisocyanate, Et$_3$N, benzene, rt; (iv) H$_2$, W-2 Raney nickel, AcOH (3 equiv) methanol/water (5:1), rt; (v) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C.	**134c**	42%	123a

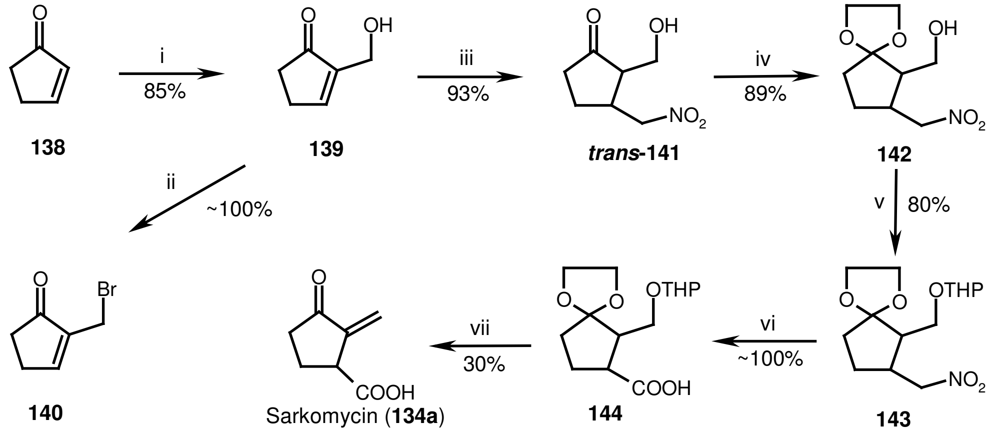
3	 2-Cyclopentenone	(i) Me_3SiCN, Et_3Al, hexane, 60 °C, 30 min; (ii) $PHSCH_2Cl$, $ZnBr_2$, CH_2Cl_2, rt, 18 h; (iii) (a) Oxone, MeOH, rt, 4 h, (b) Basic Al_2O_3, CH_2Cl_2, rt, 20 min; (iv) (a) Ethylene glycol, *p*-TSA, cyclohexane, reflux, 20 h, (b) KOH, ethylene glycol-H_2O, 120 °C, 16 h, (c) Acetone, H_2SO_4, rt, 24 h; (v) CH_2N_2, Et_2O, rt, 1h; (vi) (a) Oxone, MeOH, rt, 4 h, (b) Basic Al_2O_3, CH_2Cl_2, rt, 20 min.	**134a**	7%	123c 123d
4	 Methyl-(1*R*, 2*R*)-5-norbornene-2-carboxylate	(i) (a) LDA, THF, -75 °C, (b) $BrCH_2COOEt$, DMPU, THF; (ii) (a) LDA, THF, -75 °C, (b) 2-(2-Iodoethyl)-1,3-dioxo-lane, DMPU, THF; (iii) (a) CH_3COOH-H_2O (1:1), reflux, (b) Ag_2O, KOH, EtOH, rt; (iv) CH_2N_2, Et_2O, -10 °C; (v) *t*-BuOK, THF, -70 °C; (vi) 0.4 N NaOH in MeOH-H_2O (1:1), 100 °C; (vii) FVP: 650 °C/ 0.02 Torr.	(*S*)- and (*R*)- **134b**	29% for both (*S*)- and (*R*)- **134b**	123e
5	 2-Cyclopentenone	(i) (a) $(CH_3O)(PhS)(Me_3Si)CLi$, HMPA, THF, -78 °C, 2 h, (b) ICH_2OCH_3, 0 °C, 30 min; (ii) Bu_4NF, DMF-H_2O (8:1), rt, 1 h; (iii) CrO_3, H_2SO_4-acetone, rt, 1 h; (iv) CH_2N_2, Et_2O, 0 °C, 1 h; (v) BCl_3, CH_2Cl_2, -10 °C, 4 h; (vi) SiO_2.	**134b**	21%	123f
6	 Ethyl acrylate	(i) $(EtO)_2P(O)H$, K_2CO_3, $HSO_4N(n$-$C_4H_9)_4$ (2%), 70 °C, 8 h; (ii) NaH, THF, reflux, 1h; (iii) (HCHO)n, K_2CO_3, THF, reflux, or aq. HCHO, K_2CO_3, 20 °C, 20 min.	**134c**	35-44%	123g
7	 (1*R*, 5*R*)-Bicyclo[3.2.0]heptane-2,6-dione	Acinetobacter calcoaceticus NCIB 9871	**(1*R*, 5*S*)-137**	7% (97% *ee*)	122k

8	 1,3-Dihydroxypent-4-ene	(i) TrCl, Pyridine; (ii) Ti(O*i*-Pr)$_4$, (-)-DCHT, *t*-BuOOH; (iii) BnBr, NaH then *p*-TsOH; (iv) MsCl, Et$_3$N then NaH, CH$_2$(CO$_2$Me)$_2$; (v) I$_2$, Ti(O*t*-Bu)$_4$, CuO; (vi) KOH then xylene, reflux; (vii) H$_2$, Pd(OH)$_2$; (viii) Swern oxidation.	**(1*R*, 5*S*)-137**	16%	122l
9	 (1*R*, 5*S*)-(3,3*a*,6,6*a*)-Tetrahydro-cyclopenta[*c*]furan-1-one	(i) *m*-CPBA, CH$_2$Cl$_2$, 0 °C to rt, 12 h; (ii) TMSCl, 5 eq. Zn, Et$_2$O, 0 °C to rt, 1 h; (iii) Dess-Martin reagent, CH$_2$Cl$_2$, rt, 10 min; (iv) Zn, AcOH, rt, 15 min.	**(1*R*, 5*S*)-137**	56-60 (98% *ee*)	122m
10	 Diethyl-2-oxopropanephosphonate	(i) (a) NaH, THF, rt, (b) *n*-BuLi, 0 °C, CH$_2$=CHCH$_2$CH$_2$Br, rt, (c) H$^+$/HCl; (ii) NaH, TsN$_3$, C$_6$H$_6$-THF, 0 °C to rt; (iii) Rh$_2$(OAc)$_4$, CH$_2$Cl$_2$, reflux, 2 h; (iv) (a) O$_3$, MeOH, -70 °C, (b) Me$_2$S, -30 °C to rt, (c) CrO$_3$, H$_2$SO$_4$, acetone, 0 °C; (v) (*S*)-1-(1-Naphthyl)-ethylamine, C$_6$H$_6$, rt, 0.5 h; (vi) MeOH-H$_2$O (10:1), chromatography on ion exchanger IV Merck; (vii) NaH, THF, 0-5 °C, CH$_2$O-gas, rt to 40 °C, 1 h.	**134 and *ent*-134**	4-5% for both **134** and ***ent*-134**	122j 122n

With its promising biological activity, sarkomycin presents itself as a synthetic challenge for the organic chemist and we planned to complete a simple synthesis of (±)-sarkomycin via Michael addition of nitromethane to 2-hydroxymethyl-2-cyclopentenone, Oxone induced oxidative Nef reaction and acid catalyzed dehydration pathway (Scheme 16).

2.3A.2 Present Work: Results and Discussion

Our initial strategy towards sarkomycin was to synthesize it by the S$_N$2′ coupling reaction of 2-bromomethyl-2-cyclopentenone (**140**) with an appropriate nucleophile followed by usual transformations leading to the target molecule. Considerable interest in Baylis-Hillman reaction as a simple and versatile strategy for the α-functionalization of enone system and application of it for the synthesis of natural product or potential intermediates have been documented.[125a] We thought that this reaction could be useful for the generation of 2-hydroxymethyl-2-cyclopentenone (**139**) in substantial amount. Reaction of 2-cyclopentenone (**138**) with aqueous formaldehyde in presence of imidazole[125b] as a catalyst gave 2-hydroxymethyl-2-cyclopentenone (**139**) in 85% yield. There are a few more conditions reported[126] in the literature to obtain such type of Baylis-Hillman adducts; but we found that the present condition is most fruitful for the preparation of compound **139** (Scheme 16).[127] PBr_3 mediated bromination of compound **139** yielded the corresponding bromide **140** in quantitative yield. The bromide **140** was used immediately as it starts undergoing slow polymerization after 24 h. We tried several conditions for the S_N2' coupling reaction of **140** with nucleophiles such as sodium cyanide,[128] trimethylsilyl cyanide,[123b] and 2-lithio-1,3-dithiane[87] but all our attempts met with failure and always ended with the formation of complex reaction mixtures (Table 7).



Scheme 16 *Reagents, conditions and yields*: (i) Aq. formaldehyde, imidazole (cat.), THF, rt, 17 days (85%); (ii) PBr_3, CH_2Cl_2, 0 ºC, 1h (95%); (iii) Nitromethane, Triton B (cat.), 65 ºC, 5 h (93%); (iv) Ethylene glycol, *p*-TSA (cat.), benzene, reflux, 12 h (89%); (v) Dihydropyran, PPTS (cat.), CH_2Cl_2 rt, 5 h (80%); (vi) (a) MeOH, 0.5 N Na_2HPO_4, 1N NaOH, Oxone, rt, 2 h, (b) H^+/HCl (~ 100%); (vii) 0.5 N HCl, rt, 10 h (30%).

Table 7 Attempted S_N2' Coupling Reaction of Allylic Bromide **140**

Entry	Reagent	Reaction Condition	Conclusion
1	NaCN	NH_4Cl, DMF/H_2O (4:1), rt, 30 min	Complex reaction mixture
2	KCN	NH_4Cl, DMF/H_2O (4:1), rt, 30 min	Complex reaction mixture
3	TMSCN	HMPA, THF, -78 °C, 1 h	Complex reaction mixture

4	TMSCN	THF, -78 °C, 1 h	Complex reaction mixture
5	2-Lithio-1,3-dithiane	THF, -20 °C, 3 h	Complex reaction mixture
6	2-Lithio-1,3-dithiane	THF, -78 °C, 3 h	Complex reaction mixture

We then designed a different synthetic plan, wherein nitro compound **141** was envisaged as a key intermediate. Many bases such as DABCO, triethylamine, and tertamethylguanidine[129] were tried for the high yielding Michael addition of nitromethane to enone **139**. The best result was obtained using Triton B as a base,[130] affording *trans*-nitro compound **141** in 93% yield (Table 8).

Table 8 Conditions Used for Michael Addition of Nitromethane to enone **139**

Entry	Reagent	Reaction Condition	Conclusion
1	DABCO	nitromethane, 65 ºC, 12 h	Starting material recovered
2	Triethylamine	nitromethane, 65 ºC, 12 h	Starting material recovered
3	Tetramethyl guanidine	nitromethane, 65 ºC, 6 h	Obtained **141** with 76% yield
4	Triton B	nitromethane, 65 ºC, 5 h	Obtained **141** with 93% yield

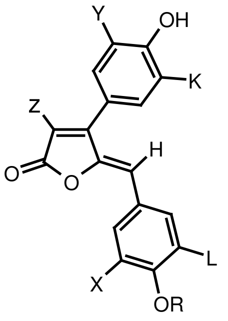
Ketalization of the carbonyl in **141** (89%) followed by protection of the hydroxy group as its THP ether yielded **143** in 80% yield. Herein we did the first very clean Oxone induced modified Nef[131] reaction on **143** to obtain **144** in ~100% yield. Being a very mild oxidizing agent, oxone (potassium hydrogen persulfate) provided better yield over the traditional Nef reaction conditions. As per the reported procedure,[122b] the treatment of **144** with dilute HCl under the Marx et al. conditions provided (±)-sarkomycin (**134a**) in 30% yield only (Scheme 16).[127] Peaks at $\delta = 5.70$ and 6.23 in ^{1}H NMR spectra of compound **134a** gave the evidence for the presence of an *exo*-methylene group. The analytical and spectral data obtained for compound **134a** were in complete agreement with reported data.[122i]

Compounds **142-144** show splitting for two/three carbon in the ^{13}C NMR spectra due to the presence of tetrahydropyranoyl group and also could be due to the formation of spiro skeleton in the ketal protected form. In this present six step synthesis, starting from 2-cyclopentenone (±)-sarkomycin was obtained with 17% overall yield.

2.3B Section C: II. An Efficient synthesis of Rubrolide E and Anlogues

2.3B.1 Background

A large number of medicinally important natural and unanatural butyrolactones are known in the literature.[132] Rubrolides are a family of biologically active marine ascidian metabolites, which have been isolated from tunicate *Ritterella rubra*[133] and *Synoicum blochmanni*.[134] The structures of rubrolides have been determined by spectroscopic and analytical methods to be butyrolactones with two *p*-hydroxyphenyl moieties with or without halogen atoms (Figure 13). [133,134] Rubrolides A-F are potent *in vitro* antibiotics and show selective inhibition of protein phosphateses 1 and 2A.[133] On the other hand, rubrolides I, K, L and M show significant cytotoxicities against four cancer cell lines, i.e. P-388 suspension culture of mouse lymphoid carcinoma, the monolayer cultures of human lung carcinoma (A-549), human colon carcinoma (HT-29) and human melanoma (MEL-28).[134] Synthesis of these bioactive natural products **145** is a challenging task of current interest.



Rubrolide A (**145a**): R = Z = H; K = L = X = Y = Br
Rubrolide B (**145b**): R = H; K = L = X = Y = Br; Z = Cl
Rubrolide C (**145c**): R = K = Y = Z = H; L = X = Br
Rubrolide D (**145d**): R = L = X = Z = H; K = Y = Br
Rubrolide E (**145e**): R = L = K = X = Y = Z = H
Rubrolide F (**145f**): R = Me; L = K = X = Y = Z = H
Rubrolide I (**145i**): R = K = H; L = X = Y = Br; Z = Cl
Rubrolide J (**145j**): R = K = Z = H; L = X = Y = Br
Rubrolide K (**145k**): R = K = L = H; X = Y = Br; Z = Cl
Rubrolide L (**145l**): R = K = Y = H; L = X = Br; Z = Cl
Rubrolide M (**145m**): R = K = L = Y = H; X = Br; Z = Cl
Rubrolide N (**145n**): R = K = L = H; Y = Cl; X= Z = Br

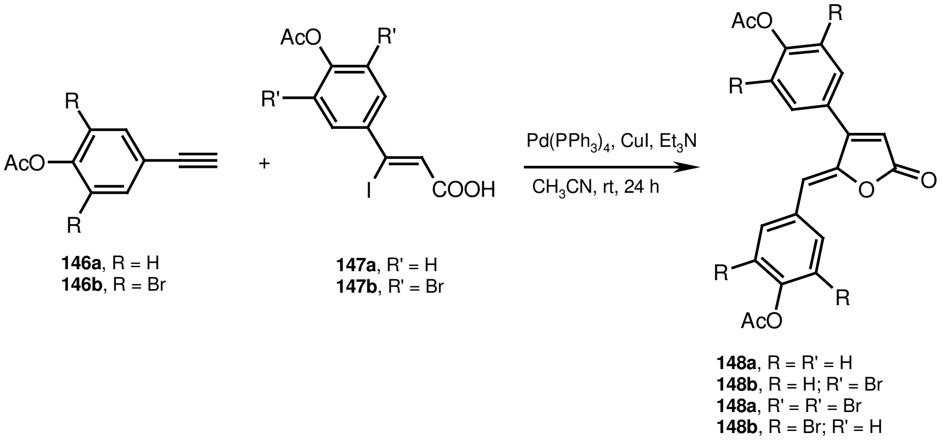
Figure 13. Naturally occurring bioactive rubrolides

2.3B.1.1 Synthetic Approaches Towards Rubrolides

Prior to our work, only one synthesis of each rubrolide A, D, M and two syntheses of rubrolide C and E were known in the literature.[135]

A] Negishi's Approach

Negishi and coworkers have reported the synthesis of diacetates of rubrolide A, C, D and E by a one pot Pd-catalyzed cross coupling-lactonization tandem reaction of alkyne **146** with β-carboxyvinyliodide **147** in 38, 54, 54 and 50% isolated yields respectively (Scheme 17).[135a] In the cross coupling-lactonization tandem process, two critical bond formation reactions take place under one set of reaction conditions. They have investigated the lactonization process separately with (*Z*)-3,5-diphenylpent-2-en-4-ynoic acid to resolve the modest yield problem and with the modified condition; they could achieve the one step process with 86% yield.



146a, R = H
146b, R = Br

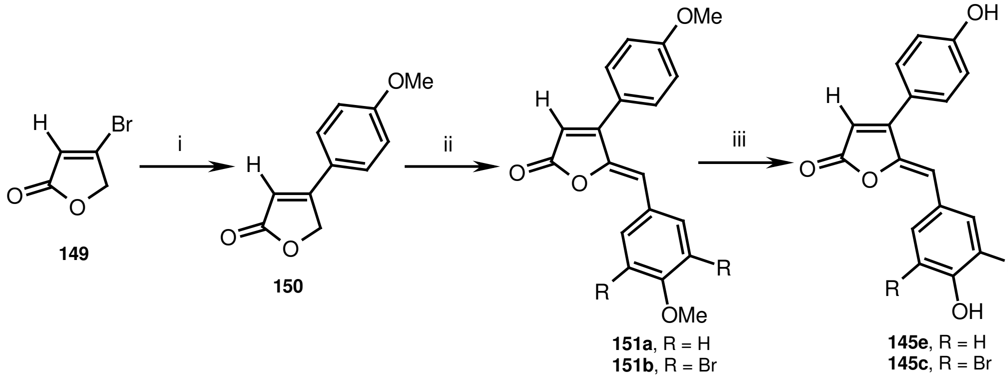
147a, R' = H
147b, R' = Br

148a, R = R' = H
148b, R = H; R' = Br
148a, R' = R' = Br
148b, R = Br; R' = H

Scheme 17

B] Boukouvalas's Approach

Boukouvalas et al. reported an efficient synthesis of rubrolide C and E starting from *β*-tetronic acid in four steps with 61 and 56% overall yield respectively (Scheme 18).[135b]

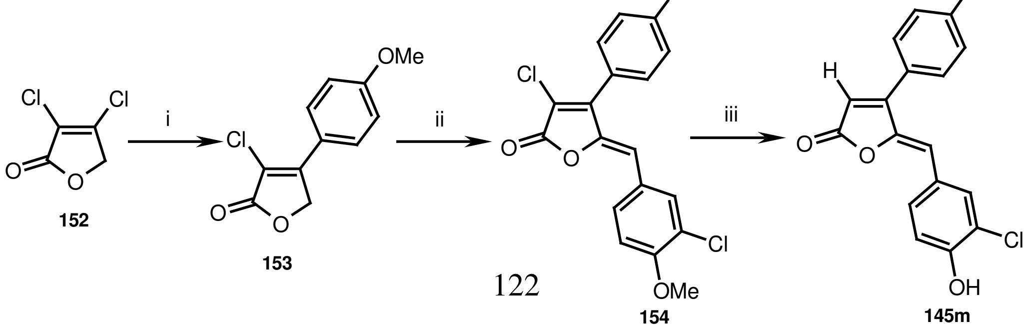


Scheme 18 *Reagents, conditions and yields*: (i) (4-$MeOC_6H_4$)$B(OH)_2$, $Pd(PPh_3)_4$, aq. Na_2CO_3, benzene/ethanol, 80 ºC, 2.5-3 h (79%); (ii) *p*-Anisaldehyde or 3,5-dibromo-4-methoxybenzaldehyde, TBDMSOTf (1.2 equiv.), *i*-Pr_2Net (3 equiv.), CH_2Cl_2, rt, 1-2 h, then DBU (2 equiv.), rt, 3 h (**151a**, 84%; **151b**, 95%); (iii) BBr_3, CH_2Cl_2, -78 to 25 ºC, 24 h (**145c**, 98%; **145e**, 95%).

They have prepared 4-bromo-2(*5H*)-furanone (**149**) from *β*-tetronic acid by Vilsmeier bromination with 86% yield and completed the synthesis via Pd-catalyzed cross coupling of butyrolactone **149** with arylboronic acid, followed by one pot sequence of silylation, aldol type condensation and DBU mediated *β*-elimination with the appropriate aldehyde and demethylation of the formed dimethoxy rubrolides (Scheme 18).[135b]

C] Rossi's Approach

Recently Rossi and coworkers reported the synthesis of rubrolide M through Pd-catalyzed regioselective formation of 4-(4-methoxyphenyl)-3-chloro-2(*5H*)-furanones (**153**) starting from 3,4-dichloro-2(*5H*)-furanone (**152**) in three steps with 27% overall yield (Scheme 19).[135e] This regioselectivity may be attributed to the extended conjugation of the lactone carbonyl gained with the aromatic ring in the formed butyrolactone **153**.

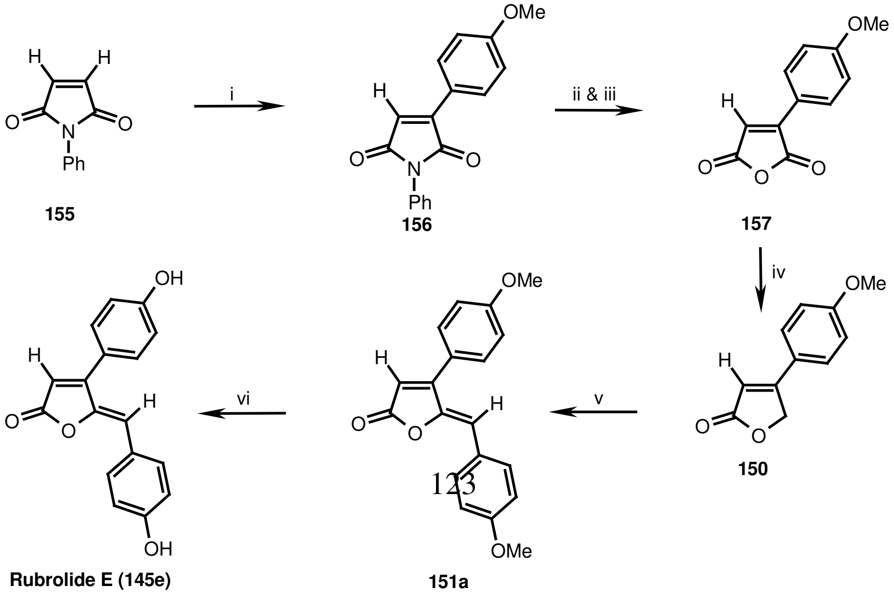


Scheme 19 *Reagents, conditions and yields*: (i) (4-$MeOC_6H_4$)$B(OH)_2$, Pd_2(dba)$_3$ (2.5 mol%), (*o*-tolyl)$_3$P (10 mol%), KF (3 equiv.), toluene 85 ºC, 21-27 h (61%) or (4-$MeOC_6H_4$)$SnBu_3$, Pd_2(dba)$_3$ (2.5 mol%), (*o*-tolyl)$_3$P (10 mol%), NMP, 85 ºC, 21-22 h (61%) (ii) 3-bromo-4-methoxybenzaldehyde (1 equiv.), TBDMSOTf (1.2 equiv.), *i*-Pr_2Net (3 equiv.), CH_2Cl_2, rt, 23 h, then DBU (2 equiv.), 20 ºC, 6 h (46%); (iii) BBr_3, CH_2Cl_2, rt, 23 h (97%).

All these synthesis presented above involve Pd-chemistry to construct the butyrolacone core unit of rubrolides. In continuation of our studies towards bioactive natural products starting from cyclic anhydrides and imides,[33,50,52,54,55,61,84,112] we felt that synthesis of naturally occurring rubrolide E would be possible starting from *N*-phenylmaleimide (**155**), using the Meerwein coupling and Knoevenagel condensation reactions for the introduction of the two *p*-anisyl units and our results are summarized in the following part (Scheme 20).[137]

2.3B.2 Present Work: Results and Discussion

We envisaged that the Meerwein coupling reaction[136] between *N*-phenylmaleimide and *p*-anisyldiazonium chloride would provide an easy access to these bioactive marine natural products **145** (Scheme 20).[137] We systematically studied the Meerwein coupling between the relatively more stable *N*-phenylmaleimide (**155**, 2 equiv.) and *p*-anisyldiazonium chloride (1 equiv.) in presence of $CuCl_2$ in aqueous acetone at pH 3, at 0 ºC to 35 ºC and obtained the desired coupled product arylmaleimide **156** in 65% yield upon column purification. The present coupling reaction efficiency is highly dependent on pH, temperature of the reaction mixture and stoichiometry of the reactants. The use of more amount (>1 equiv.) of *p*-anisyldiazonium chloride gives rise to substantial amount of



dicoupled product.

Scheme 20 *Reagents, conditions and yields*: (i) *p*-Anisyldiazonium chloride, $CuCl_2$, pH 3, aq. acetone, 0 to 35 °C, 24 h (65%); (ii) (a) 20% aq. KOH, methanol, reflux, 4 h, (b) H^+/HCl; (iii) Ac_2O, reflux, 3 h (~100%, for conditions ii & iii); (iv) $NaBH_4$, THF, 0 °C, 2 h (62%); (v) Piperidine, *p*-anisaldehyde, MeOH, rt, 15 h (78%); (vi) BBr_3, CH_2Cl_2, -78 °C to rt, 24 h (95%).

The arylmaleimide **156** on base catalyzed hydrolysis followed by acetic anhydride induced dehydrative ring closure of the thus formed intermediate arylmaleic acid furnished the *p*-anisylmaleic anhydride (**157**) in nearly 100% yield. The *p*-anisylmaleic anhydride (**157**) at 0 °C in dry THF underwent a very smooth regioselective reduction at the more reactive nonconjugated with *p*-anisyl group and hindered carbonyl carbon to yield the corresponding butyrolactone **150** in 62% yield. The Knoevenagel condensation of butyrolactone **150** with *p*-anisaldehyde exclusively gave the desired (*Z*)-butenolide **151a** in 78% yield. The borontribromide induced demethylation of both the methoxy groups in butenolide **151a** furnished the naturally occurring rubrolide E (**145e**) in 95% yield (Scheme 20).[137] Characteristic singlet peaks at $\delta = 6.31$ and 6.37 for two different vinylic protons in ^{1}H NMR spectra of compound **145e** proved the formation of the natural product. Rubrolide E (**145e**) was thus obtained in 6-steps with 30% overall yield. The analytical and spectral data obtained for rubrolide **145e** were in complete agreement with the reported data. Rubrolide E (**145e**) was fairly stable in solid state while in DMSO solution it started undergoing a slow oxidation process. Two-step conversion of intermediate lactone **150** to the naturally occurring rubrolide C (**145c**) with 90% overall yield is known in the literature.[135b] In the present six step synthesis we obtained rubrolide E with 30% overall yield starting from *N*-phenylmaleimide. All our initial attempts to transform rubrolide E (**145e**) to rubrolide A (**145a**) by selective tetrabromination with either the use of bromine in methanol or bromine/potassium bromide in dioxane plus water gave complex reaction mixture. Our efforts for conversion of rubrolide E (**145e**) to rubrolide A (**145a**) and other bromo analogues are in active progress and we feel that varying the reaction time and the amount of brominating agent used, will enable us to achieve our goal.

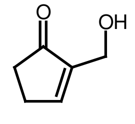
In summary, in this section we have demonstrated a simple and short synthesis of (±)-sarkomycin. The simplicity of reaction conditions used, especially the Triton B catalyzed Michael addition of nitro methane to 2-hydroxymethyl-2-cyclopentenone in

presence of free hydroxyl group and clean Oxone induced Nef reaction are noteworthy. We feel that the present approach is general and it will be useful for the synthesis of analogues homosarkomycin and bishomosarkomycin. We have also completed a concise and efficient synthesis of rubrolide E and formal synthesis of rubrolide C by taking the advantage of the Meerwein coupling reaction. In our opinion the present approach to arylsubstituted butenolides is flexible and attractive, and it will be useful for generation of libraries of rubrolide analogues for biological evaluation.

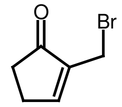
2.3C Section C: III. Experimental

Commercially available nitromethane, dihydropyran, ethylene glycol, Oxone, *p*-anisaldehyde, $CuCl_2$, acetic anhydride, $NaBH_4$, piperidine, and BBr_3 were used.

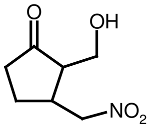
2-Hydroxymethyl-2-cyclopentenone (139). To a mixture of 2-cyclopentenone (**138**; 19.6 g, 240 mmol) and 30% aqueous formaldehyde (48 mL, 480 mmol) in THF (48 mL) was added imidazole (1.6 g, 12 mmol) and the resulting reaction mixture was stirred for 17 days at room temperature. The reaction mixture was then acidified to pH 5 with 1.5 N HCl and extracted with methylene chloride (200 mL x 3). The combined organic layer was washed with water (100 mL), brine (50 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (1:1) as eluent gave the desired 2-hydroxymethyl-2-cyclopentanone (**139**): 22.84 g (85% yield).

 **139** **$C_6H_8O_2$ (112)**	Thick oil. **IR** (Neat): ν_{max} 3448, 1693 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.75-2.25 (bs, 1H), 2.30-2.50 (m, 2H), 2.55-2.85 (m, 2H), 4.37 (bs, 2H), 7.55 (bs, 1H). **Anal. Calcd for $C_6H_8O_2$**: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.10.

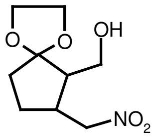
2-Bromomethyl-2-cyclopentenone (140). To a chilled solution of **139** (11.2 g, 100 mmol) in CH_2Cl_2 (100 mL), was added dropwise a freshly distilled PBr_3 (13.5 g, 50 mmol) at 0 ºC and the reaction mixture was stirred for a further 1 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and poured into water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (8:2) as eluent gave the desired bromocyclopentenone **140**: 16.6 g (95% yield).

 **140** **C_6H_7BrO (175)**	Thick oil. **IR** (Neat): ν_{max} 1732, 1547 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 200 MHz): δ 2.35-2.55 (m, 2H), 2.60-2.75 (m, 2H), 4.04 (bs, 2H), 7.71 (bs, 1H). **^{13}C NMR** (CDCl$_3$, 125 MHz): δ 21.2, 26.1, 34.1, 141.7, 161.8, 205.8. **Anal. Calcd for C_6H_7BrO**: C, 41.17; H, 4.03. Found: C, 41.23; H, 3.99.

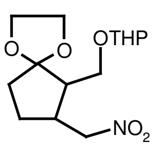
2-Hydroxymethyl-3-nitromethylcyclopentanone (141). A mixture of **139** (11.2 g, 100 mmol) and Triton B (1 mL, 40% solution in methanol) in dry nitromethane (20 mL) was heated at 65 ºC for 5 h. The reaction mixture was then allowed to cool to room temperature and poured into ice-cold water. The above mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (1:1) as eluent gave the desired cyclopentanone **141**: 16.09 g (93% yield).

 **141** **$C_7H_{11}NO_4$ (173)**	Thick oil. **IR** (Neat): ν_{max} 3423, 1736, 1551 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 200 MHz): δ 1.50-1.75 (m, 1H), 2.00-2.55 (m, 4H), 2.80-3.05 (m, 1H), 3.70-3.85 (m, 1H), 3.85-3.95 (m, 1H), 4.40-4.55 (m, 1H), 4.60-4.80 (m, 1H). **^{13}C NMR** (CDCl$_3$, 125 MHz): δ 24.9, 37.1, 37.5, 53.7, 59.3, 78.6, 217.3. **Anal. Calcd for $C_7H_{11}NO_4$**: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.47; H, 6.45; N, 8.03.

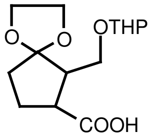
(7-Nitromethyl-1,4-dioxa-spiro[4,4]non-6-yl)-methanol (142). To a stirred solution of cyclopentanone **141** (13.84 g, 80 mmol) and ethylene glycol (7.44 g, 120 mmol) in dry benzene (80 mL) was added *p*-toluenesulfonic acid monohydrate (1.52 g, 8 mmol) and the reaction mixture was heated under reflux for 12 h using Dean and Stark apparatus containing 3 Å molecular sieves. The reaction mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with aq. $NaHCO_3$ (30 mL), brine (30 mL) and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (1:1) as eluent afforded the ketal **142**: 15.45 g (89% yield).

 **142** **$C_9H_{15}NO_5$ (217)**	Thick oil. **IR** (Neat): ν_{max} 3449, 1551,1383 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.30-1.55 (m, 1H), 1.70-2.10 (m, 4H), 2.60-2.80 (m, 1H), 3.37-3.75 (m, 4H), 3.80-4.00 (m, 2H), 4.27-4.40 (m, 1H), 4.50-4.65 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 26.0, 35.1, 39.9, 49.3, 61.3, 64.0 & 64.7 (1 carbon), 70.0 & 72.2 (1 carbon), 79.9, 116.5. **Anal. Calcd for $C_9H_{15}NO_5$**: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.81; H, 6.92; N, 6.41.

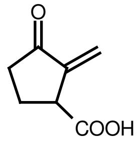
7-Nitromethyl-6-(tetrahydro-pyran-2-yloxymethyl)-1,4-dioxa-spiro[4,4]nonane (143). To a stirred solution of ketal **142** (2.17 g, 10 mmol) and dihydropyran (1.68 g, 20 mmol) in dry dichloromethane (30 mL) was added pyridinium-*p*-toluenesulfonate (251 mg, 1 mmol) and the reaction mixture was stirred at room temperature for 5 h. The organic layer was washed with water, aq. $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate mixture (7:3) afforded the THP ether **143**: 2.41 g (80% yield).

 **143** **$C_{14}H_{23}NO_6$ (301)**	Thick oil. **IR** (Neat): ν_{max} 1549, 1383 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.20-2.10 (m, 11H), 2.55-2.80 (m, 1H), 3.40-4.05 (m, 8H), 4.20-4.40 (m, 1H), 4.62 (bs, 1H), 4.75-4.90 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 19.2, 25.2, 26.1, 30.4, 35.2, 40.7, 49.0, 62.0, 64.2 & 64.7 (1 carbon), 66.4, 70.2 & 70.7 (1 carbon), 79.9, 98.7, 116.4. **Anal. Calcd for $C_{14}H_{23}NO_6$**: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.84; H, 7.63; N, 4.62.

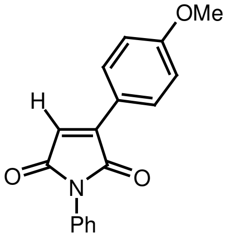
6-(Tetrahydro-pyran-2-yloxymethyl)-1,4-dioxa-spiro[4,4]nonane-7-carboxylic acid (144). To a solution of **143** (903 mg, 3 mmol) in methanol (18 mL), was added a 0.5 N solution of Na_2HPO_4 in 1 N NaOH (48 mL). After 1 h, a solution of Oxone (1.84 g, 6 mmol) in water (9 mL) was added to the stirred suspension. The resulting mixture was stirred at room temperature for 1 h, acidified with a 10% solution of HCl and immediately extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4 and concentrated in vacuo to furnish a thick yellow oil, which was purified by silica gel column chromatography using petroleum ether/ethyl acetate (1:1) to obtain the desired acid **144**: 858 mg (~ 100% yield).

 **144** **$C_{14}H_{22}O_6$ (286)**	**Mp**: 70-73 °C (ethyl acetate). **IR** ($CHCl_3$): ν_{max} 2945, 1738 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.15-2.10 (m, 10H), 2.50-2.70 (m, 1H), 2.70-2.90 (m, 1H), 3.35-4.00 (m, 8H), 4.60 (bs, 1H), 6.31 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 19.2, 25.3, 30.4, 35.6, 35.8, 46.0, 48.7, 61.9, 64.3 & 64.8 (1 carbon), 66.2, 70.2 & 70.4 (1 carbon), 98.7, 116.6, 177.1 & 178.4 (1 carbon). **Anal. Calcd for $C_{14}H_{22}O_6$**: C, 58.73; H, 7.74. Found: C, 58.77; H, 7.69.

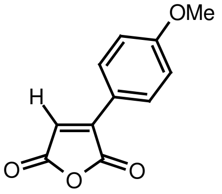
2-Methylene-3-oxo-cyclopentanecarboxylic acid [(±)-Sarkomycin, 134a]. A solution of **144** (572 mg, 2 mmol) in 0.5 N HCl (15 mL) was stirred at room temperature for 10 h and then extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was extracted with cold 5% $NaHCO_3$ (30 mL) and the aqueous layer was reacidified with dil. HCl and again extracted with $CHCl_3$ (10 mL x 2). Concentration of the organic layer gave essentially pure **134a**: 84 mg (30 % yield).

 **(±)-Sarkomycin (134a)** **$C_7H_8O_3$ (148)**	Thick oil. **IR** ($CHCl_3$): ν_{max} 2943, 1723 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.10-3.20 (m, 4H), 3.45-3.85 (m, 1H), 5.70 (d, J = 2 Hz, 1H), 6.23 (d, J = 2 Hz, 1H). **Anal. Calcd for $C_7H_8O_3$**: C, 60.00; H, 5.75. Found: C, 60.03; H, 5.70.

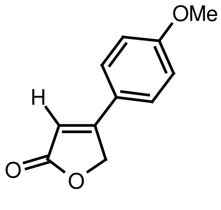
***N*-Phenyl-2-(4-methoxyphenyl)maleimide (156).** *p*-Anisidine (4.10 g, 33.3 mmol) was dissolved in a mixture of concentrated HCl (15 mL) and water (10 mL) with warming. The above solution was cooled rapidly to 0-5 ºC with stirring, 10 g of ice was added to the solution and the suspension was diazotized with 30% aqueous sodium nitrite solution (15 mL) with vigorous stirring. The filtered diazonium solution was added all at once to an ice cold suspension of *N*-phenylmaleimide (**155**, 8.65 g, 50 mmol) in acetone (20 mL) and the mixture was brought to pH 3 by addition of a saturated solution of sodium acetate. To the resulting suspension was added cupric chloride (849 mg, 5 mmol) and acetone (100 mL) to make the solution homogeneous. The reaction mixture was stirred at 0-5 ºC for 30 mins., warmed to 35 ºC and stirred for further 24 h. Acetone was removed in vacuo from the reaction mixture and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by flash silica gel column chromatographic purification using petroleum ether and ethyl acetate mixture (9:1) as an eluent gave the desired *N*-phenyl-2-(4-methoxyphenyl)maleimide (**156**): 6.04 g (65% yield).

 **156** **$C_{17}H_{13}NO_3$ (279)**	**Mp**: 148-151 ºC. **IR** (Nujol): ν_{max} 1765, 1701, 1603, 1460 cm^{-1}. ^{1}**H NMR** ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H), 6.69 (s, 1H), 6.96 (d, *J* = 8 Hz, 2H), 7.30-7.50 (m, 5H), 7.96 (d, *J* = 8 Hz, 2H). ^{13}**C NMR** ($CDCl_3$, 50 MHz): δ 55.3, 114.5, 120.9, 121.2, 126.2, 127.6, 129.0, 130.5, 131.6, 143.0, 162.1, 169.4, 169.7. **Anal. Calcd for $C_{17}H_{13}NO_3$**: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.07; H, 4.58; N, 4.96.

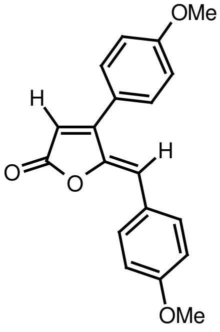
2-(4-Methoxyphenyl)maleic anhydride (157). Aqueous potassium hydroxide solution (20%, 40 mL) was added to a solution of imide **156** (6.0 g, 21.5 mmol) in methanol (10 mL) and the reaction mixture was refluxed for 4 h. The reaction mixture was then diluted with water (20 mL) and extracted with ethyl acetate (25 mL x 3). The aqueous layer was acidified to pH 2 with 2 N HCl and extracted with ethyl acetate (60 mL x 3). The combined organic layer was washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave the desired *p*-anisylmaleic acid as a yellow solid which was refluxed in acetic anhydride (20 mL) for 3 h. The reaction mixture was then concentrated in vacuo at 50 °C and the residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9:1) to furnish anhydride **157**: 4.38 g (~ 100% yield).

 **157** **$C_{11}H_8O_4$ (204)**	**Mp**: 138-139 ºC. **IR** (Nujol): ν_{max} 1763, 1720, 1605, 1462 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.90 (s, 3H), 6.84 (s, 1H), 7.01 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 55.5, 114.9, 119.5, 121.0, 131.1, 146.2, 163.3, 164.0, 165.0. **Anal. Calcd for $C_{11}H_8O_4$**: C, 64.71; H, 3.95. Found: C, 64.65; H, 3.89.

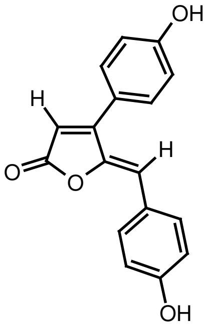
4-(4-Methoxyphenyl)-5*H*-furan-2-one (150). To a stirred solution of anhydride **157** (4.08 g, 20 mmol) in THF (50 mL) was added $NaBH_4$ (1.90 g, 50 mmol) at 0 ºC and the reaction mixture was stirred for a further 2 h. The reaction was quenched with water, acidified with dilute HCl to pH 2 and extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (8:2) to furnish the lactone **150**: 2.35 g (62% yield).

 **150** **$C_{11}H_{10}O_3$ (190)**	**Mp**: 136-139 ºC. **IR** (Nujol): ν_{max} 1738, 1622, 1607, 1462 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.88 (s, 3H), 5.21 (s, 2H), 6.25 (s, 1H), 6.98 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 55.4, 70.8, 110.4, 114.6, 122.1, 128.1, 162.3, 163.6, 174.2. **Anal. Calcd for $C_{11}H_{10}O_3$**: C, 69.46; H, 5.30. Found: C, 69.37; H, 5.32.

4-(4-Methoxyphenyl)-5*Z*-[1-(4-methoxyphenyl)methylidine]-5*H*-furan-2-one (151a). To a stirred solution of lactone **150** (1.90 g, 10 mmol) in methanol were added piperidine (595 mg, 7 mmol) and *p*-anisaldehyde (1.36 g, 10 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (9:1) furnished **151a**: 2.40 g (78% yield).

 **151a** **$C_{19}H_{16}O_4$ (308)**	**Mp**: 136-140 ºC. **IR** (Nujol): ν_{max} 1759, 1605, 1462 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 3.86 (s, 3H), 3.90 (s, 3H), 6.11 (s, 1H), 6.17 (s, 1H), 6.93 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 55.3, 55.4, 112.2, 113.6, 114.3, 114.5, 122.9, 125.9, 129.9, 132.5, 146.6, 158.3, 160.4, 161.3, 169.3. **Anal. Calcd for $C_{19}H_{16}O_4$**: C, 74.01; H, 5.23. Found: C, 74.09; H, 5.15.

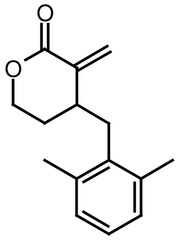
4-(4-Hydroxyphenyl)-5*Z*-[1-(4-hydroxyphenyl)methylidine]-5*H*-furan-2-one (Rubrolide E, 145e). To a stirred solution of **151a** (1.54 g, 5 mmol) in dry CH_2Cl_2 (25 mL) at –78 ºC, was added a 1 M solution of BBr_3 in CH_2Cl_2 (15 mL, 15 mmol) over a period of 15 min. The reaction mixture then allowed to warm up to room temperature and stirred for a further 24 h. The reaction was quenched with water (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate mixture (6:4) to obtain the natural product **145e**: 1.33 g (95% yield).

 **Rubrolide E (145e)** **$C_{17}H_{12}O_4$ (280)**	**Mp**: 282-283 °C. **IR** (Nujol): ν_{max} 3270, 1746, 1674, 1597 cm^{-1}. **^{1}H NMR** (DMSO-d_6, 200 MHz): δ 6.31 (s, 1H), 6.37 (s, 1H), 6.84 (d, J = 8 Hz, 2H), 6.92 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 10.04 (bs, 1H), 10.11 (bs, 1H). **^{13}C NMR** (DMSO-d_6, 50 MHz): δ 112.6, 115.2, 117.6 (2-carbons), 122.4, 126.0, 132.1, 134.3, 147.0, 159.8, 160.3, 161.3, 170.4. **UV** (MeOH): λ_{max} = 244 (12347), 257 (11867), 322 nm (10933). **Anal. Calcd for $C_{17}H_{12}O_4$**: C, 72.85; H, 4.31. Found: C, 72.66; H, 4.50.

4.1A Section D: I. Synthetic Studies on Secocrispiolide

2.1A.1 Background

In 1979, El-Emary and coworkers reported the isolation of a new seco-sesquiterpene lactone, secocrispiolide (**158**) from *Plicaria Crispa*.[138] The structure of secocrispiolide (**158**) was determined by spectroscopic methods and its core comprises an α-methylene δ-lactone unit (Figure 14).[138] Secocrispiolide (**158**) possesses a single asymmetric centre and in nature exists in *dextro* form,[138] although the absolute configuration is yet to be established. Till date, a biological role for secocrispiolide has not been established. Since the *α*-methylene ketone and lactone functionalities are found to be present in a great number of compounds having anticancer properties, it's therefore a important task for organic chemists to synthesize these natural products in considerable amount for better structure activity relationship studies. To date, only one synthesis of secocrispiolide has been reported.[139,140]

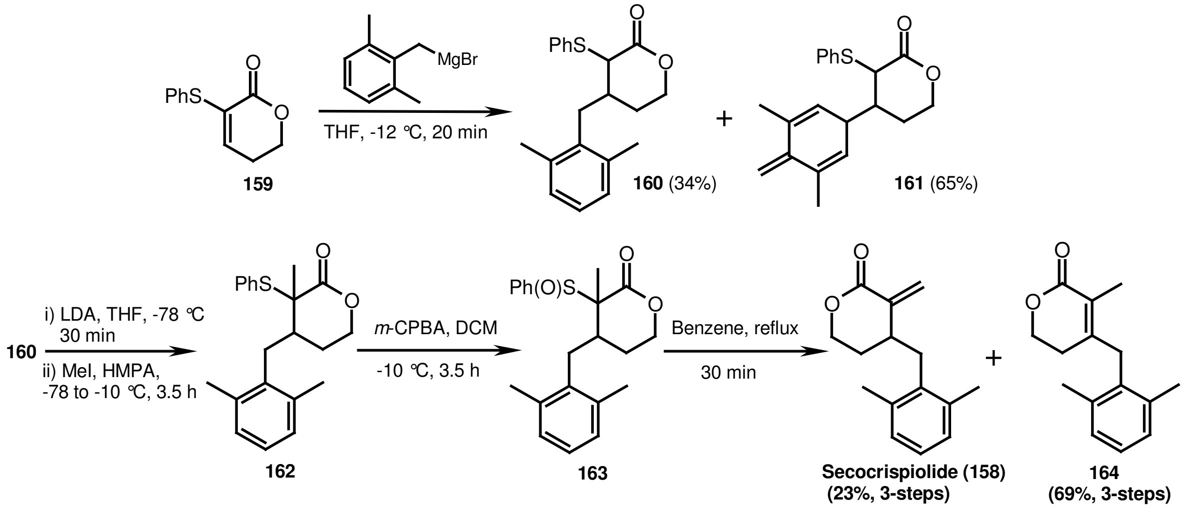


Secocrispiolide (**158**)

Figure 14

2.4A.1.1 First Synthetic Approach Towards Secocrispiolide

Yoshikoshi et al. reported synthesis of (±)-secocrispiolide (**158**) via the adduct obtained by 1,4-addition reaction of Grignard reagent prepared from 2,6-dimethylbenzyl bromide with **159**.[139,140] An unusual adduct **161** was produced along with the expected adduct **160** in ~100% combined yield. These results indicated that the steric bulk at the benzyl face would impose the conversion of the benzylic carbanion to the doubly allylic carbanion with generation of exocyclic carbon-carbon double bond, which led to the formation of adduct **161**. The procurement of synthetic intermediate **160** led to the completion of the synthesis of (±)-secocrispiolide (Scheme 21).[139,140] The lithium enolate obtained from treatment of **160** with LDA was subjected to methylation with methyl iodide in the presence of HMPA, providing the 2-methyl-δ-lactone **162**. Oxidation of **162** with equimolar amount of *m*-CPBA followed by elimination of sulfenic acid from the resulting sulfoxide **163** afforded (±)-secocrispiolide (**158**, 23%) and endo olefin **164** (69%). The overall yield of **158** starting from **159** was only 8% in four steps.

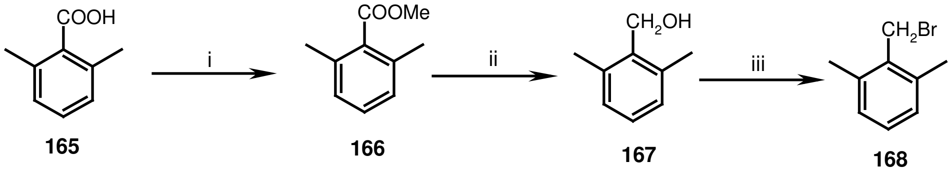


Scheme 21

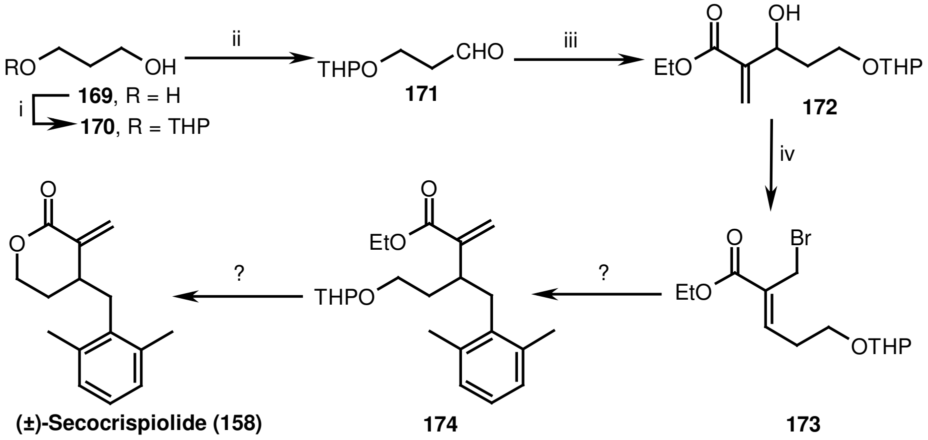
We planed for the synthesis of (±)-secocrispiolide (**158**) using the highly chemoselective S_N2' coupling reaction with allylic bromo ester **173** followed by one-pot deprotection of the THP-ether and hydrolysis of the ester leading to **158**. Thus our plan serves a double purpose of synthesis of exocyclic double bonds and 3-substituted δ-lactones as well. Since comparatively fewer methods are available for synthesis of latter, the presented work will be of interest.

2.4A.2 Present Work: Results and Discussion

Our synthetic plan required an efficient Grignard acceptor, which would give S_N2' product, which on further cyclization would result in exocyclic double bond as required in secorispiolide (**158**). The required benzylbromo compound **168** for generation of Grignard reagent was synthesized from 2,6-dimethylbenzoic acid (**165**) (Scheme 22). Acid catalyzed esterification of **165** gave the corresponding methylester **166**, lithium aluminiumhydride mediated[141] reduction of the formed ester furnished the alcohol **167** in 72% yield over two steps. Conversion[142] of alcohol **167** to the corresponding bromide **168** was achieved using PPh_3 and CBr_4 in quantitative yield.



Scheme 22 *Reagents and conditions*: (i) CH_3OH, H^+/H_2SO_4, reflux, 12 h (80%); (ii) $LiAlH_4$, dry Et_2O, rt, 3 h (90%); (iii) PPh_3, CBr_4, DCM, rt, 5 h (~100%).



Scheme 23 *Reagents, conditions and yields*: (i) DHP (0.5 eqiv.), conc. HCl (few drops), 3 h, (45%); (ii) PCC (3 equiv.), anhydrous NaOAc (10 mol%), DCM, rt, 6 h (85%); (iii) Ethyl acrylate (6 equiv.), DABCO (10 mol%), rt, 7 days (86%); (iv) NBS (1equiv.), Me_2S (1 equiv.), DCM, rt, 24 h (95%).

The compound **173** was synthesized from 1,3-propanediol (**169**) as shown in Scheme 23. 1,3-Propanediol (**169**) was monoprotected[143] as tetrahydropyranyloxy ether to give **170** (45%), which on controlled oxidation using PCC gave aldehyde **171** in 85% yield for the desired Baylis-Hillman[125a] reaction. Reaction of ethyl acrylate with aldehyde **171** in the presence of DABCO as catalyst provided the Baylis-Hillman adduct **172** in 86% yield.[142] The 3-hydroxy-2-methylenealkanoic ester **172** on brominative allylic rearrangement with *N*-bromosuccinimide/dimethyl sulfide[144] gave the proposed Grignard acceptor in our scheme, (*Z*)-2-(bromomethyl)-2-alkenoic ester **173** in 95% yield with clean allylic transposition[145,146] and *Z*-selectivity. The overall yield of bromoester **173** was 31% in four steps starting from 1,3-propanediol. However, in our hand all attempts to perform the S_N2' Grignard coupling of the allylic bromide **173** with 2,6-dimethylbenzylmagnesium bromide by varying the choice of solvent, reaction temperature and using copper salt as additive were unrewarding, providing complex reaction mixtures with minor amount of desired product (from ^{1}H NMR of the crude reaction mixture). Lack of neat generation and stability of Grignard reagent appears to be the real reason of this failure. Our efforts to come out with a suitable condition for the conversion of **173** to (±)-secocrispiolide (**158**) are under active progress and we are hopeful about the same.

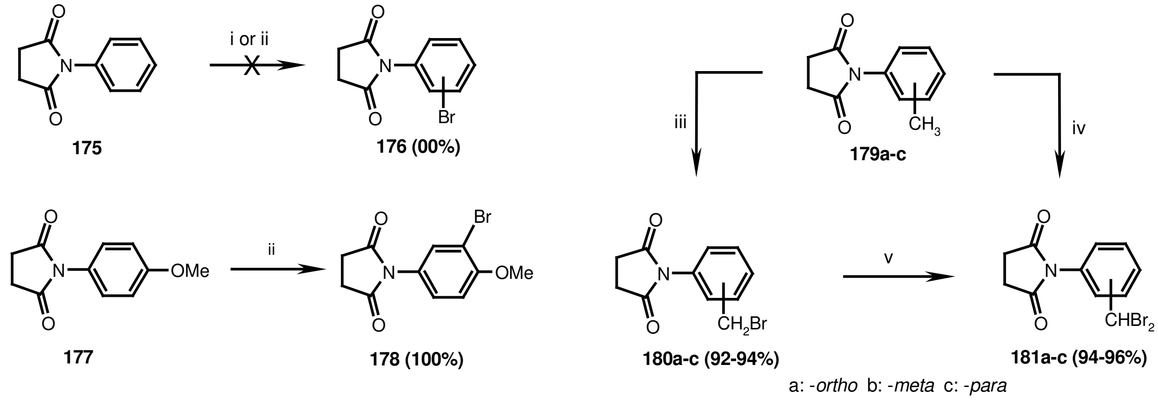
2.4B Section D: II. Synthetic Studies on Benzylic Mono- and *gem*-Dibromination of Primary Aromatic Amine Derivatives Using Molecular Bromine

2.4B.1 Background

A large number of primary aromatic amine derivatives (aniline derivatives) with variety of substituents and substituent patterns are well known in the literature and their utilities have been also well proven in practice.[147] They are generally obtained by electrophilic or nucleophilic aromatic substitution reactions and these synthetic operations are performed directly on free aniline derivatives,[147c] *N*-nitrosoaniline derivatives,[147c] *N*-haloaniline derivatives,[148] *N*-hydroxyaniline derivatives[149] or *N*-protected aniline derivatives.[147c] The free -NH_2 group protections are generally done by converting it in to (a) *N*-acyl derivatives (b) *N*-protonated salts (c) carbamates and (d) phthalimides. The latter two protecting groups have been majorly used in the chemistry of amino acids.[147c] There is no direct method to obtain aniline derivatives, wherein the electrophilic substitutions are directed by secondary activating group on the phenyl ring and also for benzylic halogenations on aniline derivatives. To date, both the aims have been achieved in a stepwise fashion by carrying out the various reactions on the corresponding less reactive nitro derivatives, followed by reduction of the nitro group to an amino group.[150] This process is quite cumbersome and may not be feasible for all the cases. For the past several years we have been using cyclic anhydrides and imides as potential starting materials for the synthesis of structurally interesting and biologically important heterocycles[56,151,152] and bioactive natural products. [26,28,33,50,52,54,55] During these studies, we noticed that the lone pair of electrons on nitrogen atom in *N*-aryl cyclic imides has no influence on the aryl ring. We reasoned and planned to take the advantage of this observation to add a new useful concept in the chemistry of primary aromatic amines.

2.4B.2 Present Work: Results and Discussion

N-phenylsuccinimide (**175**)[153] on reaction with molecular bromine in refluxing CCl_4 and with bromine in acetic acid at room temperature remained completely unreacted proving that the lone pair of electrons on nitrogen atom in phenyl succinimide **175** is fully engaged with two imide carbonyls and loses its mesomeric connectivity with aromatic ring and the phenyl ring behaves like benzene (Scheme 24).[154] The reaction of the corresponding *p*-methoxy derivative **177** with bromine in acetic acid at room temperature exclusively furnished the desired nuclear brominated product **178** in ~100% yield, thus obtaining the electrophilic substitution at an alternate site, dictated by a secondary activating $–OCH_3$ group (as compared to $–NH_2$). With suitable manipulations in substrate structures and reaction conditions, several electrophilic substitution reactions will be possible to generate an avenue of new and useful aniline derivatives. Like toluene,[147c] the *N*-(*o*/*m*/*p*)-tolylsuccinimides (**179a-c**) on treatment with 1.25 equivalents of molecular bromine in CCl_4 at room temperature, underwent a smooth monobenzylic bromination to yield the products **180a-c** respectively, in 92-94% yields, while in refluxing CCl_4 with 2.50 equivalents of bromine they furnished the corresponding *gem*-dibromo derivatives **181a-c** respectively, in 94-96% yields (Scheme 24).[154] Both these mono- and *gem*-dibenzylic bromination reactions must be following a radical pathway and the *ortho*-, *meta*- and *para*-isomers reacted in a similar manner revealing that only the benzylic relay may be operational at the reaction sites. Moreover these compounds **180a-c** and **181a-c** are clean solid materials and do not show any noticeable lachrymal properties. Thus for the first time benzylic monobrominations and *gem*-dibrominations have been achieved on the toluidine nucleus by using molecular bromine and protecting the free amino group as succinimide moiety and this concept will be amply useful for benzylic mono/*gem*-dihalogenations of several other primary aromatic amine derivatives.



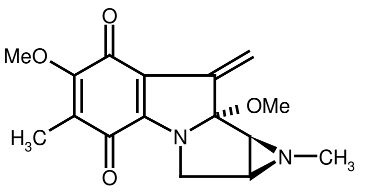
Scheme 24 *Reagents, conditions and yields*: (i) Br_2 (1.25 mmol), CCl_4, reflux, 24 h; (ii) Br_2 (1.25 mmol), AcOH, rt, 6 h (aqueous workup); (iii) Br_2 (1.25 mmol), CCl_4, rt, 4 h; (iv) Br_2 (2.50 mmol), CCl_4, reflux, 8 h; (v) Br_2 (1.25 mmol), CCl_4, reflux, 8 h.

The monobrominated products **180a-c** will provide a new simple, clean and efficient approach to *ortho*-, *meta*- and *para*-aminobenzyl nitrile,[155,156] benzyl amine,[157] benzyl alcohol,[158] benzyl thiol[159] derivatives and several other products, while *gem*-dibromo products **181a-c** will be potential starting materials for corresponding *o*/*m*/*p*-amino *gem*-diamine/imine,[147d] *gem*-diol,[160] *gem*-dithiol,[161] benzaldehyde,[162] acetal,[163] 1,3-dithiane[164] derivatives and several other products. These new potential approaches to above mentioned compounds will be highly useful in practice and depending on the substrate structure the protecting group can be detached by using hydrazine or acidic/basic reaction conditions.

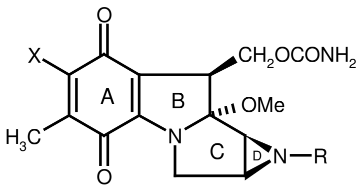
2.4C Section D: III. Synthetic Studies on Mitomycin K and C

2.4C.1 Background

Mitomycins are famous for their structural novelty and antitumor activity (Figure 15).[165-167] They were first isolated[168,169] in 1956 from *Streptomyces caespitosur* by Hata and co-workers in Japan. In 1962, they were also isolated from *Streptomyces veticillatus* and characterized[170] in United States of America. The absolute configuration of mitomycin A (**183**), mitomycin C (**184**), mitomycin K (**182**) and porfiromycin (**185**) have been formulated from X-ray crystallographic data.[171,172] Several attributes of mitomycins have served to spur multidisciplinary interest over such a long interval. Early on it was found that various mitomycins are potent antibiotics and cytotoxic agents.[173] Clinical benefits from their antiinfective properties were never realized due to unacceptable side effects. However, mitomycin C is a widely prescribed antitumor agent with demonstrated chemical value, either as a single agent, or in combination regimens.[174] Mitomycin is selective for hypoxic (O_2 deficient) cells characteristic of solid tumors,[175,176] and it is a classical example of an in situ activation mechanism that contributes to the selective cytotoxic properties of the molecule. Mode of action of mitomycin C requires either enzymatic or chemical reduction[177] or mild acidic treatment.[178] The active intermediate binds to the minor groove of DNA[179] where alkylation of the 2-aminogroup of guanine results in the formation of both monoalkylated adducts and DNA cross-links.[177a-b,180] The presence of angular oxygen functionality in mitomycin skeleton is essential for the pronounced activity of the same. The structural novelty of the mitomycins and their chemical lability constitute a formidable challenge to those who would undertake their synthesis.[165-167] The emergence of mitomycin C as a clinically useful anticancer chemotherapeutic resource promotes continuing research in this field.[181] However, inspite of the enormous amount of synthetic



Mitomycin K (**182**)



X = OCH$_3$, R = H; Mitomycin A (**183**)
X = NH$_2$, R = H; Mitomycin C (**184**)
X = NH$_2$, R = CH$_3$; Porfiromycin (**185**)

Figure 15

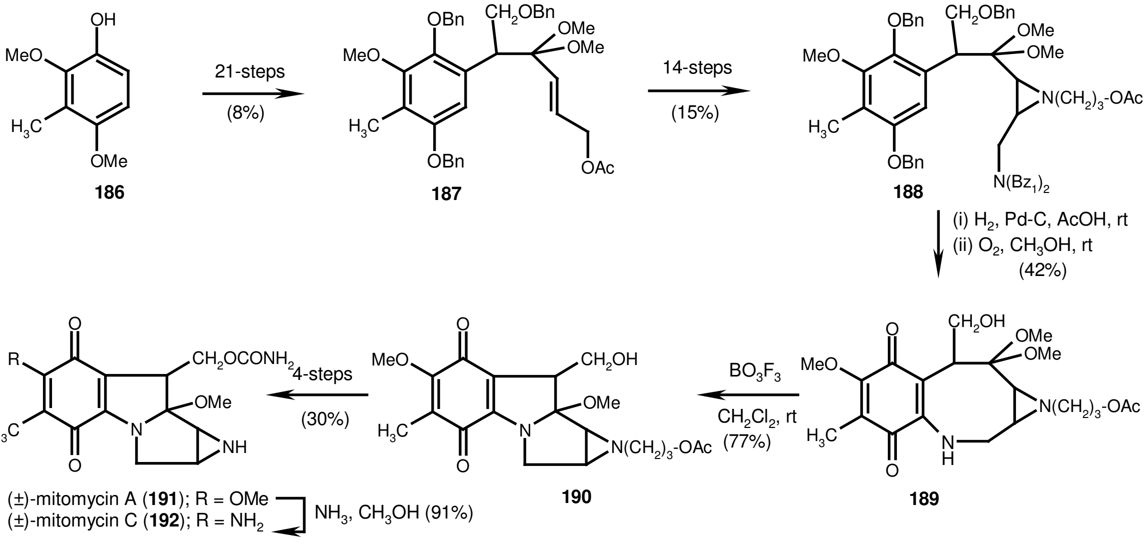
activity which the mitomycins have inspired, the only successful total synthesis of naturally occurring mitomycin C were those described by Kishi et al.[182] and Fukuyama et al.[183] In addition, the total synthesis of a related natural product mitomycin K, have been reported by Danishefsky *et al.*[184] and Jimenez *et al.*[185] Recently, several groups have also targeted the synthesis of mitomycin congeners.[186]

2.4C.1.1 Synthetic Approaches Towards Mitomycin K and C

During the past fifty years, after the isolation of these rather small size but densely functionalized natural products, the literature of synthetic studies on mitomycins and its congeners have become very large. Only two completed total synthesis of each mitomycin K and C are discussed by using the brief schemes below.

A] Kishi's Approach Towards (±)-Mitomycin C

Professor Y. Kishi reported the first racemic total synthesis of (±)-mitomycin A and C (**191** & **192**) with 0.1% overall yield starting from 2,4-dimethoxy-3-methylphenol (**186**) in 41 and 42-steps respectively (Scheme 25).[182]

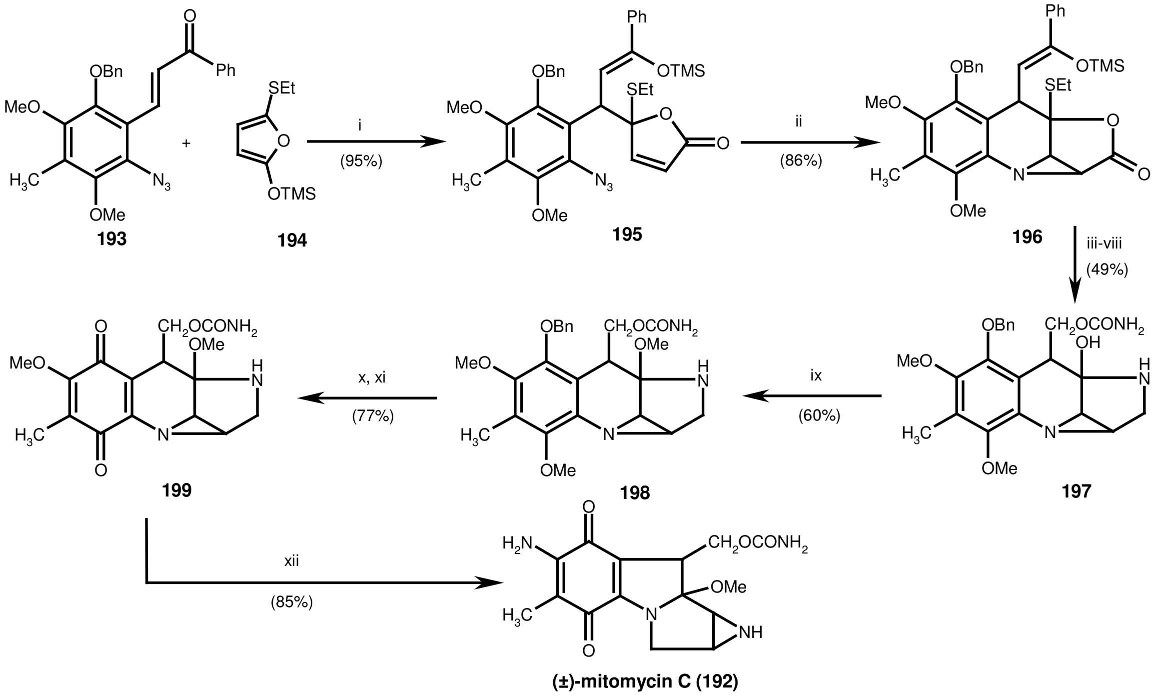


Scheme 25

The synthesis involves two key cyclizations: the intramolecular Michael reaction used to construct the eight member ring of **189** and the trans-annular cyclization of **189** to **190** under conditions mild enough to design core structure of mitomycins. The tetracyclic alcohol **190** on carbamoylation followed by deprotection of the aziridine group furnished (±)-mitomycin A (**191**) with 30% overall yield in four steps, which was subsequently converted to (±)-mitomycin C (**192**) by aminolysis in MeOH with 91% yield.

B] Fukuyama's Approach Towards (±)-Mitomycin C

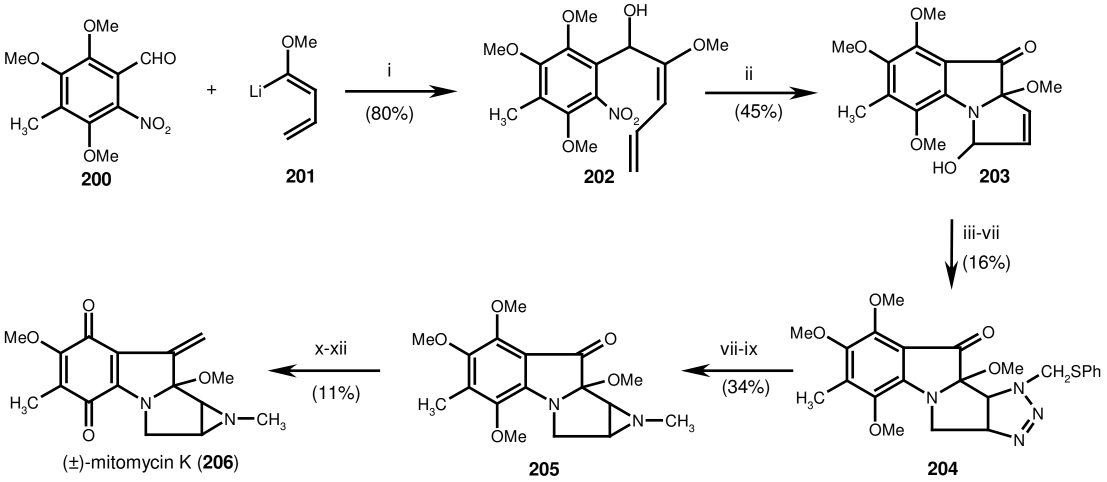
Professor T. Fukuyama reported the total synthesis of (±)-mitomycin C with 16% overall yield starting from chalcone **193** in twelve steps (Scheme 26).[183] His approach towards mitomycins includes a facile intramolecular azide-olefin cycloaddition of **195** to form the tetracyclic aziridine **196**, which on further organic transformations gave the aminal **197**. The labile methoxy group has been introduced under carefully controlled acidic conditions via highly strained bridgehead iminium ion intermediate to give **198**, which on deprotection of the benzyl ether followed by oxidation furnished (±)-isomitomycin A (**199**). Isomitomycin A (**199**) was directly converted to (±)-mitomycin C (**192**) in 85% yield by treatment with saturated ammonia in methanol at room temperature.



Scheme 26 *Reagents, conditions and yields*: (i) $SnCl_4$, CH_2Cl_2, -78 °C; Pyridine; (ii) Toluene, 110 °C, 3 h; (iii) DIBAL, THF, -78 °C; (iv) Ac_2O, Pyridine; (v) RuO_4, $NaIO_4$, $EtOAc/H_2O$ (1:1), 23 °C; (vi) $NaBH_4$, MeOH; (vii) CCl_3CONCO, CH_2Cl_2, 23 °C; (viii) NH_3, MeOH, 23 °C; $NaBH_4$; (ix) CSA, MeOH, 23 °C; (x) H_2, Pd/C, EtOH; (xi) DDQ, acetone/H_2O (20:1), -78 °C; (xii) NH_3, MeOH, 23 °C, 5 h.

C] Danishefsky's Approach Towards (±)-Mitomycin K

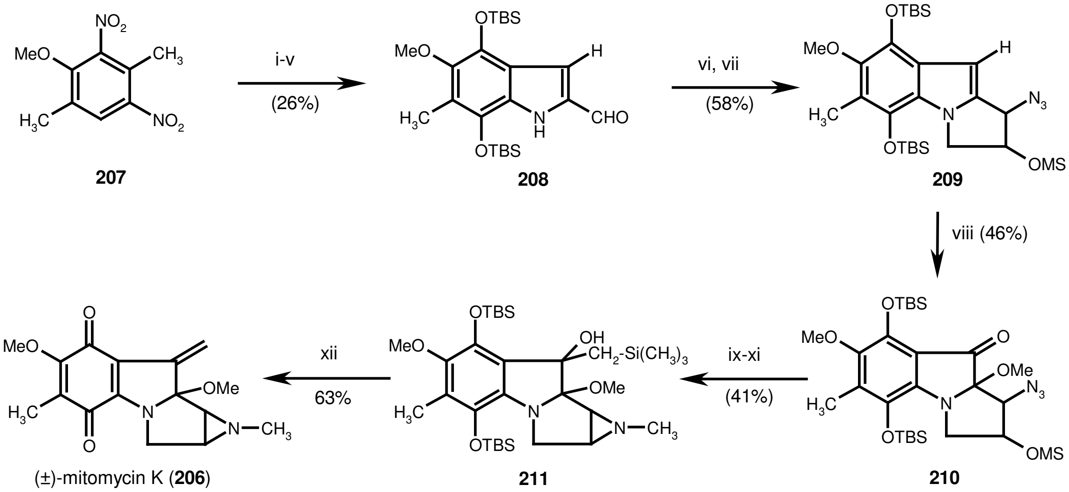
Professor S. J. Danishefsky reported the first synthesis of (±)-mitomycin K (**206**) with 0.2% overall yield starting from 2,3,5-trimethoxy-4-methyl-6-nitro-benzaldehyde (**200**) in twelve steps (Scheme 27).[184] He employed intramolecular nitroso Diels-Alder reaction of dienyl nitrobenzenemathanol **202** to produce pyrroloindole **203**, which on sequential introduction of the *N*-methylaziridine moiety by using thiophenylmethylazide, dehydroxylation followed by insertion of the exocyclic double bond by Peterson olefination and oxidation furnished the quinoid skeleton of mitomycin K.



Scheme 27 *Reagents, conditions and yields*: (i) **201**, THF, -78 °C; (ii) 350 nm lamp, THF, 15 h; (iii) PDC, CH_2Cl_2, rt, 24 h; (iv) $PhSCH_2N_3$, benzene, 80 °C; (v) L-selectride, THF, -78 °C; (vi) 1,1′-(thiocarbonyl)diimidazole, DMAP, CH_2Cl_2, 35 °C; (vii) Bu_3SNH, AIBN, bezene, 80 °C; (viii) 254 nm, Hg lamp/Vycor filter, benzene in quartz tube; (ix) Raney nickel, acetone, 60 °C; (x) [(trimethylsilyl)methyl]lithium, THF, -10 °C; (xi) Silver(II) dipicolinate, NaOAc, CH_3CN/H_2O; (xii) PPTS, CH_2Cl_2.

C] Jimenez's Approach Towards (±)-Mitomycin K

Professor L. S. Jimenez reported the racemic synthesis of (±)-mitomycin K with 1.4% overall yield starting from commercially available 2,5-dimethoxyanisole in thirteen steps (Scheme 28).[185a] They have prepared the starting dinitro compound **207** from 2,5-dimethoxyanisole via double nitration with 75% yield. His strategy involves construction of C ring of mitomycin from the aldehyde **208** by the reaction of dimethylvinylsulfonium iodide in the presence of sodium hydride followed by ring opening of the resultant tetracyclic epoxide with sodium azide and introduction of the angular oxygen functionality by the use of (hexamethylphosphoramido)-oxodiperoxomolybdenum (VI) as an oxidizing agent. In a later communication,[185b] they have introduced dimethyldiixoirane to effect the same oxidation in a completely stereoselective manner with better yield.

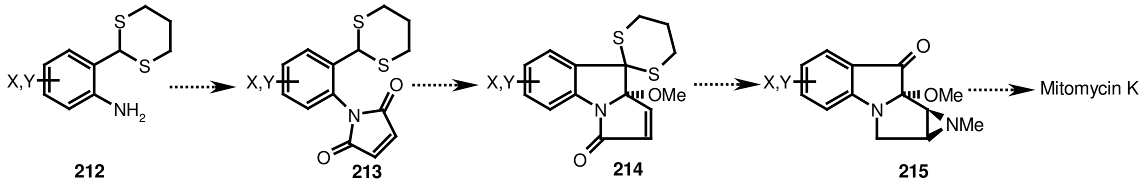


Scheme 28 *Reagents, conditions and yields*: (i) (a) Dimethyl oxalate, *t*-BuOK, Et_2O, (b) Zn/HCl, MeOH-Et_2O, reflux; (ii) Fermy's salt, Et_2O; (iii) H_2, Pd/C then TBSOTf, Et_3N, CH_2Cl_2; (iv) DIBAL, THF; (v) MnO_2, CH_2Cl_2; (vi) Diisopropylvinylsulfonium iodide, NaH, THF 0 °C; then NaN_3, acetone-H_2O; (vii) MsCl, Et_3N, CH_2Cl_2; (viii) MoO_5.HMPA, MeOH, 5-10 °C, 3 days; (ix) PPh_3, Et_3N, THF-H_2O, rt; (x) CH_3OTf, pyridine, CH_2Cl_2, 0 °C; (xi) 1.0 M $(CH_3)_3SiCH_2Li$, THF, -10 °C; (xii) PCC, CH_2Cl_2, 0 °C.

Appearance of a stream of publications on synthetic studies on mitomicinoid family of natural products, suggests that there is an urgency to synthesize mitomycins and the congeners in a fully stereoselective manner. We have discussed our synthetic efforts for the attempted synthesis of mitomycin K and C ring skeleton in the following part.

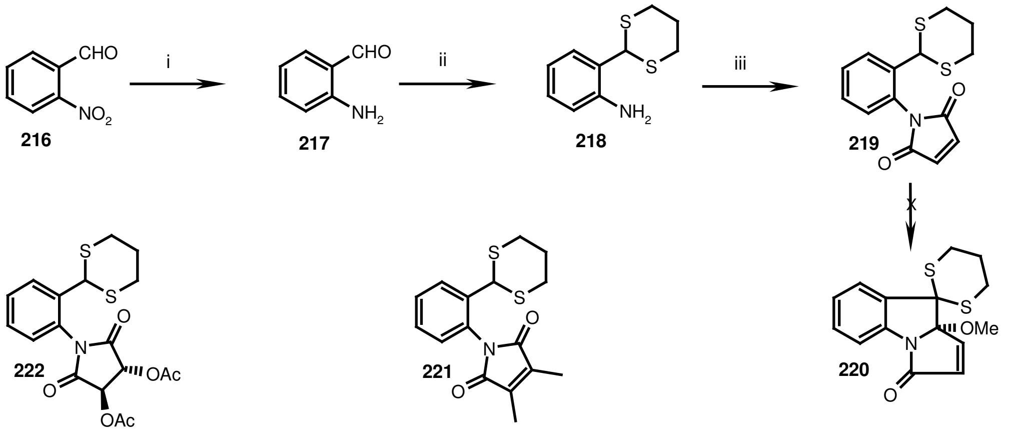
2.4C.2 Present Work: Results and Discussion

Initially we focused our synthetic plan towards the construction of core structure of mitomycins. A retrosynthetic analysis of the mitomycin systems reveals that the suitably substituted *o*-dithianylmaleimide can be a potential precursor for synthesis of mitomycin skeleton via an intramolecular ring closure with an introduction of angular oxygen functionality (Scheme 29).



Scheme 29

To check the feasibility, we first synthesized the suitable intermediate imide **219** starting from *o*-nitrobenzaldehyde (**216**) (Scheme 30). Iron catalyzed reduction[187] of **216** furnished *o*-aminobenzaldehyde (**217**) in 75% yield and was essentially pure to proceed for next step without any further purification. Dithianyl protection of the aldehyde **217** using $BF_3.Et_2O$ as catalyst gave the *o*-dithianylaniline **218** in 96% yield. Reaction of **218** with maleic anhydride followed by dehydrative ring closure of the formed anilic acid using acetic anhydride gave the desired maleimide **219** in 87% yield over the two steps. All our attempts to ring close[188] dithianylmaleimide **219** with an introduction of angular oxygen function to construct pyrrolidinone skeleton met with failure.



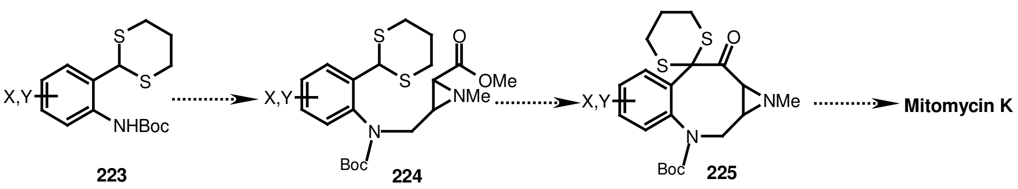
Scheme 30 *Reagents, conditions and yields*: (i) Fe/HCl, EtOH-CH_3COOH-H_2O (2:2:1), reflux, 15 min, (75%); (ii) 1,3-Dithiol, $BF_3.Et_2O$, dioxane, rt, 6 h (96%); (iii) (a) Maleic anhydride, Et_2O, rt, 2 h, (b) Ac_2O, NaOAc, reflux, 2 h (2-steps, 87%).

At this point we reasoned that, instability of the maleimide under basic condition might be the cause of such a failure. We prepared maleimides **221** and **222** from amine **218** using dimethylmaleic anhydride and L-diacetoxytartaric anhydride with 91% and 83% yields respectively and subjected them to ring closing conditions (Table 9). Such a ring closing proved to be unrewarding in our hands, resulting only in complex reaction mixtures or decomposition of starting material.

Table 9 Attempted Intramolecular cyclization of Imides **219**, **221**, **222**

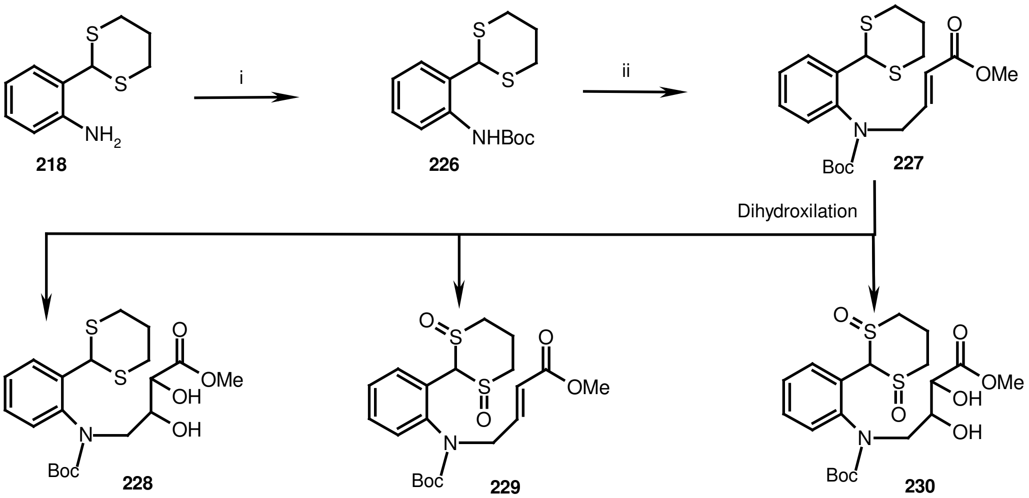
Entry	Substrate	Reagent	Reaction Condition	Conclusion
1	**219**	*n*-BuLi	THF, -78 °C, 1 h	Decomposition of starting material
2	**219**	*n*-BuLi	THF, -78 °C, 1 h then Ac_2O	Decomposition of starting material
3	**219**	*n*-BuLi	THF, HMPA, -78 °C, 1 h	Decomposition of starting material
4	**219**	*t*-BuLi	THF, HMPA, -78 °C, 1 h	Decomposition of starting material
5	**219**	*t*-BuLi	THF, HMPA, -78 °C, 1 h then Ac_2O	Decomposition of starting material
6	**221**	*n*-BuLi	THF, -78 °C, 1 h	Decomposition of starting material
7	**221**	*t*-BuLi	THF, -78 °C, 1 h	Complex reaction mixture
8	**222**	*n*-BuLi	THF, -78 °C, 1 h	Decomposition of starting material
9	**222**	*t*-BuLi	THF, -78 °C, 1 h	Decomposition of starting material

The above failure led to a change in our synthetic plan. Our modified synthetic approach involved *N*-allylation of suitably substituted monoprotected aniline **223** with methyl 4-bromo crotonate followed by suitable functionalization of the double bond and intramolecular condensation to get the eight-member precursor of mitomycins (Scheme 31).



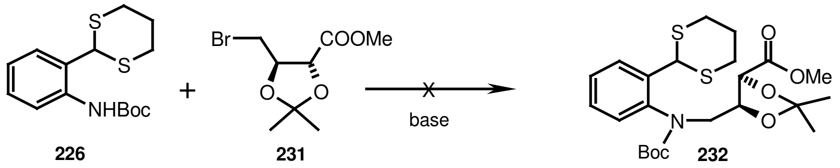
Scheme 31

Reaction of amine **218** with Boc-anhydride in THF at room temperature gave the monoprotected amine **226** in 89% yield. The *N*-Boc dithianylaniline **226** on reaction with methyl 4-bromocrotonate gave the corresponding *N*-allylated product **227** in 68% yield.[189] Unfortunately all our attempts for dihydroxylation[190] of **227** gave a complex mixture of all possible dihydroxylated and sulfur oxidised products. We could separate our desired product **228** by column chromatography but in only 5-10% yield (Scheme 32).



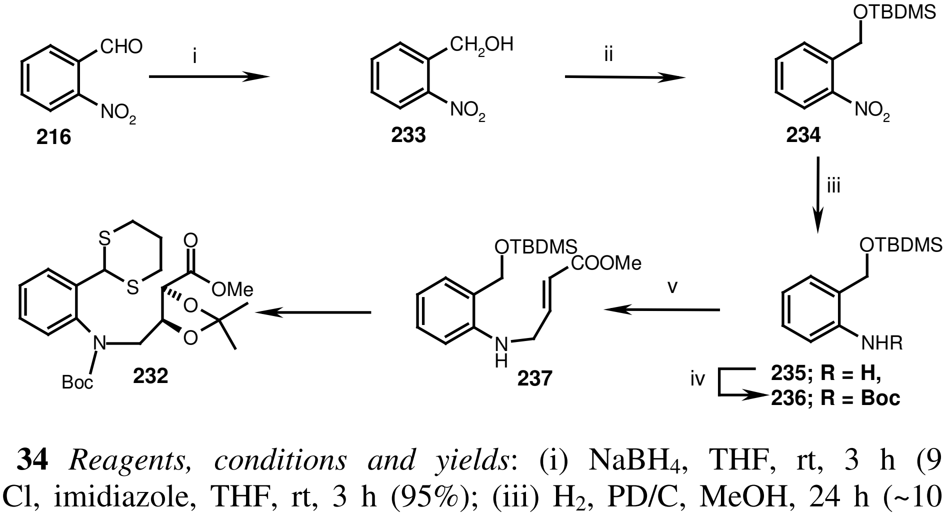
Scheme 32 *Reagents, conditions and yields*: (i) $(Boc)_2O$, THF, rt, 24 h (89%); (ii) methyl-4-bromocrotonate, anhydrous K_2CO_3, DMF, rt, 48 h (68%).

An alternate chiral pool strategy was planned to circumvent the above problem posed by sulfur atom's oxidation. We prepared the bromoester **231** starting from L-ascorbic acid using known literature procedure.[191] All our efforts for bringing about non allylic coupling of *N*-Boc dithianylaniline **226** with **231** using different bases (K_2CO_3, Na_2CO_3, Cs_2CO_3, NaH) met with failure (Scheme 33).



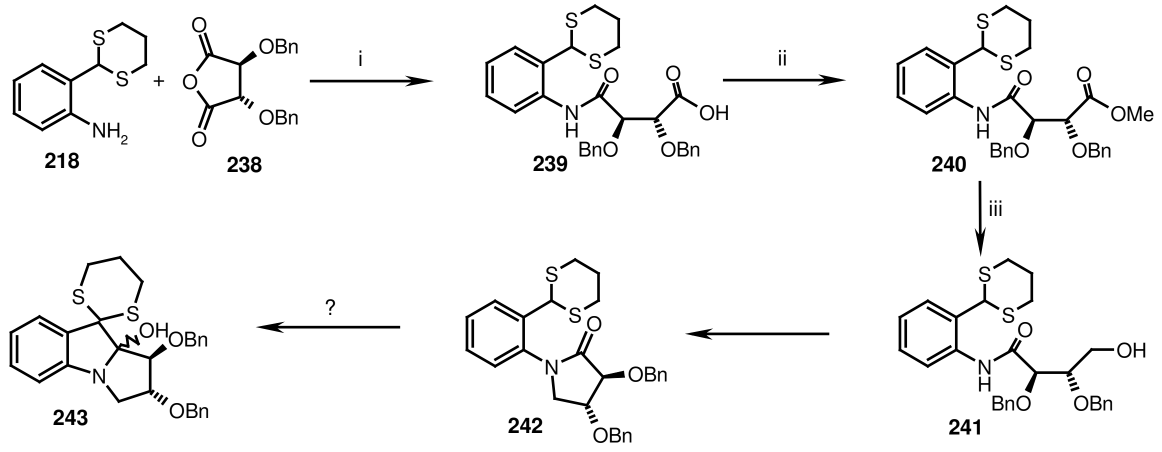
Scheme 33

At this stage, we reasoned that insertion of dithiane-functionality after *N*-allylation and dihydroxylation might solve this problem. So to check the feasibility of our synthetic plan, we synthesized the intermediate **235** and **236** starting from commercially available *o*-nitrobenzyl alcohol (**233**), which can also be prepared conveniently from *o*-nitrobenzaldehyde by $NaBH_4$ reduction with 97% yield (Scheme 34). Silylether protection of *o*-nitrobenzyl alcohol (**233**) gave the nitro compound **234** in 95% yield, which on Pd-C catalyzed hydrogenation afforded the corresponding amine **235** in quantitative yield. Careful *N*-allylation of **235** with 1.5 equivalent 4-bromocrotonate using K_2CO_3 as base in DMF yielded the *N*-allylated product **237**. All our efforts to convert compound **237** to its Boc-protected form were unrewarding, leading to complete recovery of the starting material. We also tried the N-allylation of monoprotected amine **236**, but all our efforts met with failure.



Scheme 34 *Reagents, conditions and yields*: (i) $NaBH_4$, THF, rt, 3 h (97%); (ii) TBDMSCl, imidiazole, THF, rt, 3 h (95%); (iii) H_2, PD/C, MeOH, 24 h (~100%); (iv) $(Boc)_2O$, THF, 24 h (79%); (v) Methyl-4-bromocrotonate, anhydrous K_2CO_3, DMF, rt, 18 h (68%).

Failure of Boc-protection led us to explore the lactam **242** as a probable precursor for the synthesis of mitomycin core structure via reactivity Umpolung. We planned to synthesize lactam **242** starting from dithianylaniline **218** and dibenzyltartaric anhydride **238**. Reaction of dithianylaniline **218** with dibenzyltartaric anhydride **238**[192] in ether gave the corresponding anilic acid **239** in quantitative yield, which was subjected without any further purification to esterification in ether with in situ generated diazomethane to give anilic ester **240** in 85% yield. Reduction of **240** with lithium aluminiumhydride, followed by the treatment of the formed alcohol **241** with *p*-TsCl and sodium hydride furnished the desired lactam **242** in 67% yield over two steps (Scheme 35). In our hands, several attempts to introduce the labile angular oxygen functionality via intramolecular cyclization of the lactam **242** to produce **243** varying the base and reaction conditions met with failure (Table 10). Literature reports reveal that there are very few examples known, wherein the intramolecular additions of 1,3-dithianyl carbanion has been realized.[188] Any base strong enough to deprotonate a dithiane-group, can also react with the carbonyl group either as a base or as a nucleophile. To affect such a cyclization, use of a protected carbanion *e.g.* 2-silyl-1,3-dithiane, which can be unmasked under relatively milder conditions may provide a better solution. Our efforts to synthesize such an intermediate are in active progress.



Scheme 35 *Reagents, conditions and yields*: (i) Dibenzyl-L-tartaric anhydride, Et_2O, 2 h (~100%); (ii) CH_2N_2, Et_2O, rt, 4 h (85%); (iii) (a) LAH, THF, 0 °C, 2 h, (b) NaH, *p*-TsCl, THF, 4 h (2-steps, 67%).

Table 10 Attempted Intramolecular cyclization of Lactam **242**

Entry	Reagent	Reaction Condition	Conclusion
1	*n*-BuLi	THF, -78 °C, 1 h	Complex reaction mixture
2	*n*-BuLi	THF, -78 °C, 1 h then Ac_2O	Complex reaction mixture

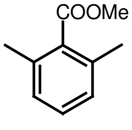
3	*n*-BuLi	THF, HMPA, -78 °C, 1 h	Complex reaction mixture
4	*t*-BuLi	THF, HMPA, -78 °C, 1 h	Complex reaction mixture
5	*t*-BuLi	THF, HMPA, -78 °C, 1 h then Ac_2O	Complex reaction mixture
6	*t*-BuLi	THF, -78 °C, 1 h	Complex reaction mixture

In summary, in this section we have presented our studies on the attempted synthesis of (±)-secocrispiolide, mitomycin K and C. We have efficiently synthesized the intermediate ethyl-5-(tetrahydropyranyloxy)-2-(bromomethyl)-2-pentenoate with good overall yield in order to test the feasibility of our synthetic plan. We feel that the use of organo-lithium species, might give a straightforward way to (±)-secocrispiolide. We have also described a simple route to achieve benzylic mono/*gem*-dibrominations of aromatic amine derivatives using molecular bromine. To the best of our knowledge, this is the first time *N*-arylsuccinimides have been treated as aniline derivatives rather than succinic anhydride derivatives to demonstrate a simple method for nuclear bromination at an alternate site and benzylic mono/*gem*-dibrominations using molecular bromine. In future this concept will be highly useful to demonstrate plenty of new applications in the subject. We have also presented our preliminary studies towards the synthesis mitomycin K and C skeletons using cyclic anhydrides and imides as probable precursors. We feel that the labile oxygen functionality as well as all the four rings present in mitomycin skeletons can be generated following our synthetic strategy (reactivity Umpolung) and further reasoned efforts are required. The logical extension of the same strategy will also be applicable for the total synthesis of Mitomycin K and C and analogues and our efforts for the same are in active progress in our laboratory.

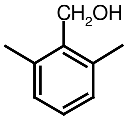
3.3C Section D: IV. Experimental

Commercially available 2,6-dimethylbenzoic acid, 1,3-propane diol, ethyl acrylate, dihydropyran, pyridinium chlorochromate, succinic anhydride, *p*-anisidine, *o*,*m*,*p*-toluidine, *o*-nitobenzaldehyde, 1,3-propanedithiol, di-*t*-butyldicarbonate, methyl-4-bromocrtonate, TBDMSCl, imidiazole, acetic anhydride, $BF_3.OEt_2$, $LiAlH_4$, NaH, PPh_3, $NaBH_4$, CBr_4, were used.

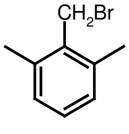
Methyl-2,6-dimethyl benzoate (166). A solution of 2,6-dimethylbenzoic acid (**165**, 3 g, 20 mmol) in methanol (20 mL) and H_2SO_4 (0.25 mL) mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether/ethyl acetate (9:1) as eluent furnished pure ester **166**: 2.62 g (80% yield).

 **166** $C_{10}H_{12}O_2$ (164)	Thick oil. **IR** (Neat): ν_{max} 1732, 1437, 1076, 773 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.33 (s, 6H), 3.93 (s, 3H), 7.00-7.30 (m, 3H).

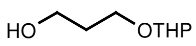
2,6-Dimethylbenzyl alcohol (167). To a slurry of lithium aluminium hydride (565 mg, 15 mmol) in anhydrous ether (20 mL) was added dropwise a solution of the ester **166** (1.64 g, 10 mmol) in anhydrous ether (10 mL) with efficient stirring under nitrogen atmosphere. The reaction mixture was stirred for 3 h. Moist ether (10 mL), water (10 mL) and saturated ammonium chloride solution (10 mL) was sequentially added to the reaction mixture. The ether layer was separated, washed with brine (20 mL), dried over anhydrous Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (4:1) as eluent gave the desired alcohol **167**: 1.22 g (90% yield).

 **167** **$C_9H_{12}O$** (136)	Mp: 84 °C. **IR** (Neat): ν_{max} 3421, 1472, 989, 756 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.44 (s, 6H), 4.74 (s, 2H), 7.00-7.20 (m, 3H).

2,6-Dimethylbenzyl bromide (168). To a stirred solution of alcohol **167** (680 mg, 5 mmol) and CBr_4 (2.49 g, 7.5 mmol) in 30 mL of dry DCM was added a solution of PPh_3 (1.31 g, 5 mmol) in 10 mL of dry DCM during a period of 30 min. at room temperature. After an additional 4.5 h stirring, the reaction mixture was diluted with *n*-hexane and the resulting precipitate was removed by filtration and was washed several times with *n*-hexane. The combined organic layer was washed with 5% $NaHCO_3$ solution (10 mL), water (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (9:1) as eluent gave **168**: 992 mg (~100% yield).

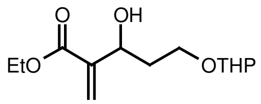
 **168** **$C_9H_{11}Br$** (199)	Thick oil. **IR** (Neat): ν_{max} 1472, 1215, 758 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.41 (s, 6H), 4.57 (s, 2H), 6.95-7.15 (m, 3H). **Anal. Calcd for $C_9H_{11}Br$**: C, 54.30; H, 5.57. Found: C, 54.22; H, 5.51.

3-(Tetrahydropyranyloxy)propanol (170). To a stirred solution of 1,3-propanediol (**169**, 3.80 g, 50 mmol) containing few drops of concentrated HCl was added dihydropyran (2.86 g, 34 mmol), the temperature rose to about 40 °C. After 3 hours of stirring at room temperature, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with 10% KOH (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer under vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (4:1) as eluent gave 3-(tetrahydropyranyloxy)propanol (**170**): 2.45 g (45% yield).

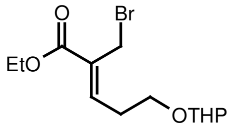
 **170** $\mathbf{C_8H_{16}O_3}$ (160)	Thick oil. **IR** (Neat): ν_{max} 3404, 1121, 1072, 1034 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 1.30-1.95 (m, 8H), 2.72 (bs, 1H), 3.30-3.80 (m, 6H) 4.43 (bs, 1H). **Anal. Calcd for $\mathbf{C_8H_{16}O_3}$**: C, 59.97; H, 10.07. Found: C, 59.93; H, 10.11.

5-(Tetrahydropyranyloxy)-3-hydroxy-2-methylenepentanoic acid ethyl ester (172). 3-(Tetrahydropyranyloxy)propanol (**170**, 1.26 g, 7.9 mmol) in 5 mL DCM was added quickly to a suspension of PCC (2.66 g; 12.36 mmol) in 30 mL DCM, containing sodium acetate (190 mg). The mixture quickly turned black and after 1.5 h of stirring, it was diluted with ethyl acetate. The supernatant solution was decanted from tarry residue, which was again extracted using ethyl acetate (30 mL x 5). The combined organic extracts were filtered through basic alumina and solvent was concentrated under vacuo to give the aldehyde **171** (1.07 g, 85%), which was used immediately for the next step.

Compound **171** (1.07 g, 6.7 mmol) was mixed with ethyl acrylate (1.5 mL) and DABCO (75 mg, 0.67 mmol) was added with dissolution. The reaction was monitored by TLC and was discontinued after 10 days. The excess of acrylate was removed under vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (10 mL x 3) to remove DABCO and was dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (4:1) as eluent gave **172**: 1.48 g (86% yield).

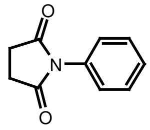
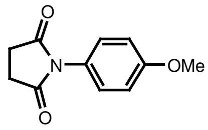
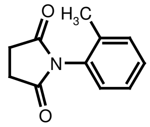
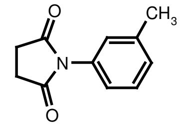
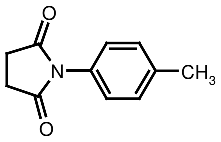
 **172** **$C_{13}H_{22}O_5$** (258)	Thick oil. **IR** (Neat): ν_{max} 3439, 1720, 1120, 1034 cm^{-1}. **^{1}H NMR** ($CDCl_{3,}$ 500 MHz): δ 1.20 (t, *J* = 10 Hz, 3H), 1.35-2.00 (m, 8H), 3.35-3.55 (m, 2H), 3.70-3.90 (m, 2H), 4.12 (q, *J* = 10 Hz, 2H), 4.45-4.60 (m, 2H), 5.82 (d, *J* = 3 Hz, 1H), 6.18 (s, 1H). **Anal. Calcd for $C_{13}H_{22}O_5$**: C, 60.45; H, 8,58. Found: C, 60.41; H, 8.54.

5-(Tetrahydropyranyloxy)-2-(bromomethyl)-2-pentenoic acid ethyl ester (173). To a solution of NBS (480 mg; 2.64 mmol) in DCM (10 mL) was added a solution of dimethyl sulfide (172 mg, 2.88 mmol) in DCM (5 mL) at 0 °C under N_2 atmosphere, after 10 min. of stirring a solution of **172** (619 mg, 2.4 mmol) in DCM (5 mL) was added dropwise and the resulting mixture was stirred at room temperature for a further 24 h. The reaction mixture was diluted with ether and was poured in to ice cold solution of NaCl. The organic layer was separated and the aqueous layer was extracted with DCM (20 mL x 2). The combined organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (9:1) as eluent gave **173**: 732 mg (95% yield).

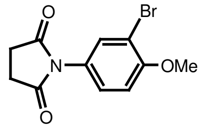
 **173** **$C_{13}H_{21}BrO_4$** (321)	Thick oil. **IR** (Neat): ν_{max} 1726, 1643, 1070, 1034, 734 cm^{-1}. **^{1}H NMR** ($CDCl_{3,}$ 200 MHz): δ 1.29 (t, *J* = 8 Hz, 3H), 1.40-1.95 (m, 6H), 2.50-2.65 (m, 2H), 3.40-3.60 (m, 2H), 3.75-3.95 (m, 2H), 4.15-4.30 (m, 4H), 4.58 (t, *J* = 6 Hz, 1H), 6.99 (t, *J* = 6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 13.8, 19.0, 24.0, 25.0, 29.1, 30.2, 60.6, 61.8, 64.6, 98.3, 130.6, 144.0, 164.9. **Anal. Calcd for $C_{13}H_{21}BrO_4$**: C, 48.61; H, 6.59. Found: C, 48.57; H, 6.62.

General procedure for preparation of *N*-arylsuccinimides. To a stirred solution of succinic anhydride (5 g, 50 mmol) in benzene plus 1,4-dioxane mixture (60 mL, 2:1) was added a solution of primary aromatic amine (50 mmol) in ether (40 mL) in a dropwise fashion at room temperature over a period of 20 min. and the reaction mixture was further stirred for 2 h. The formed solid product was filtered, washed with ether (25 mL) and vacuum dried to obtain succinanilic acids in quantitative yield, which were used for the next step without any further purification.

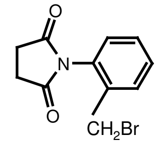
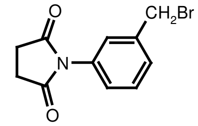
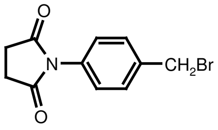
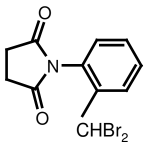
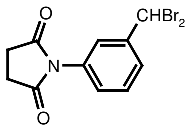
A mixture of succinanilic acid (45 mmol), acetic anhydride (30 mL) and fused sodium acetate (500 mg) was heated on water bath at 60 °C for 2 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The precipitated product was filtered, washed with water and dried in vacuo to obtain succinimides in 90-95% yield.

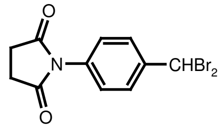
 **175** **$C_{10}H_9NO_2$** (175)	**Mp**: 158-159 °C. **IR** (Nujol): ν_{max} 1776, 1709, 1595 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.91 (s, 4H), 7.20-7.60 (m, 5H).
 **177** **$C_{11}H_{11}NO_3$** (205)	**Mp**: 165-167 °C. **IR** (Nujol): ν_{max} 1770, 1705, 1607 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.88 (s, 4H), 3.82 (s, 3H), 6.99 (d, J = 10 Hz, 2H), 7.20 (d, J = 10 Hz, 2H).
 **179a** **$C_{11}H_{11}NO_2$** (189)	**Mp**: 99-102 °C. **IR** (Nujol): ν_{max} 1770, 1705, 1600 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.15 (s, 3H), 2.93 (s, 4H), 7.08 (d, J = 6 Hz, 1H), 7.25-7.45 (m, 3H).
 **179b** **$C_{11}H_{11}NO_2$** (189)	**Mp**: 103-105 °C. **IR** (Nujol): ν_{max} 1767, 1705, 1607 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.39 (s, 3H), 2.88 (s, 4H), 7.00-7.50 (m, 4H).
 **179c** **$C_{11}H_{11}NO_2$** (189)	**Mp**: 158-160 °C. **IR** (Nujol): ν_{max} 1770, 1705, 1600 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.38 (s, 3H), 2.87 (s, 4H), 7.15 (d, J = 6 Hz, 2H), 7.28 (d, J = 6 Hz, 2H).

***N*-(3-Bromo-4-methoxy)phenylsuccinimide (178).** To a stirred solution of imide **177** (2.84 g, 10 mmol) in acetic acid (20 mL) was added molecular bromine (2.00 g, 12.5 mmol) and the reaction mixture was stirred at room temperature for 6 h. Aqueous workup, followed by filtration of the formed precipitate and vacuum drying gave pure **178**: 3.62 g (100% yield).

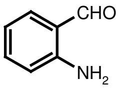
 **178** **$C_{11}H_{10}BrNO_3$** (284)	**Mp**: 178-180 °C. **IR** (Neat): ν_{max} 1782, 1717, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): 2.89 (s, 4H), 3.93 (s, 3H), 6.99 (d, *J* = 10 Hz, 1H), 7.24 (dd, *J* = 10 & 2 Hz, 1H), 7.51 (d, *J* = 4 Hz, 1H). **MS** (*m/e*): 285, 283, 270, 268, 257, 255, 240, 239, 214, 212, 204, 186, 158, 140, 132, 106, 90, 76, 63. **Anal. Calcd for $C_{11}H_{10}BrNO_3$**: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.62; H, 3.41; N, 5.01.

General Procedure for benzylic monobromination and *gem*-dibromination of 179a-c: To a stirred solution of succinimide **179a/b/c** (5 mmol) in CCl_4 (40 mL) was added bromine (6.25 mmol) in CCl_4 (10 mL) at room temperature in a dropwise fashion over a period of 10 to 15 min. and the reaction mixture was further stirred for 4 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL), the organic layer was washed with water, 5% aqueous sodium metabisulphite (10 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo furnished respectively the desired monobromo products **180a/b/c** in 92-94% yields. Similarly the starting materials **179a/b/c** (5 mmol) with bromine (12.5 mmol) on refluxing in CCl_4 (50 mL) for 8 h gave respectively the *gem*-dibromo compounds **181a/b/c** in 94-96% yields. The ^{1}H NMR spectra of isolated monobromo products **180a/b/c** revealed that 2-3% of starting material remains unreacted and/or formation of corresponding *gem*-dibromo products. The analytically pure products were obtained by recrystalization.

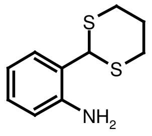
 **180a** **$C_{11}H_{10}BrNO_2$ (268)**	**Mp**: 126-128 °C (CCl_4). **IR** (Nujol): ν_{max} 1782, 1717, 1595 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.96 (d, J = 2 Hz, 4H), 4.38 (s, 2H), 7.17 (d, J = 6 Hz, 1H), 7.30-7.65 (m, 3H). **MS** (*m/e*): 269, 267, 188, 160, 142, 132, 118, 104, 91, 77, 63. **Anal. Calcd for $C_{11}H_{10}BrNO_2$**: C, 49.28; H, 3.76; N, 5.23. Found: C, 49.11; H, 3.58; N, 5.08.
 **180b** **$C_{11}H_{10}BrNO_2$** (268)	**Mp**: 126-128 °C (CCl_4). **IR** (Nujol) ν_{max} 1778, 1700, 1600 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.90 (s, 4H), 4.50 (s, 2H), 7.20-7.55 (m, 4H). **MS** (*m/e*): 269, 267, 188, 160, 146, 132, 106, 91, 77, 65. **Anal. Calcd for $C_{11}H_{10}BrNO_2$**: C, 49.28; H, 3.76; N, 5.23. Found: C, 49.15; H, 3.82; N, 5.36.
 **180c** **$C_{11}H_{10}BrNO_2$ (268)**	**Mp**: 186-187 °C (ethyl acetate). **IR** ($CHCl_3$): ν_{max} 1782, 1718, 1610 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.90 (s, 4H), 4.50 (s, 2H), 7.29 (d, J = 8 Hz, 2H), 7.51 (d, J = 8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 28.4, 32.3, 126.7, 129.8, 131.8, 138.1, 175.9. **MS** (*m/e*): 269, 267, 188, 132, 106, 89, 77. **Anal. Calcd for $C_{11}H_{10}BrNO_2$**: C, 49.28; H, 3.76; N, 5.23. Found: C, 49.16; H, 3.70; N, 5.19.
 **181a** **$C_{11}H_9Br_2NO_2$ (347)**	**Mp**: 200-203 °C ($CHCl_3$). **IR** (Nujol): ν_{max} 1771, 1709, 1595 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.99 (d, J = 2 Hz, 4H), 6.55 (s, 1H), 7.05 (dd, J = 8 & 2 Hz, 1H), 7.45 (dt, J = 8 & 2 Hz, 1H), 7.57 (dt, J = 8 & 2 Hz, 1H), 8.12 (dd, J = 10 & 2 Hz, 1H). **MS** (*m/e*): 349, 347, 345, 268, 266, 186, 158, 130, 103, 76. **Anal. Calcd for $C_{11}H_9Br_2NO_2$**: C, 38.07; H, 2.61; N, 4.04. Found: C, 37.93; H, 2.55; N, 3.81.
 **181b** **$C_{11}H_9Br_2NO_2$ (347)**	Waxy solid. **IR** (Nujol): ν_{max} 1780, 1715, 1607 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.93 (s, 4H), 6.65 (s, 1H), 7.29 (d, J = 8 Hz, 1H), 7.40-7.70 (m, 3H). **MS** (*m/e*): 349, 347, 345, 268, 266, 210, 187, 158, 130, 117, 103, 89. **Anal. Calcd for $C_{11}H_9Br_2NO_2$**: C, 38.07; H, 2.61; N, 4.04. Found: C, 37.88; H, 2.43; N, 4.02.

 **181c** **$C_{11}H_9Br_2NO_2$ (347)**	**Mp**: 212-213 °C (ethyl acetate) **IR** (Nujol): ν_{max} 1774, 1707, 1603 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 2.93 (s, 4H), 6.65 (s, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 8 Hz, 2H). **^{13}C NMR** (Acetone-d_6, 50 MHz): δ 29.2, 41.6, 127.8, 127.9, 135.2, 142.8, 177.0. **MS** (*m/e*): 349, 347, 345, 268, 266, 210, 184, 158, 130, 104, 77, 63. **Anal. Calcd for $C_{11}H_9Br_2NO_2$**: C, 38.07; H, 2.61; N, 4.04. Found: C, 37.97; H, 2.58; N, 3.76.

2-Aminobenzaldehyde (217). A mixture of 2-nitrobenzaldehyde (**216**, 5.25 g, 34.8 mmol), iron powder (14.6 g, 26.1 mmol) and concentrated HCl (0.15 mL) in 300 mL of a mixture of ethanol, acetic acid and water (2:2:1) was refluxed for 15 minutes with mechanical stirring. The solution was filtered, diluted with water (600 mL), and extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with saturated aqueous sodiumbicarbonate (300 mL), water (200 mL x 2) and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave essentially pure 2-aminobenzaldehyde (**217**): 3.16 g (75%). The above scale reaction was repeated to prepare required amount of aminobenzaldehyde (**217**).

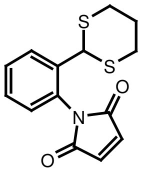
 **217** **C_7H_7NO** (121)	Thick oil. **IR** (Neat): ν_{max} 3502, 3354, 1673, 1619, 1204, 1158 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 6.17 (bs, 2H), 6.60-6.80 (m, 2H), 7.32 (t, *J* = 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 9.87 (s, 1H).

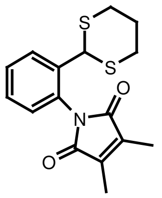
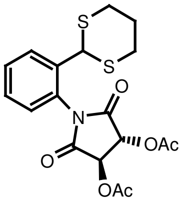
2-[1,3]Dithian-2-yl-phenylamine (218). To a stirred solution of 2-aminobenzaldehyde (**217**) (847 mg, 7 mmol) and 1,3-propanedithol (833 mg, 7.7 mmol) in dry dioxane (20 mL) was added $BF_3.Et_2O$ (0.3 mL) and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was then concentrated under vacuum and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with saturated aqueous sodiumbicarbonate (30 mL) and water (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (3:2) as eluent gave the desired dithyanyl amine **218**: 1.42 g (96% yield).

 **218** **$C_{10}H_{13}NS_2$** (211)	Thick oil. **IR** ($CHCl_3$): ν_{max} 3389, 3346, 1215 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.70-2.15 (m, 2H), 2.75-3.00 (m, 4H), 3.77 (bs, 2H), 5.21 (s, 1H), 6.75-7.35 (m, 4H).

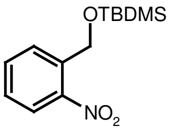
General procedure for preparation of maleimides (219, 221 and 222). To a stirred solution of anhydrides (2 mmol) in diethyl ether (10 mL) was added a solution of amine **218** (422 mg, 2 mmol) in ether (10 mL) in a dropwise fashion at room temperature over a period of 20 min. and the reaction mixture was further stirred for 2 h. The formed solid product was filtered, washed with ether (25 mL) and vacuum dried to obtain maleanilic acids in quantitative yield, which were used for the next step without any further purification.

A mixture of maleanilic acid (2 mmol), acetic anhydride (10 mL) and fused sodium acetate (10 mg) was heated on water bath at 60 °C for 2 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The precipitated product was filtered, washed with water and dried in vacuo to obtain maleimides (**219**, **221** and **222**) in 83-91% yield.

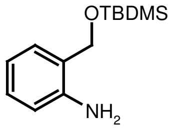
 **219** **$C_{14}H_{13}NO_2S_2$** (291)	**Mp**: 160 °C. **IR** ($CHCl_3$): ν_{max} 1718, 1215, 1150 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.80-1.95 (m, 1H), 2.05-2.15 (m, 1H), 2.80-3.00 (m, 4H), 4.99 (s, 1H), 6.91 (s, 2H), 7.12 (d, J = 6 Hz, 1H), 7.35-7.55 (m, 2H), 7.82 (d, J = 6 Hz, 1H). **Anal. Calcd for $C_{14}H_{13}NO_2S_2$**: C, 57.71; H, 4.50; N, 4.81. Found: C, 57.66; H, 4.43; N, 4.83.

 **221** **$C_{16}H_{17}NO_2S_2$** (319)	**Mp**: 142 °C. **IR** (CHCl$_3$): ν_{max} 1707, 1391, 1094 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 500 MHz): δ 1.85-1.95 (m, 1H), 2.00-2.15 (m, 1H), 2.10 (s, 6H), 2.80-3.00 (m, 4H), 5.02 (s, 1H), 7.08 (d, J = 10 Hz, 1H), 7.35-7.45 (m, 2H), 7.82 (d, J = 10 Hz, 1H). **Anal. Calcd for $C_{16}H_{17}NO_2S_2$**: C, 60.16; H, 5.36; N, 4.38. Found: C, 60.19; H, 5.31; N, 4.27.
 **222** **$C_{18}H_{19}NO_6S_2$** (409)	**Mp**: 132 °C. **IR** (CHCl$_3$): ν_{max} 1737, 1641, 1215, 1094 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 300 MHz): δ 1.80-2.15 (m, 2H), 2.25 (s, 3H); 2.28 (s, 3H), 2.70-3.30 (m, 4H), 5.25-5.32 (m, 2H), 5.85 (d, J = 6 Hz, 1H), 7.15-7.20 (m, 1H), 7.35-7.55 (m, 2H), 7.80-7.90 (m, 1H). **Anal. Calcd for $C_{18}H_{19}NO_6S_2$**: C, 52.80; H, 4.68; N, 3.42. Found: C, 52.74; H, 4.61; N, 3.47.

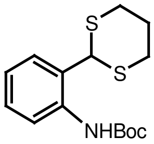
t-Butyl-dimethyl-(2-nitro-benzyloxy)silane (234). **To a stirred ice cold solution of alcohol** 233 **(1.53 g, 10 mmol) and imidiazole (1.70 g, 25 mmol) in dry THF (20 mL) was added a solution of *t*-butyl-dimethylsilylchloride (2.31 g, 15 mmol) in dry THF (10 mL) and the resulting reaction mixture was stirred at room temperature for a further 3 h. The reaction mixture was diluted with ethyl acetate (30 mL) and it was washed with water (20 mL x 3), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (9:1) as eluent gave** 234**: 2.54 g (95% yield).**

 **234** **$C_{13}H_{21}NO_3Si$** (267)	**Thick oil.** **IR** (Neat): ν_{max} 1526, 1340, 1107, 839 cm^{-1}. **^{1}H NMR** (CDCl$_3$, 200 MHz): δ 0.15 (s, 6H), 0.98 (s, 9H), 5.11 (s, 2H), 7.42 (t, J = 8 Hz, 1H), 7.68 (t, J = 8 Hz, 1H), 7.93 (d, J = 8Hz, 1H), 8.10 (d, J = 8 Hz, 1H). **Anal. Calcd for $C_{13}H_{21}NO_3Si$**: C, 58.39; H, 7.92; N, 5.24. Found: C, 58.31; H, 7.97; N, 5.18.

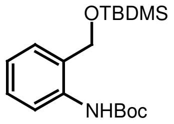
2-(*t*-Butyl-dimethyl-silanyloxymethyl)-phenylamine (235). A mixture of **234** (2.14 g, 8 mmol) and catalytic amount of Pd/C in methanol (20 mL) was subjected to hydrogenation at 65-psi hydrogen pressure for 24 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate and (7:3) to furnish **235**: 1.89 g (~100% yield).

 **235** **$C_{13}H_{23}NOSi$** (237)	**Thick oil.** **IR** ($CHCl_3$): ν_{max} 3462, 3377, 1620, 1462, 1215, 837 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.09 (s, 6H), 0.92 (s, 9H), 4.15 (bs, 2H), 4.70 (s, 2H), 6.70 (t, J = 6 Hz, 2H), 7.00-7.15 (m, 2H). **Anal. Calcd for $C_{13}H_{23}NOSi$**: C, 65.77; H, 9.76; N, 5.90. Found: C, 65.65; H, 9.71; N, 5.83.

(2-[1,3]Dithian-2-yl-phenyl)-carbamic acid *t*-butyl ester (226). To a solution of amine **218** (633 mg, 3 mmol) in dry THF (20 mL) was added a solution of di-*t*-butyldicarbonate (982 mg, 4.5 mmol) in dry THF (20 mL) and the reaction mixture was stirred at room temperature for a further 24 h. The reaction mixture was then concentrated under vacuum. Water (20 ml) was added to the residue and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (7:3) as eluent gave the desired Boc-protected amine **226**: 830 mg (89% yield).

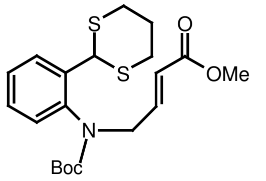
 **226** **$C_{15}H_{21}NO_2S_2$** (311)	**Mp**: 145 °C. **IR** ($CHCl_3$): ν_{max} 3352, 1732, 1506, 1225 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 1.54 (s, 9H), 1.90-2.00 (m, 1H), 2.15-2.25 (m, 1H), 2.90-2.97 (m, 2H), 3.05-3.15 (m, 2H), 5.30 (s, 1H), 7.07 (t, J = 5 Hz, 1H), 7.25-7.35 (m, 2H), 7.40 (d, J = 5 Hz, 1H), 7.81 (bs, 1H). **Anal. Calcd for $C_{15}H_{21}NO_2S_2$**: C, 57.84; H, 6.80; N, 4.50. Found: C, 57.77; H, 6.73; N, 4.53.

[2-(*t*-Butyl-dimethyl-silanyloxymethyl)-phenyl]-carbamic acid *t*-butyl ester (236). **Repetition of the above procedure using amine** 235 **(711 mg, 3 mmol) and di-*t*-butyldicarbonate (982 mg, 4.5 mmol) gave the corresponding monoprotected amine** 236**: 798 mg (79%).**

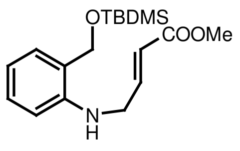
	**Thick oil.** **IR** (Neat): ν_{max} 3363, 1718, 1215, 839 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.11 (s, 6H), 0.94 (s, 9H), 1.52 (s, 9H), 4.72 (s, 2H), 6.90-7.10 (m, 2H), 7.20-7.35 (m, 1H), 8.05 (d, J = 8 Hz, 1H), 8.21 (bs, 1H).

236 **$C_{18}H_{31}NO_3Si$** (337)	**Anal. Calcd for $C_{18}H_{31}NO_3Si$**: C, 64.05; H, 9.26; N, 4.15. Found: C, 63.97; H, 9.18; N, 4.21.

4-[*t*-Butoxycarbonyl-(2-[1,3]dithian-2-yl-phenyl)-amino]-but-2-enoic acid methyl ester (227). To a slurry of Boc-protected amine **226** (622 mg, 2 mmol) and finely divided potassium carbonate (1.1 g, 8 mmol) in dry DMF (10 mL) was added methyl-4-bromocrotonate (716 mg, 4 mmol) and the reaction mixture was stirred at room temperature for 24 h. Another portion of methyl-4-bromocrotonate (358 mg, 2 mmol) was added to the reaction mixture and stirring was continued for a further 24 h. Then the reaction mixture was poured into ice-cold water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (7:3) as eluent gave the desired *N*-allylated amine **227**: 556 mg (68% yield).

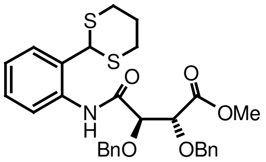
 **227** **$C_{20}H_{27}NO_4S_2$** (409)	Thick oil. **IR** (Neat): ν_{max} 1724, 1655, 1435, 1274, 1165, 1043 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 1.36 (bs, 9H), 1.80-2.00 (m, 1H), 2.15-2.20 (m, 1H), 2.80-3.10 (m, 4H), 3.73 (s, 3H), 4.05-4.15 (m, 1H), 4.50-4.55 (m, 1H), 5.17 (s, 1H), 5.92 (d, *J* = 15 Hz, 1H), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 2H), 7.67 (d, *J* = 5 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 25.0, 27.9, 32.1, 32.3, 46.2, 51.4, 80.8, 122.9, 128.3, 128.6, 128.8, 129.3, 136.8, 139.2, 143.2, 143.6, 154.5, 166.3. **Anal. Calcd for $C_{20}H_{27}NO_4S_2$**: C, 58.65; H, 6.64; N, 3.42. Found: C, 58.61; H, 6.57; N, 3.35.

4-[2-(*t*-Butyl-dimethyl-silanyloxymethyl)-phenylamino]-but-2-enoic acid methyl ester (237). **To a slurry of amine** 235 **(711 mg, 3 mmol) and finely divided potassium carbonate (1.65 g, 12 mmol) in dry DMF (30 mL) was added methyl-4-bromocrotonate (806 mg, 4.5 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (8:2) as eluent gave the desired *N*-allylated amine** 237**: 683 mg (68% yield).**

 **237** **$C_{18}H_{29}NO_3Si$** (335)	**Thick oil.** **IR** (Neat): ν_{max} 3369, 1722, 1215, 839 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.07 (s, 6H), 0.89 (s, 9H), 3.73 (s, 3H), 3.95-4.05 (m, 2H), 4.72 (s, 2H), 5.27 (bs, 1H), 6.00-6.15 (m, 1H), 6.55 (d, *J* = 8 Hz, 1H), 6.68 (t, *J* = 8 Hz, 1H), 7.20-7.25 (m, 3H). **Anal. Calcd for $C_{18}H_{29}NO_3Si$**: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.37; H, 8.75; N, 4.12.

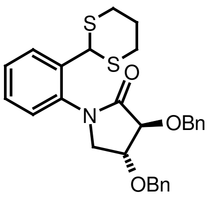
(2*R*,3*R*)-2,3-Bis-benzyloxy-*N*-(2-[1,3]dithian-2-yl-phenyl)-succinamic acid methyl ester (240). **To a stirred solution of anhydride** 238 **(1.25 g, 4 mmol) in ether (20 mL) was added a solution of amine** 218 **(844 mg, 4 mmol) in ether (20 mL) in a dropwise fashion at room temperature over a period of 20 min. and the reaction mixture was further stirred for 2 h. The formed solid product was filtered, washed with ether (25 mL) and vacuum dried to obtain maleanilic acid** 239 **(2.08 g) in quantitative yield, which was used for the next step without any further purification.**

A solution of **239** (1.83 g, 3.5 mmol) in ether (20 mL) was treated with a solution of diazomethane in ether at 0 °C until the starting material was completely consumed (4 h). The excess diazomethane was quenched with acetic acid (0.5 mL) and the reaction mixture was concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (7:3) to give **240**: 1.6 g (85% yield).

 **240** **$C_{29}H_{31}NO_5S_2$** (537)	**Thick oil.** **IR** (Neat): ν_{max} 3283, 3248, 1726, 1458, 1219, 825 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 1.55-1.95 (m, 2H), 2.40-2.85 (m, 4H), 3.70 (s, 3H), 4.45-4.65 (m, 4H), 4.80-4.90 (m, 2H), 5.29 (s, 1H), 7.20-7.50 (m, 14H). **Anal. Calcd for $C_{29}H_{31}NO_5S_2$**: C, 64.78; H, 5.81; N, 2.61. Found: C, 64.73; H, 5.72; N, 2.65.

1-(2-[1,3]Dithian-2-yl-phenyl)-(2*R*,3*R*)-3,4-diphenoxy-pyrrolidin-2-one (242). To a slurry of lithium aluminium hydride (228 mg, 6 mmol) in anhydrous THF (10 mL) was added dropwise a solution of the ester **240** (1.6 g, 3 mmol) in anhydrous THF (20 ml) at 0 °C under constant stirring. The reaction mixture was stirred at the same temperature for a further 2 h. Saturated ammonium chloride solution (10 ml) was added to the reaction mixture and diluted with THF (20 mL). The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude **241** (1.1 g), which was used for the next step without further purification.

To a stirred slurry of NaH (115 mg, 4.8 mmol) in THF (10 mL) was added a solution of crude alcohol **241** (1.22 g, 2.4 mmol) in THF (20 mL). To the above reaction mixture a solution of *p*-toluenesulfonyl chloride (915 mg, 4.8 mmol) in THF (10 mL) was added in a drop-wise fashion over a period of 15 min. and the reaction mixture was further stirred at rt for 30 min. Reaction was quenched with water (10 mL), concentrated in vacuo and extracted with ethyl acetate (100 mL). The organic layer was washed with aqueous sodium bicarbonate solution (20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification using petroleum ether/ethyl acetate (3:2) as eluent gave the desired lactam **242**: 988 mg (67% yield).

 **242** **$C_{28}H_{29}NO_3S_2$** (491)	**Thick oil.** **IR** (Neat): $\nu_{\max}$ 1713, 1637, 1217, 1103 cm^{-1}. ^{1}**H NMR** (CDCl$_3$, 200 MHz): δ 1.75-2.10 (m, 2H), 2.65-2.95 (m, 4H), 3.65-3.85 (m, 1H), 3.95-4.05 (m, 1H), 4.25-4.40 (m, 2H), 4.62 (d, *J* = 4 Hz, 2H), 4.88 (d, *J* = 12 Hz, 1H), 5.13 (d, *J* = 12 Hz, 1H), 5.23 (s, 1H), 7.10-7.20 (m, 1H), 7.25-7.60 (m, 12H), 7.65-7.85 (m, 1H). **Anal. Calcd for $C_{28}H_{29}NO_3S_2$**: C, 68.40; H, 5.95; N, 2.85. Found: C, 68.34; H, 5.87; N, 2.92.

2.5 Summary

In the present chapter, we have described our studies on total synthesis of several small to medium size bioactive natural products. We have presented an efficient synthesis of chaetomellic acid A anhydride, 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid, 2-carboxymethyl-3-hexylmaleic anhydride, 2-(*β*-carboxyethyl)-3-alkylmaleic anhydrides, maculalactone A-C and nostoclide I using highly chemo and regioselective S_N2' coupling reaction of appropriate Grignard reagents with dimethyl bromomethylfumarate as one of the key steps. Our present synthesis of chaetomellic acid A anhydride and 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid are noteworthy because without using any catalyst we have achieved high chemo- and regioselectivity in the present S_N2' Grignard coupling reaction by employing HMPA as cosolvent. In the present synthesis of 2-carboxymethyl-3-hexylmaleic anhydride and 2-(*β*-carboxyethyl)-3-alkylmaleic anhydrides we have demonstrated an alternate route to brominate the less active allylic methyl carbon in the presence of active methyl group to generate (bromomethyl)alkylmaleic anhydrides. We feel that these bromoanhydrides and their analogues will be potential building blocks for synthesis of several important natural/synthetic products bearing maleic anhydride moieties. We have also developed straightforward route to bioactive butyrolactones maculalctones A-C, nostoclide I, rubrolide E by simple conversion of corresponding anhydrides using regioselective reduction to lactone followed by Knoevenagel condensation reactions with appropriate aldehydes. The present approach is very much general in nature and will be useful to design diverse butyrolactone skeletons for the structure-activity relationship studies. The simplicity of reaction conditions used in the synthesis of simple but rather unstable natural product (±)-sarkomycin, especially the

Triton B catalyzed Michael addition of nitro methane in presence of free hydroxyl group and clean Oxone induced Nef reaction are noteworthy.

We have developed an efficient methodology to achieve the quantitative benzylic mono- and *gem*-dibromination of primary aromatic amine derivatives using molecular bromine instead of NBS by protecting the amino group as a succinimide moiety. We have also presented the role of NBS-DBP/AIBN as a reagent to induce *Z*- to *E*- carbon-carbon double bond isomerization with several types of olefins having a variety of substituents. The NBS-bromination condition is sufficient for both allylic bromination and isomerization of carbon-carbon double bonds, when the allylic sites are not available in substrates; only the isomerization of carbon-carbon double bond takes place. The present conditions for isomerization of carbon-carbon double bonds are mild and general in nature.

We have presented our studies on the attempted synthesis of (±)-secocrispiolide and mitomycins. Work is in progress for the search of suitable condition for the S_N2' coupling reaction of proper nucleophile with ethyl-5-(tetrahydropyranyloxy)-2-(bromomethyl)-2-pentenoate to complete the synthesis of (±)-secocrispiolide. Intramolecular ring closing reaction using reactivity Umpolung to generate the mitomycin skeleton and to complete the total synthesis of mitomycin K and C continues to be a challenge in our synthetic endeavors. In short, in the present studies we got a nice opportunity to design several useful cyclic anhydrides and butyrolactones by performing very selective reactions of carbon nucleophiles on cyclic anhydride and their analogues/derivatives, which also provided us an elegant way to learn lot of new chemistry during these studies.

Large numbers of cyclic anhydrides are known and starting from couple of them we have designed in our group concise synthesis of several bioactive natural (30 plus) and unnatural (25 plus) products using variety of new synthetic strategies, without using much of protection-deprotection chemistry. In design of these useful compounds we have performed very selective addition, elimination, substitution, oxidation, reduction reactions and nucleophilic ring opening reactions with variety of nucleophiles (carbon, nitrogen, oxygen and sulfur). We feel that development of new routes to several desired cyclic anhydrides and performing selective intermolecular and intramolecular reactions on them will provide a broad way to several new complex target molecules. We also feel that the chemistry developed will be of interest to large number of chemist from theoretical and practical point of view. In conclusion, the cyclic anhydride chemistry will continue to have a rich history, bright present and future to its credit.

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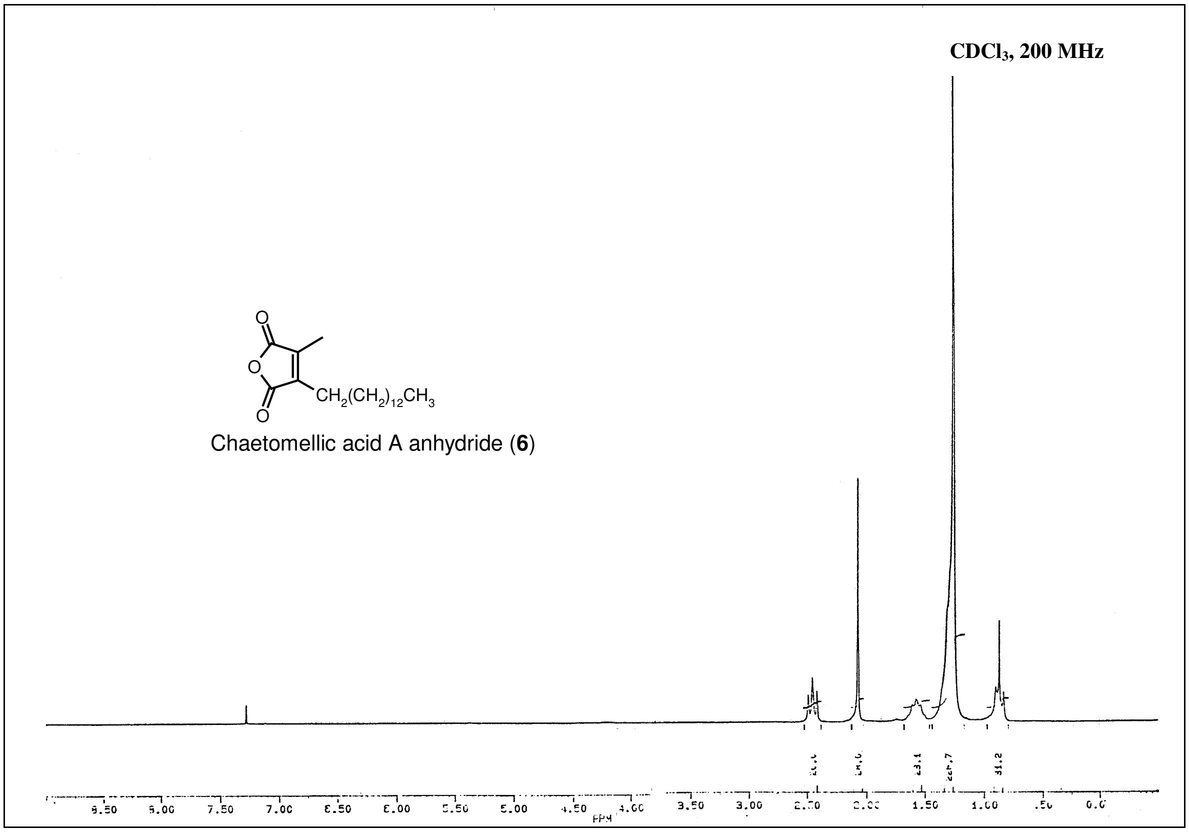
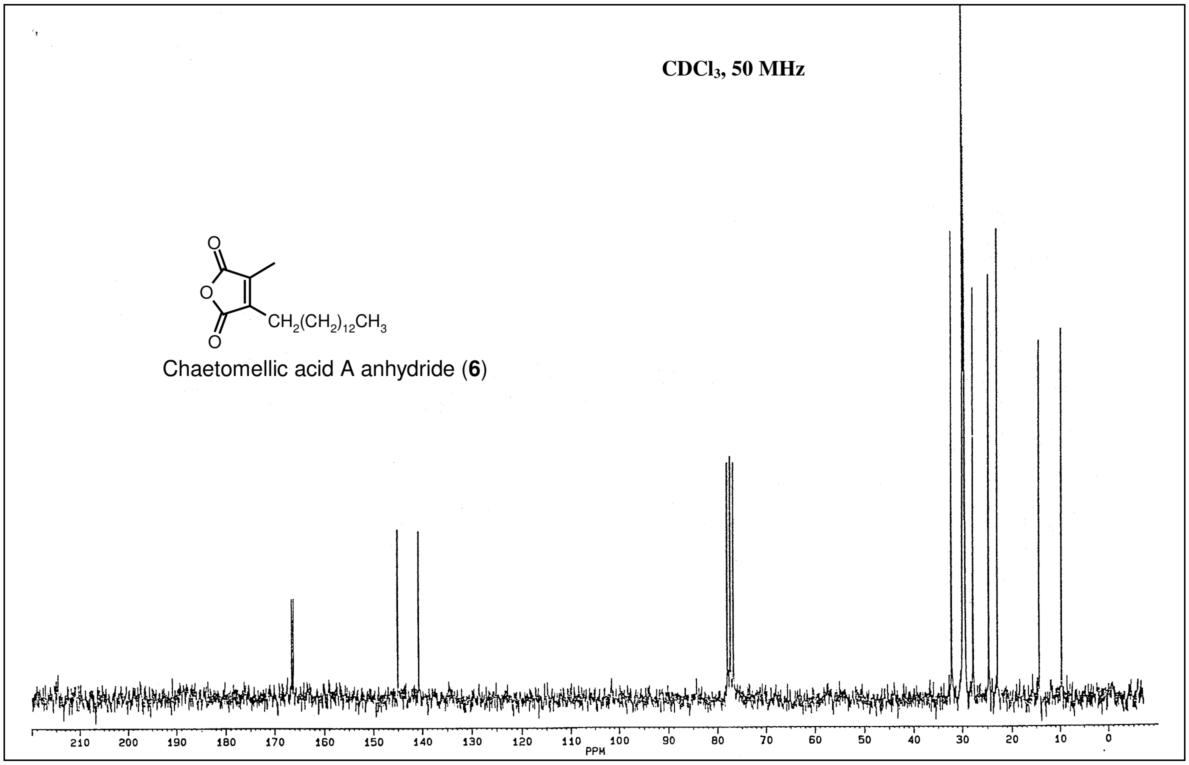


CDCl$_3$, 200 MHz

Chaetomellic acid A anhydride (**6**)



CDCl$_3$, 50 MHz

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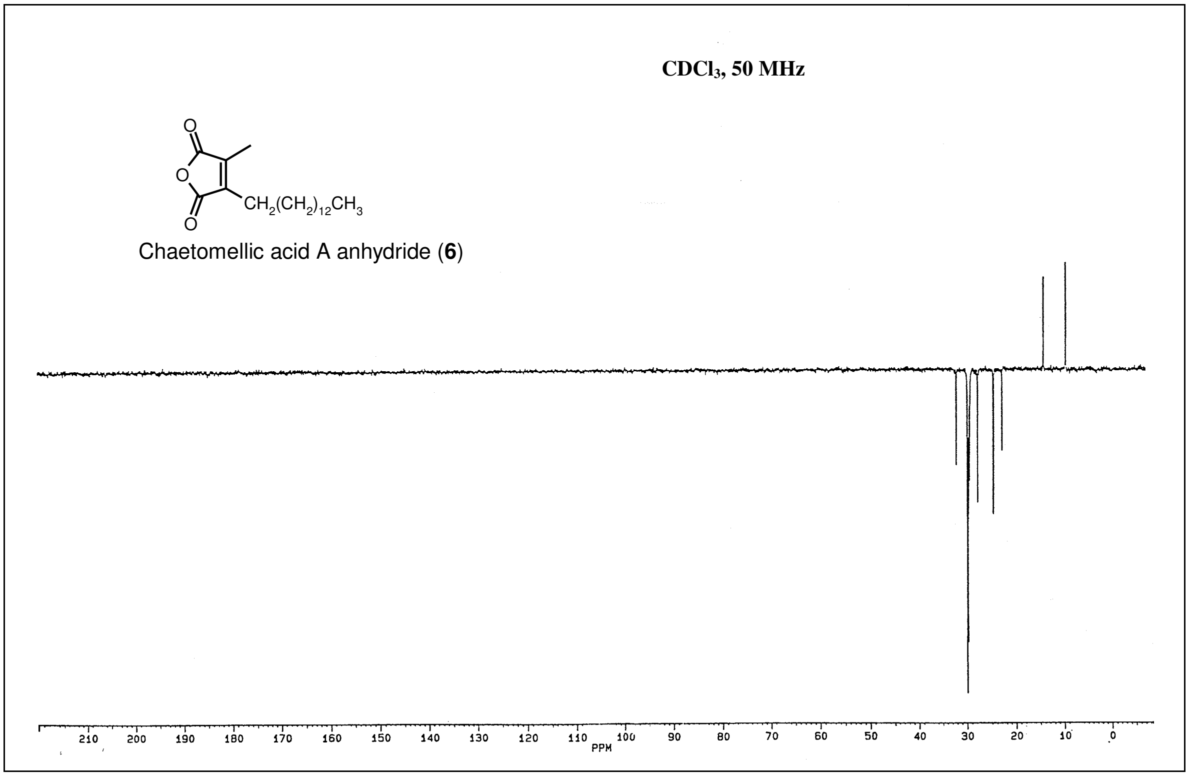
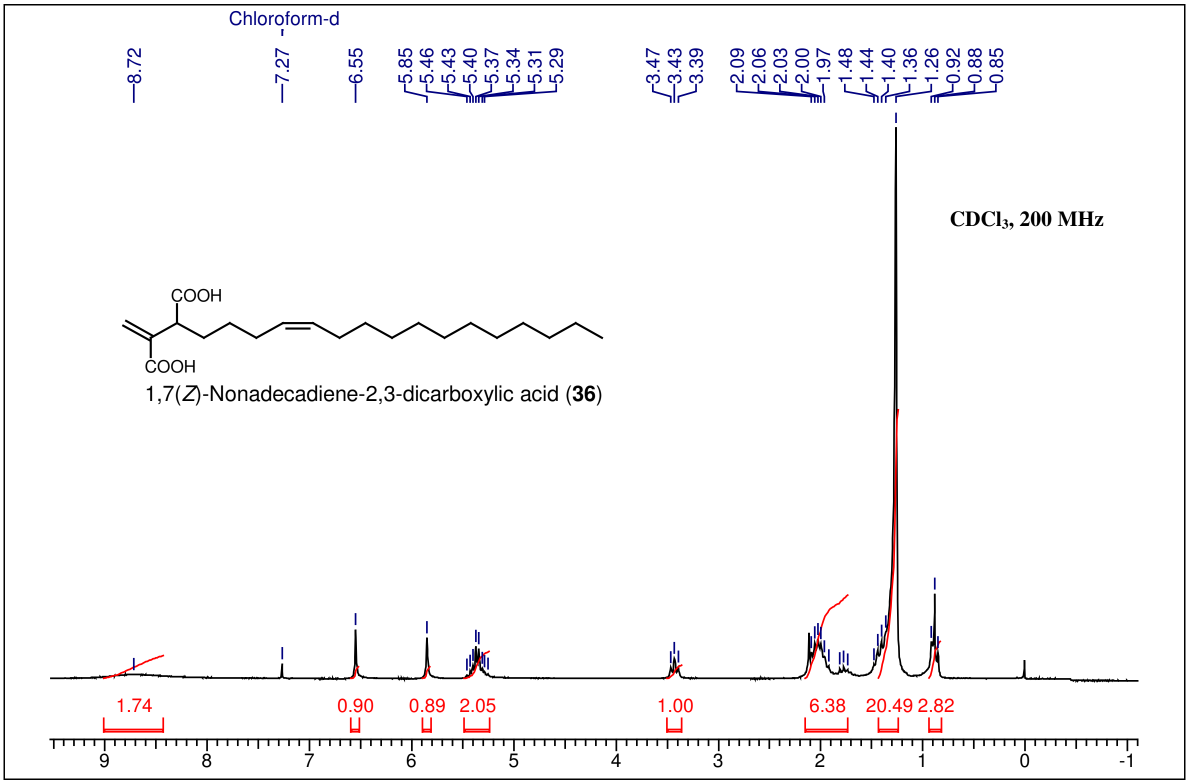
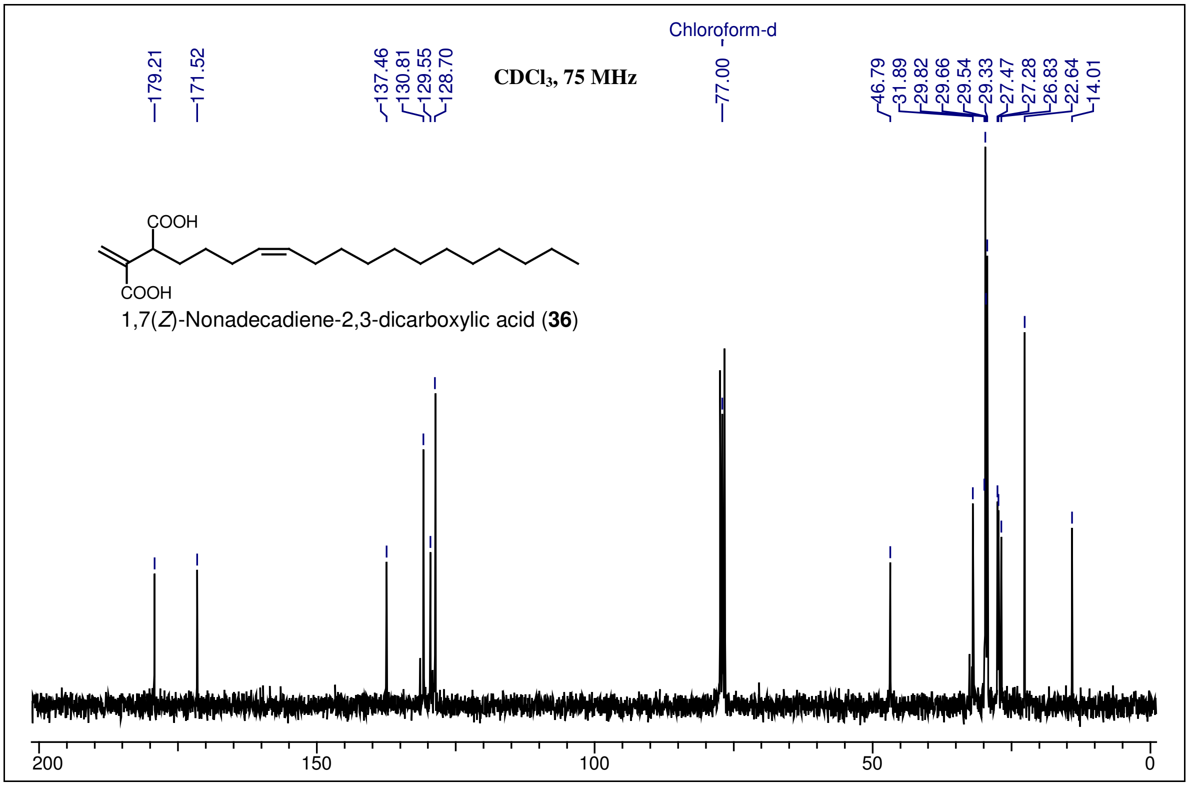
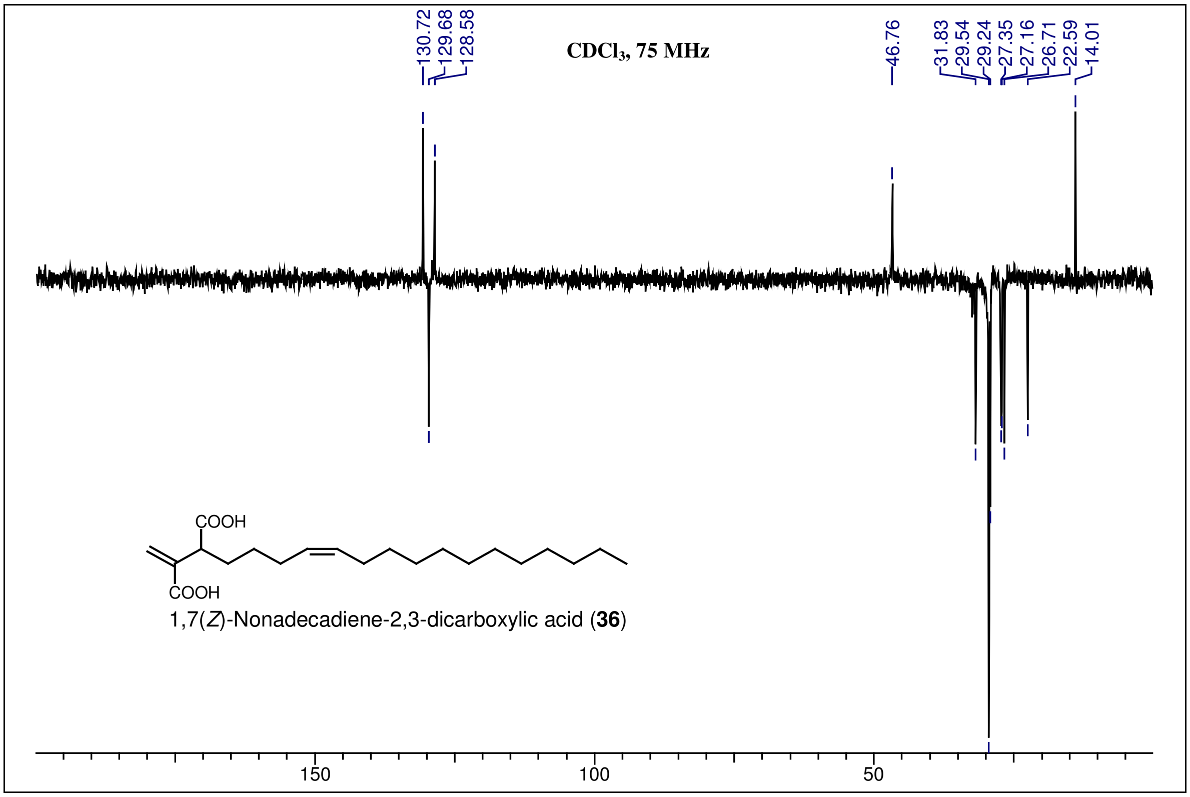


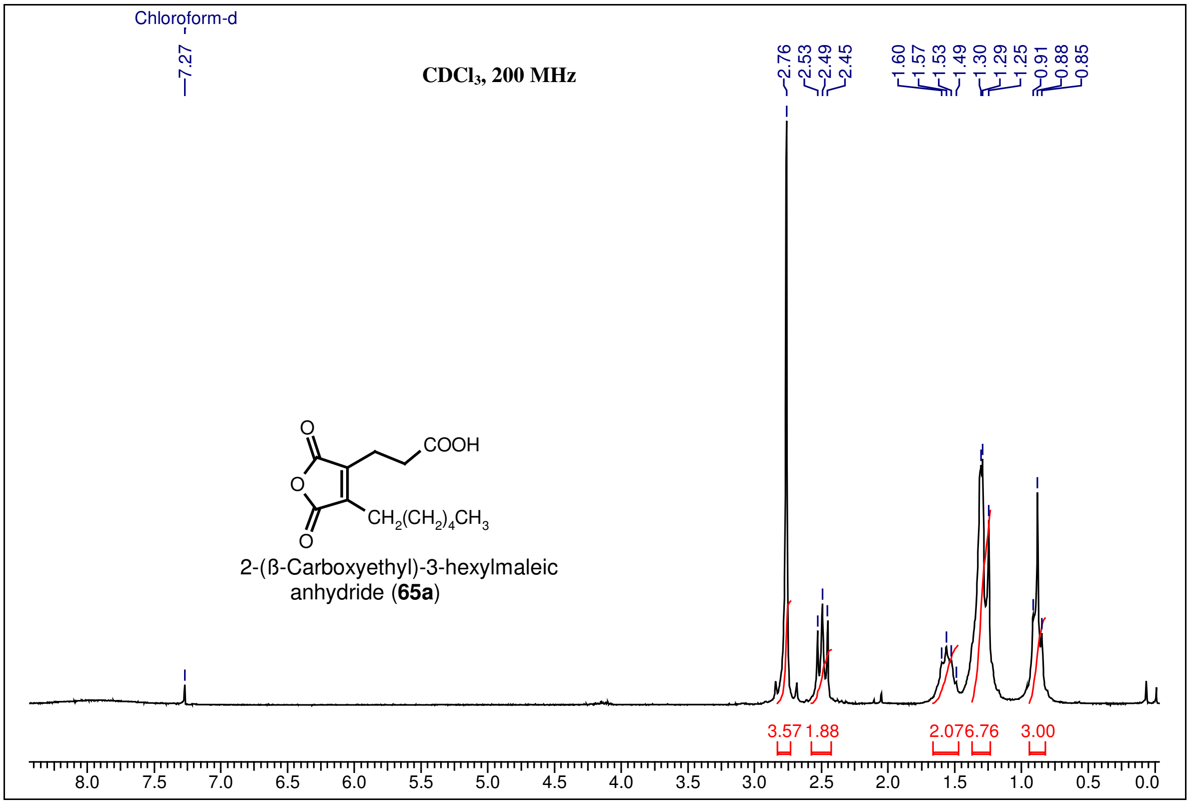
Chaetomellic acid A anhydride (**6**)

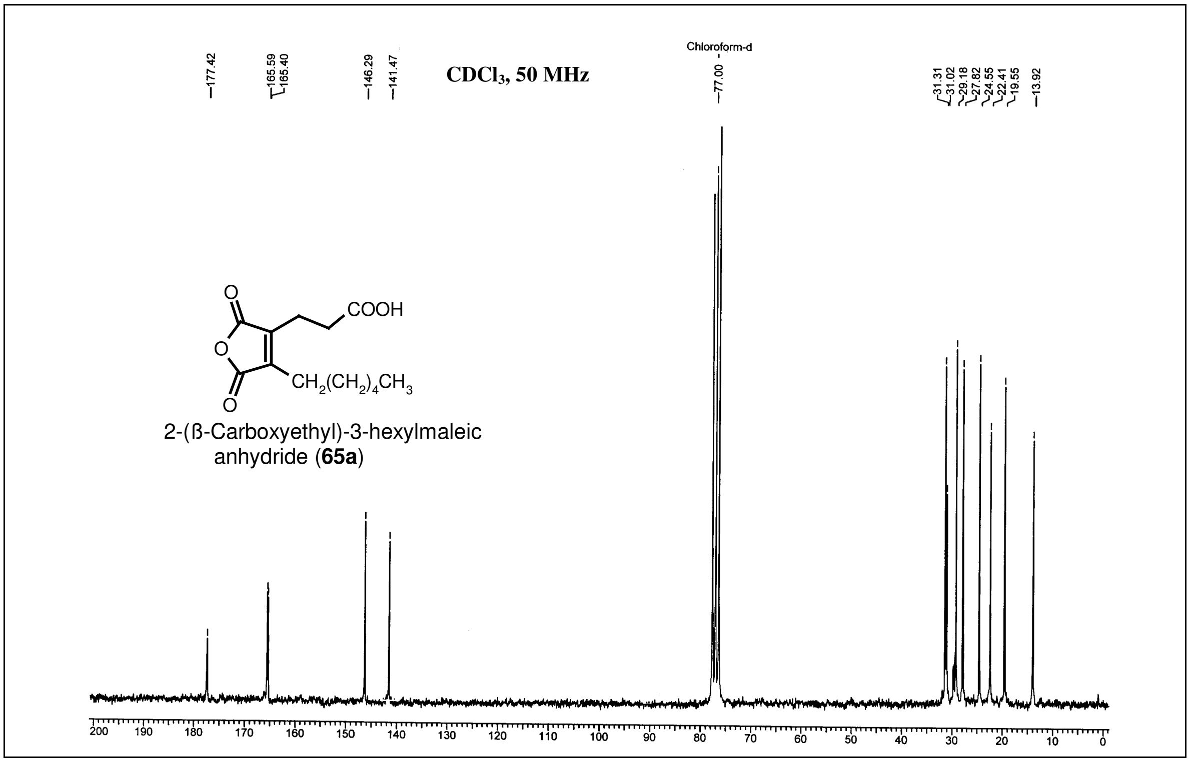


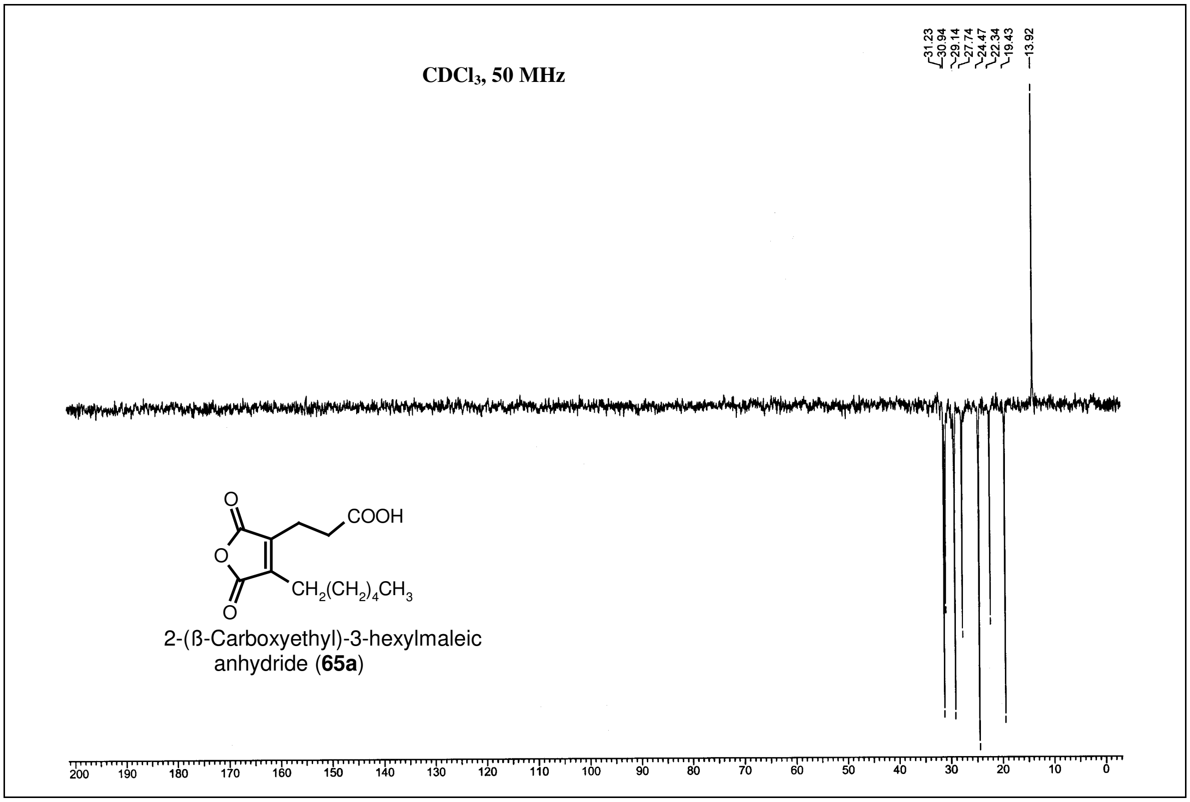
1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic acid (**36**)


Chloroform-d
179.21
171.52
137.46
130.81
129.55
128.70
CDCl₃, 75 MHz
77.00
46.79
31.89
29.82
29.66
29.54
29.33
27.47
27.28
26.83
22.64
14.01
COOH
COOH
1,7(Z)-Nonadecadiene-2,3-dicarboxylic acid (36)
200
150
100
50
0

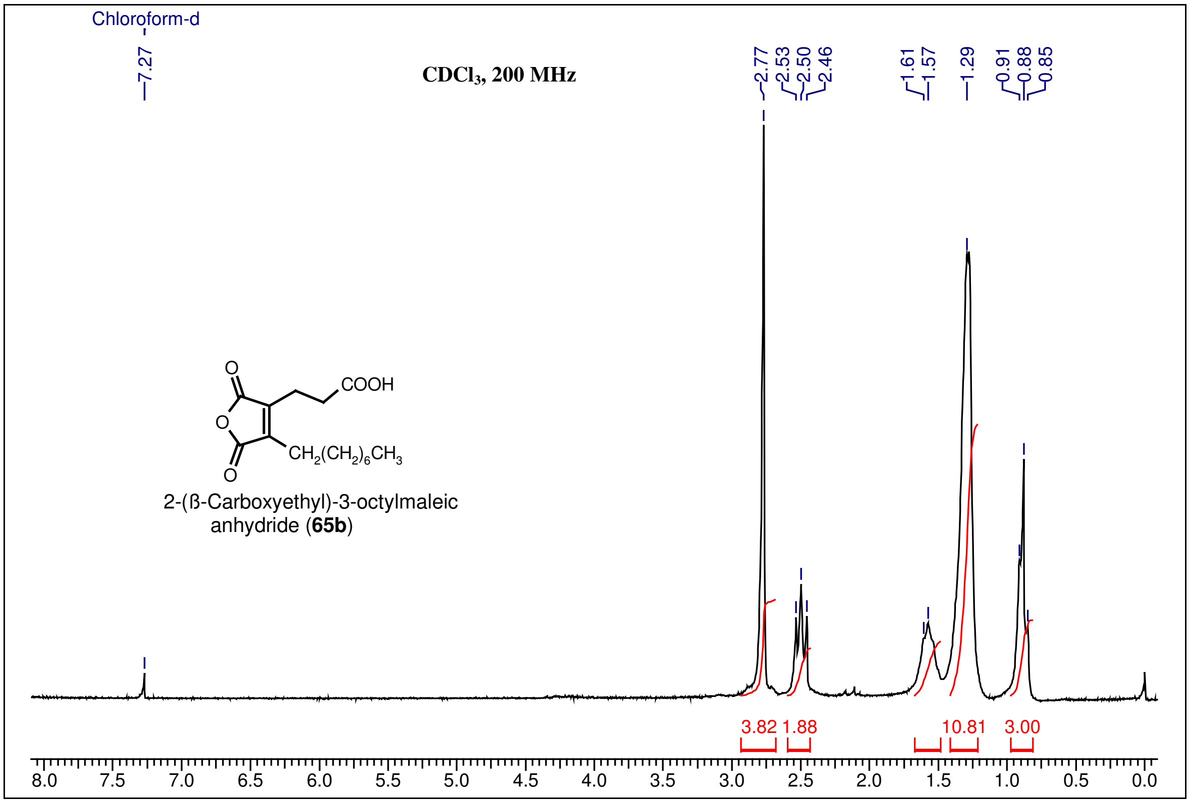

130.72
129.68
128.58
CDCl₃, 75 MHz
46.76
31.83
29.54
29.24
27.35
27.16
26.71
22.59
14.01
COOH
COOH
1,7(Z)-Nonadecadiene-2,3-dicarboxylic acid (36)
150
100
50


Chloroform-d
7.27
CDCl₃, 200 MHz
2.76
2.53
2.49
2.45
1.60
1.57
1.53
1.49
1.30
1.29
1.25
0.91
0.88
0.85
O
COOH
O
CH₂(CH₂)₄CH₃
O
2-(ß-Carboxyethyl)-3-hexylmaleic anhydride (**65a**)
3.57
1.88
2.07
6.76
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

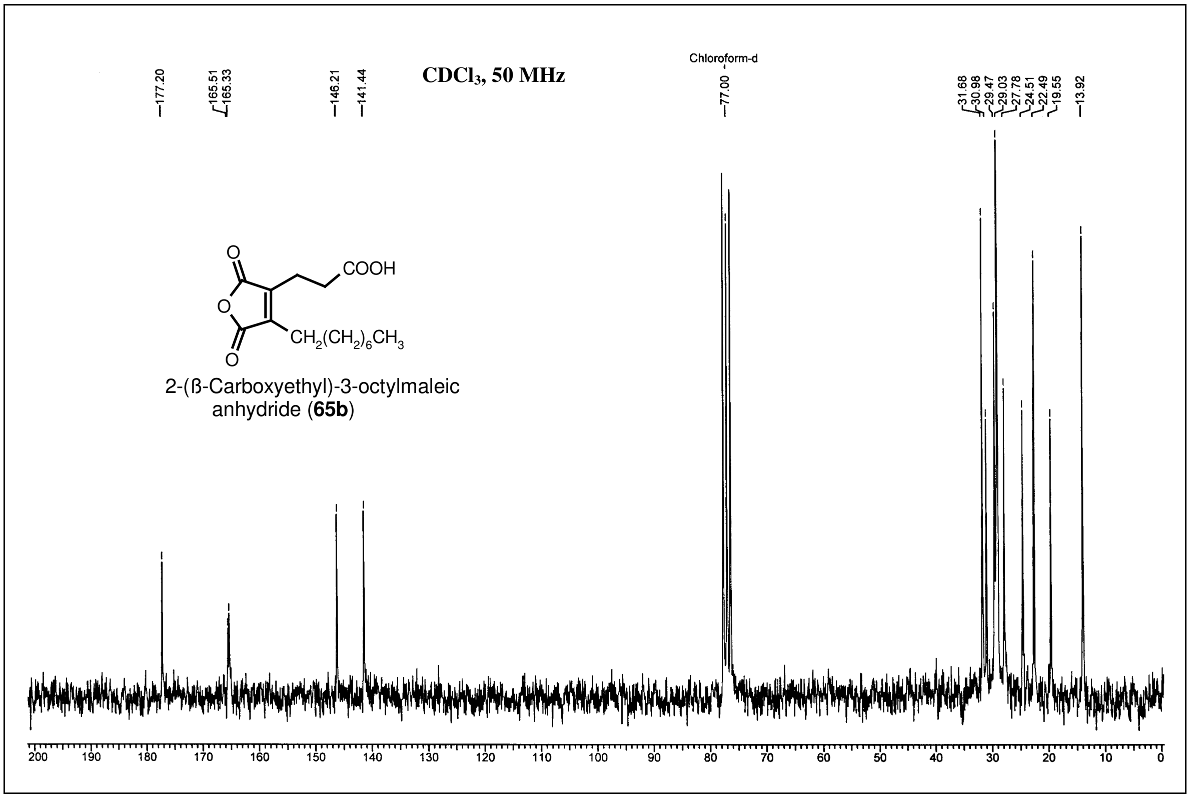

177.42
165.59
165.40
146.29
141.47
CDCl₃, 50 MHz
Chloroform-d
77.00
31.31
31.02
29.18
27.82
24.55
22.41
19.55
13.92
O
COOH
O
CH₂(CH₂)₄CH₃
O
2-(ß-Carboxyethyl)-3-hexylmaleic anhydride (**65a**)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

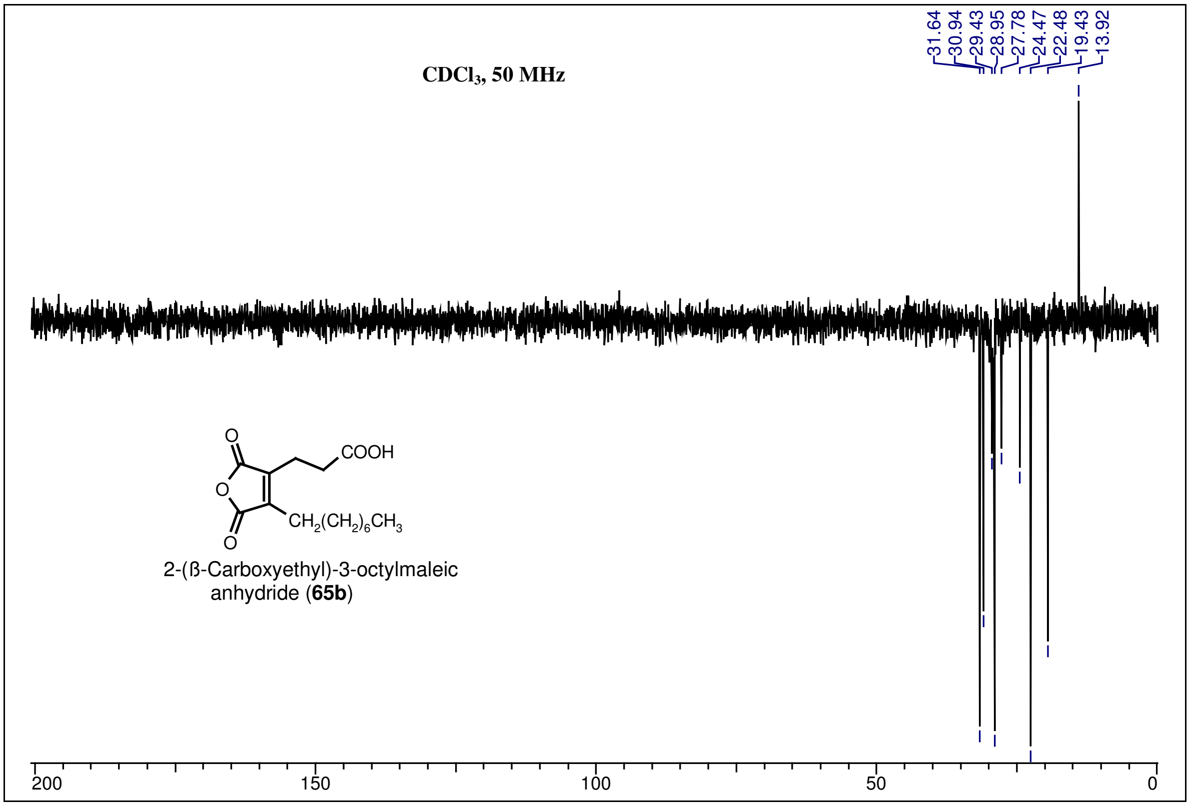


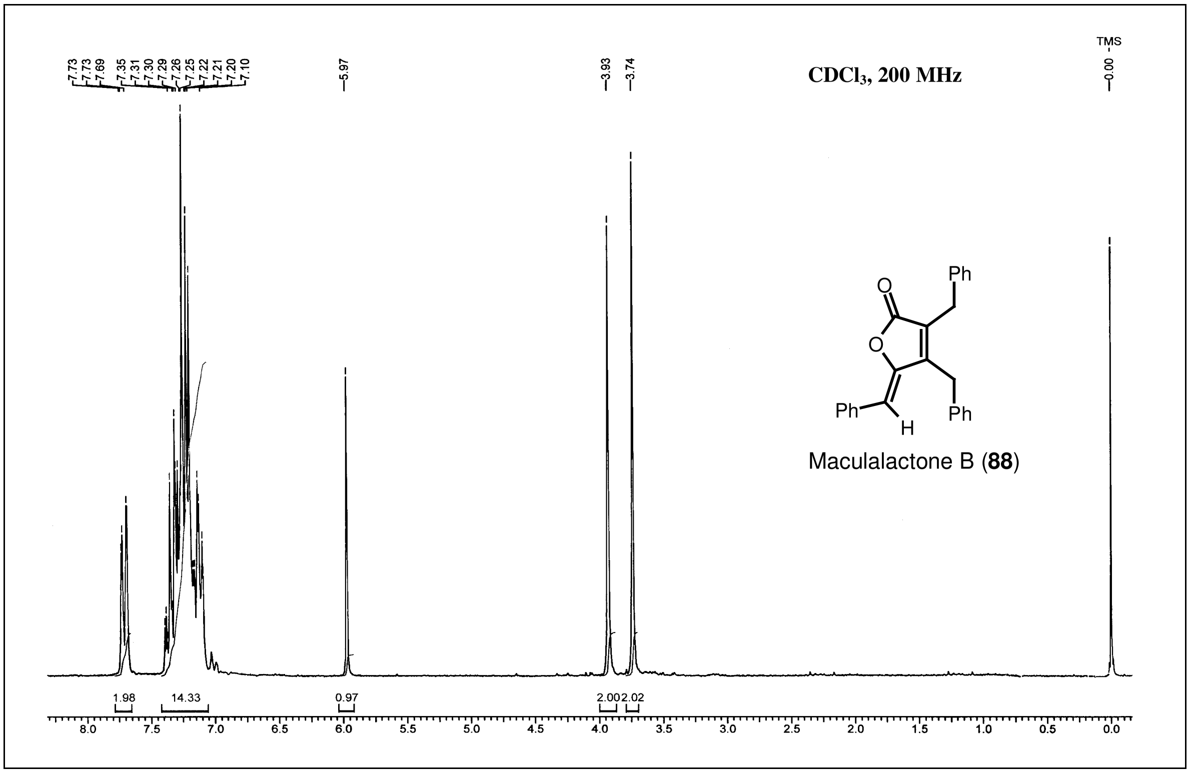
2-(β-Carboxyethyl)-3-hexylmaleic anhydride (**65a**)

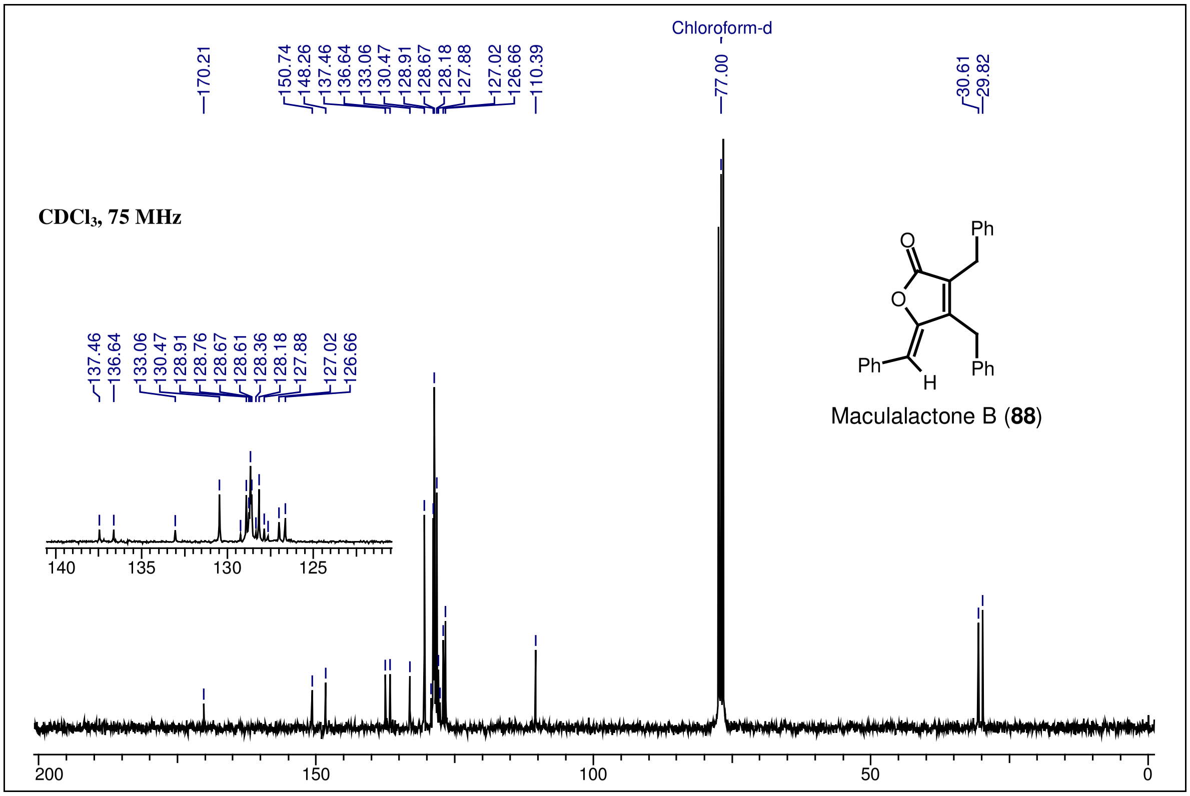


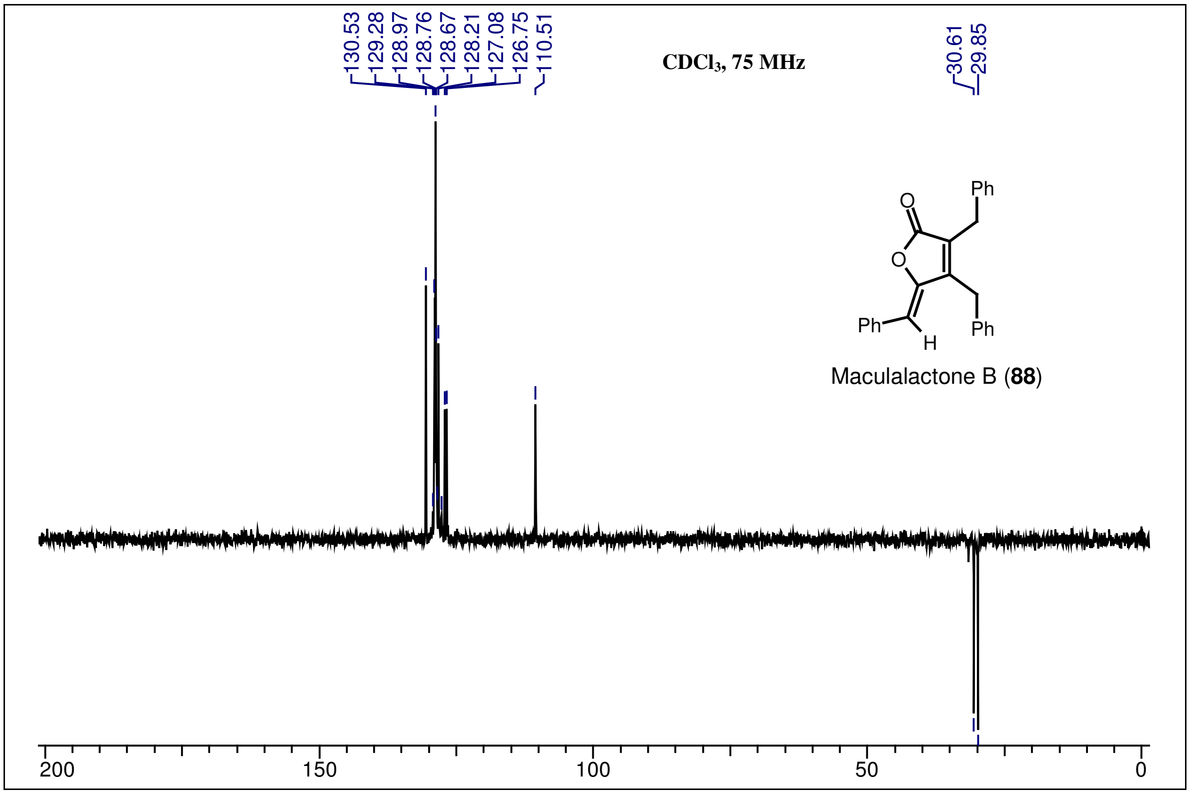
2-(β-Carboxyethyl)-3-octylmaleic anhydride (**65b**)


CDCl₃, 50 MHz
Chloroform-d
177.20
165.51
165.33
146.21
141.44
77.00
31.68
30.98
29.47
29.03
27.78
24.51
22.49
19.55
13.92
O
O
O
COOH
CH₂(CH₂)₆CH₃
2-(ß-Carboxyethyl)-3-octylmaleic anhydride (65b)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

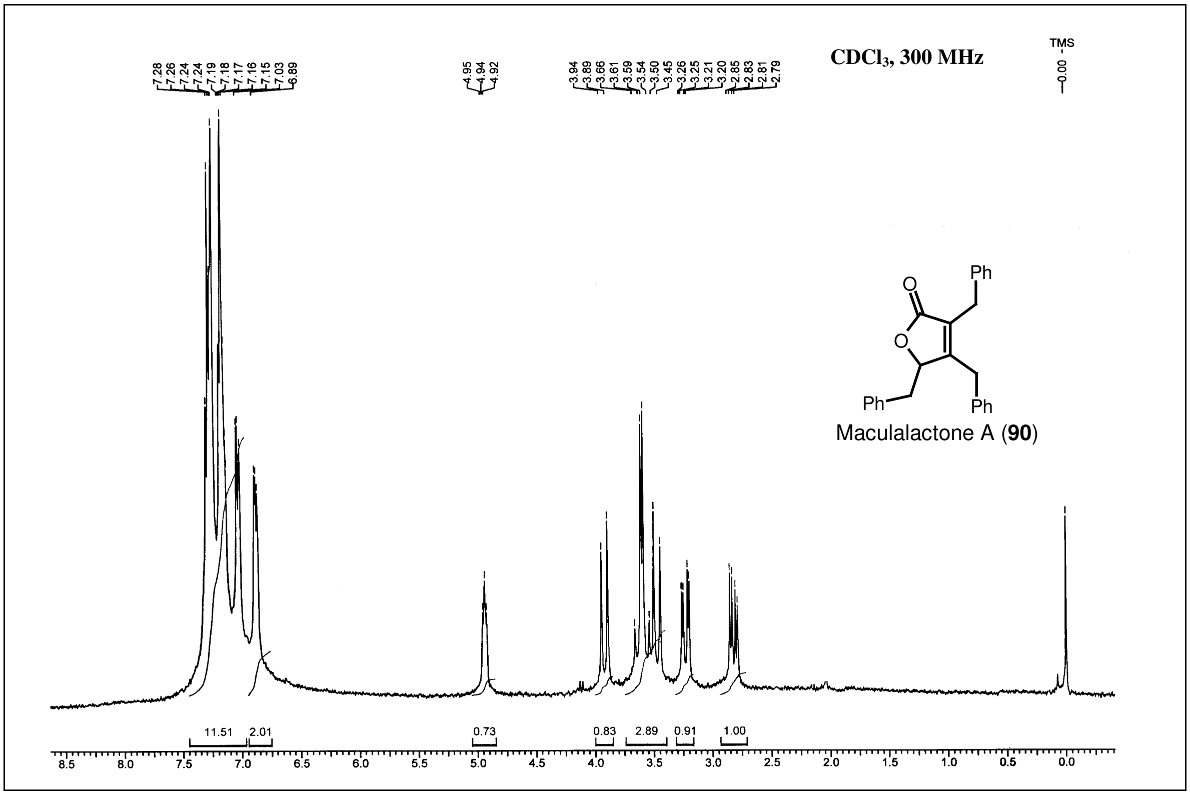

CDCl₃, 50 MHz
31.64
30.94
29.43
28.95
27.78
24.47
22.48
19.43
13.92
O
O
O
COOH
CH₂(CH₂)₆CH₃
2-(ß-Carboxyethyl)-3-octylmaleic anhydride (65b)
200
150
100
50
0


7.73
7.73
7.69
7.35
7.31
7.30
7.29
7.26
7.25
7.22
7.21
7.20
7.10
5.97
3.93
3.74
TMS
0.00
CDCl$_3$, 200 MHz
O
O
Ph
Ph
Ph
H
Maculalactone B (88)
1.98
14.33
0.97
2.00
2.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

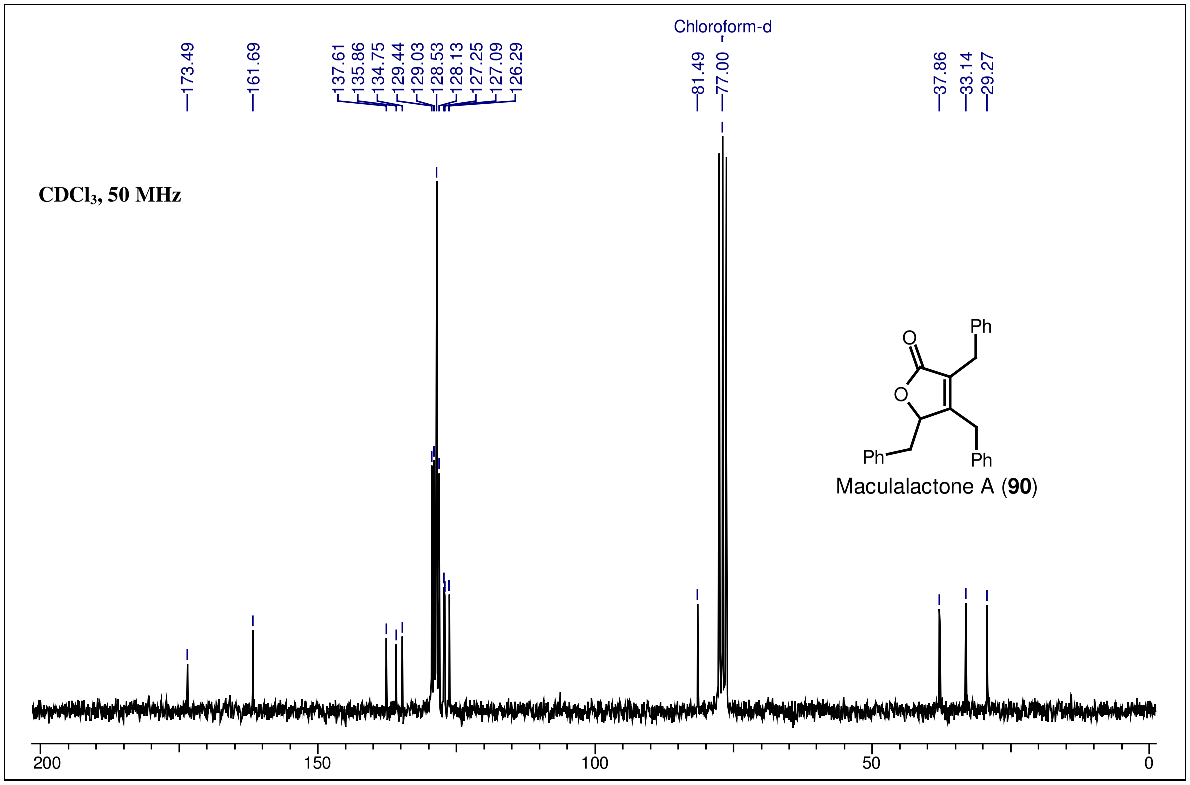

Chloroform-d
170.21
150.74
148.26
137.46
136.64
133.06
130.47
128.91
128.67
128.18
127.88
127.02
126.66
110.39
77.00
30.61
29.82
CDCl$_3$, 75 MHz
137.46
136.64
133.06
130.47
128.91
128.76
128.67
128.61
128.36
128.18
127.88
127.02
126.66
140
135
130
125
O
O
Ph
Ph
Ph
H
Maculalactone B (88)
200
150
100
50
0

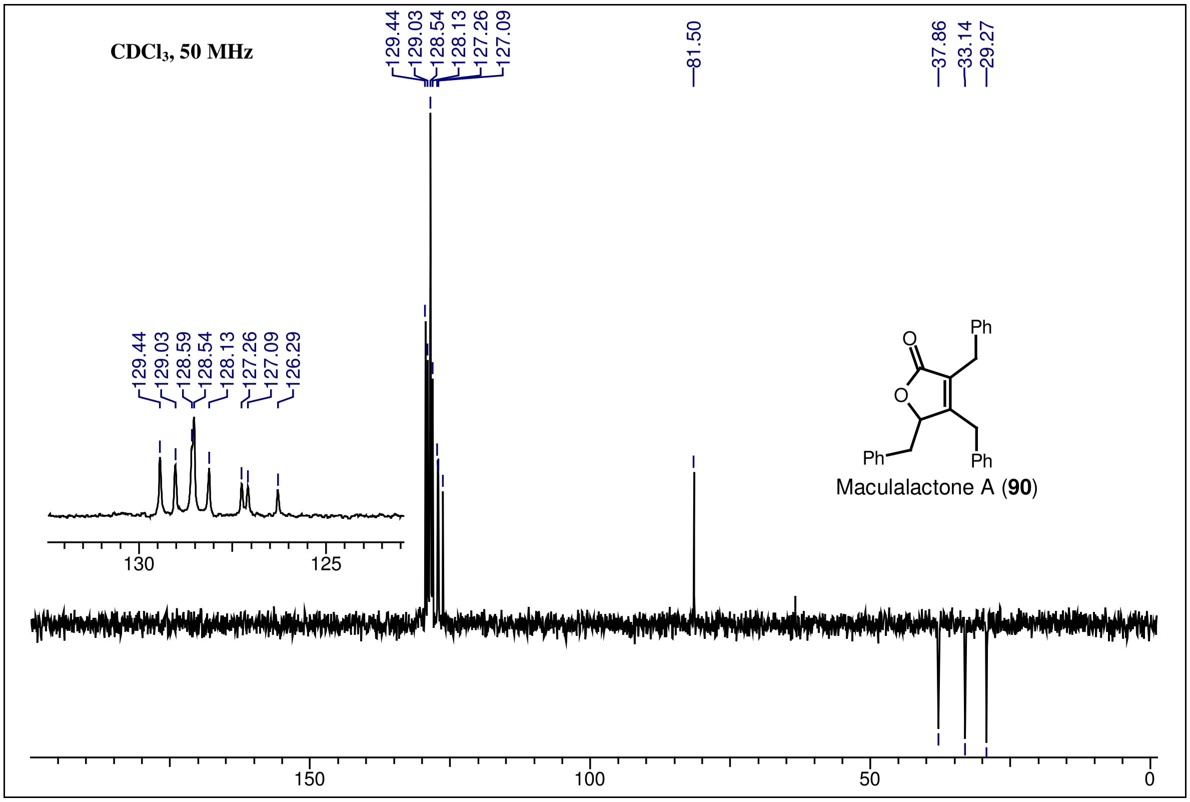


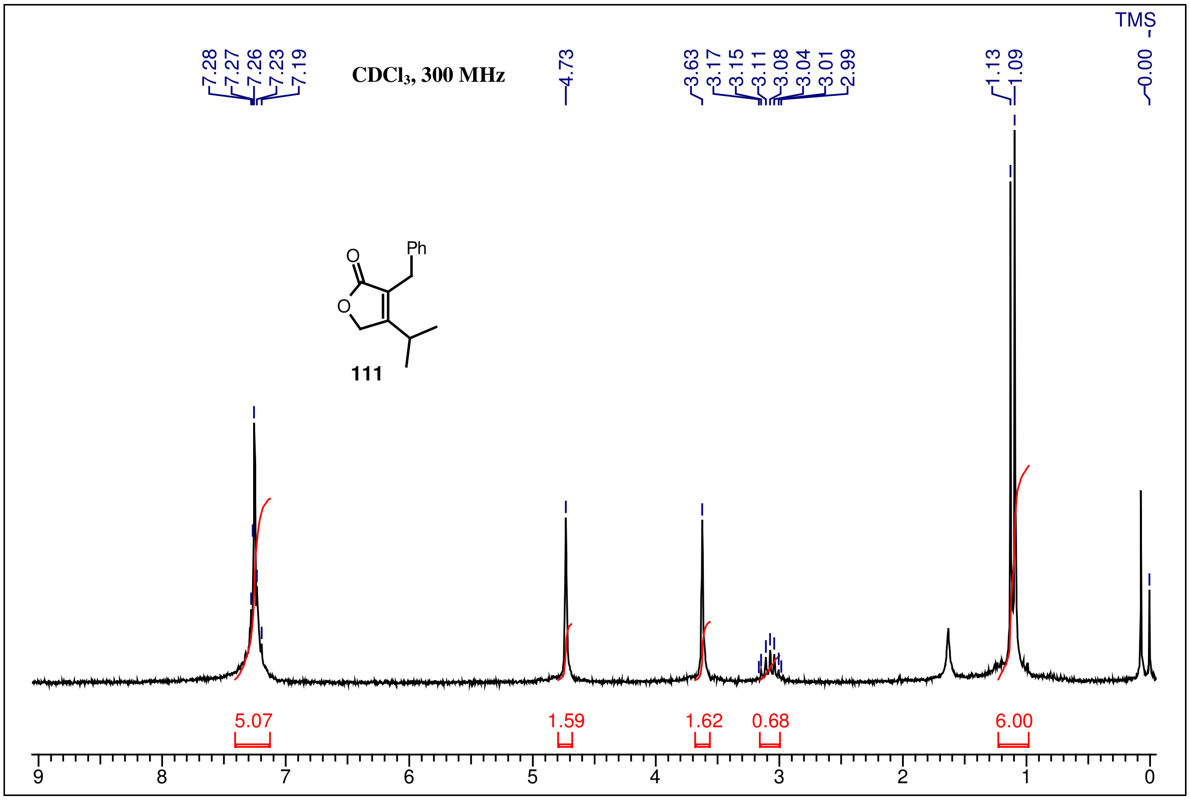
Maculalactone B (**88**)

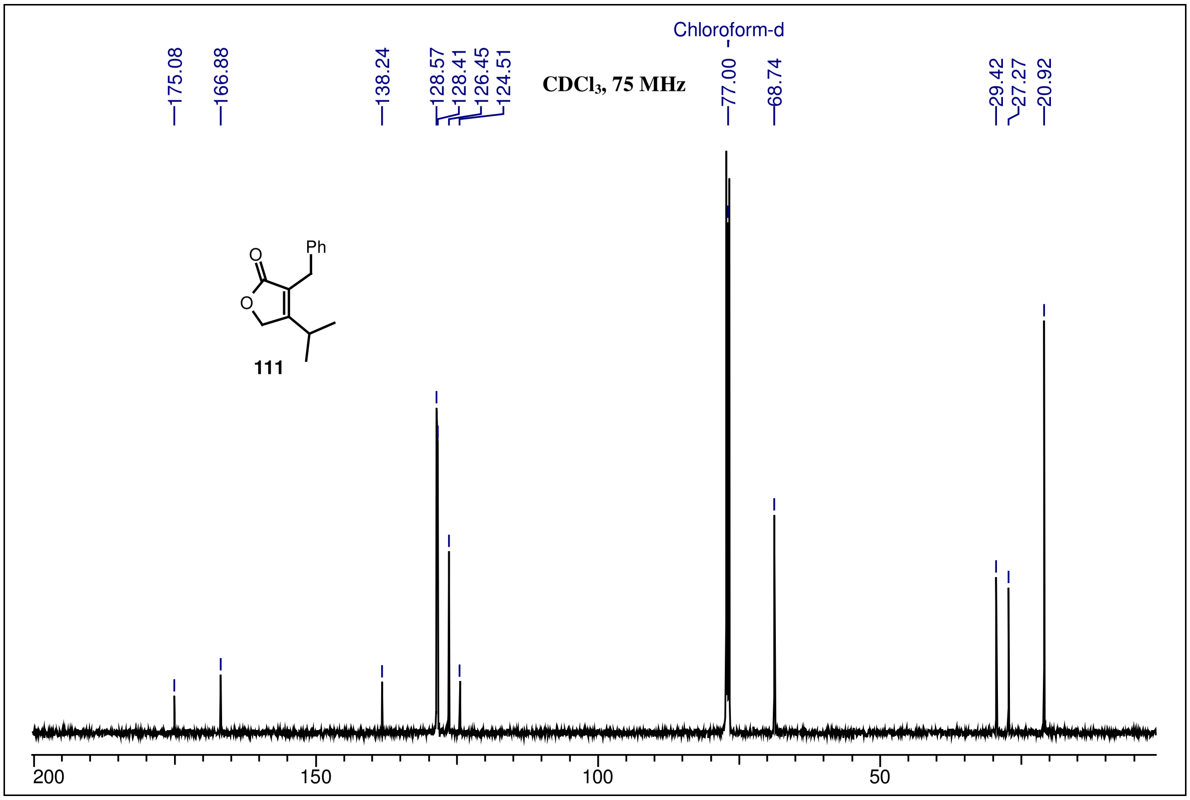


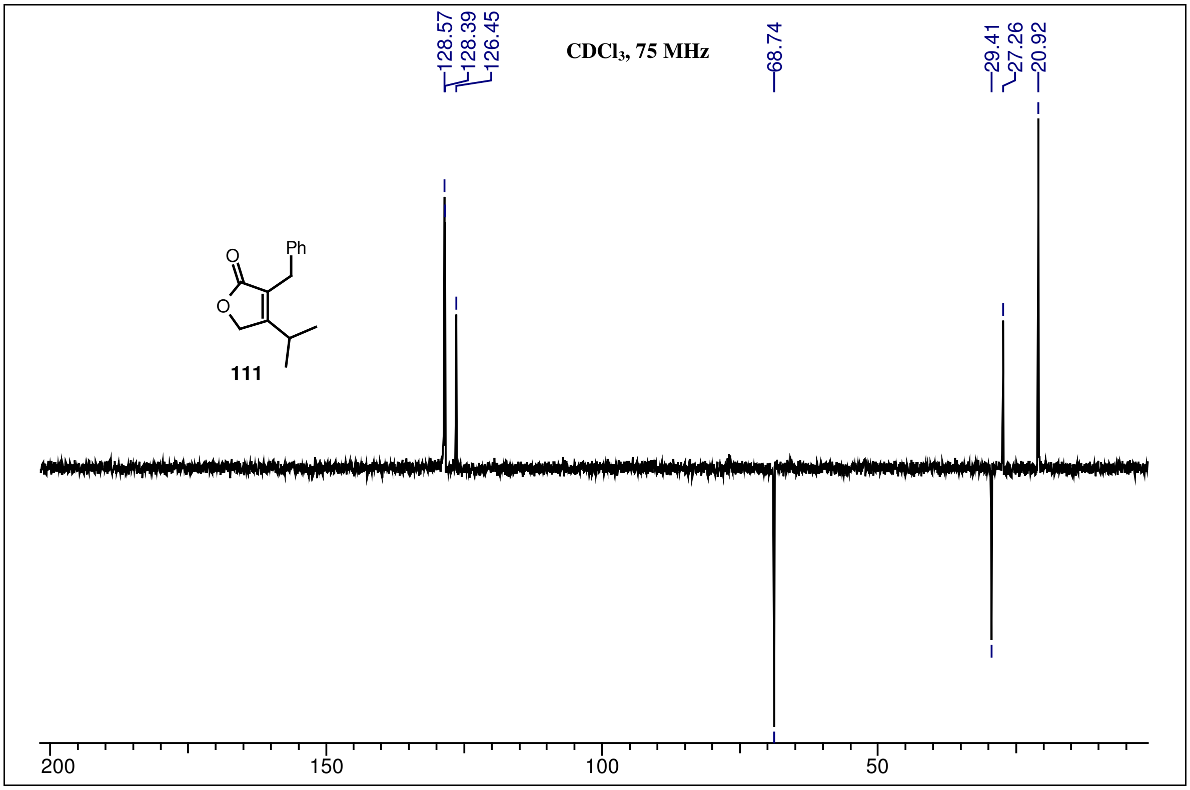
Maculalactone A (**90**)

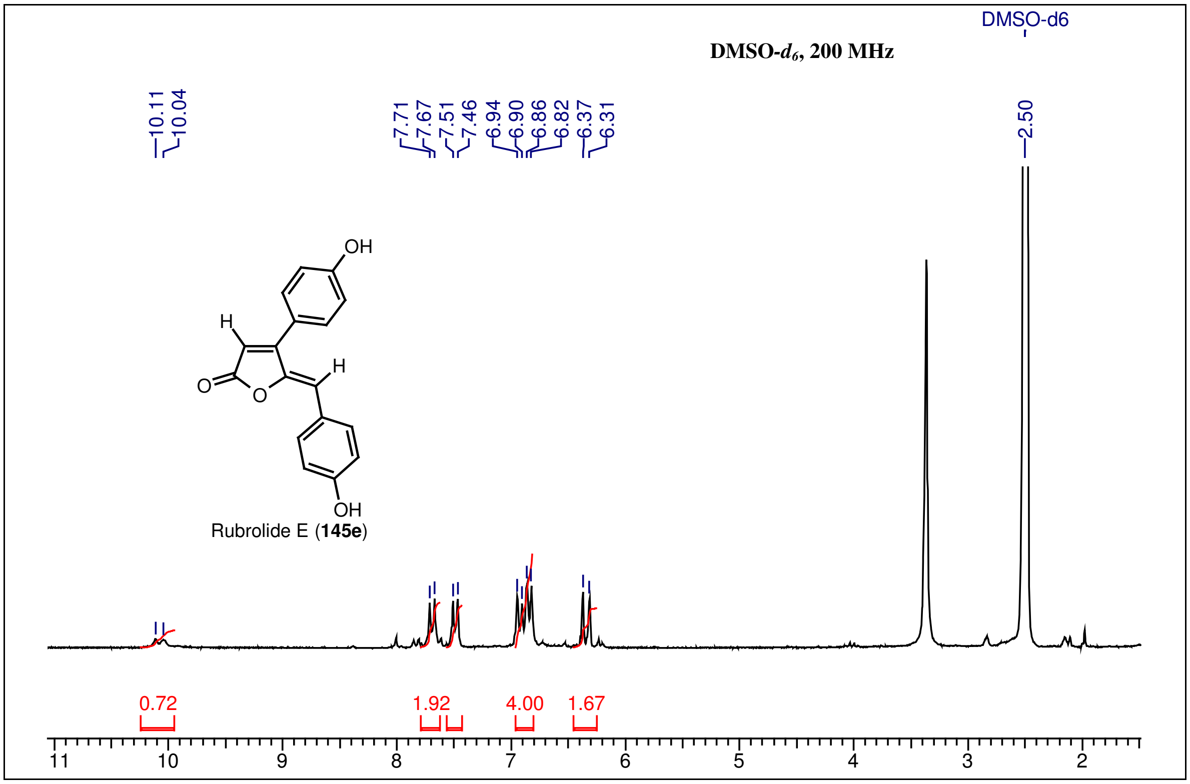

CDCl₃, 50 MHz
173.49
161.69
137.61
135.86
134.75
129.44
129.03
128.53
128.13
127.25
127.09
126.29
Chloroform-d
81.49
77.00
37.86
33.14
29.27
O
O
Ph
Ph
Ph
Maculalactone A (90)
200
150
100
50
0

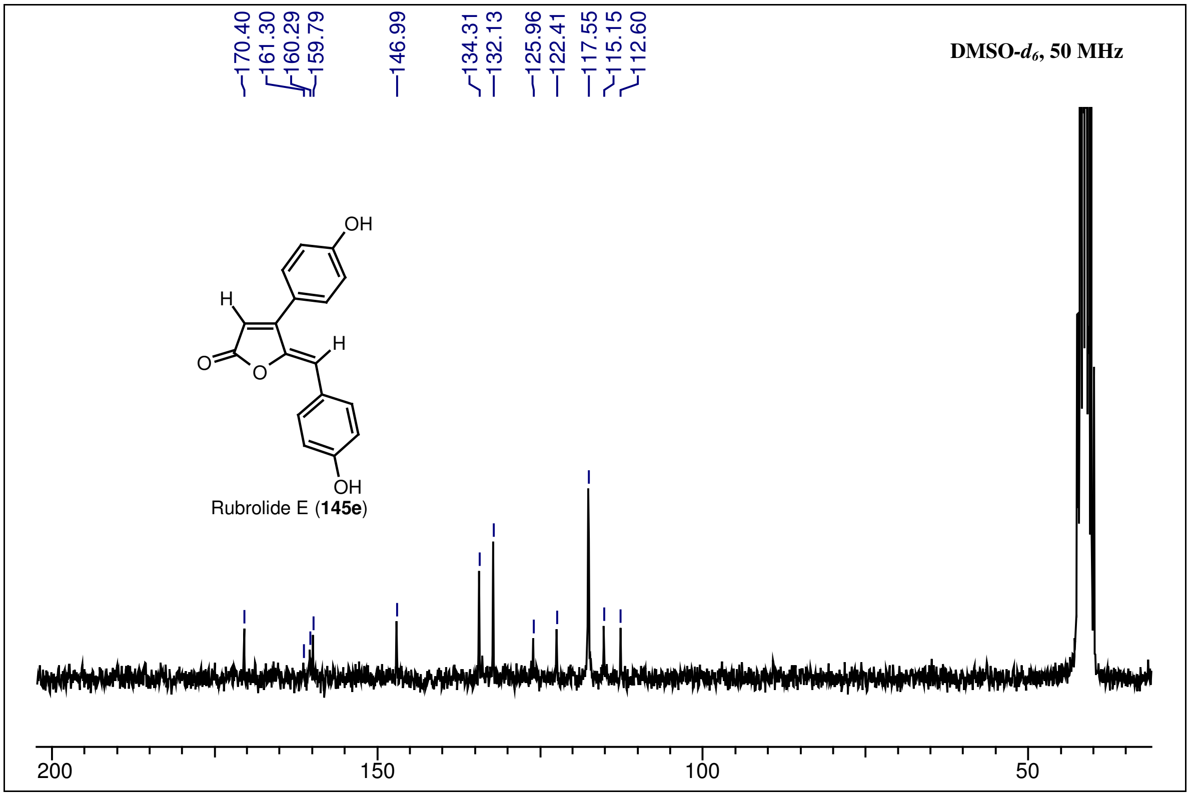

CDCl₃, 50 MHz
129.44
129.03
128.54
128.13
127.26
127.09
81.50
37.86
33.14
29.27
129.44
129.03
128.59
128.54
128.13
127.26
127.09
126.29
130
125
O
O
Ph
Ph
Ph
Maculalactone A (90)
150
100
50
0

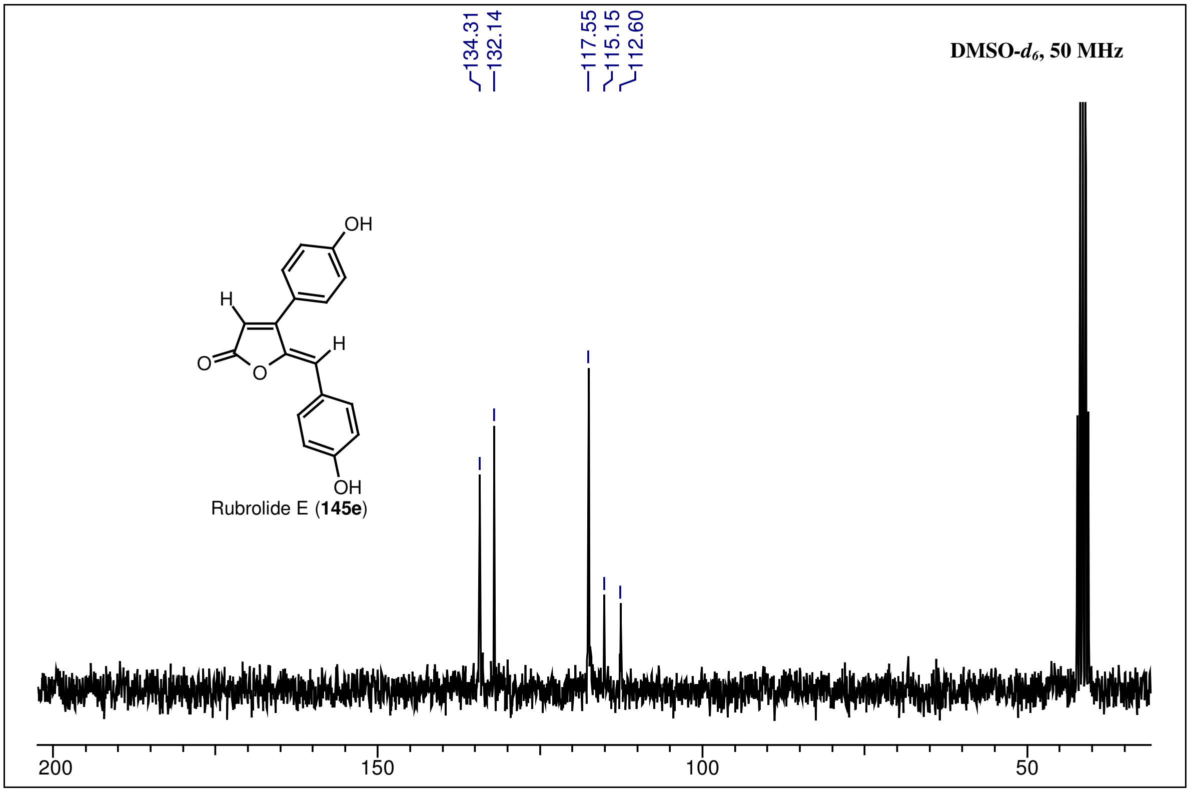

7.28
7.27
7.26
7.23
7.19
CDCl3, 300 MHz
4.73
3.63
3.17
3.15
3.11
3.08
3.04
3.01
2.99
1.13
1.09
TMS
0.00
Ph
O
O
111
5.07
1.59
1.62
0.68
6.00
9
8
7
6
5
4
3
2
1
0

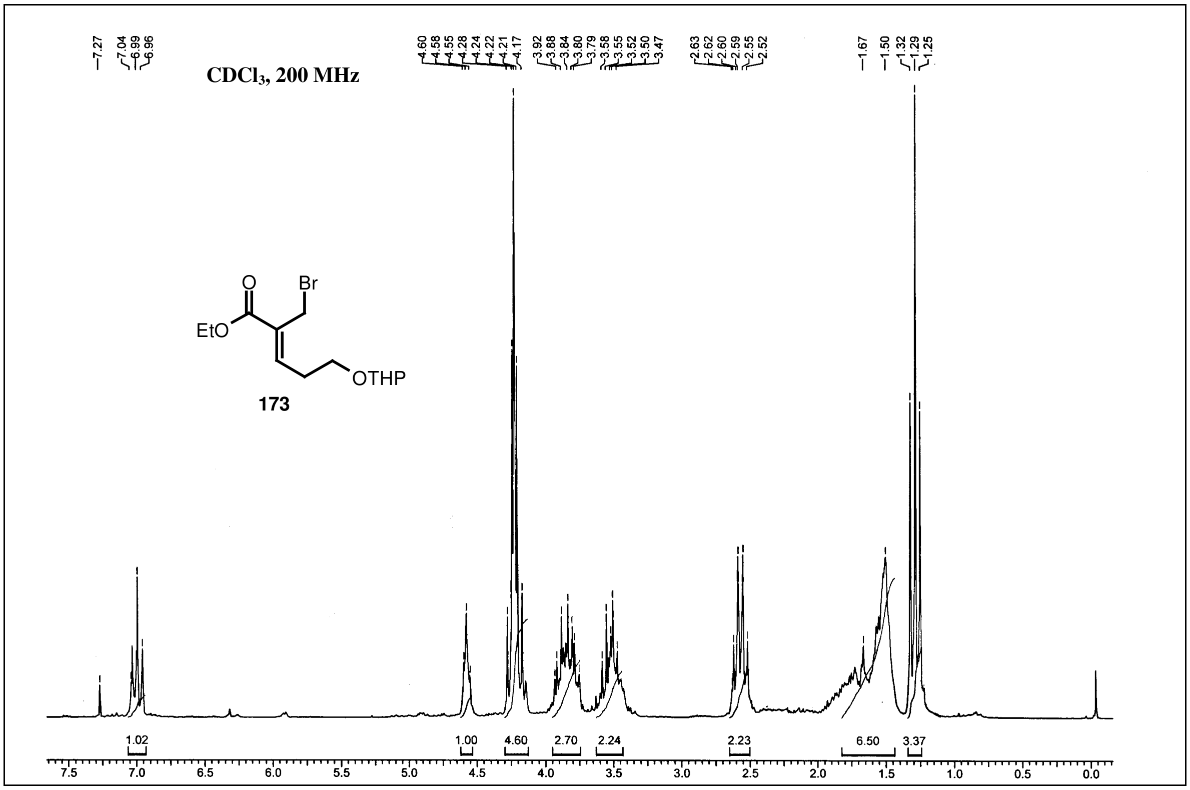

Chloroform-d
175.08
166.88
138.24
128.57
128.41
126.45
124.51
CDCl3, 75 MHz
77.00
68.74
29.42
27.27
20.92
Ph
O
O
111
200
150
100
50

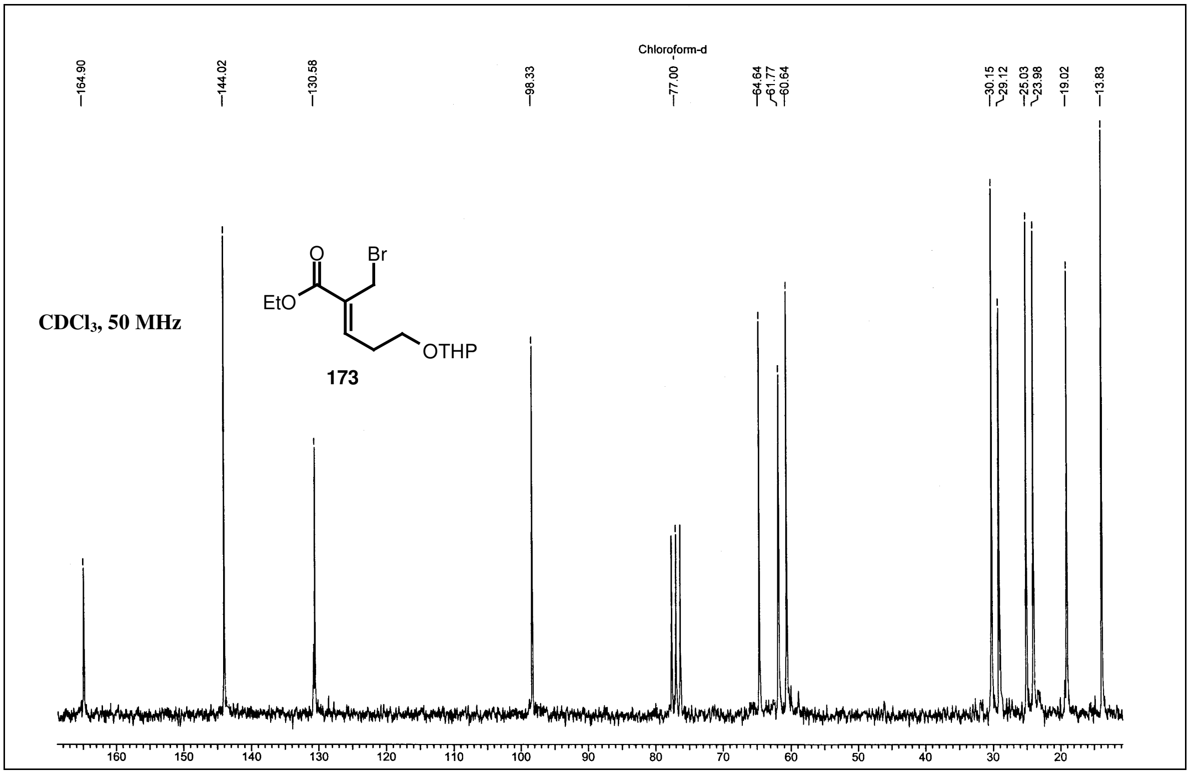

CDCl$_3$, 75 MHz
128.57
128.39
126.45
68.74
29.41
27.26
20.92
O
Ph
O
111
200
150
100
50

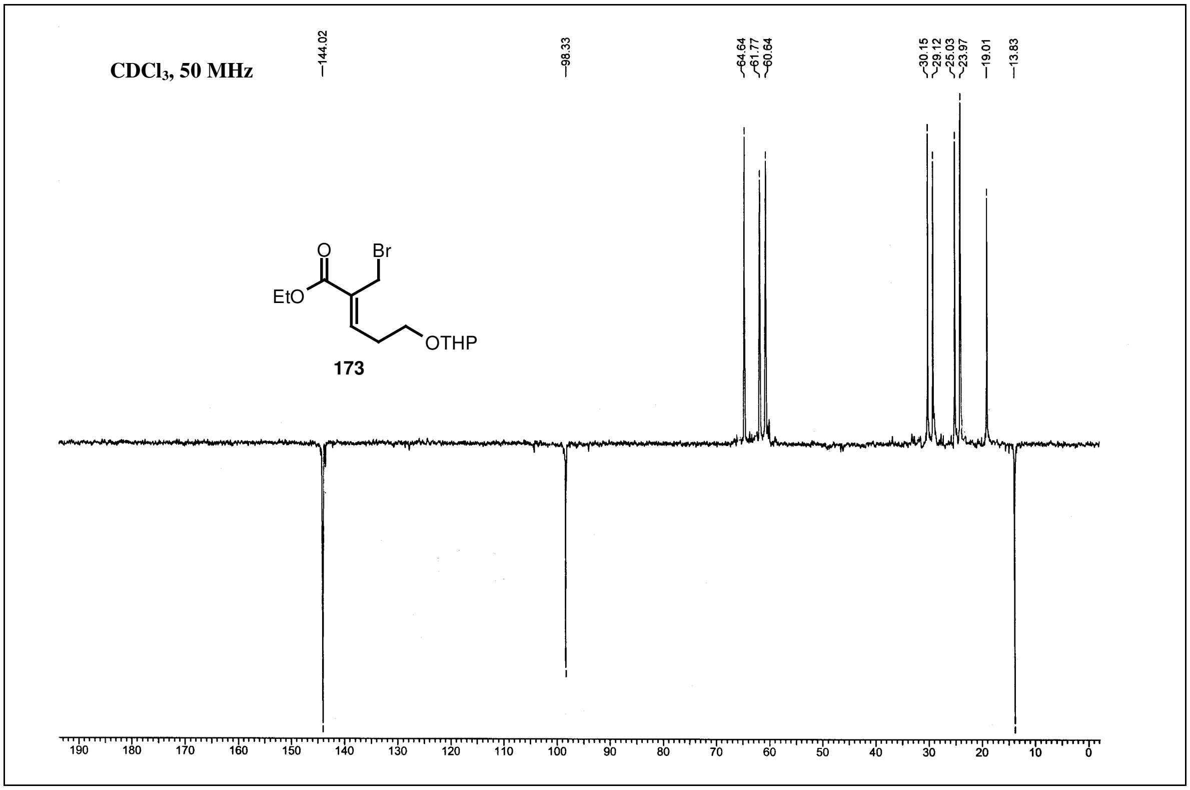

DMSO-d6
DMSO-d_6, 200 MHz
10.11
10.04
7.71
7.67
7.51
7.46
6.94
6.90
6.86
6.82
6.37
6.31
2.50
OH
H
H
O
O
OH
Rubrolide E (145e)
0.72
1.92
4.00
1.67
11
10
9
8
7
6
5
4
3
2


170.40
161.30
160.29
159.79
146.99
134.31
132.13
125.96
122.41
117.55
115.15
112.60
DMSO-d_6, 50 MHz
OH
H
H
O
O
OH
Rubrolide E (**145e**)
200
150
100
50

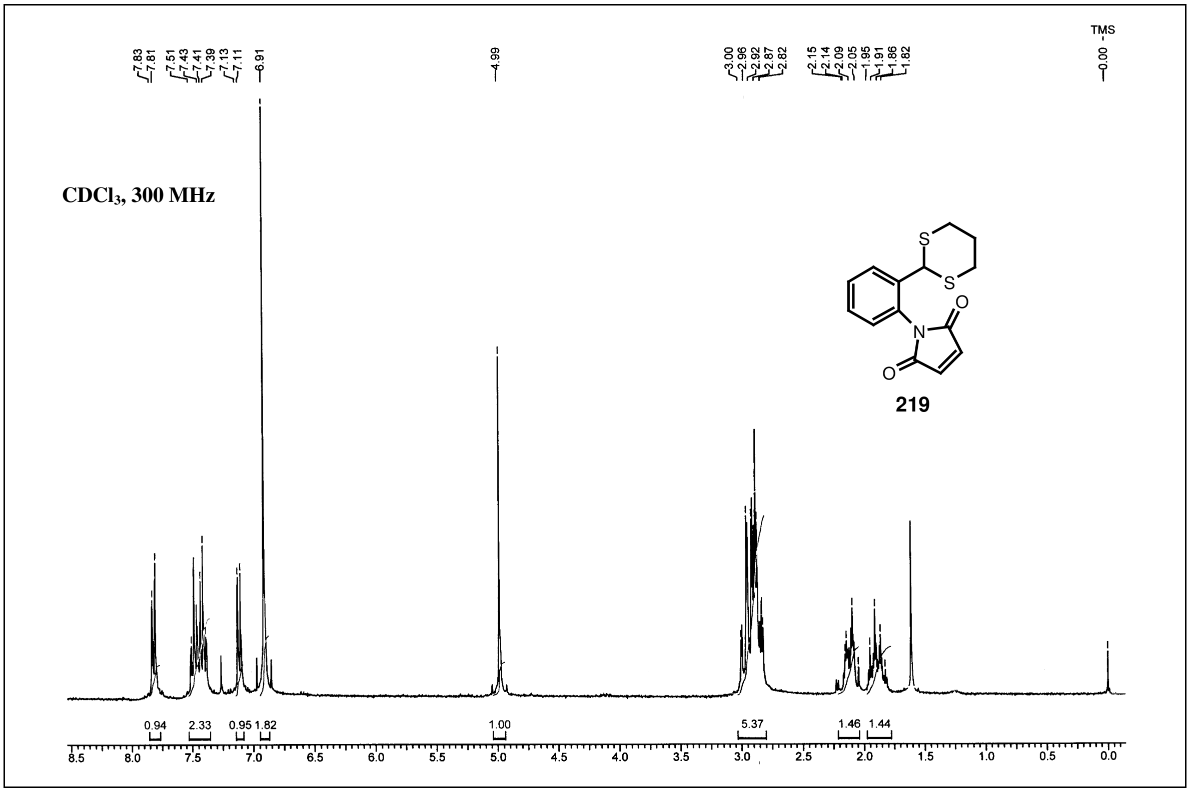

134.31
132.14
117.55
115.15
112.60
DMSO-d_6, 50 MHz
OH
H
H
O
O
OH
Rubrolide E (**145e**)
200
150
100
50


CDCl₃, 200 MHz
7.27
7.04
6.99
6.96
4.60
4.58
4.55
4.28
4.24
4.22
4.21
4.17
3.92
3.88
3.84
3.80
3.79
3.58
3.55
3.52
3.50
3.47
2.63
2.62
2.60
2.59
2.55
2.52
1.67
1.50
1.32
1.29
1.25
O
Br
EtO
OTHP
173
1.02
1.00
4.60
2.70
2.24
2.23
6.50
3.37
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

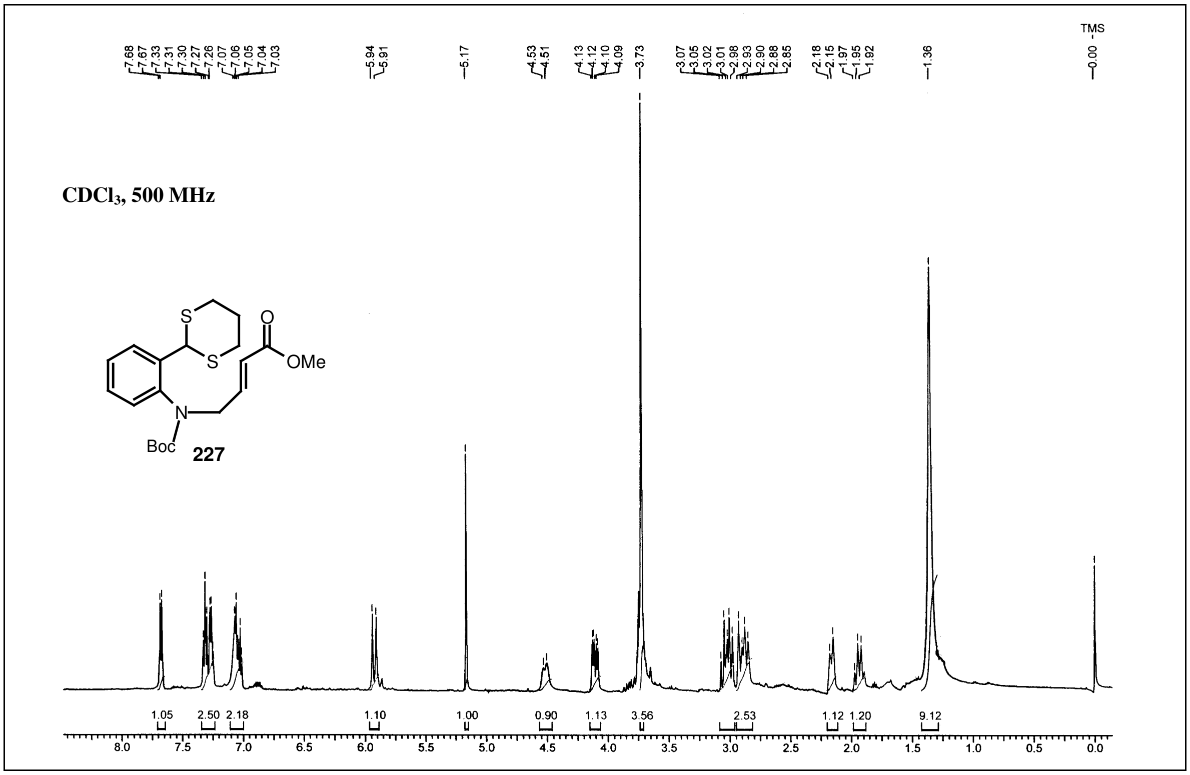

Chloroform-d
164.90
144.02
130.58
98.33
77.00
64.64
61.77
60.64
30.15
29.12
25.03
23.98
19.02
13.83
CDCl₃, 50 MHz
O
Br
EtO
OTHP
173
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

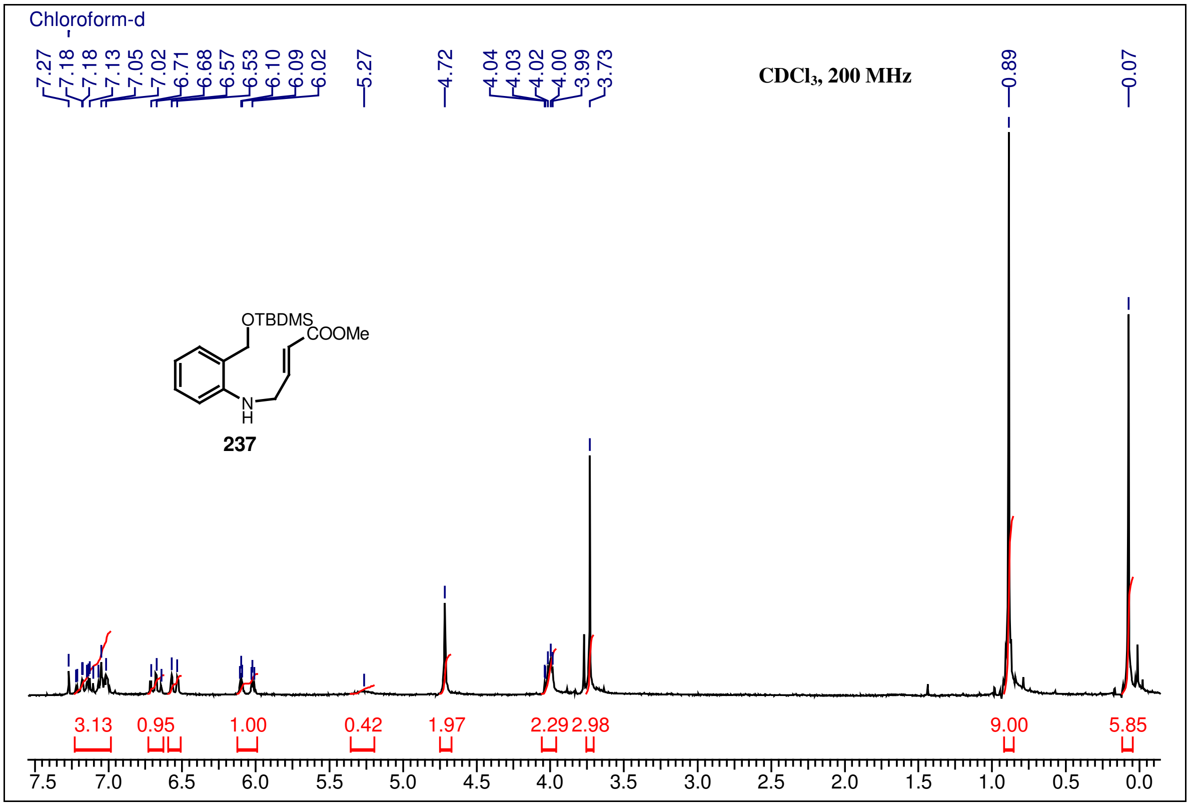

CDCl₃, 50 MHz
144.02
98.33
64.64
61.77
60.64
30.15
29.12
25.03
23.97
19.01
13.83
O
Br
EtO
OTHP
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

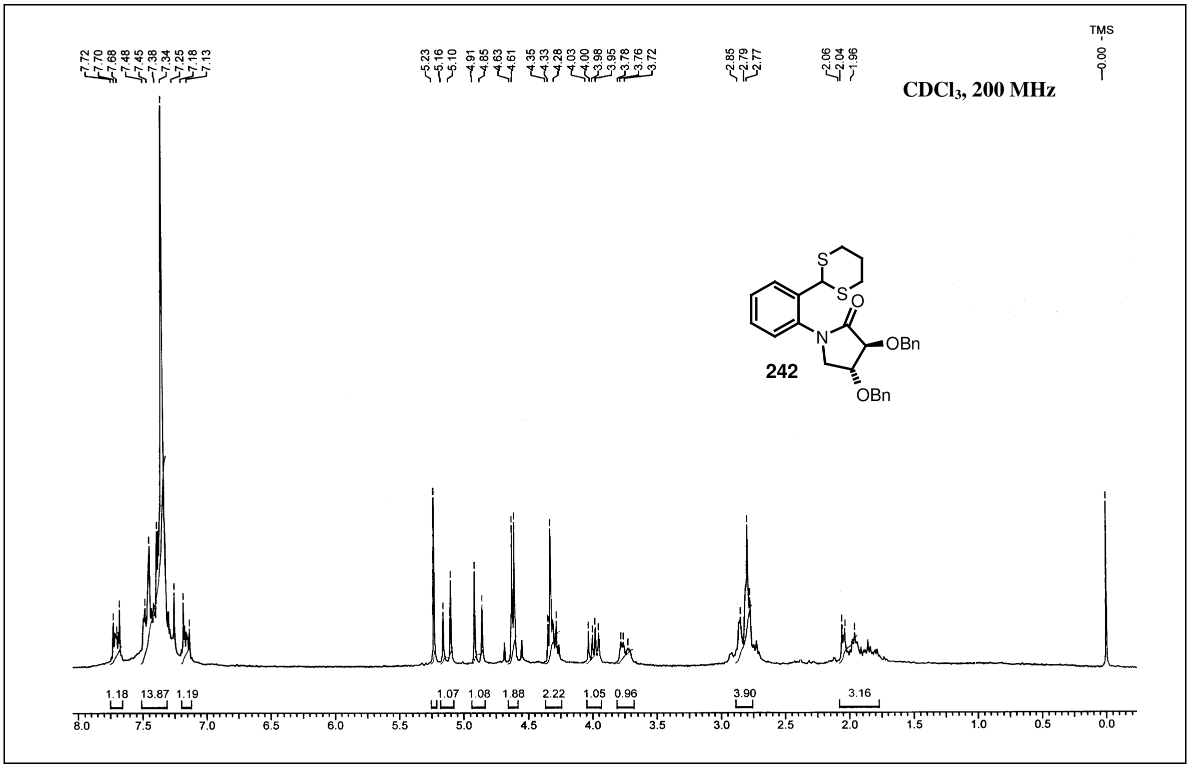
173


CDCl₃, 300 MHz
7.83
7.81
7.51
7.43
7.41
7.39
7.13
7.11
6.91
4.99
3.00
2.96
2.92
2.87
2.82
2.15
2.14
2.09
2.05
1.95
1.91
1.86
1.82
TMS
0.00
S
S
N
O
O
0.94
2.33
0.95
1.82
1.00
5.37
1.46
1.44
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

219


7.68
7.67
7.33
7.31
7.30
7.27
7.26
7.07
7.06
7.05
7.04
7.03
5.94
5.91
5.17
4.53
4.51
4.13
4.12
4.10
4.09
3.73
3.07
3.05
3.02
3.01
2.98
2.93
2.90
2.88
2.85
2.18
2.15
1.97
1.95
1.92
1.36
TMS
0.00
CDCl₃, 500 MHz
S
S
O
OMe
N
Boc
227
1.05
2.50
2.18
1.10
1.00
0.90
1.13
3.56
2.53
1.12
1.20
9.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
7.27
7.18
7.18
7.13
7.05
7.02
6.71
6.68
6.57
6.53
6.10
6.09
6.02
5.27
4.72
4.04
4.03
4.02
4.00
3.99
3.73
CDCl₃, 200 MHz
0.89
0.07
OTBDMS
COOMe
N
H
237
3.13
0.95
1.00
0.42
1.97
2.29
2.98
9.00
5.85
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



In the present chapter, we have provided selected ^{1}H NMR (13) and ^{13}C NMR (9) spectra along with DEPT (9) spectra. The structures and structure numbers of compounds from Chapter Two have been depicted on all the spectra. The procedures for preparation and tabulated spectral data for all these compounds have been described in the experimental parts of Section A-D in Chapter Two.