Chapter I
Synthetic Studies towards Quassinoids
Introduction
Organic synthesis can be classified into two broad categories: (i) Natural product synthesis and (ii) synthesis of non-natural compounds. The distinction between the two has been very clearly spelt out by Professor D. J. Cram in one of his articles. He observed: "Synthetic organic chemists fall into two groups: those who prepare old naturally occurring compounds and those who prepare new compounds. The synthetic targets of the former group are provided by the evolutionary chemistry of Nature. The synthetic targets of the latter group are designed by the investigator". Synthetic organic chemists all over the world are pursuing the synthesis of both classes of compounds very actively. In the first category, some of the notable achievements in recent times include the synthesis of erythromycin, palytoxin, calicheamicin, and taxol. On the other hand, some of the interesting non-natural products that have been synthesized over the past decade are pentaprismane, dodecahedrane and a host of new supramolecules like the dendritic hydrocarbon C_{n}H_{m}. All these have been made possible by the availability of sophisticated synthetic, analytical, spectroscopic and chromatographic techniques. The presence of computers has given a new dimension to synthetic planning.

Among the natural products, synthesis of steroids, alkaloids, prostaglandins and terpenes have been the subject of several investigations. In recent years, compounds having diverse physiological and pharmacological activity have received
considerable attention from synthetic chemists worldwide. Some typical examples are the ene-diyne antibiotics\textsuperscript{10} \textit{taxol} and imununosuppresants such as \textit{rapamycin} and \textit{FK-506}.

Quassinoids, like many other group of naturally occurring compounds, have also been the subject of many synthetic endeavours.

The quassinoids are a broad group of bitter principles isolated from the botanical family of \textit{Simaroubaceae}. Extracts from the \textit{Simaroubaceae} plants have been used in the folk medicine of Asia and Africa for centuries in the treatment of various ailments. Although the structure of the first quassinoid quassin (1) was established in 1962\textsuperscript{14}, there was no systematic investigation of these substances before the discovery in 1970 that halocanthone, a member of this family, possessed antineoplastic activity. Later, in 1973, Kupchan reported an investigation of \textit{Brueca antidysenterica}. Eight new quassinoids were isolated and several of them were found to have significant antitumour and antileukemic activity. Kupchan's disclosure about the antineoplastic activity of bruceantin 2 generated
considerable interest in quassinoids. A brief discussion of the biological activity of quassinoids is presented in the following paragraphs.

![Structures of Bruceantin (2), Simalikalactone D (3), and Bruceantinol (4)]

Most of the quassinoids are biologically active. Bruceantin (2), simalikalactone D (3) and Bruceantinol (4) are most active against P - 388 lymphocytic leukemia. Bruceantin shows activity over a wide dose range and, in addition, is active against solid tumours. It was also found that Bruceantin was active against L - 1210 lymphoid leukemia, Lewis lung carcinoma and B - 16 melanocarcinoma, resulting in it being selected for clinical trials by the US National Cancer Institute.

Structure - activity studies reveal some of the structural requirements essential for optimal antineoplastic activity. They are a) ring A with either an \( \alpha,\beta \)-unsaturated ketol at positions C1 and C2 or a diosphenol group at positions C2 and
C3 (structures a and b of chart 1) b) ring C with an epoxymethano bridge between C8 and C11 or between C8 and C13 (structures c and d) and c) a free hydroxyl group in ring C at C12 in addition to α-ester group at C15.

Among other pharmacological properties, the growth of chloroquine resistant blood parasite *Plasmodium falciparum* was markedly inhibited *in vitro* by certain quassinoids. Bruceantin (2) and simalikalactone (3) and some other quassinoids displayed activity against the parasite *Entamoeba histolytica* in Gillin's and Reiner's extensive study.

The highly oxygenated carbon skeleton and wide ranging biological activity of quassinoids have attracted the attention of synthetic chemists in a big way. As a result, total syntheses of tetracyclic quassinoids like quassin, castalanolide, amarolide and kleineanone have been achieved. Besides this, there was also a great interest in the synthesis of pentacyclic quassinoids like bruceantin. Bruceantin has a complex structure with several different functional groups and has ten asymmetric centres. Despite its failure in phase II of the clinical trials at the National Cancer Institute, bruceantin still attracts intensive synthetic efforts from chemists all over the world.
To date, only two total syntheses of bruceantin have been achieved, despite intensive efforts by several research groups. A short summary of the efforts that culminated in the total synthesis of bruceantin is presented in the following paragraphs.

In a sustained effort lasting several steps, Murae and co-workers achieved a relay total synthesis of bruceantin. Based on the previous experience gained during the synthesis of a pentacyclic intermediate, compound 5 was chosen as the starting material for the total synthesis.

Reagents and conditions: a) thexylborane, THF, 0; NaOH, H₂O₂; b) MOMCl, (iPr)₂NEt, CH₂Cl₂, 0°; c) CrO₃Py, CH₂Cl₂; d) Li, NH₃.

Compound 5 was transformed into the tetracyclic ketone 6 by routine functional group manipulations. Selective reduction
of the ketone 6 to the desired 1α alcohol 7 was achieved under chelation controlled conditions employing 1 eq. of LiBr along with the reducing agent LiEtBH.

Efforts were then directed to the introduction of C11 - C12 diol unit via the C11 - C12 double bond. For this, alcohol 7 was converted to the ketone 8 in 3 steps. The tosylhydrazone of ketone 8 when subjected to the Shapiro reaction afforded the hydroxy olefin 9 in 92% yield.

**Reagents and conditions:** a) AcO, DMAP, Py, CHCl3; b) n-BuNF, THF, 50; c) CrO2Py.

The C11 - C12 olefin was osmylated after protecting the hydroxy group in 9 as trichloroethylcarbonate (TCC) to give the
diol 10. Next, efforts were concentrated on building the $S$ lactone moiety. To achieve this, the diol 10 was protected as its diacetate and the methoxymethyl protecting groups were cleaved using ethanedithiol and BF $\cdot$EtO. This resulted in concomittant transthioetalization of the C3 carbonyl group. The thioketal 11 was then converted to the pentacyclic lactone 12 in several steps.

Py, THF, NaHSO$_3$; c) Ac$_2$O, DMAP, CH$_2$Cl; d) (CH$_2$SH)$_2$, BF$_3$EtO, CH$_2$Cl$_2$, 0°->rt.

Reagents and conditions: a) NBS, CaCO$_3$, H$_2$O-CH$_3$CN; b) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -78°->rt; c) CrO$_3$, H$_2$SO$_4$, acetone d) CH$_2$N$_2$, Et$_2$O, EtOAc, 0°; e) (CH$_2$OH)$_2$, TsOH, C$_6$H$_5$CO$_2$H, reflux; f) Zn-AcOH-THF (1:9), Py.
Inversion of the hydroxy group at C11 in 12 was brought about by routine reactions. Functionalization of the A ring was taken up next. This was accomplished in a 5 step sequence from lactone 13. Lactone 14 thus obtained was converted to the C15-C16 enol ether 15 by reducing the lactone carbonyl selectively with NaBH4 and dehydrating the lactol with POCl3. This enol ether 15 was converted to α-hydroxy lactol 16 in one step by epoxidation with MCPBA and in situ ring opening of the reactive 15,16 epoxide.
with water. The 3,4 epoxide was also obtained as an inseparable by-product in this reaction. The lactol 16 was oxidized with silver oxide to furnish the \( \alpha \)-hydroxy lactone 17. Total synthesis of bruceantin was achieved by acylating the C15 hydroxyl group in 17 with 3,4-dimethyl-2-pentenoic acid and deacetylating the product, 11,12-di-O-acetyl-3-O-(tert.butyldimethylsilyloxy)-bruceantin.

Reagents and conditions: a) \( \text{NaBH}_4, \text{EtOH, CH}_2\text{Cl}_2, 0 \); b) \( \text{POCl}_3, \text{Py, 100°} \); c) \( \text{mCPBA, NaHCO}_3, \text{CH}_2\text{Cl}_2-\text{H}_2\text{O,d) Ag}_2\text{O, CH}_3\text{CN,reflux; e) DCC, DMAP, (Me)}_2\text{CH(Me)}_2\text{C=CHCOOH, CH}_2\text{Cl}_2; f) 3\text{H}_2\text{SO}_4, \text{MeOH (1:1), reflux.} \)

Grieco's synthesis starts from tricyclic ketone 18, which was recognized by many groups as the logical starting point for the synthesis of bruceantin. Compound 18 was trans-
formed into an activated tricyclic \( \alpha, \beta \)-unsaturated ketoester 19 by routine reactions.

Reagents and conditions: a) \(2\text{-methoxypropene}, \ PPTS, \ 0\)  
b) \(\text{NaH}, \ (\text{MeO})_2\text{CO}, \ \text{MeOH(cat.}, \ \text{THF, reflux; c) NaH, PhSeCl, THF, }0^{\circ}; \  \)  
d) \(\text{mCPBA, THF, }-78^{\circ}-0^{\circ}\).

\(\beta\)-Alkylation of the \(\alpha, \beta\)-unsaturated ketoester 19 was achieved with excess of 1-methoxy-1-(tert-butyl(dimethyl)silyloxy)ethylene at 40\(^{\circ}\)in the presence of 1M LiClO -1,2-dimethoxyethane as promoter when other methods failed to give the desired results. This was followed by deprotection of the hydroxyl group to give 20. The C8 - C13 epoxymethano bridge was constructed based on a previous observation made in connection with quassinoid model studies. Thus, on bromination (NBS,THF,0 ) 20 gave bromosilylated hemiketal 21 which upon heating (DMF, collidine, 130\(^{\circ}\)) rearranged to 22. Introduction of the C11-C12 trans diaxial unit into ring C was accomplished in 9 steps starting from 22. This is shown in the accompanying scheme.
Reagents and conditions: a) 1-methoxy-1-(tert.butyldimethyl-silyloxy) ethylene, 1M LiClO -1,2-dimethoxyethane, 40°; b) MeOH, PPTS, 0°; c) NBS, THF, 0°; d) collidine, DMF, 130°.

Reagents and conditions: a) KF-MeOH; b) LAH, THF; c) TBDPSCI, imidazole, DMF; d) PCC, NaOAc, CH₂Cl₂, celite; e) TsNHNH₂, MgSO THF; f) LDA, DIPA, THF, -78°->0°->rt; g) OsO₄, Py, NaHSO₃; h) (COC₁)₂, DMSO, CH₂Cl₂, -78° -> rt; i) NaBH₄, MeOH-THF.
With all the C ring functionality in place, attention was focussed on the construction of the D ring 6 lactone, which was accomplished in several steps from 23 as outlined below.

Reagents and conditions: a) MOMCl, iPr NEt, (CH Cl) ; b) CrO . 3,5-dimethylpyrazole, -25°; c) Li, NH , t-BuOH, THF, -78°; d) 1.0M Superhydride, THF, -78°; e) n-Bu NF, THF; f) (COCl) , DMSO, Et N, -78°->rt; g) Jones' reagent, 0°; h) CH N , Et O.

In the next stage of the synthesis, the C15 hydroxyl group was introduced into 24 by a) reduction of the lactone to lactol, b) dehydration with POCl to dihydropyran, c) osmylation of the 15,16 double bond which took place from the desired β face, and d) oxidation with a periodinane reagent.

At this stage the tasks needed to be accomplished for the total synthesis of bruceantin are: a) acylation of the C15 hydroxyl group with 3,4-dimethyl-2-pentenoic acid b) introduction of the diosphenol unit into ring A and c) deprotection of the hydroxyl groups at C11 and C12. These were done in 6 steps from the pentacyclic lactone 25. Thus, the total synthesis of bruceantin was achieved.
Reagents and conditions: a) NaBH$_4$, EtOH-CH$_2$Cl$_2$ (2:1); b) POCl$_3$, Py, 85°; c) OsO$_4$, Py, 0°, NaHSO$_3$; d) HBTBO, CH$_2$Cl$_2$.

Reagents and conditions: a) 1M HCl, THF; b) 3, 4-dimethyl-2-pentenoic acid, DCC, DMAP, THF; c) TMSOTf, Et$_3$N, CH$_2$Cl$_2$, -10°; d)

Other noteworthy efforts towards the pentacyclic skeleton of bruceantin are those by Kametani$^3$, Ganem$^34$, Ziegler and Fuchs. Recently, Fuchs and co-workers have published their work on the synthesis of 15-deoxy,16-ethoxy

In our laboratory, we have been engaged in model studies towards the synthesis of quassinoids in general and
bruceantin in particular. In a study related to the model BCD ring system of quassinoids, tertiary alcohol 26 was synthesized as a precursor for an intramolecular Diels–Alder reaction. This compound, however, could not be converted to the tricyclic compound 28 in satisfactory yields. The tertiary alcohol 26 could not be dehydrated to the diene 27 under several conditions tried. Under drastic conditions, the tricyclic compound 28 was obtained in very low yields presumably via the diene 27. It was then believed that the methyl group at C2 was providing steric hindrance to the reaction as, the unmethylated compound underwent smooth intramolecular Diels–Alder reaction under dehydrating conditions.
In another approach\textsuperscript{39}, a model AB ring system was constructed starting from the Wieland–Miescher ketone (31) in several steps which included stereoselective osmylation of the olefin 32. This is shown schematically below.

Compound 32 was transformed into 34 via the enone 33 in several steps. Meanwhile, difficulties surfaced in the dehydration of 26. Anticipating that a similar fate might befall the tertiary alcohol 34, further studies in this direction were not carried out.

It was at this stage that we decided to synthesize a model system comprising the BCD rings and the results of this approach are presented in the next section.
Results and Discussion
A brief discussion about the Diels - Alder reaction would be appropriate at this juncture. The Diels - Alder reaction, first discovered in 1928, has become one of the most important reactions for the construction of six membered rings. In this reaction, an olefin and a 1,3 diene undergo thermal..
cycloaddition to give a six membered ring. In general, the reaction takes place readily, simply by mixing the components at room temperature or by heating in a suitable solvent, although in some cases drastic conditions have been used.

\[
\text{\begin{tikzpicture}
  \draw[thick] (0,0) -- (1,0) to[bend right] (1.5,0.5); \end{tikzpicture}}
\]

The rate of the Diels - Alder reaction is significantly altered by the presence of electron donating or withdrawing substituents on either the diene or dienophile. Based on the substituent attached, the reaction can be classified as type I or the normal mode, in which the diene has electron donating groups and is therefore electron rich, and the olefin (also called the dienophile) has electron withdrawing groups and hence, electron deficient. In type II or the inverse mode, the diene is electron deficient and the dienophile electron rich. The essential feature, therefore, is that the two components have complementary electronic character.

Frontier molecular orbital calculations reveal that for the type I reaction, HOMO-diene-LUMO-dienophile interactions are the most important. For the type II reactions, HOMO-dienophile-LUMO-diene energy separation is the dominating factor. These calculations also show that electron donating groups increase the energy level of the orbital concerned and electron withdrawing groups decrease it. The ease with which the reaction takes place
is determined by the HOMO-LUMO energy separation

For the normal mode reaction, electron donating groups increase the HOMO energy of the diene and electron withdrawing groups decrease the LUMO energy of the dienophile. In the case of the inverse electron demand reactions, favourable conditions can be created either by increasing the HOMO energy level of the dienophile by putting electron donating groups or by decreasing the LUMO energy level of the diene with electron withdrawing groups. Some typical examples of the inverse electron demand Diels - Alder reactions are given below.

As is evident from the above examples, enol ethers, ketene acetal and enamines all react with $\alpha,\beta$ unsaturated carbonyl compounds to give dihydropyrans. In the intramolecular
version, both diene and the dienophile are in the same molecule thus forming two or more rings in one single operation.

Tietze and coworkers in their work on tandem Knoevenegal - hetero Diels - Alder reactions\(^4\)\(^5\), have rationalized the formation of different ring fusions by examining the four possible transition states that lead to products. These transition states are shown below.

They observed that aromatic aldehydes such as 35 gave cis cycloadducts via an endo-E-syn transition state.

On the other hand, aliphatic \(\omega\)-unsaturated aldehydes, for example 37, gave trans annelated products passing through an exo-E-anti transition state.
Based on the above observations, we anticipated that the hetero Diels–Alder reaction envisaged in the retrosynthetic analysis could give a trans fused product which would have to be epimerized to the desired cis stereomer during the course of the synthesis.

We thought it would be better to work on a model system before embarking on the total synthesis itself, and for this purpose, omitted the A ring. The retrosynthetic analysis for the model BCD rings is shown below. We envisaged a tandem Knoevenegal–hetero Diels–Alder reaction as key the step. This would furnish the BCD rings in one step.

4-(2-methyl-2-cyclohexen-1-yl)-butyraldehyde 42 was arrived at as the suitable starting material. This aldehyde could, in principle, be transformed into a suitable Diels–Alder reaction substrate following Tietze's protocol. It has been
reported in the literature that $\alpha, \beta$ - unsaturated carbonyl compounds having an additional electron withdrawing group behave as excellent substrates for the hetero Diels - Alder reaction. In the intramolecular version, the heterodiene moiety was appended to the $\omega$ - unsaturated aldehydes by a Knoevenegal reaction. In most cases, the condensation product underwent spontaneous Diels - Alder reaction to furnish the cycloadducts. This methodology has been advantageously used in the construction of cannabinoids by Tietze and coworkers.

Our synthesis of aldehyde 42 began from 2-methyl-2-cyclohexen-1-ol (43). Alcohol 43 was converted to (2-methyl-2-cyclohexen-1-yl)-acetaldehyde (45) via the Claisen rearrangement of its enol ether 44 in excellent yields. Aldehyde 45 was homologated to aldehyde 42 by two different routes. In the first route, aldehyde 45 was subjected to a Knoevenegal condensation with dimethyl malonate in the presence of piperidine and acetic acid as catalysts. The reaction proceeded well giving the alkyldiene malonate 46 in good yields (75-80%). The product was characterized from its IR and $^1H$ NMR spectral data. In the IR spectrum, the carbonyl group absorption was observed at 1740 cm$^{-1}$.

\[ \text{alcohol 43} \xrightarrow{a} \text{enol ether 44} \xrightarrow{b} \text{aldehyde 45} \]
and the characteristic aldehyde C-H absorption at 2750 cm⁻¹ of 45 was absent. In the H NMR spectrum, apart from other signals, a triplet at 7.0 ppm was seen. This was assigned to the (3 proton of the alkylidene malonate. The activated double bond in 46 was reduced with sodium borohydride to furnish the malonate 47, in very good yield. Compound 47 did not have 7.0 ppm signal in its H NMR spectrum. This indicated the absence of the activated double bond. A triplet at 3.32 ppm was attributed to the proton of the malonate group.

Reagents and conditions: a) $\text{CH}_2(\text{CO}_2\text{Me})_2\cdot\text{piperidine}$, AcOH, $\text{C}_6\text{H}_6$ reflux; b) $\text{NaBH}_4$, MeOH, 0°; c) $\text{NaCl}$, $\text{H}_2\text{O}$-DMSO, reflux, d) LAH, ether, 0°; e) PCC, $\text{CH}_2\text{Cl}_2$, 0°.

Decarboxylation of 47 was effected following Krapcho's protocol and a good yield of the butyrate 48 was obtained. Characterization of 48 was done based on its H NMR spectrum. The triplet at 3.32 ppm in the $^1\text{H}$ NMR spectrum of the starting
material was shifted upfield and now merged with other high field signals. The methoxyl signal now integrated only for three protons indicating loss of one methoxycarbonyl group. Next, ester 48 was transformed into aldehyde 42 in two steps by reduction with lithium aluminum hydride followed by oxidation of the resultant alcohol 49 with pyridinium chlorochromate to the aldehyde 42. The structural identity of 40 was readily established from its spectral data. The aldehydic proton resonated at 9.74 ppm and in the C nmr, the carbonyl carbon appeared at 207.8 ppm.

The second route to 42 had one step less. In this route, aldehyde 45 was homologated by a Wittig reaction. Surprisingly, 45 did not react efficiently with (carbethoxy methylene) triphenyl phosphorane. However, it underwent a clean Horner - Wadsworth - Emmons reaction with triethyl phosphonoacetate. Thus, when treated with triethyl phosphonoacetate and sodium hydride, aldehyde 45 furnished the $\alpha,\beta$-unsaturated ester reagents and conditions: a) triethylphosphonoacetate, NaH, ether, $0^\circ \rightarrow$ reflux.

50 in about 80% yield. Compound 50 was identified from its spectral characteristics. The C NMR spectrum has 13 lines of
which 5 are in the 100 - 170 ppm region. The signal at 166.6 ppm was assigned to the carbonyl carbon and the other four lines to the olefinic carbons. The \( \alpha \) hydrogen of the \( \alpha,\beta \) - unsaturated ester was seen as a doublet at 5.84 ppm with a coupling constant of 16 Hz. This indicated that the double bond has the trans geometry. The \( \beta \) proton of the \( \alpha,\beta \) - unsaturated ester was observed at 6.82 ppm and was consistent with its nature. Following the report by Narisada and co-workers on the selective reduction of \( \alpha,\beta \)-unsaturated carbonyl compounds using sodium borohydride and cuprous chloride, we reduced the \( \alpha,\beta \)-unsaturated ester 50 to the saturated ester 51. Best yields were obtained when the solvents (MeOH, THF) were removed before work up. The compound was characterized from its spectral properties. The signals due to the protons of the activated double bond in 50 at 6.82 and 5.84 ppm were absent in the \( ^1H \) NMR spectrum of 51. This compound was converted to aldehyde 42 as described above for 48.

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{H} & \quad \text{CHO}
\end{align*}
\]

reagents and conditions: a) \( \text{NaBH}_4, \text{CuCl, MeOH-THF (5:2)}, \text{rt} \); b) \( \text{LAH, ether}, \text{0°} \); c) \( \text{PCC, CH}_2\text{Cl}_2, \text{0°} \).

With the target aldehyde 42 available, we now set out to perform the crucial hetero Diels - Alder reaction following the conditions reported by Tietze and Kiedrowski . When treated
with Meldrum's acid (34), in the presence of ethylenediammonium diacetate, our aldehyde 42 furnished only the Knoevenegal product 52 and none of the cycloadduct 53. However, the yield of 52 was very good (90-95%). The structure of 52 rests on its IR and H NMR data. In the IR spectrum, carbonyl groups in 52 showed absorptions at 1740 cm⁻¹. The alkylidene proton showed up at 7.92 ppm in H NMR as expected for β olefinic proton on an electron deficient alkene. Also, it was observed that there was no signal corresponding to the aldehyde proton in the H NMR spectrum. Longer reaction times also gave only the condensation product, with no evidence for the formation of the hetero Diels-Alder reaction adduct.

\[ \text{CHO} \quad \rightarrow \quad \text{52} \]

\[ \text{53} \]

**reagents and conditions:**  a) ethylenediammonium diacetate, \( CH_4Cl_2 \), rt.

Proceeding on the assumption that the hetero Diels-Alder reaction may require a higher temperature, the condensation product was dissolved in benzene and heated at 140° in a sealed
tube for 3h. At this temperature also no cycloaddition was observed. At 160°, the material decomposed to many intractable products and no efforts were made to purify this mixture. Under classical Knoevenegal conditions employing piperidine and acetic acid, 42 and Meldrum’s acid gave only a complex mixture. With the failure of these methods to yield the cycloadducts, further studies based on this strategy were not carried out.

It is not clear to us at the moment the reasons for the failure of this reaction. The present system is unique because both the diene and dienophile are cyclic systems linked by a carbon chain. One ring may sterically impede the approach of the other, creating unfavorable conditions for the reaction. In literature examples of this reaction, the dienophile component was always acyclic, though highly substituted double bonds have also been used. To the best of our knowledge, no cyclic olefin has been used as a dienophile in hetero Diels-Alder reaction. Since, cyclic olefins do not have the conformational flexibility of the acyclic ones this could be one of the reasons for the failure. In the present case, the methyl group on the cyclohexene ring could also be the cause of failure as past experience in our laboratory has indicated that highly substituted olefins were not good substrates for intramolecular Diels-Alder reactions.

The presence of the methyl group is essential for the construction of E ring in the later stages of the synthesis and it would be of very little use trying to experiment without the methyl group. Therefore, alternative approaches have to be found
We elected to use cyclopropanes that are geminally substituted with two electron withdrawing groups for two reasons. i) the nucleophilic ring opening of the cyclopropane was expected to be facile with double activation and ii) further functionalization of the compound would be accomplished easily. It is known in the literature that cyclopropanes having geminal electron withdrawing groups undergo ring opening reaction in a homo - Michael 1,5 fashion with nucleophiles.

With the failure of the intramolecular hetero Diels - Alder approach, an entirely different strategy was planned. The BCD rings were proposed to be constructed by intramolecular cyclopropanation of an appropriate substrate followed by ring opening of the cyclopropane with suitable nucleophiles. This is presented schematically below. This leads to 2-methyl-2-cyclohexen-1-ol as the appropriate starting material. This would have to be esterified with a suitable acid to perform this sequence of reactions.
Different nucleophiles have been used to open electron
deficient cyclopropanes and these include amines, mercaptans,
enamines, cuprates and malonate anion. Except for organometallic
nucleophiles, the reaction conditions for others are quite
drastic. When there is double activation, the ring opening
reaction is very facile and takes place under mild conditions. A
high degree of stereoselectivity has been observed in these ring
openings. This has been explained by invoking orbital
interactions. It has been shown that the bond which is cleaved is
the one best situated for simultaneous overlap with both
carbonyl groups.

In order to experimentally test our strategy, we
selected 2-methyl-2-cyclohexen-1-ol as the starting material. The
necessary side chain was built by acylating this alcohol with
phenylsulfonyl acetic acid. This furnished the phenylsulfonyl
acetate 55 in good yields. 55 was characterized from its spectral
data. The carbonyl group showed an absorption at 1720 cm⁻¹ in the
IR spectrum and a singlet at 4.12 ppm in the H NMR spectrum was
assigned to the active methylene group. It is to be noticed that
compound 55 has two different electron withdrawing groups. This
has two advantages. 1) This enables functional group
differentiation between the two electron withdrawing groups and
2) sulfones can be removed, if necessary, under mild conditions during the course of the synthesis.

reagents and conditions: a) PhSO₂CH₂CO₂H, DCC, DMAP, CH₂Cl₂, 0°–rt. b) TsN₃, DBU, CH₂Cl₂, 0–5°.

The active methylene group of 55 was converted into a diazo group following a procedure developed in our laboratory. Thus, compound 55, when treated with tosyl azide and DBU in dichloromethane, underwent facile diazo group transfer giving rise to the diazo compound 56 in very good yields. The reaction product was identified from its spectral characteristics. A very strong IR absorption at 2150 cm⁻¹ indicated the presence of the diazo group and the carbonyl group absorption was seen at 1700 cm⁻¹. Also, the 4.12 ppm signal in H NMR of 55 was absent.

The stage was now set for the decomposition of the diazo sulfone ester 56 and intramolecular capture of the resulting carbene by the alkene to give a doubly activated cyclopropane. No reaction was observed when 56 was heated in benzene at 130° for 5 min. At 150°, only a complex mixture was obtained. It is to be noted here that Kuwajima reported that diazosulfones when heated in n-decane, underwent decomposition to
give products, which were explained based on the formation of carbene and ketene intermediates. With the uncatalyzed thermolysis not being useful, we felt the need to use catalysts for the decomposition of 56. A search in the literature revealed that many transition metal salts and complexes catalyze the decomposition of diazo compounds.

Of the many metals that catalyze the decomposition of diazo compounds, we used copper and its salts because they are cheap and readily available and are reported to give good yields. With Cu(acac) and at room temperature in benzene, no reaction was observed. At higher temperatures and with varying reaction times, only a complex mixture was obtained. No attempts were made to separate and identify the products.

During the course of his prostaglandin synthesis, Corey reported the use of copper powder for the decomposition of diazo compound 57 to the corresponding cyclopropane 58. Under similar conditions, when 56 was heated in chlorobenzene as the solvent, only an intractable mixture was obtained. The same was
the result when the decomposition was carried out in cyclohexane.

Later, in 1984, Corey reported another catalyst, bis(salicylaldiminato) copper(II) and he showed it to be a superior catalyst than copper powder for the decomposition of diazo compounds. We performed the experiment by adding a toluene solution of the diazo compound 56 over a period of 12h to a refluxing solution of this catalyst in toluene and obtained a mixture of products which also contained some starting material. Apart from the recovery of about 10% starting material, no other well defined products were isolable.

![Catalyst Structure](image)

With copper and its salts failing to give any useful reaction, we turned our attention to the more expensive Rh. (OAc). This has been widely used in the decomposition of diazo carbonyl compounds. Unfortunately, there was no decomposition of 56 at room temperature in ether. In refluxing chloroform, extensive decomposition of the diazo compound was observed. This is surprising in the light of observations made by Monteiro on the decomposition of 59. Good yields of cyclopropane 60 were obtained when 59 was treated with Rh₄(OAc) in dichloromethane at room temperature.
However, 61 gave allylic CH insertion as the major product along with minor amounts of the cyclopropane. The results of our decomposition experiments on 56 are collectively presented in the following table.

Table I

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05M C₆H₅; 150°;</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>0.05M C₆H₅; 130°; 5min;</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>0.05M C₆H₅; Cu(acac)₂, reflux, rt.</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>0.056M C₆H₅M; Cu(acac)₂, reflux, 8h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>0.01M C₆H₅; Cu(acac)₂, reflux, 5h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>0.05M C₆H₅; Cu powder, reflux</td>
<td>complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>0.05M C₆H₅Cl; Cu powder; reflux 90min</td>
<td>complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>0.01M Corey's cat.; reflux 12h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>9</td>
<td>0.01M ether; Rh₂(OAc)₄</td>
<td>no reaction</td>
</tr>
<tr>
<td>10</td>
<td>0.01M CHCl₃; Rh₆(OAc)₃; reflux</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

With the diazosulfone ester 56 failing completely to
meet our expectations, we chose to use a diazo malonate which has been used extensively for intramolecular cyclopropanation. Therefore, we prepared the malonate ester 62 by acylating 2-methyl-2-cyclohexen-1-ol with the half ester of malonic acid. Good yields of the ester 62 were obtained (77%). Compound 62 showed a carbonyl absorption at 1720 cm⁻¹ in the IR spectrum. In the NMR spectrum, the active methylene protons were observed at 3.32 ppm. The diazo transfer reaction of 62 proceeded uneventfully and in quantitative yields to provide 63. In the IR spectrum, compound 63 showed a very strong absorption at 2150 cm⁻¹ indicative of the presence of a diazo group. Now, we were ready for the cyclopropanation reaction. Thermolysis of 63 in benzene without any catalyst was not useful once again and an intractable mixture was the result.

![Chemical structures](image)

reagents and conditions: a) EtO CCH CO H, DCC, DMAP, CHCl₃, 0°→rt; b) TsN₃, DBU, CH₂Cl₂, 0°.

We then followed Corey's conditions, and used copper powder as the promoter of cyclopropanation. To our relief, this provided the cyclopropane 64 in low yields (<40%). However, this happiness was short-lived as the yield of the product 64
could not be improved in subsequent trials and was also non-reproducible, presumably due to the heterogeneity of the reaction conditions. When the decomposition of 63 was carried out with Rh$_2$(OAc)$_3$ as the catalyst in chloroform at room temperature for 32h, (the time required for the complete disappearence of the starting material), no well defined product could be isolated. Further studies were not be carried out as the cyclopropanation could not be optimized.

We hoped that the carbenes 65 and 66 generated by the decomposition of 56 and 63 would be more stable because of the electron withdrawing substituents attached to them and therefore more selective in their reactions than alkyl carbenes. It appears that these carbenes are also non-selective as evidenced by the formation of several products. We believe that the methyl group...
on the double bond provides steric hindrance for the reaction to proceed in the case of these carbenes. With the methyl group blocking the approach of the carbene to the double bond and thus decreasing the rate of cyclopropanation, other side reactions become predominant, giving rise to a mixture of products. This argument finds support from the work of Ziegler, who reported that the diazomalonate 67 underwent intramolecular cyclopropanation in the presence of CuI.P(OMe) complex in 65% yield. Another reason to believe that the methyl group is probably the culprit is based on some findings in our laboratory. As it was pointed out in the introduction, alcohol 26 gave a very low yield of the cycloadduct 28 while its unmethylated counterpart gave good yields of the cycloadducts. In another instance, compound 69 did not undergo intramolecular Pauson–Khand reaction under several conditions tried, while its unmethylated counterpart 70 gave good yields of the cyclopentenone 71. Further experiments have to be performed to hit upon the right set of conditions for the cyclopropanation reaction in synthetically useful yields with the vinylic methyl group intact.
Once again, we had to revise our strategy for the construction of BCD rings. This time, we chose to use an intramolecular Michael reaction as the key step for the formation of the BD rings. The C ring was proposed to be formed later by alkylation cyclization on the aldehyde functionality. The retrosynthetic analysis on these lines is shown below.

Li and Wu have applied the intramolecular Michael addition strategy for the synthesis of a forskolin intermediate. 3-Hydroxy-α-cyclocitral (73) when treated with diketene furnished an unstable product 74 which on reaction with sodium hydride in DMF underwent intramolecular Michael addition to produce 75 in 60% yield.
We carried out preliminary studies using 3-hydroxy-α-cyclocitral as the starting material. We planned to use a side chain that would lead to six **membered** ring upon the Michael reaction. We chose 3-carbethoxysuccinic acid 4-ethyl ester as a suitable side chain. Thus, 73 on acylation with 3-carbethoxy succinic acid 4-ethyl ester gave 76 in 80% yield. It is to be noticed that this substrate would provide the D ring α lactone moiety that lacks only the α hydroxy group, if the Michael reaction is successful. First, we attempted the Michael reaction under mild conditions employing DBU as the base at room temperature. However, no reaction was observed. Next, we used a stronger base sodium hydride and performed the reaction in a polar aprotic solvent DMF. Unfortunately, no reaction was observed in this case also. Probably the malonate anion was not nucleophilic enough to add to the α,β-unsaturated aldehyde to furnish the 5 lactone 77.
reagents and conditions: a) \((\text{EtO}_2\text{C})\text{CHCH}_2\text{CO}_2\text{H}, \text{DCC}, \text{DMAP}, \text{CH}_2\text{Cl}_2\).

We did not pursue the synthesis of quassinoids further, in the light of all these failures.
Experimental
General techniques:

All reactions were conducted under nitrogen atmosphere unless otherwise mentioned. Reagents were transferred using standard septa-syringe techniques. All solvents were distilled from appropriate drying agents just before use. All the reagents were purified by appropriate methods before use. All the organic extracts after workup were dried using anhydrous magnesium sulfate, unless otherwise mentioned.

Solvents used for chromatography were of commercial grade and were fractionally distilled before use. Hexane refers to the petroleum fraction boiling between 60 - 70°. Column chromatography was performed using ACME 100 - 200 mesh silica gel using appropriate mixtures of hexane and ethyl acetate for elution. Analytical thin layer chromatography (tlc) was performed on home made plates using ACME silica gel GF254 grade containing 13% calcium sulfate as binder and were developed in appropriate solvent systems. Developed plates were visualized by shining ultraviolet light and/or by exposure to iodine vapours.

Infrared spectra were recorded on Perkin - Elmer infrared spectrophotometers models 1310 or 297. Solid samples were recorded as KBr wafers and liquid samples as thin films between NaCl plates. The spectra are calibrated against polystyrene absorption at 1601 cm⁻¹. NMR spectra were recorded on a JEOL FX-100 fourier transform spectrometer operating at 23.5 Tesla magnetic field strength in chloroform - d as solvent with tetramethylsilane (TMS) as internal reference unless otherwise
mentioned. Chemical shifts are given downfield of tetramethylsilane in parts per million (ppm). Coupling constants are measured in Hertz. The multiplicity of the signals are denoted by the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Elemental analyses were performed on a Perkin-Elmer model 240C elemental analyzer.

2-Methyl-2-cyclohexen-1-ol vinyl ether (44):
To a stirred solution of mercuric acetate (11.2 g, 35.1 mmol) in ethyl vinyl ether (150 ml) was added a solution of 2-methyl-2-cyclohexen-1-ol (43) (5.0 g, 44.6 mmol) in ethyl vinyl ether (30 ml) and the solution was heated under reflux for 40h. The solution was concentrated, diluted with ether, washed with 5% aqueous potassium hydroxide (4x25 ml) and dried over anhydrous potassium carbonate. The residue after solvent evaporation was distilled under reduced pressure to yield the vinyl ether 44 as a colourless volatile liquid.
yield: 6.05 g (98%)
b.p.: 60° (oil bath)/1mm/Hg.
IR (neat): 2950, 1620, 1240, 1180, 1140, 1040, 920, 820 cm⁻¹.

(2-Methyl-2-cyclohexen-1-yl) acetaldehyde (45):
The vinyl ether 44 (6.0 g) was taken in a thick walled glass tube, sealed under nitrogen and maintained at 190-195° for 1h. The tube was cooled to room temperature and the contents were
distilled under reduced pressure to give pure 45 as a colourless volatile liquid.

yield : 5.6g (93%)
b.p. : 60° (oil bath)/1mm/Hg.
IR (neat) : 2900, 2800, 2750, 1720, 1440, 1020, 800 cm⁻¹.

Dimethyl 2-(2-methyl-2-cyclohexen-1-yl) ethylidene malonate (46):

A solution of 45 (303 mg, 2.2 mmol), dimethyl malonate (264 mg, 2.0 mmol), piperidine (7 mg, 0.08 mmol) and acetic acid (24 mg, 0.4 mmol) in benzene (2ml) was heated under reflux for 2h, cooled to room temperature, diluted with ether, washed several times with water and dried. The residue was purified by silica gel column chromatography. This furnished 46 as a colourless oil.

yield : 454 mg (82%) .
IR (Neat) : 2900, 1720, 1440, 1260, 1240, 1060 cm⁻¹.

$^1$H NMR : 8 1.20 - 2.60 (m, 12H), 3.80 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 5.40 (br, 1H, olefinic), 7.0 (t, J = 8 HZ, 1H, olefinic).

Dimethyl 2-(2-methyl-2-cyclohexen-1-yl)ethyl malonate (47):

To a stirred solution of the alkylidene malonate 46 (226 mg, 0.9 mmol) in methanol (1 ml) at 0° was added sodium borohydride (60 mg, 1.5 mmol) in portions and the reaction mixture was stirred at 0° for 90 min, diluted with water (5 ml), acidified to pH 1 with dilute hydrochloric acid and extracted several times
with ether. The organic layer was dried and concentrated to
furnish the product 47 as an oil.
yield : 218 mg (95%)
IR (neat) : 2900, 2850, 1740, 1420, 1340 cm⁻¹.
¹H NMR : δ 1.20 - 2.12 (m, 14H) , 3.32 (t, J = 8Hz, 1H, CH
(COOME)₂), 3.72 (s, 6H, OCH₃), 5.40 (br, 1H, olefinic).

Methyl 4-(2-methyl-2-cyclohexen-1-yl)-butanoate (48):
The malonate ester 47 (190 mg, 0.75 mmol) was dissolved in
dimethyl sulfoxide (1.5 ml) and water (13 μl) and sodium chloride (88 mg, 1.5 mmol) were added. The mixture was heated
under reflux for 2h, cooled to room temperature, diluted with water (15 ml) and the solution extracted with ether (4x10 ml).
The solution was concentrated, the residue was dissolved in hexanes (15 ml) and washed several times with water. The hexane
solution was dried and concentrated to give the product 48 as an oil.
yield : 110 mg (74%)
IR (neat) : 2900, 2850, 1740, 1440, 1180 cm⁻¹.
¹H NMR : δ 1.20 - 2.40 (m, 16H) , 3.64 (s, 3H, OCH₃), 5.40 (br, 1H, olefinic).

4-(2-Methyl-2-cyclohexen-1-yl)-butan-1-ol (49):
To a stirred suspension of lithium aluminum hydride (100 mg, 2.5 mmol) in ether (2 ml) was added a solution of the
ester 48 (380 mg, 1.94 mmol) in ether (2 ml). The reaction mixture was stirred for 10h at room temperature, then cooled in ice and quenched with saturated aqueous sodium sulfate solution. The solids were filtered and washed several times with ethyl acetate. The filtrate was dried and concentrated. The residue was purified by chromatography.

yield : 307 mg (94%).

IR (neat) : 3340, 2920, 2840, 1450, 1060, 800 cm⁻¹.

¹H NMR : δ 0.80 - 2.08 (m, 16H), 3.64 (t, CH₂OH), 5.40 (br, 1H, olefinic).

¹³C NMR : 19.65, 22.12, 23.41, 25.53, 27.30, 32.41, 33.00, 38.47, 62.70, 122.42, 137.30 ppm.

4-(2-Methyl-2-cyclohexen-1-yl)-butan-1-al (42):

A solution of the alcohol 49 (307 mg, 1.83 mmol) in dichloromethane (3 ml) was added to a stirred suspension of pyridinium chlorochromate (595 mg, 2.75 mmol) in dichloromethane (3 ml). After 1h, the reaction mixture was diluted with ether (20 ml) and filtered through a short column of fluorisil. The ether solution was concentrated to obtain the aldehyde 42.

yield : 207 mg

IR (neat) : 2910, 2860, 2720, 1720, 1440, 800 cm⁻¹.

¹H NMR : δ 1.40 - 2.20 (m, 14H), 2.52 (m, 2H), 5.40 (m, 1H, olefinic), 9.74 (t, 1H, CHO).

¹³C NMR : 15.53, 22.00, 21.35, 27.12, 32.00, 38.18, 44.06, 122.72, 134.59, 207.77 ppm.
Ethyl 4-(2-methyl-2-cyclohexen-1-yl) crotonate (50):

To a stirred suspension of sodium hydride (washed with hexanes to remove oil) (156 mg, 6.5 mmol) in dry ether (5 ml) at 0° was added triethyl phosphonoacetate (1.23 g, 5.5 mmol). After 15 min, aldehyde 42 (690 mg, 5 mmol) was added. The reaction mixture was stirred at 0° for 15 min and then heated under reflux for 15 min. The reaction mixture was cooled, quenched with water and extracted with ether (3x20 ml). The ether solution was dried and concentrated. The product was purified by column chromatography.

yield : 910 mg (88%).

IR (neat) : 2980, 2920, 2860, 1720, 1650, 1450, 1370, 1260, 1180, 1040, 800 cm⁻¹.

¹H NMR : 6 1.0-2.20 (m, 15H), 3.20 (q, 2H, OCH₂CH₃), 5.40 (br, 1H, olefinic) 5.84 (d, J=16 Hz, 1H, H-2), 6.82 (m, 1H, H-3).

¹³C NMR : 14.18, 15.41, 19.29, 22.00, 25.30, 27.53, 36.65, 60.06, 122.59, 123.77, 135.48, 148.42, 166.60 ppm.

Ethyl 4-(2-methyl-2-cyclohexen-1-yl) butanoate (51):

To a stirred solution of the unsaturated ester 50 (750 mg, 3.7 mmol) in 5:2 methanol-tetrahydrofuran (70 ml) was added cuprous chloride (527 mg, 5.32 mmol) and sodium borohydride (1.37 g, 36 mmol). After 30 min, the solvent was removed under reduced pressure and the residue was taken up in water and extracted with ether (4x15 ml). The organic layer was dried, concentrated and
the residue was purified by chromatography.

yield : 500 mg (66%).

\textbf{IR (neat)}: 2950, 1740, 1440, 1380, 1160, 1040, 800 cm$^{-1}$.

$^1$H NMR : $\delta$ 1.0 - 2.40 (m, 16H), 1.24 (t, 3H, CH$_3$CH$_2$), 4.12 (q, 2H, OCH$_2$CH$_3$), 5.40 (br, 1H, olefinic).

Condensation of aldehyde 42 with Meldrum's acid:

Ethylenediammonium diacetate (32 mg, 0.18 mmol) was added to a stirred solution of Meldrum's acid (52 mg, 0.36 mmol) in dichloromethane (0.4 ml). After 5 min, a solution of the aldehyde 42 (60 mg, 0.36 mmol) in dichloromethane (0.4 ml) was added. After 15 min, the reaction mixture was diluted with dichloromethane (5 ml), washed with water (2x5 ml) and dried. The condensation product was obtained on evaporating the solvent.

yield : 97 mg (92%)

IR (neat): 3000, 2920, 2860, 1740, 1630, 1450, 1400, 1380, 1280, 1210, 810, 740 cm$^{-1}$.

$^1$H NMR : $\delta$ 1.20 - 2.04 (m, 14H), 2.0 (br, 2H), 5.40 (br, 1H, olefinic), 7.92 (t, J=8 Hz, 1H, olefinic).

Attempted Diels - Alder reaction of 52:

trial 1:

A solution of the compound 52 (20 mg, 0.07 mmol) in benzene (1 ml) was heated in a sealed tube at 140° for 3h. The reaction mixture was cooled to room temperature and the solvent evaporated. TLC of the reaction mixture showed the presence of
mainly the starting material. The material recovery was 17 mg.

trial 2:
A solution of the compound 52 (70 mg, 0.24 mmol) in toluene (2 ml) was heated in a sealed tube at 160° for 2h. The reaction mixture was cooled, solvent evaporated and the residue analyzed by tlc. TLC of this mixture was very complex. No attempts were made to purify this mixture.

Attempted tandem Knoevenegal - hetero Diels - Alder reaction of aldehyde 42:

The reaction mixture containing aldehyde 42 (23 mg, 0.14 mmol), Meldrum’s acid (20 mg, 0.14 mmol), piperidine (1 drop) and acetic acid (1 drop) in benzene (0.5 ml) was heated under reflux for 2h. TLC analysis of the reaction mixture at this stage showed the presence of a complex mixture. No attempts were made to isolate the products.

2-Methyl-2-cyclohexen-1-yl phenylsulfonylacate (55):

To a stirred solution of 2-methyl-2-cyclohexen-1-ol (43) (336 mg, 3 mmol) in dichloromethane (20 ml) at 0° was added sequentially phenylsulfonylacetic acid (900 mg, 4.5 mmol), DCC (927 mg, 4.5 mmol) and 4-dimethylaminopyridine (37 mg, 0.3 mmol). The reaction mixture was stirred overnight at room temperature. It was then poured into water (25 ml), layers separated and the aqueous phase extracted with dichloromethane (3x20 ml). The
combined organic layers were washed with aqueous sodium bicarbonate solution and dried. The residue after solvent evaporation was purified by silica gel column chromatography.

yield : 747 mg (85%)

IR (neat) : 2900, 1720, 1440, 1380, 1320, 1280, 1100, 1080, 980, 920, 800, 720, 680 cm$^{-1}$.

$^1$H NMR : 6 1.20 - 2.08 (m, 9H), 4.12 (s, 2H, CH$_2$SO$_2$Ph), 5.20 (m, OCH), 5.64 (m, 1H, olefinic), 7.44 - 8.0 (m, 5H, Ar).

$^{13}$C NMR : 17.70, 20.29, 24.82, 28.35, 60.94, 73.06, 128.41, 128.89, 129.18, 130.48, 134.18, 138.89, 162.24 ppm.

 Elemental analysis:
Calculated for C$_{15}$H$_{18}$O$_4$S : C = 61.20, H: 6.16.

The diazo transfer reaction:

To a stirred solution of the sulfone ester 55 (320 mg, 1.0 mmol) in dichloromethane (1.5 ml) at 0-5 °C, was added DBU (228 mg, 1.5 mmol) followed by dropwise addition of a solution of tosyl azide (197 mg, 1 mmol) in dichloromethane (1 ml). After 15 min, the reaction mixture was diluted with dichloromethane, washed with 5% aqueous HCl (3x5 ml), dried and concentrated. The residue was purified by silica gel column chromatography to furnish the diazo compound 56 as a pale yellow oil.

yield : 275mg (79%)

IR (neat) : 2900, 2150, 1700, 1440, 1340, 1280, 1140, 1100, 960,
900, 740, 600 cm$^{-1}$.

$^1$H NMR: 0.60 - 2.0 (m, 9H), 5.20 (m, 1H, OCH), 5.64 (m, 1H, olefinic), 7.60 - 8.0 (m, 5H, Ar).

Elemental analysis:
Calcd for C$\text{H}_\text{N}_4\text{O}_4\text{S}$: C = 56.23, H = 5.03, N = 8.76.

Decomposition experiments on the diazo compound 56:

All solvents used in these experiments were dried using appropriate drying agents and were degassed by bubbling nitrogen through them.

1. **Thermolysis** in benzene:

A solution of the diazo compound 56 (56 mg, 0.18 mmol) in benzene (3 ml) was heated at 150° in a sealed tube for 2h. The reaction mixture was cooled and analyzed by tlc. A complex tlc pattern was observed. No attempts were made to separate and identify the individual components.

2. A solution of the diazo compound 56 (50 mg, 0.16 mmol) in benzene (3 ml) was heated in a sealed tube at 130° for 5 min. The cooled reaction mixture was analyzed by tlc. Only the starting material was seen. No other products were observed.

Decompositions in the presence of Cu(acac)$_2$:

3. The benzene solution (2 ml) of 56 (35 mg, 0.11 mmol) and Cu(acac)$_2$ (4 mg) was stirred at room temperature for 10h.
Tlc of the reaction mixture at the end of this period showed only
the starting material. Thus, no reaction was observed under these
conditions.

4. A solution of 56 (447 mg, 1.29 mmol) and Cu(acac)
(45 mg) in benzene (25 ml) was heated under reflux for 8h. Only a
complex mixture was seen on the tlc plate. Therefore, no attempts
were made to analyze the products.

5. A 0.01M solution of 56 (30 mg, 0.09 mmol) and
Cu(acac) (3 mg) in benzene was heated under reflux for 5h. At
this stage the tlc indicated the absence of the starting
material. However, several other spots were also seen making the
separation difficult. No characterizable product was isolated
from this mixture.

Decomposition experiments with copper powder:

6. A solution of 56 (100 mg, 0.31 mmol) in
chlorobenzene (7 ml) was heated at 160° in the presence of copper
powder (electrolytic grade, 992 mg, 15.5 mmol) in a sealed tube
for 90 min. The cooled reaction mixture was analyzed by tlc. A
complex mixture was noticed. However, no attempts were made to
separate and identify the components of the mixture.

7. A solution of the diazo compound 56 (115 mg, 0.36
mmol) in cyclohexane (0.5 ml) was slowly added to a refluxing
slurry of copper powder (0.912 g, 14.4 mmol) in cyclohexane (6 ml). Heating was continued for 6 h and the reaction mixture was cooled, filtered and concentrated. Tlc of the reaction mixture revealed many spots which could not be separated.

**Decomposition** experiment with Corey's catalyst:

8. To a refluxing solution of bis (tert-butyl-salicylaldiminato) copper(II) (3 mg) in toluene (5 ml) was added a solution of 56 (45 mg, 0.14 mmol) in toluene (4 ml) over a period of 12 h. The reaction mixture was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column. The only isolable material was the starting diazo compound in 8% yield.

Experiments with rhodium acetate as catalyst for **cyclopropanation**:

9. A 0.01 M solution of 56 (100 mg, 0.31 mmol) and rhodium acetate (2 mg) in ether was stirred at room temperature for 24 h. No reaction was observed as indicated by tlc analysis.

10. To a refluxing solution of rhodium acetate (2 mg, 0.0033 mmol) in alcohol free chloroform (1 ml) was added a solution of the diazo compound 56 (107 mg, 0.33 mmol) in chloroform (2 ml) over a period of 5 min. Heating was continued for 48 h. At this stage tlc indicated the presence of starting material along with many other products.
Ethyl 2-methyl-2-cyclohexen-1-yl malonate (62):

To a stirred solution of 2-methyl-2-cyclohexen-1-ol (45) (112 mg, 1.0 mmol) in dichloromethane (1 ml) at 0° was added a solution of monoethyl malonate (198 mg, 1.5 mmol) in dichloromethane (1 ml) followed by DCC (309 mg, 1.5 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol). After stirring overnight at room temperature, the reaction mixture was worked up as described for 55.

yield : 173 mg (77%)

IR (neat) : 2900, 1720, 1300, 1160, 1040, 1000, 940 cm⁻¹.

¹H NMR : δ 1.28 (t, 3H, CH₂CH₃), 1.40 - 2.08 (m, 9H), 3.32 (s, 2H, CH₂COOEt), 4.20 (q, 2H, OCH₂CH₃), 5.20 (m, 1H, OCH), 5.64 (m, 1H, olefinic).

Diazotransfer reaction of 62:

The diazotransfer reaction of 62 was conducted as described for 55 to provide the diazomalonate 63.

yield : 100%

IR (neat) : 2950, 2150, 1760, 1720, 1680, 1380, 1300, 1260, 1100, 920, 760 cm⁻¹.

Cyclopropanation experiments of 63:

1. With copper powder:

To a boiling suspension of copper powder (500 mg, 7.8 mmol) in xylene (1 ml) was added a solution of the diazomalonate 63 (50 mg, 0.2 mmol) in xylene (1 ml). The reaction mixture was
heated under reflux for 6h, cooled and filtered. The filtrate was concentrated and chromatographed on a silica gel column. The only isolable product was that of the cyclopropane 64.

**yield:** 17 mg (39%)

**IR (neat):** 2950, 1740, 1440, 1240, 1060, 720 cm\(^{-1}\).

**\(^1\)H NMR:** 5.0 - 2.40 (m, 13H), 4.24 (q, 2H, OCH\(_2\)CH\(_3\)), 4.60 (br s, 1H, OCH).

2. With Cu(acac)\(_2\):  
A solution consisting of the diazo compound 63 (40 mg, 0.16 mmol), Cu(acac) (4 mg) in benzene (2 ml) was heated in a sealed tube for 30 min. The cooled reaction mixture was filtered and concentrated. TLC of this revealed an intractable mixture. Therefore no purification was attempted.

3. With rhodium acetate:  
To a stirring solution of 63 (33 mg, 0.13 mmol) in alcohol free chloroform (1 ml) at room temperature was added rhodium acetate (2 mg) and the mixture was stirred for 32h, by which time the starting material was completely consumed. The reaction mixture was concentrated and analyzed by tlc. A complex mixture was seen.

Esterification of 3-hydroxy-α-cyclocitral (73) with 3-carbethoxy succinic acid 4-ethyl ester.

To a stirred solution of the alcohol 73 (100 mg, 0.6
mmol) in dichloromethane (2 ml) at 0° was added dropwise a solution of 3-carboxethoxysuccinic acid 4-ethyl ester (195 mg, 0.9 mmol) followed by DCC (184 mg, 0.9 mmol) and 4-dimethylamino pyridine (7 mg, 0.06 mmol). The resulting mixture was stirred overnight at room temperature. Water (5 ml) was added, layers separated and the aqueous layer extracted with hexanes (3x10 ml). The organic extracts were combined, dried and concentrated. The product was purified by chromatography to furnish 76 as an oil.

yield : 180 mg (82%)

IR (neat) : 3000, 2950, 2800, 1720, 1700, 1440, 1380, 1280, 1180, 1040, 860, 740 cm⁻¹.

Attempted Michael reactions of 76:

1. With DBU:

   The substrate 76 (100 mg, 0.27 mmol) in benzene (1.5 ml) was treated with DBU (2 drops) and stirred at room temperature for 24h. No reaction was noticeable by tlc analysis.

2. With sodium hydride:

   A solution of the substrate 76 (72 mg, 0.2 mmol) in dimethylformamide (0.5 ml) was added to an oil free suspension of sodium hydride (6 mg, 0.25 mmol) in dimethylformamide (0.5 ml) at room temperature. The reaction was monitored by tlc and no observable change was noticed even after 24h.
References


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Chapter II

Some Reactions of Unsaturated Sugars