NOVEL HALOGEN-SUBSTITUTED CYCLOHEXA-2,4-DIENONES AS DIENES FOR THE INTER MOLECULAR DIELS-ALDER REACTION. SYNTHESIS AND CHARACTERIZATION OF BICYCLO[2.2.2.] OCTENONE DERIVATIVES

A DISSERTATION

Submitted in partial fulfilment of the requirement for the award of the degree of

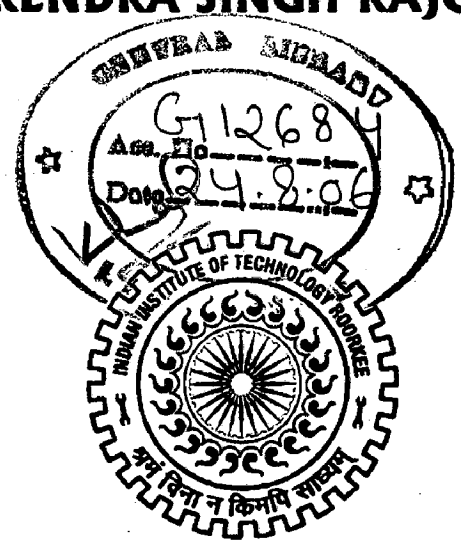
MASTER OF TECHNOLOGY

in

ADVANCED CHEMICAL ANALYSIS

By

VIRENDRA SINGH RAJORA



DEPARTMENT OF CHEMISTRY

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JUNE, 2006

CANDIDATE'S DECLARATION

I hereby declare that the work which is being presented in the dissertation entitled, **"NOVEL HALOGEN-SUBSTITUTED CYCLOHEXA-2,4-DIENONES AS DIENES FOR THE INTER MOLECULAR DIELS-ALDER REACTION. SYNTHESIS AND CHARACTERIZATION OF BICYCLO[2.2.2]OCTENONE DERIVATIVES"** in partial fulfillment of the requirement for the award of the degree of **"MASTER OF TECHNOLOGY"** submitted in the Department of Chemistry, I. I. T. Roorkee. This work has been carried out during the period from July 2005 to June 2006 under the supervision of Dr. R. K. Peddinti, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

I have not submitted the material presented in this dissertation report for the award of any other degree or diploma of this or any other institute/university. In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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ABSTRACT

Utilization of easily available and less expensive starting materials for the rapid construction of complex molecules with defined stereochemistry is an exciting and challenge for the synthetic organic chemists. In this connection the synthesis of bicyclo[2.2.2]octenone derivatives using 4-halo-2-methoxyphenol as an inexpensive starting material is described. The synthesis of bicyclo[2.2.2]octenone derivatives from the reactions of 4-halo-2-methoxyphenol (217, 221) with methyl acrylate and methyl methacrylate have been carried out using hypervalent iodine reagent diacetoxyiodobenzene. Bicyclo[2.2.2]octenone derivatives that are potential intermediate for the total synthesis of natural products are obtained.

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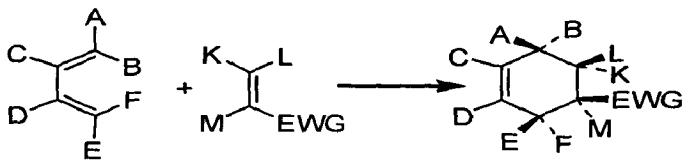
INTRODUCTION

1.1 *GENERAL ASPECTS*

The Diels-Alder reaction is one of the most powerful methods of carbon-carbon bond construction in synthetic organic chemistry [1,2]. It enables, in a one-step inter- or intramolecular reaction, the rapid preparation of cyclic compounds having a six-membered ring. The Diels-Alder reaction has several attractive features that have resulted in its use in innumerable synthesis of natural products: the high regio- and stersoselectivity typically displayed by this reaction, the easy of its execution, and the ability of creating up to four new stereocenters during the course of the reaction [3]. It may be classified into one of three types of $\pi^{2s} + \pi^{4s}$ cycloaddition reaction: the normal HOMO diene-controlled reaction using an electron rich-diene and electron-deficient dienophile, the neutral Diels-Alder reaction, and the inverse electron demand or LUMO diene-controlled Diels-Alder reaction. If a concerted reaction is assumed, both a *cis* addition (suprafacial mode) and a preffered *endo* orientation (Alder rule) can be expected. The Diels alder reaction has both enabled and shaped the art and science of total synthesis over the last few decades to an extent which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire. With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and programmed cascade sequences facilitating complex molecule construction, the Diels- Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products. Many different versions of the Diels-Alder reaction were elaborated, including intramolecular [4+2] cycloadditions, hetero Diels-Alder reactions, pressure-accelerated Diels-Alder reactions, and Lewis acid accelerated Diels-Alder reactions [2]. If one chemical reaction had to be selected from all those in the repertoire of synthetic organic chemists as the most useful and powerful synthetic construction, it was clear by 1970 that the Diels-Alder reaction would be the logical choice. Its application not only leads to a strong increase in molecular complexity (molecular size, topology, stereochemistry, functionality, and

appendages), but also can result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic reactions. The Diels-Alder reaction is a widely used protocol in organic synthesis since it generates a wide variety of polyfunctionalized cyclic compounds with up to four new contiguous stereogenic centers in a highly stereoselective and predictable manner in a single laboratory operation [2, 4-5].A large number of dienes and dienophiles with a plethora of functionalities has been used to construct various types of ring structures [4]. A wide variety of ring structures have been constructed by using various dienes and dienophiles bearing an array of functionalities in the Diels-Alder reactions [6]. Its versatility has been further enhanced with the introduction of its intramolecular version, i.e., the intramolecular Diels-Alder reaction, [7] which stands out from the intermolecular reaction both in aesthetic sense and usefulness. The reaction requires efficient designing and stitching together of the two reacting moieties prior to the reaction. It produces a minimum of two rings in a highly regioselective and stereocontrolled manner. The advantages offered by intramolecular reactions over their intermolecular counterparts have generated much interest in finding ways to intramolecularize the reactions [8]. Attempts toward intramolecularization of a variety of reactions including Diels-Alder reactions using disposable tethers have resulted in considerable success [9, 10]. In recent years, "domino" or "tandem" processes have gained considerable importance as a means to achieve synthesis of molecules with high complexity in a rapid and efficient manner [11-14]. As evidenced by a large number of reports in recent literature, the intramolecular Diels- Alder reactions are among the few that are commonly employed in combination with other reactions in domino/tandem processes [14]. In tandem processes, synthesis of the triene precursors required for intramolecular Diels-Alder reactions has been generally achieved via one of two strategies: (i) in situ tethering of diene and alkene via alkylation, acylation, condensation, etc.; (ii) in situ generation of either diene or alkene via oxidation, elimination, retrogradation, etc. [11, 12]. The intramolecular Diels-Alder (IMDA) reaction has been proved to be a very useful strategy in the regio- and stereoselective construction of highly substituted bicyclic and polycyclic ring systems [15]. One important difference between intramolecular and intermolecular is that the decreased entropic demands in IMDA reactions often render them to proceed under

milder conditions with higher reaction rates. Second, the reduction in the degrees of freedom of the unimolecular transition state often results in superior selectivities when compared to the intermolecular reactions. The original version of the Diels-Alder reaction (Scheme 1) joins together a wide variety of conjugated dienes and alkenes with electron withdrawing groups (the dienophiles), to produce a cyclohexene ring in which practically all six carbon atoms can be substituted as desired. The reaction may be executed under relatively simple reaction conditions by heating together the two components, diene and dienophile, in non-polar solvents, followed by evaporation which leads usually to high yields of the product(s). The reaction is disciplined by the Woodward-Hoffmann rules [2] as a $[_{\pi}4_{s}+_{\pi}2_{s}]$ cycloaddition occurring in a concerted but probably not symmetrically synchronous fashion, thus leading to highly predictable product structures in which two new carbon-carbon sigma bonds are formed in a stereospecific manner with the creation of up to four new stereogenic centres. The classical empirical rules have now found strong theoretical basis in the Woodward- Hoffmann rules, with regards to regiochemistry ("ortho" and "para" orientations) and stereochemistry (endo transition state kinetically favoured over the exo transition state in most of the reactions) [2].



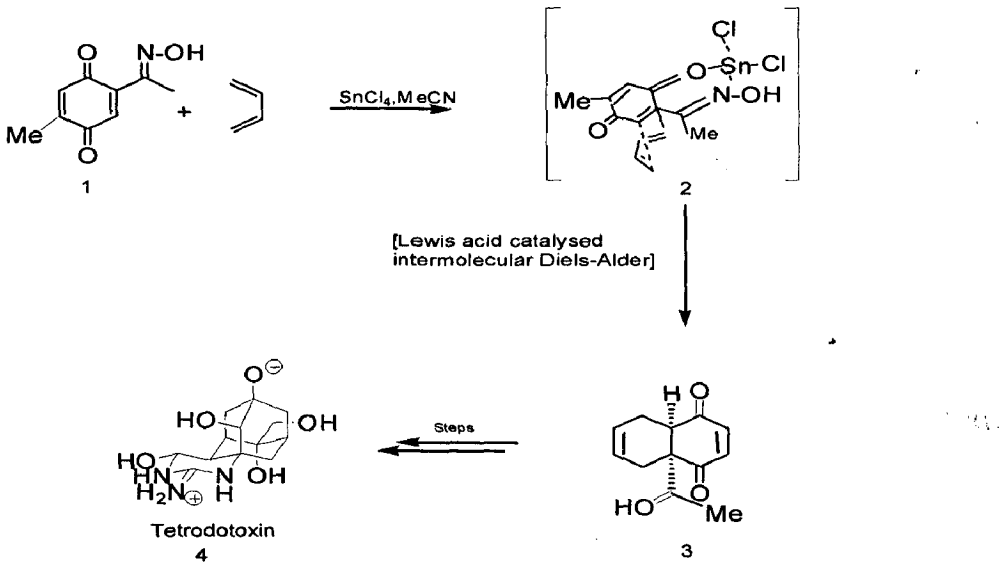
A-F and K-M: substitute;
EWG: electron withdrawing group

SCHEME 1

The Diels-Alder reaction has now become an important research area for theoretical chemists, with regard to the finer details of the transition state and the energetics of the process, and with special concern for entropy and activation energies [16-18]. On a completely different front it is now well accepted that the Diels-Alder reaction can be an important biosynthetic process [17, 19-23] and several publications include discussions on the existence of the enzyme Diels-Alderase [17, 20-23]. A powerful synthetic strategy of Diels-Alder chemistry as a protecting group and temporary

scaffold (or template), for the manipulation of the sensitive multiple functionalities of diene or dienophile types. In this approach the sensitive diene or dienophile portions of the molecules are tied up with a convenient partner in a Diels-Alder reaction, the cycloadduct is then chemically modified in accordance with the synthetic plan and finally undergoes a retro Diels-Alder reaction to liberate the desired product [24]. For example, the cycloaddition product of a reactive α,β-enone function with cyclopentadiene, can be submitted to the required chemo-, regio- and stereoselective reactions, dominated in part by the expected endo-cycloadduct structure, before retro Diels-Alder reaction unravels a much more complex product. There are three basic straregies for the control of the desired products in Diels-alder reaction: the use of a chirally modified diene, a chirally modified dienophile or a chiral catalyst. In the past few years, a numbers of chiral auxiliaries and catalysts for asymmetric Diels-Alder reaction have been developed [25, 26]. One of the requirements for the design of enantioselective Diels-Alder catalysts is achiral Lewis Acid-C=O complex. This coordination of Lewis acid to the dienophile serves as the activation process and provides a chiral environment that affects facial selectivity. The understanding of enantioselectivity requires knowledge of the detailed structure and concentration of each dienophile-Lewis acid complex present in equilibrium and the relative rates for the reaction of each with the diene. Even if the catalyst has a single fixed geometry in the complex with the α,β-unsaturated carbonyl compounds, the production of *s-cis* and *s-trans* α,β-unsaturated complexes must be controlled, since these will lead to enantiomeric products. As a result of the region- and stereospecific nature of the Diels-Alder reaction (always a *cis* addition) and the diastereoselectivity of the union based on the Alder endo rule [27] (where a more sterically crowded and seemingly less thermodynamically stable transition state results when the dienophile possesses a suitable conjugating substituent), the formation of these chiral elements is often predictable in a relative sense. In addition, although Woodward's Diels-Alder reactions elegantly achieved regioselectivity, results which can be rationalized successfully on the basis of frontier molecular orbital theory these examples do not reflect the challenges faced in attempting to achieve such control in certain contexts where particular unsymmetrical diene and/ or dienophile units having specific steric and electronic properties are employed. A classical method to enhance regioselectivity is

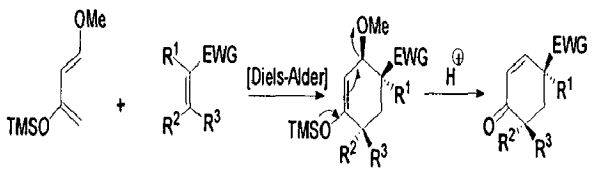
based on the use of Lewis acid catalysts. Upon complexation of such species to the dienophile, the normal demand Diels-Alder reaction is promoted since the energy gap between the lowest unoccupied molecular orbital (LUMO) of the dienophile and the highest occupied molecular orbital (HOMO) of the diene is reduced, thus decreasing the activation energy required to achieve the cycloaddition. Moreover, as this stabilization is greater for the endo transition state, as a result of beneficial enhancement of secondary orbital overlap that is unobtainable in an exo mode of reaction, the use of Lewis acids favors an increased ratio of endo: exo products. More valuable synthetically, however, is the fact that Lewis acids can often reverse the regiochemical course of a Diels-Alder addition and generate products that would not otherwise be observed in a simple, thermally induced reaction [28]. An early and elegant example of this concept is provided by the total synthesis of tetrodotoxin (**4**, Scheme 2) by Kishi et al [28].



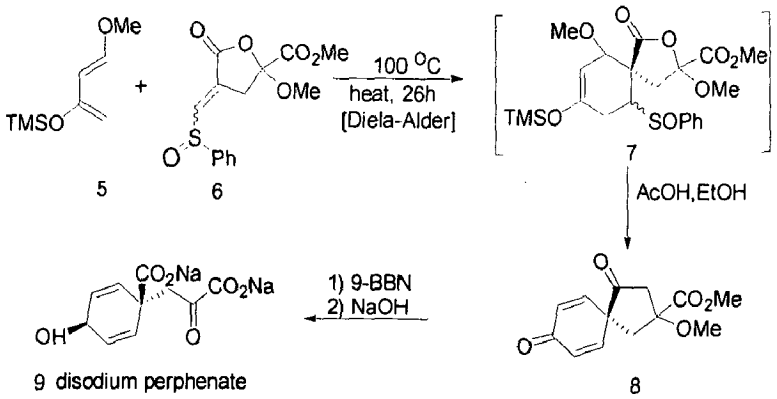
SCHEME 2

As in the Woodward paradigm, an initial Diels-Alder union between quinone and butadiene was employed to generate a preliminary set of rings and stereocenters for subsequent elaboration. However, the intriguing feature of this example is that the use of $SnCl_4$ in the Diels-Alder reaction proved critical for the chemoselective engagement of butadiene with the oxime-bound dienophile, in the absence of the Lewis acid, the other olefinic bond of quinone reacted exclusively. Although oximes normally behave

mesomerically as electron-donating substituents, thus deactivating the neighboring olefin for Diels-Alder reaction, coordination of the Lewis acid reverses this behavior by drawing electron density away from this group, which leads to an adjacent highly competent electron-deficient dienophile [29]. Thus, Lewis acid activation nicely affected regiochemical control in the employed [4+2] cycloaddition that could not have been achieved otherwise. Among other methods introduced to achieve excellent regioselectivity, as well as to incorporate useful functional groups, Danishefsky's widely applicable diene system (Scheme 3a) represents one of the most important advances in this regard within the past quarter century [30]. Initially developed as part of a method to selectively generate pyran rings upon reaction with aldehyde dienophiles [31], the power of the prototype diene rests in the synergistic effects of the two incorporated oxygen groups, which provide mutually reinforcing electronic contributions to the diene system such that regiospecific formation of a lone endo adducts results upon reaction with most dienophiles. In addition, upon treatment with mild acid after the Diels-Alder reaction, cleavage of the silyl protecting group residing within the product and the strategic location of the methoxy leaving group enables an ensuing cascade sequence that results in the formation of an α,β-unsaturated system. An early demonstration of this strategy in total synthesis can be found in the route used by Danishefsky et al. to form disodium prephenate (**9**, Scheme 3b), [32] where, although the target may not seem to possess great molecular complexity, application of this designed diene technology provided a highly elegant and concise solution to the synthetic problem at hand. As illustrated, after regioselective formation of Diels-Alder product, in situ treatment of this compound with acetic acid formed the desired α,β-unsaturated system which concurrently eliminated phenyl sulfoxide to provide a product which was easily elaborated to the target structure.



SCHEME 3a

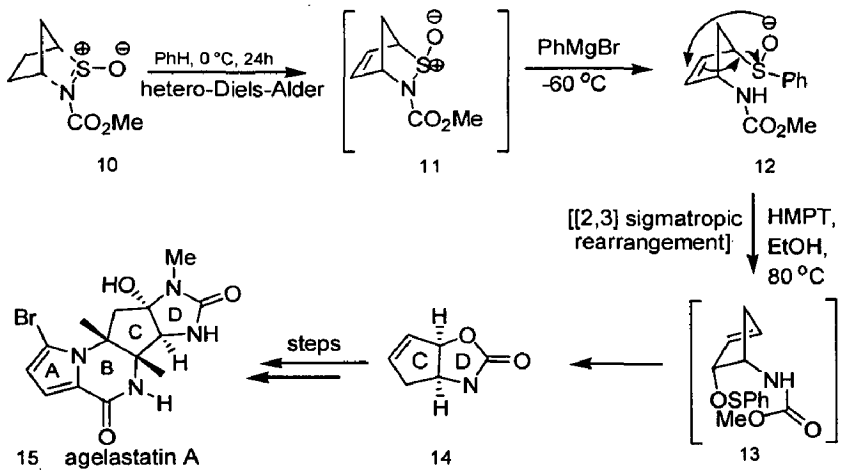


SCHEME 3b

HETERO-DIELS-ALDER REACTION

The ability to incorporate various heteroatoms at any of the six possible positions in the diene and dienophile components of the reaction constitutes a challenge which has occupied the hearts and minds of synthetic chemists since the discovery of the Diels-Alder reaction [33]. In fact, one of the first examples of a hetero- Diels-Alder reaction was disclosed by Alder himself in 1943 when he discovered, purely by serendipity, that an imine tautomer could engage appropriate dienes in a productive [4+2] cycloaddition [34]. The overall power of this hetero-Diels-Alder-based methodology is beautifully illustrated in the total synthesis of agelastatin A (**15**, Scheme 4) by Weinreb and co-workers, [35] the climax of extensive mechanistic studies and several creative syntheses achieved in this arena by this research group [36]. In the initial step of this synthesis; N-sulfinylmethylcarbamate (**10**) smoothly engaged in a hetero- Diels-Alder union with cyclopentadiene at 0 ^{0}C to provide **11**. In general, the addition process with this class of hetero dienophile is particularly reversible, and, as such, the observed products often do not reflect the kinetics of the initial addition. Additionally, the resultant sulfoxide stereochemistry in the Diels-Alder products is often difficult to predict or control. Since **11** was prone to retro-Diels-Alder reaction at ambient temperature, the compound was treated immediately upon formation with phenylmagnesium bromide and furnished **12** as a result of nucleophilic attack on the sulfur atom and concurrent lysis of the S-N bond. Heating a solution of this compound in HMPT and Et_3N induced the anticipated conversion into sulfenate ester **13** by a [2,3] sigmatropic rearrangement. Subsequent

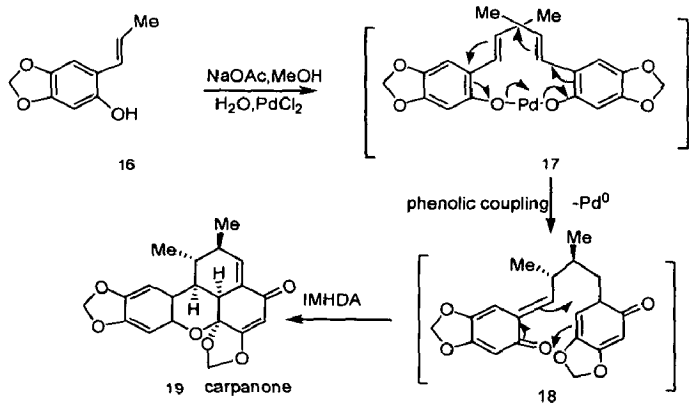
attack by the resulting nucleophilic oxygen atom on the pendant ester then led to carbamate formation and afforded **14**. As such, the net transformation accomplished by this programmed hetero- Diels-Alder/rearrangement sequence was the regioselective syn addition of an oxygen and a nitrogen atom across one of the double bonds of cyclopentadiene to provide a 1,2-aminoalcohol, a motif which is found in numerous natural products besides agelastatin A (**15**) [37].



SCHEME 4

CLOAKED DIENES AND DIENOPHILES

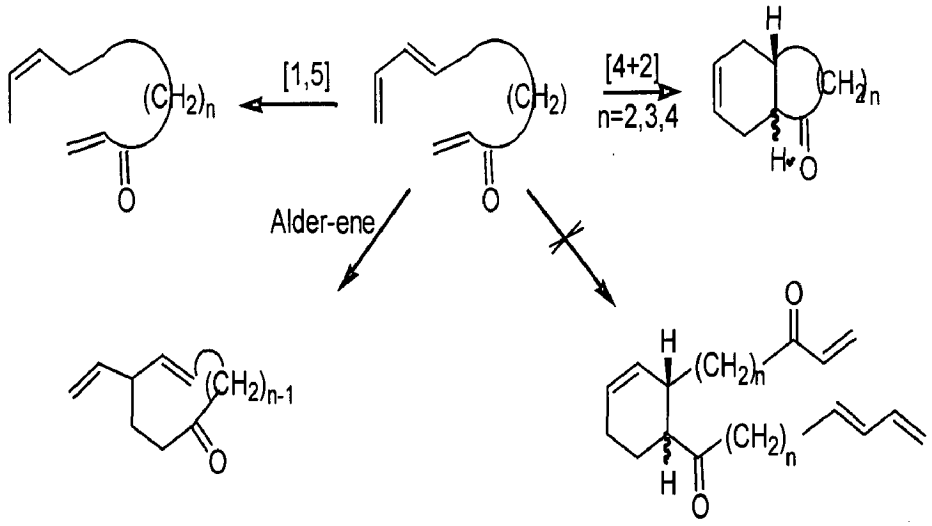
In the majority of applications of the Diels-Alder reaction in total synthesis the diene and dienophile moieties represent inherent parts of the molecular scaffold, readily visible to the naked eye throughout the synthetic sequence. An often more intriguing strategy, however, is the masking of such units until the key juncture in the synthesis, at which time they are uncloaked for the desired Diels-Alder reaction. Significantly, such approaches often constitute the only feasible method for realizing the desired Diels-Alder union when one or both components are fleeting intermediates or highly reactive species. The group of cascade-based total syntheses in which the generation of a highly reactive Diels-Alder component sets the stage for a subsequent immediate [4+2] cycloaddition reaction includes the classic biomimetic synthesis of carpanone (**19**, Scheme 5) in 1971 by Chapman et al. [38] In this example, exposure of monomeric phenol **16** to $PdCl_2$ in basic media effected a phenolic dimerization to **18** via reactive intermediate **17**.



SCHEME 5

INTRAMOLECULAR DIELS-ALDER REACTION

With the basic and relevant empirical facts well established, and the Woodward-Hoffmann rules allowing predictability of the expected structures to be produced in the classical intermolecular reaction, it became of interest to study ways to alter or circumvent the observed chemo-, regio- and stereoselectivities, and induce enantioselectivity [39]. The first reports on the IMDA reaction appeared in the fifties and sixties and were based upon the desire to produce polycyclic structures incorporating this cycloaddition as the key step (Scheme 6). The triene precursor strongly suggests a carbonyl group conjugated to the alkene dienophile partner. As the initial and principal objective was the synthesis of bicyclic products containing the expected cyclohexene ring fused to a five, six, or seven membered ring, the accumulated knowledge of the IMDA reaction provided detailed information about the diene portion, the dienophile portion and the kind of carbon chain (with or without heteroatoms) necessary for a successful reaction [40-42].



SCHEME 6

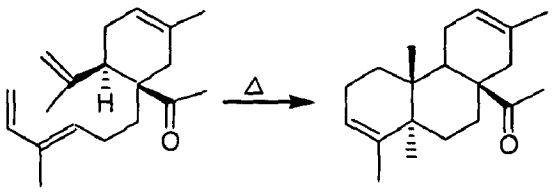
COMPETING REACTIONS

The question of the IMDA reaction acting in competition with the bimolecular intermolecular reaction does not seem to have been specifically investigated, which suggests that the IMDA is kinetically much more favored and therefore the intermolecular reaction products are not observed in significant amounts (Scheme 6). Brocksom et al. have however noted that many IMDA reactions are run at relatively low concentrations (generally around 10^{-3} mol.L^{-1}) perhaps with an intuitive respect for the possibility of competing intermolecular reactions. Also, [4+2] cycloadditions can co-exist with [1,5] sigmatropic hydrogen shifts and Alder-ene rearrangements (Scheme 6), under normal thermolytic conditions, and these other two pericyclic reactions are quite relevant in the intramolecular situation.

ELECTRONIC EFFECTS

The Diels-Alder reaction is a pericyclic reaction under complete stereoelectronic control, but is strongly influenced by electronic and steric effects in both diene and dienophile. However, the importance of these two effects is quite different in the intermolecular version and in the intramolecular and transannulear Diels-Alder reactions. As to the basic electronic loading on the dienophile partner, which requires conjugated

electron withdrawing groups for activation, this is not necessarily the case in the intramolecular and transannulear Diels-Alder reactions. Simple substituted ethylenes and ethynes do not give Diels-Alder products in good yields in the intermolecular version even at very high pressures, whereas convenient linkage to the diene partner allows cycloaddition. For example (Scheme 7), the Abad group in Spain has made very interesting use of the unactivated isopropenyl group present in suitably substituted and chiral carvone derivatives, in the synthesis of polycyclic higher terpenoids [43]. The synthesis of himandravine involves the IMDA reaction of a diene tethered through an ester group to a relatively unactivated dienophile which is also a diene [44], thus demonstrating chemoselectivity as well.

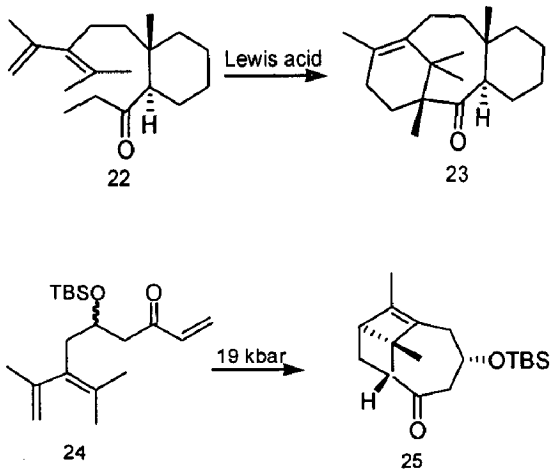


20 21

SCHEME 7

STERIC EFFECTS

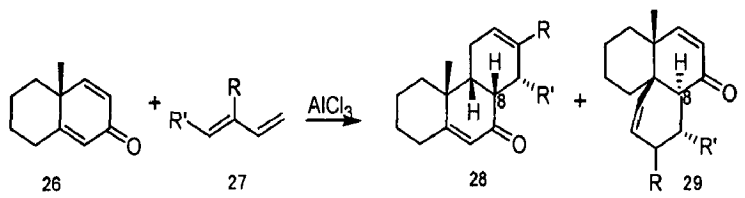
Steric effects can also be pronounced in the intermolecular version, specially at the terminal carbon atom of the diene. The *E*-substituted dienes react normally whereas their *Z* isomers are notoriously sluggish, requiring special conditions of high pressure or catalysis [45]. The definitive case is the terminally gem-disubstituted diene which usually defies all attempts at [4+2] cycloaddition, usually preferring the [1,5] hydrogen shift and posterior Diels-Alder reaction of the new diene. Scheme 8 shows two examples which demonstrate approaches to taxol synthesis involving the IMDA reaction as the key step, and where Lewis acids [46] and very high pressure [47] were essential for effective reactions.



SCHEME 8

CHEMOSELECTIVITY

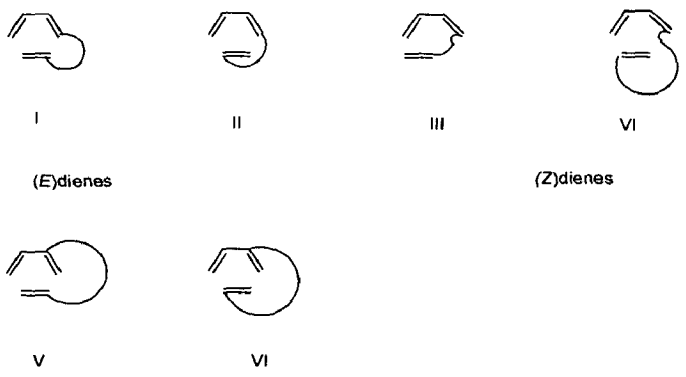
The electronic and steric effects which define diene and dienophile reactivity in the intermolecular situation are well known, so that molecules containing more than one diene function can be reacted chemoselectively with molecules containing more than one dienophile moiety, and many interesting experiments have been devised and conducted with this objective in mind. The dienes can be present as a conjugated triene or as separate dienes, while the dienophiles can also be in extended conjugation or in two different sites in the molecule. For instance, the Wenkert-Fringuelli-Taticchi groups have performed extensive investigations on the extended and double dienophile situations, as can be seen in the example in Scheme 9. The general case for diene chemoselectivity has been reviewed.



SCHEME 9

REGIOSELECTIVITY

In a very similar sense, the diene-dienophile chain combinations determine the regiochemistry of cycloaddition between the two possible orientations. These relationships have been formalised as modes or types [41] and are shown in Scheme 10. Modes I through IV are denominated type I (or 1) where the chain is linked from the terminal carbon atom of the diene, whereas modes V and VI are named type II (or 2) as the chain is linked from the non-terminal carbon atom of the diene. Mode I is generally much preferred over mode II, as is mode V over mode VI, for obvious strain reasons, although lengthening the chain between the diene and the dienophile will finally allow modes II and VI to participate. In the case of the Z-dienes as in modes III and IV, there is clear evidence of preference for mode III, while once again a longer chain may favor mode IV. This leads to the important conclusion that the dominant regiochemistry, as defined by the coefficients of atomic orbitals in intermolecular reactions, can be overruled by linking the partners in the opposite orientation as long as the chain is not too long.

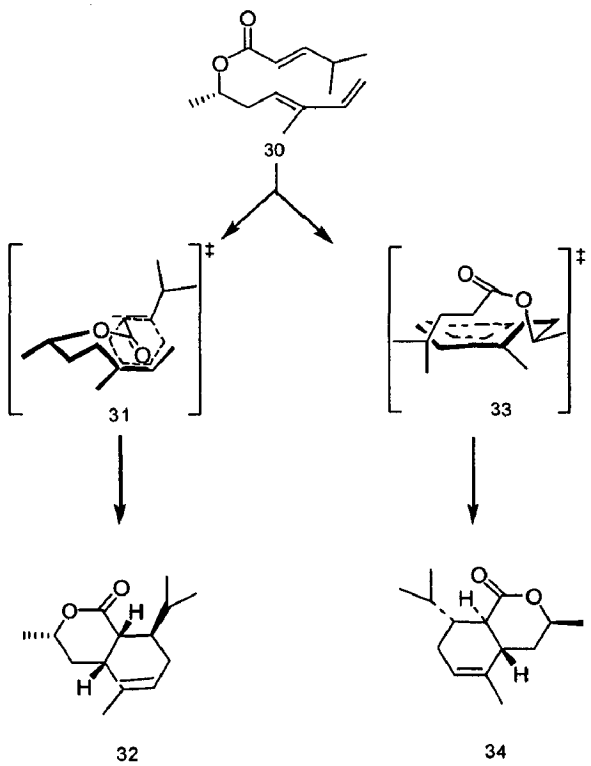


SCHEME 10

STEREOSELECTIVITY

The stereochemistries of diene to chain and dienophile to chain are extremely relevant for defining the stereochemistry of the cycloadduct, with special reference to the ring junctions. The stereoselective transfer of alkene stereochemistry (sp^2 carbon) to

create new sp^3 stereogenic centres is a very well established and fundamental concept in synthesis, as is the opposite process, and well demonstrated in the case of the Diels-Alder reaction. The kinetically preferred intermolecular endo transition state can be overruled by conformational requirements which demand an exo transition state. Thus different stereoselectivities can be pre-ordained by the judicious choice of the diene, the dienophile and principally how the chain links them together. This point has been very well treated in reviews with special attention being given by Craig [42] (Scheme 11).

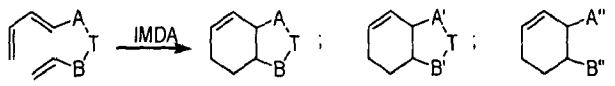


SCHEME 11

CHAINS, BRIDGES, TETHERS, SPACERS, AND LINKERS

The developments in this area have opened up new possibilities for application of the IMDA reaction which are now becoming more and more commonplace. This involves the very basic question of the nature of the chain (or bridge), which at first sight was, and still is, to be an intrinsic part of the product structure and therefore a highly important component of the cycloaddition precursor. However, it was soon realised that

the functionalities present and the length of the chain were also important for the success of the IMDA reaction. This is now so true that the chain may be incorporated into the final product as is, or by functional group modification, or simply discarded after having served its purpose.



SCHEME 12

(Scheme 12; A and B are the original substituents linked by a tether T, while A', B', A" and B" are transformed functionalities). This last analysis brings in the concepts of spacers, linkers, and tethers instead of the chain, where the spacer (or linker) has the function of separating, in a flexible fashion, the diene and the dienophile by the correct distance for accommodation into the requisite transition state conformation. The tether is perhaps the most common word used now, and includes the concept of the spacer together with more subtle details about functional groups present. The combination of the requisite distance together with the organisation of the tether into preferred conformations, can secure the diene and dienophile units into more tightly structured relationships and therefore more appropriate transition states. Finally, the tether can also include modifiers at the termini which are chosen and incorporated for the specific purpose of fine-tuning the electronic situation of the diene and/or dienophile. Thus the concept of the tether can be conveniently subdivided into the following;

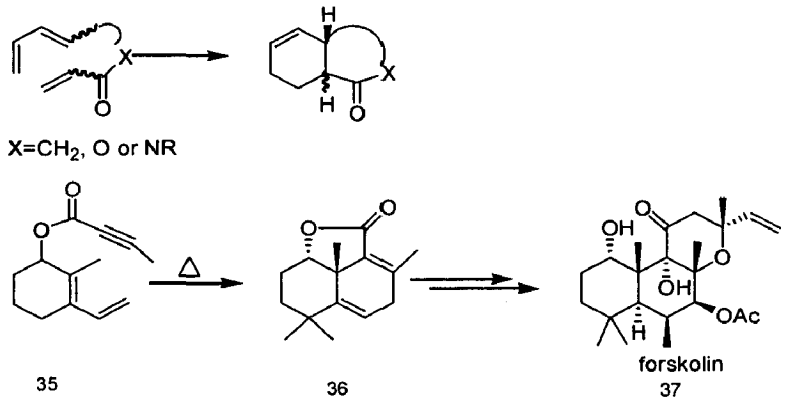
a) The tether is permanent in that it is to be used in the cycloaddition reaction and also is present in the product, with perhaps minor functional group modifications occurring after the IMDA reaction.

b) The tether is still permanent in that it also uses strong covalent bonds, and a portion will be retained in the product. The tether is also to be chosen for some steric effect, such as the tether control group effect or the buttressing effect [45], which are used to advantage to force the diene and dienophile groups into greater proximity.

c) The tether is less permanent and not to be used in the cycloadduct's further chemistry, as is the case with the protecting group strategy [46] involving silyl ether tethers [42-44].

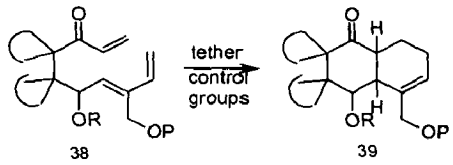
d) The tether is temporary to the point of being created in situ during the reaction, leading to the transition state, and being removed from the cycloadduct at the end of the reaction.

The permanent type of tether is the dienophile linked to an electron withdrawing group, and then to the diene by a methylene chain, preferably with the functional groups which are present in the desired cycloadduct. The electron withdrawing group most frequently chosen is the carbonyl group (Scheme 13), as a ketone or as an ester or amide. However, it is important to recognise that there is a big difference between ketones and the other two groups due to preferred conformational requirements of the ester and amide groups, with their heteroatom non-bonding electrons being in overlap with the p orbital of the carbonyl group.



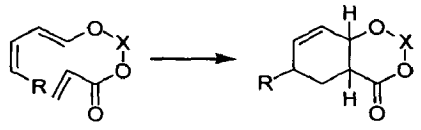
SCHEME 13

The second type of tether that has been developed more recently involves two different solutions to the same basic question of how to force the diene and dienophile components into closer proximity by the use of a steric control element. Scheme 14 (equation 1) presents the solution which Fallis and co-workers have named the tether control group [47-49], and which works by incorporation of rigidity. This rigidity can be imposed on the tether by a simple cis-double bond or its di-hydroxyl derivatives, and also by different kinds of aromatic rings. The second solution involves the buttressing effect [45], whereby a conveniently located quaternary carbon atom is substituted by the diene chain, the dienophile chain and two substituents which reduce the conformational liberties of the two chains. The exchange of simple methylene groups in the tether (group X) for more highly substituted carbon atoms has been studied (Scheme 14; equation equation 2) with convincing results as to the buttressing effect [50].



38 39

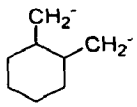
eq. 1



40 41

X=-$(CH_2)_3$-, -$CH_2CMe_2CH_2$-, -$CHMeCH_2CHMe$-

R = H, Me

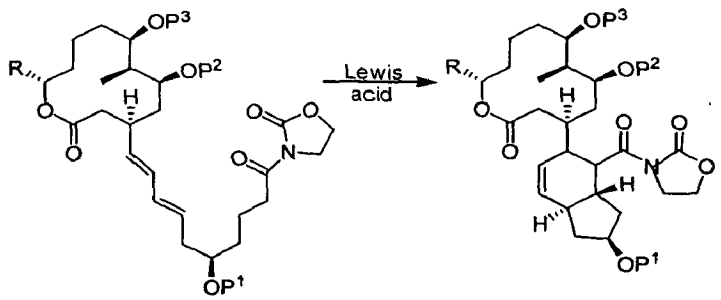


eq. 2

SCHEME 14

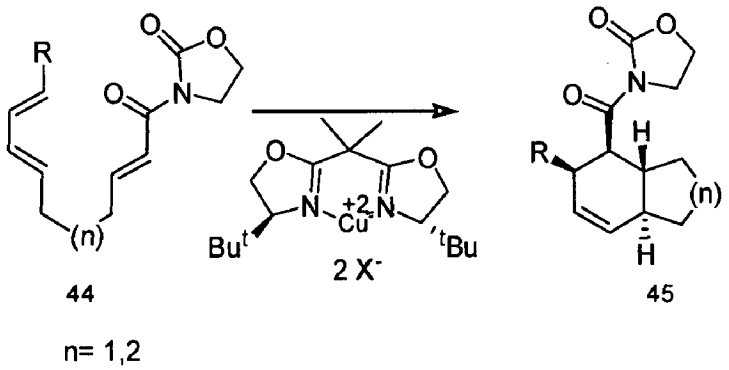
IMDA REACTION IN TOTAL SYNTHESIS

Many total syntheses now include at least one pericyclic reaction as a key step, preferably in a tandem combination with another pericyclic reaction, and where the Diels-Alder reaction is the most popular choice for the preparation of six membered rings. The Evans group has used the IMDA reaction both in total synthesis and as a vehicle for demonstrating the success of bis-oxazoline chiral catalysis, as for example in generating the hydrindene nucleus of more complex natural products (Scheme 15, equations 1 and 2) [51,52].



42 43

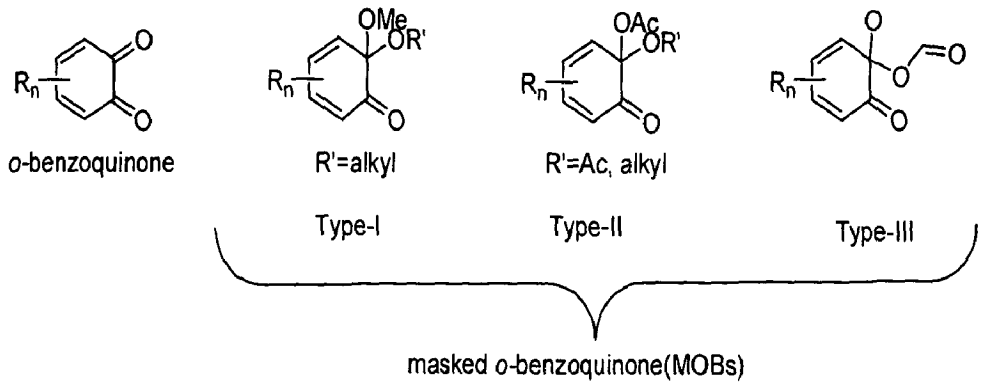
eq. 1



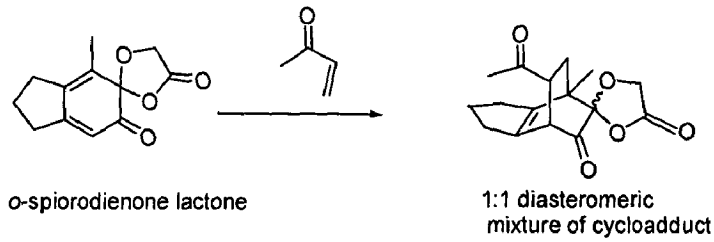
eq. 2

SCHEME 15

Masked o-benzoquinones (MOBs,), a type of cyclohexa-2,4-dienones, are a relatively under-utilized class of compounds [53,54]. MOBs, which are linearly conjugated cyclohexadienones, can potentially participate in cycloaddition and nucleophilic addition reactions. The double bonds of the diene moiety, being positioned between a carbonyl and an acetal functions, are electronically differentiated and can be elaborated regioselectively in various reactions. In addition, the acetal moiety serves as monoprotection for the vicinal carbonyl system. Despite their remarkable synthetic potential, MOBs are relatively underexploited in organic synthesis as compared to their counterparts derived from p-benzoquinones. This dearth of MOB chemistry may be attributed to their high reactivity, resulting in great propensity toward dimerization. Furthermore, lack of efficient methods for the preparation of MOBs appears to be another main deterrent to their use in organic synthesis. Intrigued by the unexploited synthetic potential of this class of synthons, Liao and Peddinti have embarked on a research program on "chemistry of masked o-benzoquinones" with the main aim of evolving new synthetic methodologies, especially based on the Diels-Alder reactivity of MOBs. It is worth mentioning that Deslongchamps opened the field in 1969 by reporting the first example [55] (shown in Scheme 17) which led later on the total synthesis of (+)-ryanodol [56].



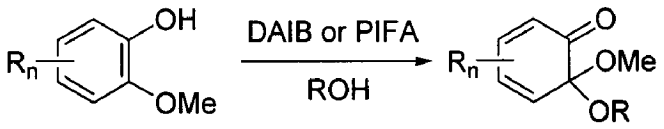
SCHEME 16

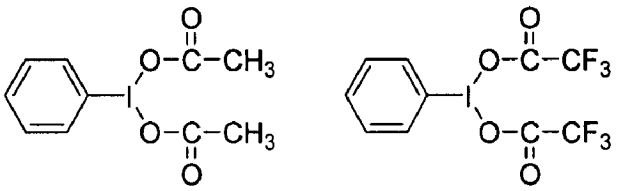


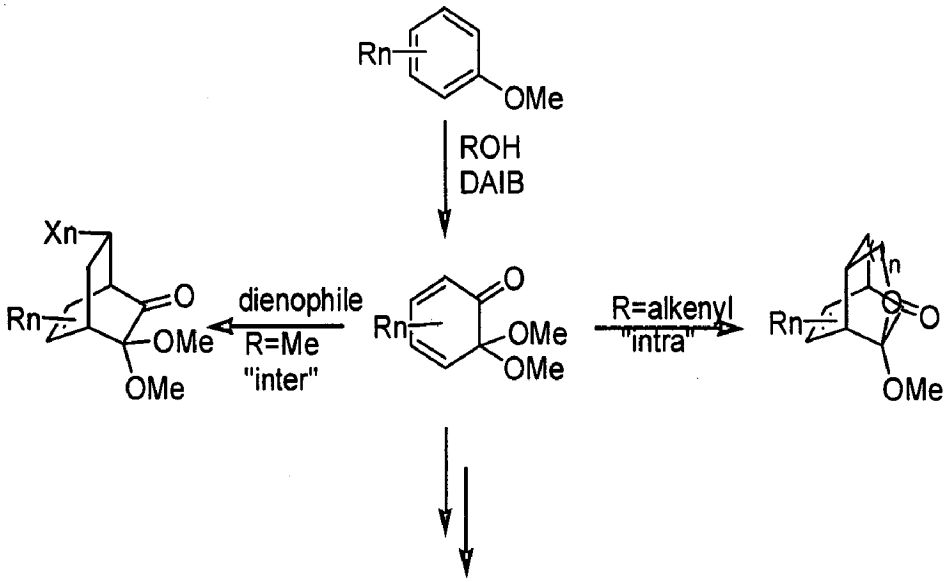
SCHEME 17

MOBs can be easily generated in situ by the oxidation of the corresponding 2-methoxyphenols [54] with hypervalent iodine reagents such as (diacetoxy)iodobenzene (DAIB) or phenyliodonium(III) bis(trifluoroacetate) (PIFA) in the presence of an alcohol. In situ generated MOBs undergo rather facile intermolecular Diels-Alder reactions in a regio- and stereocontrolled manner with electron-deficient dienophiles, [57, 58], acyclic dienes [59] and cyclopentadiene [60] to produce the corresponding bicyclo[2.2.2]octenone derivatives derived via endo-addition. Very recently, Liao et al. have demonstrated the dienophilic behaviour of heteroaromatics namely, furans [61], and indoles [62] in the Diels-Alder cycloadditions with MOBs. When the oxidation of 2-methoxyphenols was carried out in the presence of an alkenol, MOBs undergo facile intramolecular cycloaddition reactions via a tandem oxidative acetalization [63] (Scheme 18). The inter and intramolecular Diels-Alder reactions of MOBs have already utilized as a key step in the stereoselective synthesis of various compounds, including polysubstituted cyclohexene derivatives, [64] cis-decalins, [65] bicyclo[4.2.2]decenones,

[65] tricyclo[3.3.0.0^{2,8}]octenones, [66] and bicyclo[4.2.0]-octenones [66]. In addition, these reactions were employed as the key step in the total syntheses of cleradone diterpenic acids, [67] forsythide aglucone dimethyl ester [68] and pallescensin B [69] and in a formal synthesis of reserpine [70].







SCHEME 18

6,6,-Dialkoxycyclohexa-2,4-dienones often known as orthobenzoquinone monoketals or masked *o*-benzoquinones remain underutilized class of substrates in preparative organic synthesis, in contrast to their *para*-counterparts - 4,4,-dialkoxycyclohexa-2,5-dienones whose chemistry has been well explored [71]. Unlike *p*-benzoquinone monoketals, which are cross-conjugated dienones, orthobenzoquinone

monoketals with linearly conjugated dienone moiety are highly reactive and often undergo self dimerization [58]. The dimerization event itself is a Diels-Alder process, in which one molecule acts as diene and the other as dienophile. This Diels-Alder reaction proceeds in a highly selective manner to provide a single Diels-Alder cycloadduct. The propensity of dimerization mainly depends on the substitution pattern on the aromatic nucleus. The nature and the position of the substituent dictate the reactivity and stability of a particular cyclohexa-2,4-dienone. For instance, when an electron-withdrawing group is present at C4 of the cyclohexadienone, the propensity toward dimerization is increased. On contrary, the electron-releasing group at that position exerts an opposite effect.

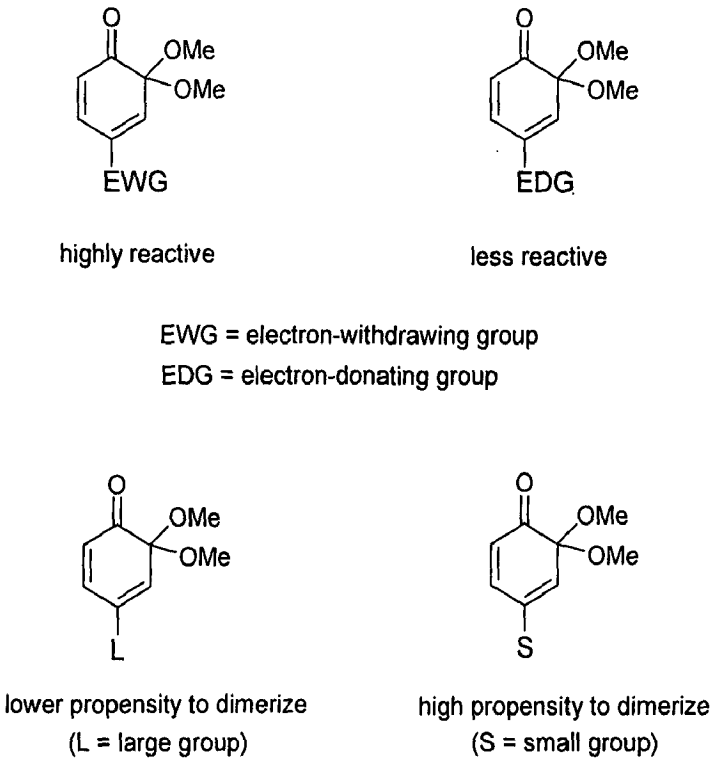


FIGURE 1: Effect of substituents on the propensity of dimerization of cyclohexa-2,4-dienones.

The presence of bulky substitutent at C4 of cyclohexadienone also retards the Diels-Alder dimerization and a small substituent increases the tendency of dimerization (Figure 1) [58]. The propensity to dimerize via [4 + 2] cycloaddition can be significantly diminished by having either a bromine substituent at the 4-position or a small alkyl or alkoxy group at the 5-position of the cyclohexa-2,4-dienone system. Some of the isolable

orthobenzoquinone monoketals, which are relatively stable, are shown in figure 2 [58, 72-73].

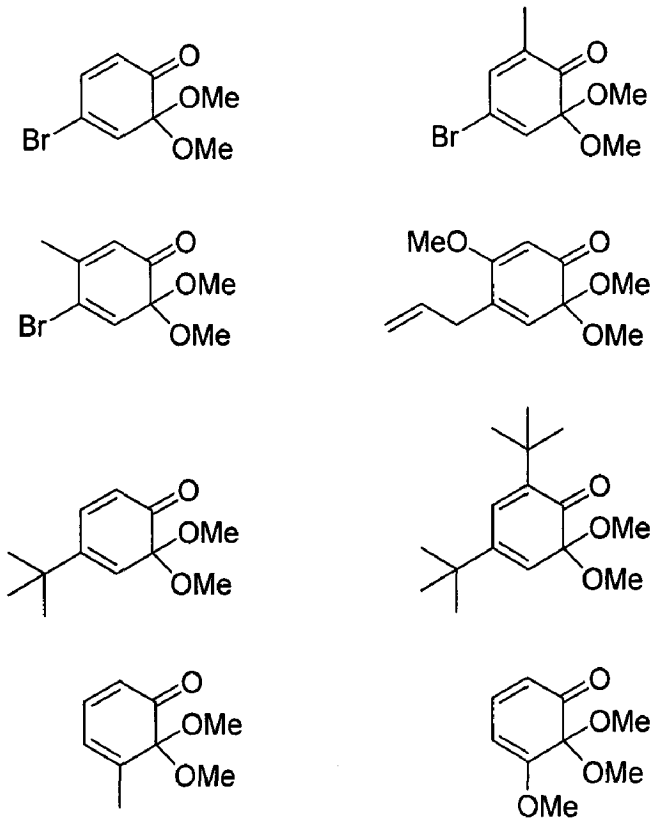
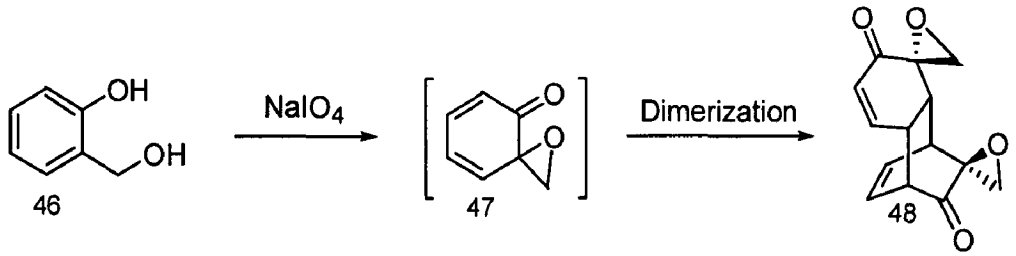


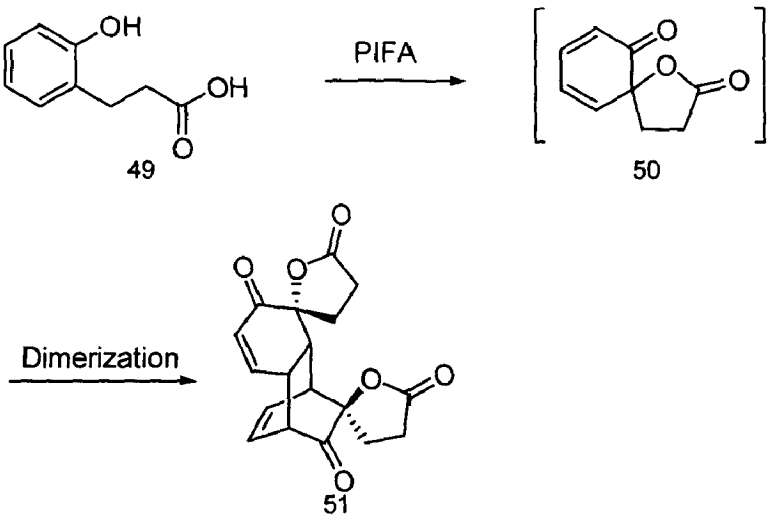
FIGURE 2: Stable orthobenzoquinone monoketals.

It is known from literature that the parent 6-alkyl-6-alkoxy-cyclohexa-2,4-dienones without any substitutions are also unstable and undergo Diels-Alder dimerization and provide the corresponding dimeric adducts. 6-Spiroepoxycyclohexadienones are easily obtained by Alder-Becker oxidation ($NaIO_4$) of salicyl alcohols. The dimerization usually occurs at room temperature, through a *syn-endo* Diels-Alder reaction (Scheme 19) [74].



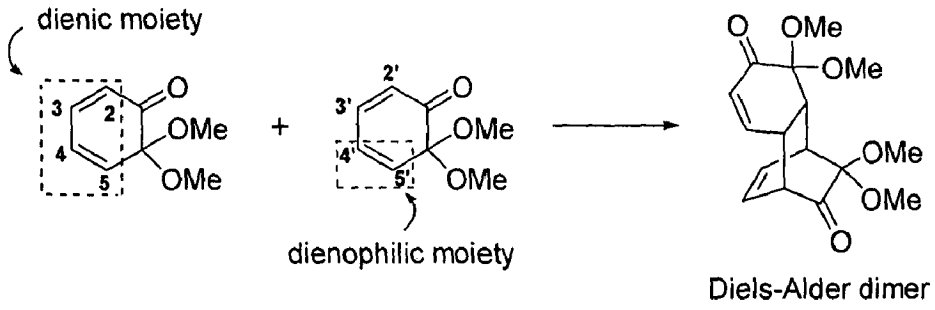
SCHEME 19: Generation and dimerization of a 6-spiroepoxycyclohexa-2,4-dienone.

The oxidation of 3-(2-hydroxyphenyl)propionic acid with phenyliodonium(III) bistrifluoroacetate produces spirolactodienone, which dimerizes at room temperature to afford the corresponding dimer (Scheme 20).



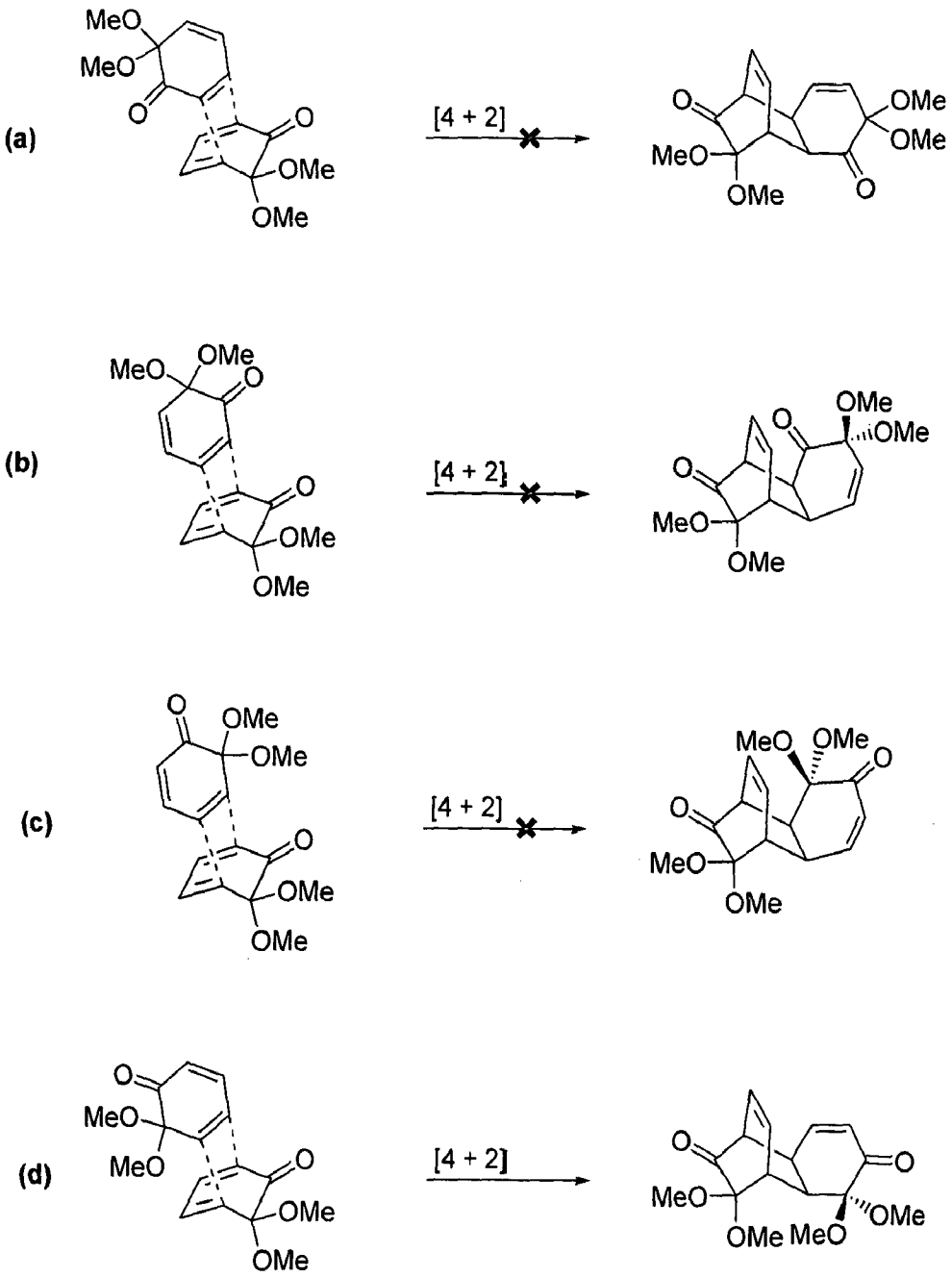
SCHEME 20: Generation and dimerization of a 6-spirolactocyclohexa-2,4-dienone.

The orthobenzoquinone monoketals, by virtue of their structure, can react as both diene and dienophile which render them to involve in self-dimerization via Diels-Alder reaction. The Diels-Alder reaction proceeds in highly stereo-, regio-, chemo-selective manner. Although there are a priori many possible modes of [4 + 2] cycloadditions, the dimerization provides a single isomer. Among the two double bonds, the $C_{4'}$=$C_{5'}$ bond of orthobenzoquinone monoketal acts as dienophilic component. The dienophilic orthobenzoquinone monoketal approaches the dienic orthobenzoquinone monoketal to yield the cycloadduct with *endo*-selectivity. The dimers possess ortho-regiochemistry *i.e.*, the $C_{2'}$=$C_{3'}$ bond is adjacent to the C_1 carbonyl group of the dimer (Scheme 21) [75].



SCHEME 21: Dimerization of parent orthoquinone monoketal.

Several research groups performed theoretical calculations on molecular orbitals at both semi-empirical and ab initio RHF at various levels with the aim of identifying some reasons that might explain the dimerizing and non-dimerizing behaviours of these orthoquinone monoketals as well as their high stereo- and regioselectivities [58b,75b,76-78a,]. The findings indicate that calculations based on such simple terms of FMO theory are not enough to delineate any general trends in the reactivity/selectivity profile of orthoquinone monoketals with external dienophiles. For the sake of simplicity, the four transition states of the dimerization event of the parent orthoquinone monoketal are shown in scheme 22. The first two possibilities (**a**) and (**b**) can be ruled out on the basis that the remaining C4-C5 double bond loses its conjugation with the electronic demanding C1 carbonyl group in the process, thus probably affecting the extent of any participation of this double bond in secondary orbital interactions (SIOs) with the C3 and C4 p orbitals of the orthoquinone monoketal unit. Among the possibilities (**c**) and (**d**), the latter appears to have the lowest dipole moment of the transition state and the formation of dimer through this path is expected [78].

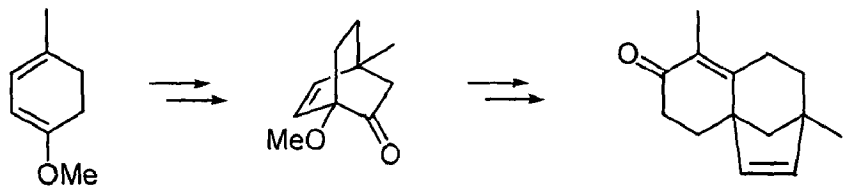


SCHEME 22: Four modes of dimerization of parent orthobenzoquinone monoketal.

2,4-cyclohexadienones themselves are very important compounds from both synthetic and biological points of view [79-81]. They were recently identified as a potential new class of receptor tyrosine kinase inhibitors [80]. They can in principle participate in (i) cycloaddition reactions, [79] (ii) nucleophilic, electrophilic, and radical addition reactions, [82] and (iii) photochemical reactions [83]. Despite their vast

potential, they are a relatively underutilized class of compounds. Although not extensively, the Diels-Alder chemistry of cyclohexadienones has been studied and used in the total synthesis of natural products [79, 84-90]. The use of cyclohexadienones in a general way is constrained in that their preparation requires strategic placement of substituents, which cannot be removed easily. On the other hand, masked *o*-benzoquinones (MOBs) could be ideal compounds for use in Diels-Alder reactions because the unavoidable acetal group, being positioned next to a keto group, could be removed by reduction if not required or modified into a desired functionality at a latter stage with relative ease [85-86]. Bicyclo-[2.2.2]octenones obtained via the Diels-Alder reactions are useful synthons for polysubstituted cyclohexanes, [70] bicyclo[3.2.1]octenones, bicyclo[4.2.0]octenones, [91,92] tricyclo-[3.3.0.$0^{2,8}$]octanones,[91] variously fused triquinanes,[93] cis decalins, [94] and bicyclo[4.2.2]decenones [95]. Bicyclo[2.2.2]octenones derivatives, which have a wide range of applications in the synthesis of natural products, [96,97] can be accessed easily by using the Diels-Alder reaction of 2,4-cyclohexadienones with activated alkenes [4,98]. Similarly, bicyclo[2.2.2]octadienones derivatives can be conveniently generated by reaction of activated alkynes with 2,4-cyclohexadienones [99-103]. Both bicyclo[2.2.2]octadienones and bicyclo[2.2.2]octenones can undergo interesting and useful photochemical reactions, viz., di-π-methane (DPM) and oxa-di-π-methane (ODPM) rearrangements, and 1,3-acyl migration and ODPM rearrangement, respectively. Unlike bicyclo[2.2.2]octenones, the only general method for preparing bicyclo[2.2.2]octadienones is the Diels-Alder reaction of 2,4-cyclohexadienones with acetylene derivatives [99-103]. The ground and excited state reactions of bicyclo[2.2.2]octenones lead to complex polycyclic systems, which have served as precursors for diverse natural products [96,97]. The bicyclo[2.2.2]octanes or bicyclo[2.2.2]octenones may be transformed by subsequent molecular reorganizations involving a fragmentation to give cyclohexanes or via pinacolonic rearrangement to give bicyclo[3.2.1]octanes. Since the structures of a number of types of natural products incorporate a bicyclo[3.2.1]octane ring system, a general method for its construction by rearrangement of bicyclo[2.2.2]octanes would be useful. One such sequence is used in an

elegant synthesis of stachenone (54) which was obtained from the transformation of bicyclo[2.2.2]octenone (53) [104] (Scheme 23).

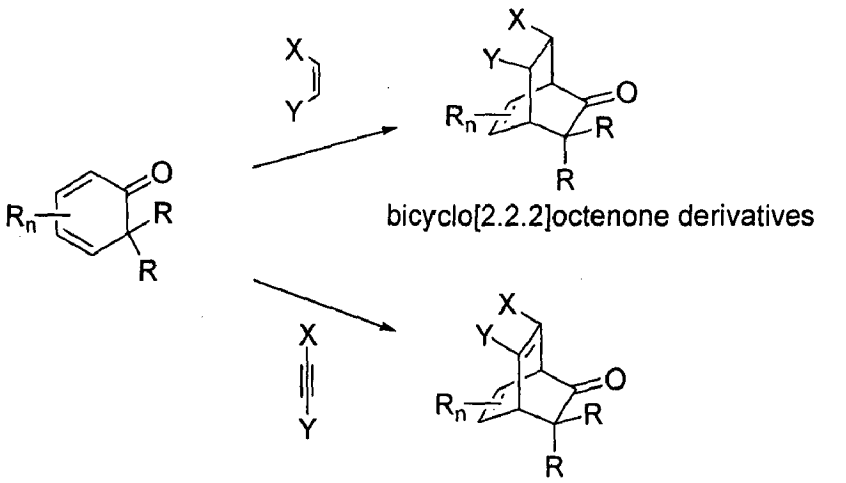


52 53 54

stachenone

SCHEME 23

A large number of dienes and dienophiles with a plethora of functionalities has been used to construct various types of bicyclo[2.2.2]octenones. These ring systems can be accessed easily by using the Diels-Alder reaction of 2,4-cyclohexadienones with activated alkenes [6]. Similarly, bicyclo[2.2.2]octadienones can be conveniently generated by reaction of activated alkynes with 2,4-cyclohexadienones (Scheme 24) [99].

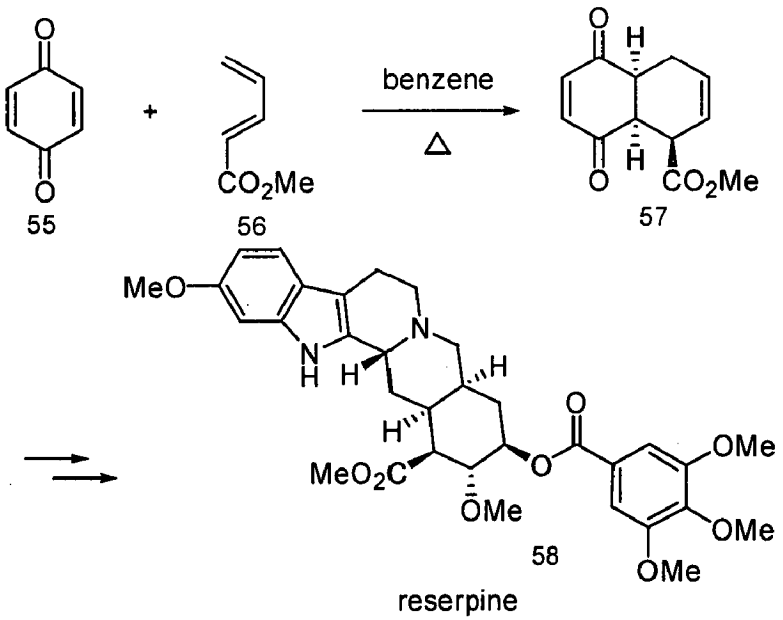


R = alkoxy, alkyl, acyloxy
R_n = groups
X, Y = electron-withdrawing groups

SCHEME 24

1.2 *LITERATURE SURVEY*

Liao and coworker have proved the synthetic utility of masked o-benzoquinones. The inter- and intramolecular Diels-Alder reactions of in situ generated masked o-benzoquinones produced cycloadducts in excellent selectivities. New synthetic methodologies have been developed for the synthesis of highly substituted ring systems including bicyclo[2.2.2]octenones, oxatricycles, triquinanes, polysubstituted cyclohexanes, and bicyclo[4.2.2]decenones with complete stereocontrol from easily accessible 2-methoxyphenols via the Diels-Alder reaction of masked o-benzoquinones. The Diels-Alder reaction with quinones as dienophiles has provided a powerful construction for functionalized *cis*-fused decalin systems. Many syntheses of complex natural products have been recorded in which the quinone Diels-Alder reaction has been used to set in place an initial arrangement of rings and stereocenters that paves the way for elaboration of the final target structure by subsequent transformations. The notable examples are steroids, reserpine, ibogamine, dendrobine, gibberellic acid, trichodermol and euonyminol [105].

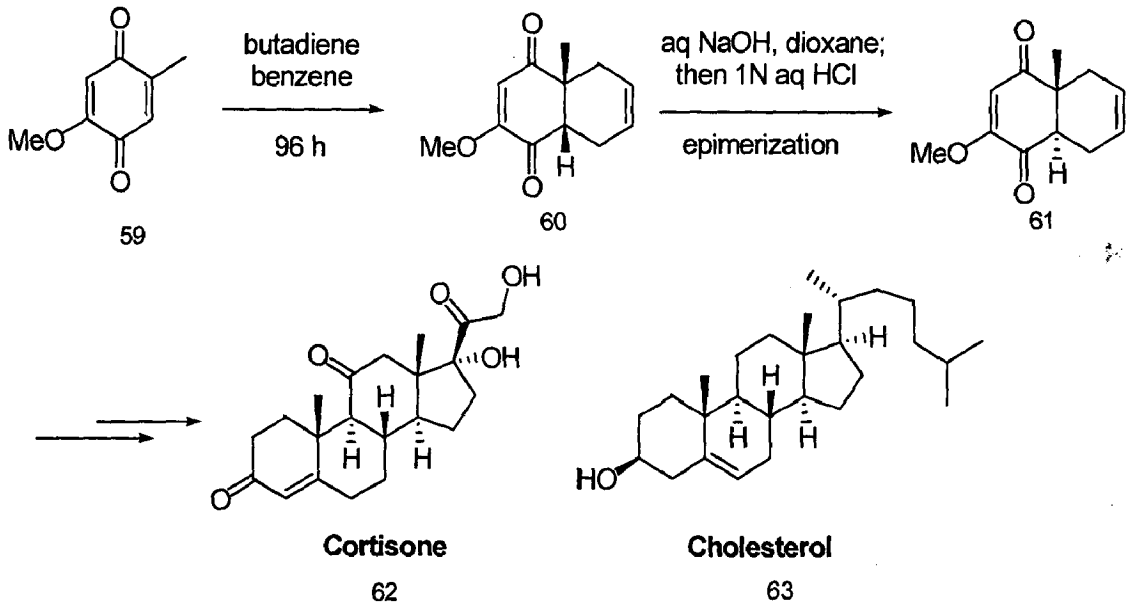


SCHEME 25

The Diels-Alder cycloadduct obtained from the reaction of *p*-benzoquione with a butadiene derivative was utilized as an intermediate for the famous Woodward synthesis

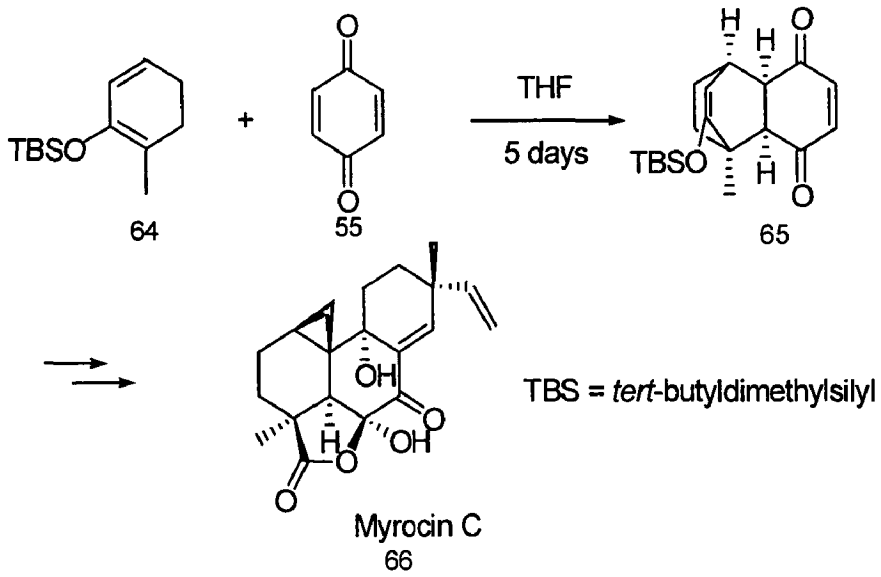
of reserpine [105]. The use of Diels-Alder strategy to form an initial array of rings and stereocenters, elements which pave the way for the subsequent stereocontrolled elaboration to the final target molecule represents distinctive hallmark of Woodward's synthetic acumen (Scheme 25).

In 1952, Woodward *et al.* disclosed their historic routes to the steroids cortisone and cholesterol, where in the initial step reaction, 2-methoxy-5-methylquinone underwent Diels-Alder cycloaddition with butadiene to form a *cis*-fused bicyclic adduct [105]. The *cis*-fused adduct was first converted into *trans*-fused bicyclic system and later on transformed into cortisone **(62)** and cholesterol **(63)** (Scheme 26).



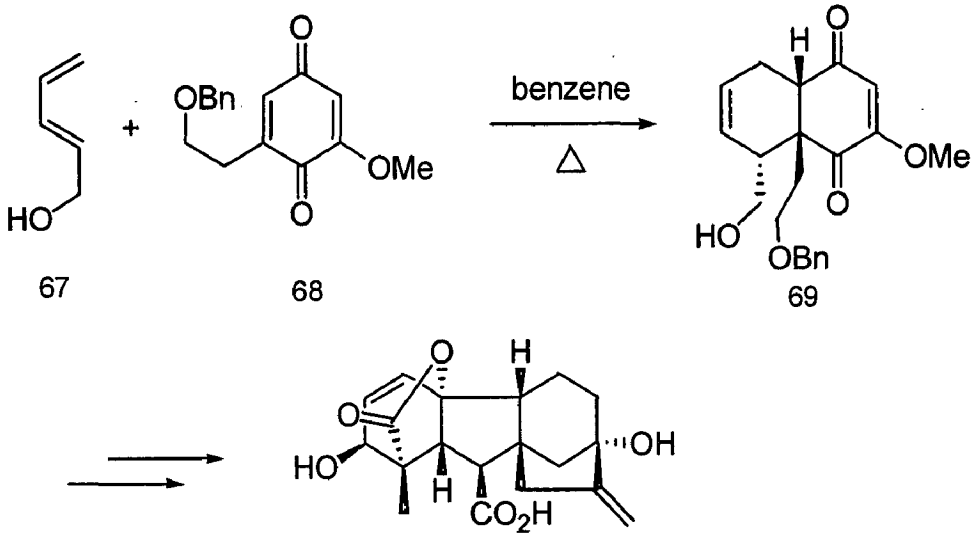
SCHEME 26

Danishefsky and his co-workers controlled the stereochemical outcome of the intermolecular Diels-Alder reaction (diastereoselectivity) in the total synthesis of Myrocin C **(66)** (Scheme 27) [32]. It is pertinent to mention here that the complete selectivity realized in this inter molecular event is common for substrate controlled intramolecular reactions.



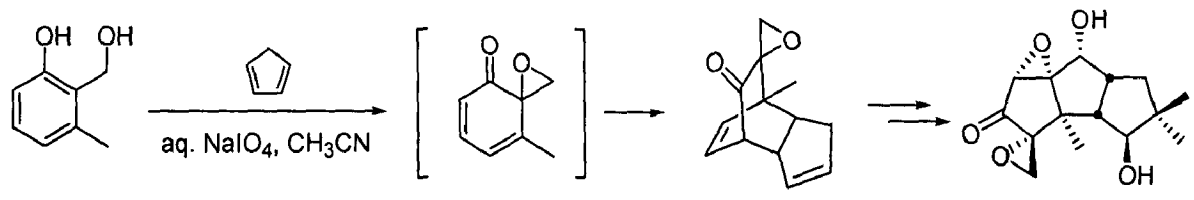
SCHEME 27

The power of strategies that exert sterochemical control is similarly reflected in the brilliant total synthesis of gibberellic acid by Corey et al. [105, 106] wherein an initial chemo- and regioselective Diels-Alder union between diene and quinone forged the relative stereochemistry in *cis*-decalin (Diels-Alder adduct), and subsequent elaboration to diene intermediate enabled a substrate controlled intramolecular Diels-Alder reaction to proceed with selective formation of the expected product (Scheme **28**).



SCHEME 28

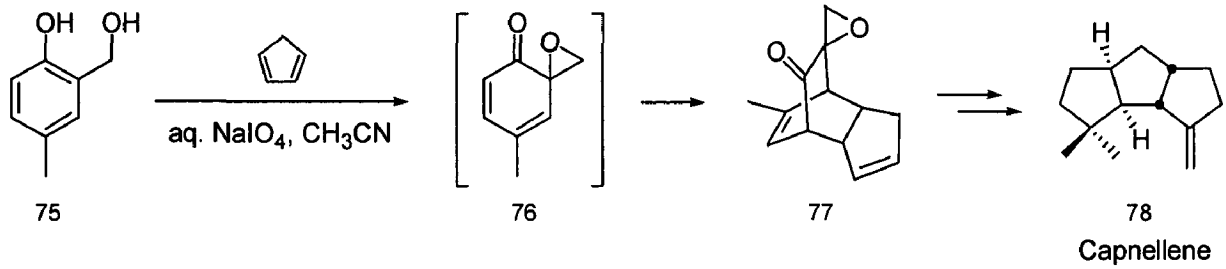
A classical method to enhance regioselectivity is based on the use of Lewis-acid catalysts. Upon complexation of such species to the dienophile, the normal demand Diels-Alder reaction is promoted since the energy gap between the LUMO of the dienophile and the HOMO of the diene is reduced, thus decreasing the activation energy required to achieve the cycloaddition. Furthermore, as the stabilization is greater for the *endo*-transition state, as a result of beneficial enhancement of secondary orbital overlap that is unobtainable in an *exo* mode of reaction. The use of Lewis-acids favours an increased ratio of *endo:exo* products. It is worthwhile to mention that Lewis-acids can often reverse the regiochemical course of a Diels-Alder addition and generate products that would not otherwise be observed in a simple, thermally induced reaction. Recent investigations in Corey's group have focused on the use of 1,4-monoketals rather than the corresponding quinones, for reasons which include the following. i) The monoketals are expected to be more Lewis-basic; ii) the monoketals would provide adducts that do not undergo facile aromatization, in contrast to the 1,4-quinone adducts, which are known to aromatize readily and to be difficult to handle; iii) the monoketals lead to adducts in which one of the two carbonyl groups of the 1,4-quinone is already protected, thus simplifying the task of further selective transformations, and iv) the monoketals are accessible synthetically either from oxidative *p*-ketalization of phenols or from transketalization starting from 4,4-dimethoxy-2,5-cyclohexadienones. Corey reported catalytic enantioselective Diels-Alder reaction of 1,4-quinone monoketals. Singh *et al.* reported a formal total synthesis of coriolin (**74**) from 6-methylsaligenin (**71**) and cyclopentadiene. The cyclohexadienone derivative **72,** which was generated *in situ* by the Becker-Alder oxidation of phenol **71** underwent Diels-Alder reaction with cyclopentadiene to provide the cycloadduct **73** Subsequently, the dienone **73** was converted into coriolin (**74**) (Scheme **29**) [107].



71 72 73 74
Coriolin

SCHEME 29

A *p*-cresol derivative **75** was used as the starting phenol, which was submitted to Becker-Alder oxidation in the presence of cyclopentadiene. The *endo*-annulated bicyclic ketone **77** obtained by the Diels-Alder reaction of in situ generated cyclohexa-2,4-dienone **76**, was transformed into the target capnellene (**78**) (Scheme **30**) [108].

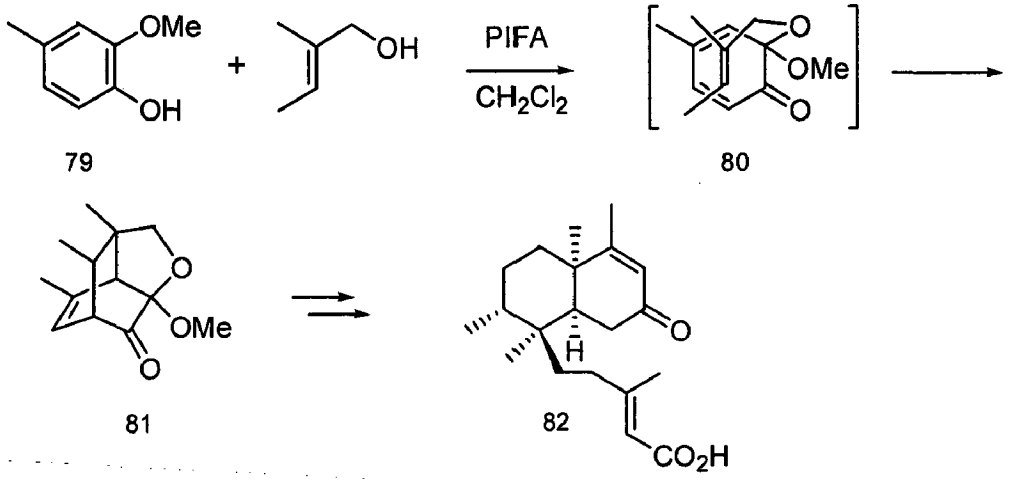


75 76 77 78

Capnellene

SCHEME 30

Liao and co-workers have applied their orthobenzoquinone monoketal based route to bicyclo[2.2.2]octenones in the synthesis of two diastereomeric but naturally occurring *cis*-clerodane diterpenic acids **82** (*Eperua purpurea*) and **85** (*Aristolochia vrasiliensis*) in racemic forms (Schemes 31 and 32). The first synthesis featured the oxidative ketalization of the creosol (**79**), with the allyl alcohol using phenyliodonium(III) bistrifluoroacetate (PIFA) followed in situ by an intramolecular Diels-Alder reaction of orthobenzoquinone monoketal **80** to furnish the oxatricyclic ketone **81**. This compound was then transformed into the α-*cis*-clerodane derivative **82** [109].

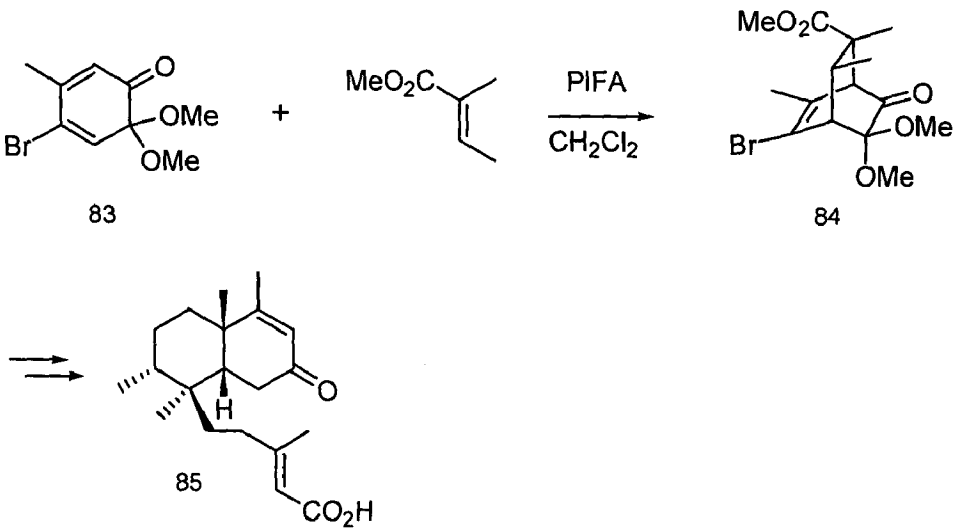


79 80 81 82

a *cis*-Clerodane diterpenic acid

SCHEME 31

The synthesis of the diastereomeric diterpenic acid **85** made use of the improved intramolecular Diels-Alder reaction of non-dimerizing orthoquinone monoketal **80** depicted in scheme 28 [110]. Thus, 6,6-dimethoxy-4-bromo-3-methylcyclohexa-2,4-dienone (**83**) was cycloadded to the dienophile to afford the cycloadduct **84**. Further elaboration of **84** led to the formation of β-*cis*-clerodane derivative **85**.

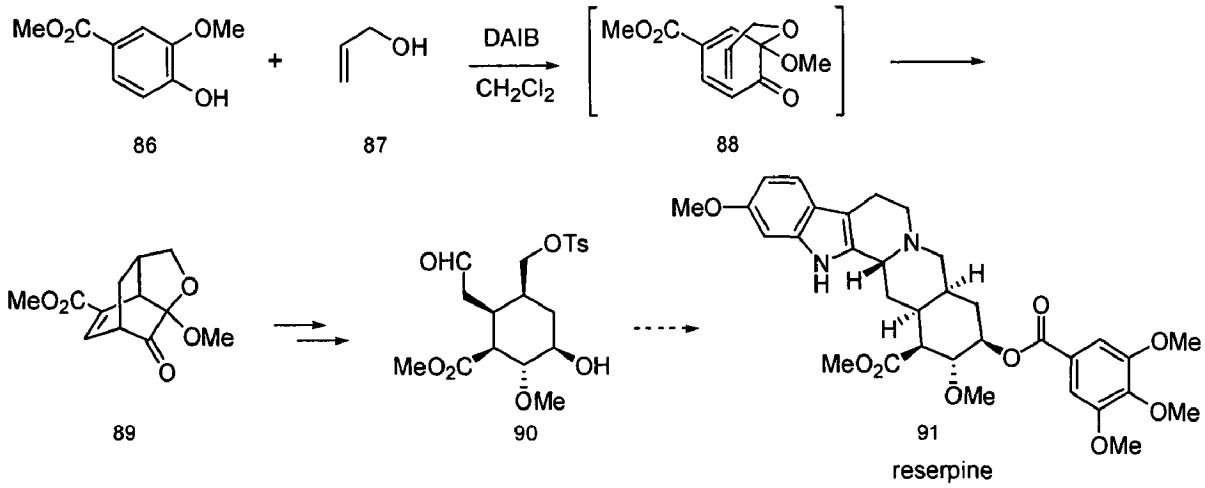


83 84 85

a *cis*-Clerodane diterpenic acid

SCHEME 32

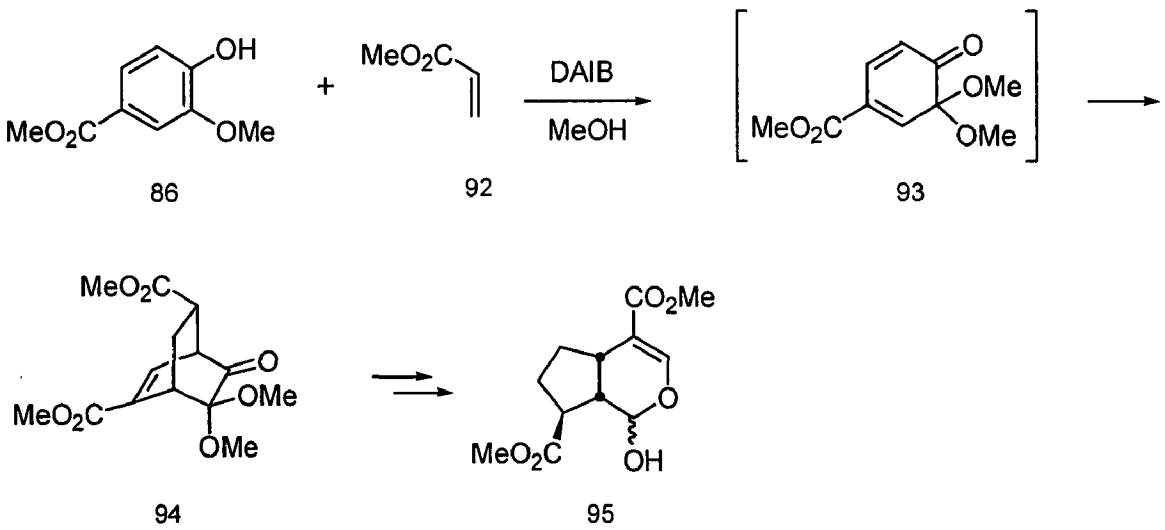
Starting from methyl vanillate, a key intermediate **90** in Stork's synthesis of (+/-)-reserpine (**91**) [111] was achieved by Liao's research group (Scheme 33). Tandem oxidative acetalization of methyl vanillate (**86**) with allylic alcohol produced orthoquinone monoketal **88**, which underwent intramolecular Diels-Alder reaction to furnish cycloadduct **89**. The enone **89** was further elaborated into cyclohexane **90**, which can be transformed into (+/-)-reserpine (**91**) in two synthetic operations [70].



86 87 88 89 90 91

SCHEME 33

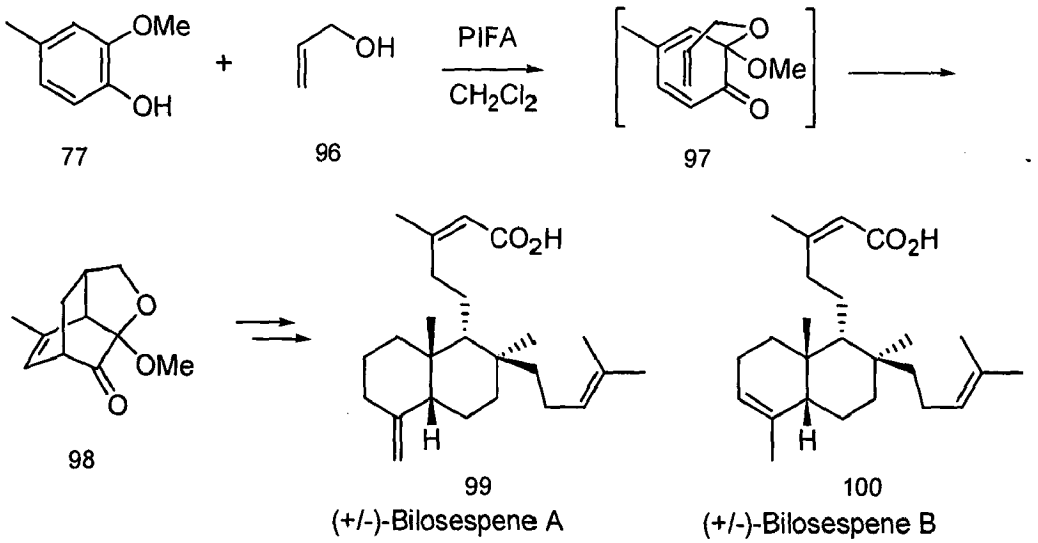
Synthesis of iridoid (+/-)-forsythide aglucone dimethyl ester **95** was accomplished via orthobenzoquinone monoketal strategy as shown in scheme 34. The Diels-Alder reaction of in situ generated cyclohexa-2,4-dienone **93** furnished bicyclo[2.2.2]octenone derivative **94**. The enone **94** was further transformed into the target **95**. It may be noted that all the carbon atoms required were introduced in a single operation *i.e.*, Diels-Alder reaction [68].



86 92 93 94 95

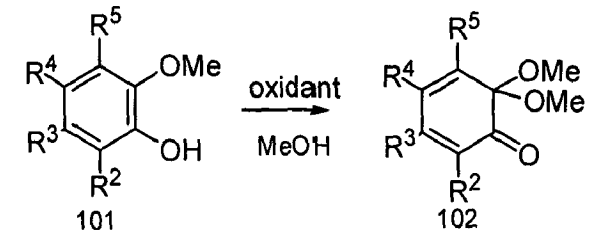
SCHEME 34

Recently, the total syntheses of alleged structures of two sesterpenic acids bilosespenes A and B (**99** and **100**) were accomplished. The intramolecular Diels-Alder reaction of *in situ* generated orthobenzoquinone monoketal **97** provided bicyclo[2.2.2]octenone derivative **98**. Subsequently, the cycloadduct **98** was transformed into the target sesterpenic acids **99** and **100** (Scheme 35).



SCHEME 35

Orthobenzoquinone monoketals can be easily generated by the oxidation of 2-alkoxyphenols in the presence of an alcohol (Scheme 36).



SCHEME 36

The commercially available diacetoxyiodobenzene (DAIB) and phenyliodonium(III) bistrifluoroacetate (PIFA) are the most frequently used hypervalent iodine reagents for the oxidation of phenols, quinols and catechols. Hypervalent iodine reagents have become more popular in organic synthesis owing to their low toxicity, ready availability and easy handling [115]. MOBs are most frequently generated by chemical oxidation of 2-methoxyphenols [112-114] (Scheme 36). This oxidation is a two-electron process [115]. Simple MOBs are found to be highly reactive and dimerize rapidly to produce dimers **103** in high yields (Figure 3).

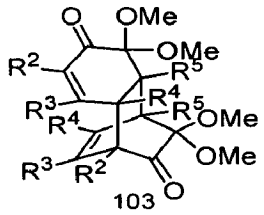
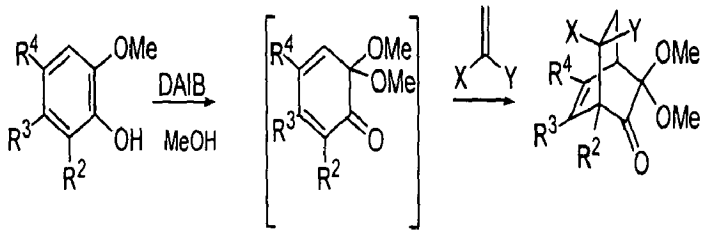


FIGURE 3

The dimerization occurs in a highly regio-, and stereoselective manner via the Diels-Alder reaction. It results from the cycloaddition of a molecule of MOB as the diene and $C_{4'}=C_{5'}$ double bond of the other as the dienophile. The dimers of MOBs possess ortho-regiochemistry and anti-stereochemistry (the $C_{3'}=C_{2'}$ bond is adjacent and anti to the C_1 carbonyl group in 103). As the dimerization of MOB and the Diels-Alder reaction between MOB and an external dienophile are competitive reactions, a high-dilution technique was employed to prevent/minimize the formation of dimmers by generating MOBs in situ at low concentration in the presence of large excess of dienophile [57]. The cycloaddition reaction of these MOBs with electron-deficient dienophiles such as methyl acrylate (MA), methyl methacrylate (MMA), and methyl vinyl ketone (MVK) afforded the bicyclo[2.2.2]-octenone derivatives via endo addition in good to excellent yields [57, 58]. (Scheme 37)

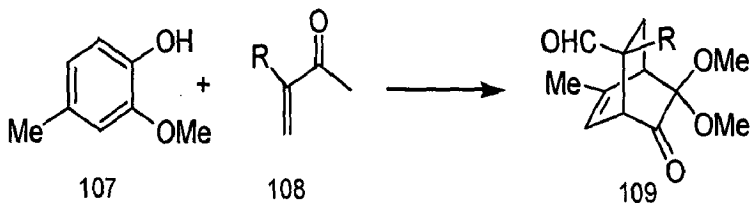


104 105 106

R^n= H.CO_2Me,COMe,Me
X= CO_2Me,COMe
Y= H,Me

SCHEME 37

The reaction of the MOB derived from creosol (2-methoxy-4-methylphenol) with acrolein under usual conditions produced the Diels-Alder adduct in rather low yields, apparently due to the undesired side reaction of DAIB with acrolein. In a parallel fashion, acrolein and methacrolein could undergo cycloaddition with MOBs derived from creosol, methyl vanillate, and methyl isovanillate to provide the corresponding adducts in good yields (Scheme 38) [95].

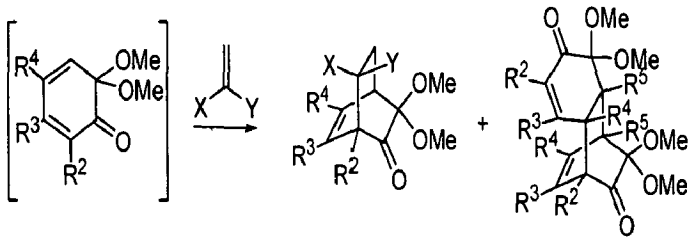


107 108 109

R= H,Me

SCHEME 38

The Diels-Alder reactions of the parent MOB and its 2-Me and 3-Me derivatives with MA, MMA, and MVK provided the corresponding cycloadducts in low to moderate yields along with substantial amounts of dimers.



110 111 112

SCHEME 39

Though in principle, there are four possible modes of [4+2] cycloaddition, Liao's group found that ortho,anti-adduct (the electron withdrawing group X is adjacent and anti to the carbonyl function of the bicyclo[2.2.2]octenone moiety) is the sole product in each case indicating that the Diels-Alder reaction is highly regio- and stereoselective. Liao and Peddinti carried out theoretical calculations to rationalize the observed selectivities on the basis of the frontier molecular orbital (FMO) theory. Consequently, calculations on the transition-state structures for the reaction between parent MOB and methyl vinyl ketone based on the ab initio RHF/3-21G method have been performed. The calculations have also suggested that this cycloaddition is a nonsynchronous concerted reaction and the formation of the C_5-$C_{2'}$ bond is faster than that of the C_2-$C_{1'}$ bond. The Diels-Alder reactions of various MOBs with electron-rich dienophiles such as benzyl vinyl ether (BVE), dihydrofuran (DHF), styrene, and phenyl vinyl sulfide (PVS) were investigated [46]. These cycloadditions were both regio- and stereoselective and furnished ortho,anti-adducts (Figure 4) as in the cases of electron-deficient dienophiles.

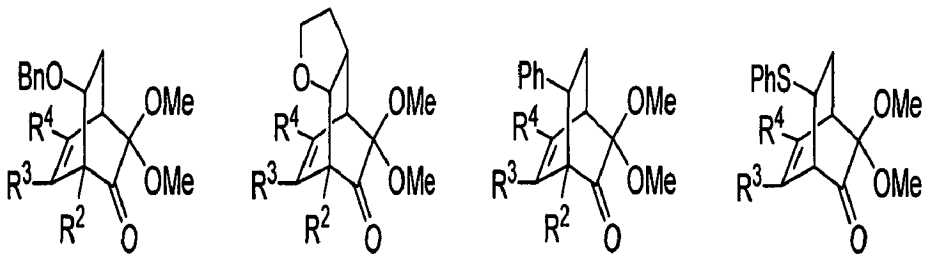
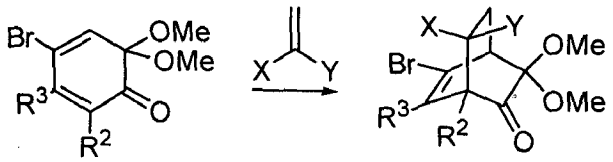


FIGURE 4

The MOBs derived from 2-methoxyphenols such as methyl vanillate, methyl isovanillate, and acetovanillone bearing EWGs displayed excellent reactivities in general with BVE and DHF. The reactions of the MOBs derived from guaiacol and creosol are slower than those of other 2-methoxyphenols bearing EWGs. Unlike the above electron-rich dienophiles, the reactions of vinyl acetate with MOBs were found to be inefficient and nonstereoselective [57]. On the basis of FMO theory, the theoretical calculations suggested that these are inverse-electron demand processes and also supported the observed selectivities in most cases [46]. To overcome the dimerization event in the cases of MOBs of guaiacol and its 5- and 6-methyl derivatives, a bromine atom was introduced as an additional removable substituent at position-4 of MOB, assuming that 4-bromo MOBs would gain stability by retarding the dimerization pathway. As anticipated, the reactions of MOBs derived from 4-bromo-2-methoxyphenols with electron-deficient dienophiles, in stoichiometric quantities or slight excess, proceeded efficiently to produce the adducts in good to excellent yields as the single stereoisomer in each case (Scheme 40).



113 114

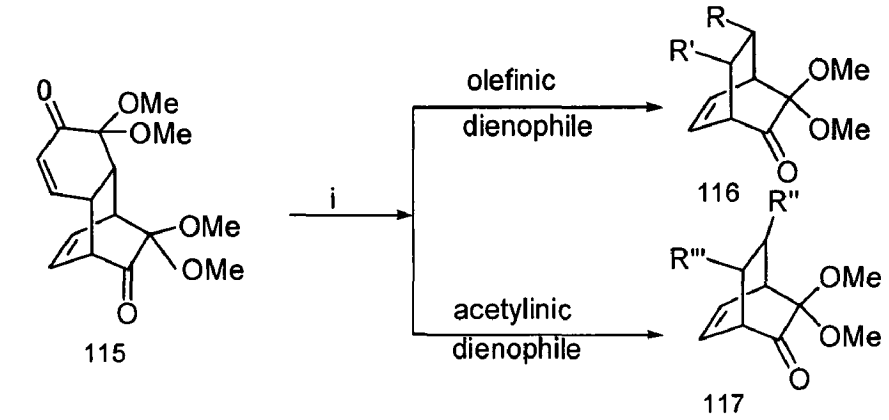
R^n= H,Me

X= CO_2Me, COMe,

Y= H, Me

SCHEME 40

Liao *et al.* used the domino retro-Diels-Alder/Diels-Alder strategy in MOB chemistry to produce bicyclo[2.2.2]octenones from the parent dimer, as an alternative to the aforementioned detour method involving bromination and debromination. (Scheme 41)

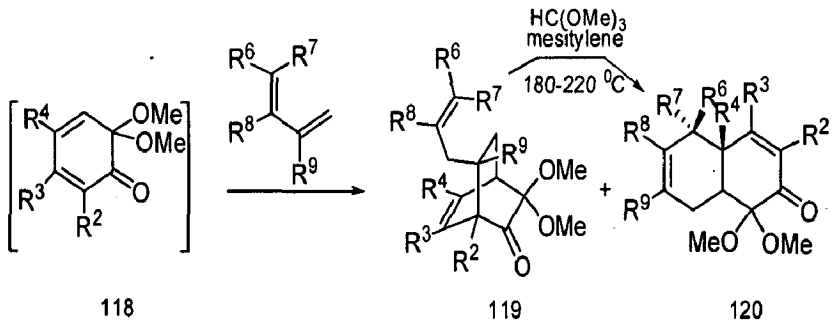


i= mesitylene, sealed tube,220 ^{0}C

dienophile= MVK, BVE, DHF, PVS

SCHEME 41

The dienophilic behavior of MOBs in their reactions with unactivated 1,3-butadienes was found for the first time in Liao's laboratories [59]. The MOBs, derived from creosol, methyl vanillate, methyl isovanillate, and methyl syringate, upon reaction with substituted 1,3-butadienes provided Diels-Alder adducts 119 and 120 (Scheme 42).

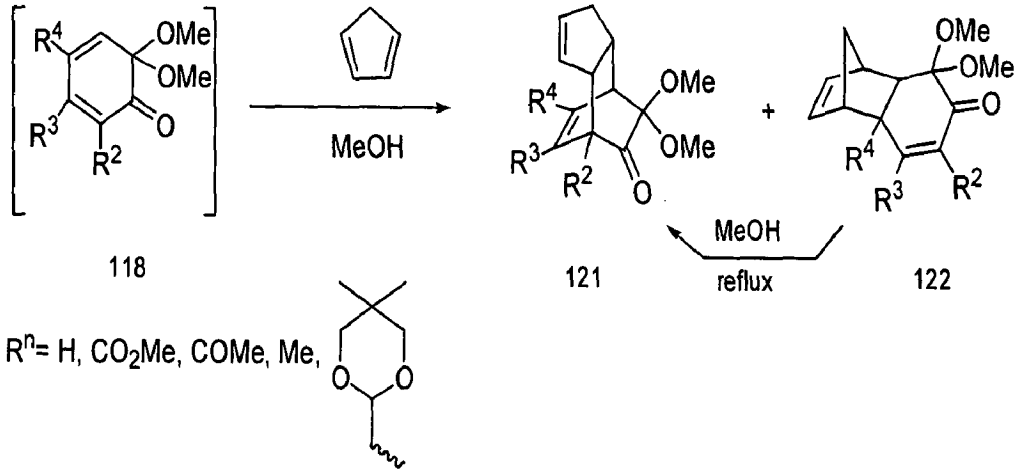


118 119 120

SCHEME 42

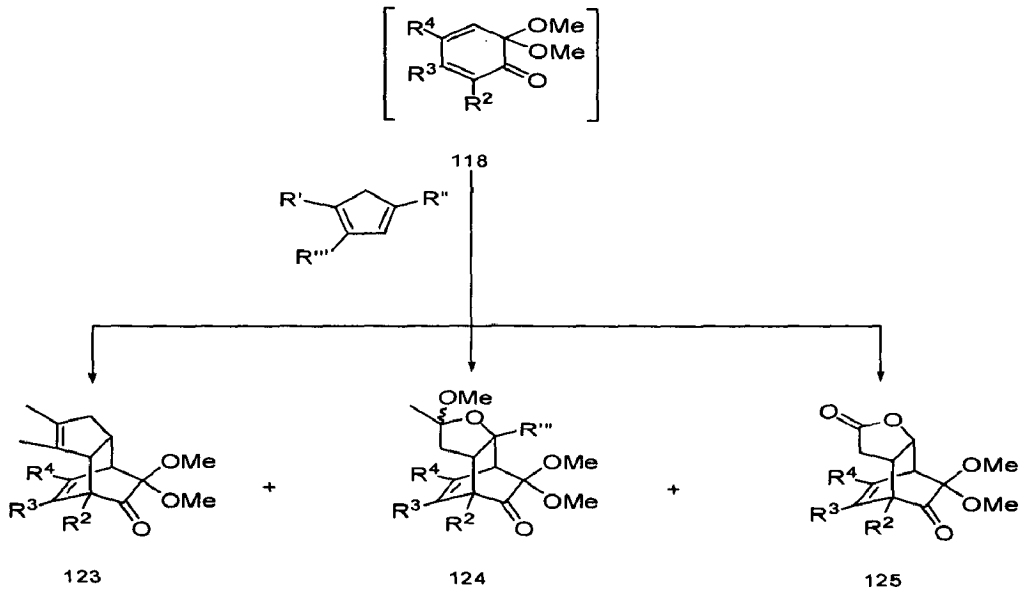
The ratio of adducts **119** and 120 depends on the nature and position of the substituents on both the MOBs and the dienes. The formation of **119** and **120** indicates the dual character of MOB as a diene and a dienophile. When some of the adducts **119** were separately heated in methanol in the presence of acetic acid and the corresponding 1,3-diene, no appreciable change was noticed. This indicates that **119** and **120** are generally primary products. Liao et al. also used the cyclopentadiene, as a cycloaddition

partner in the reactions with in situ generated MOBs. The reaction of guaiacol and its 3-methyl derivative in the presence of DAIB in refluxing methanol provided **121** and **122,** whereas at higher temperature it afforded solely adducts **121**. In contrary, the MOBs derived from other 2-methoxyphenols reacted with cyclopentadiene in refluxing methanol to produce exclusively adducts **121** in high yields (Scheme 43).



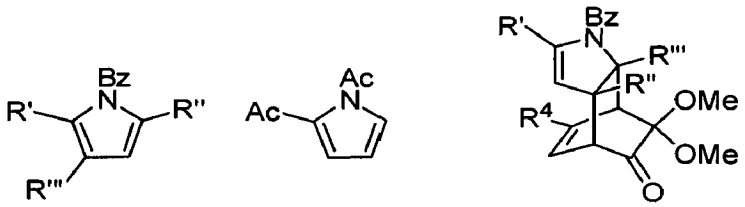
SCHEME 43

Despite their aromaticity, furans participate in the Diels-Alder cycloaddition essentially as 4 π partners (Scheme 44).



SCHEME 44

Nevertheless, MOBs compelled furans to act as dienophiles in the Diels-Alder reactions [117]. The cycloadditions of pyrroles are generally less efficient than those of furans due to the higher resonance energy of the former. In addition, pyrroles undergo Michael additions. Despite these obstacles, N-acyl pyrroles, in their capacity as dienophiles, underwent extremely facile Diels-Alder reaction with 4-EWG substituted MOBs.

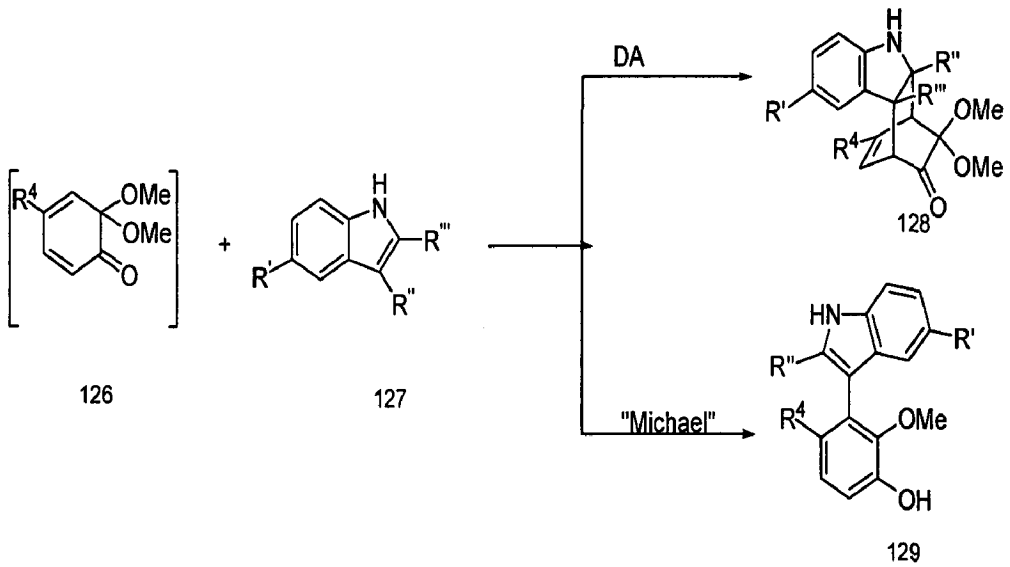


R^n= H,Me

Diels-Alder adducts of MOBs with *N*-acyl pyrroles

FIGURE 5

Interestingly, MOBs **126** in their reactions with indoles behaved as both dienes and Michael acceptors depending on the reaction temperature and the substitution pattern on indoles and produced hydrocarbazoles and 3-arylindoles, respectively (Scheme 45).



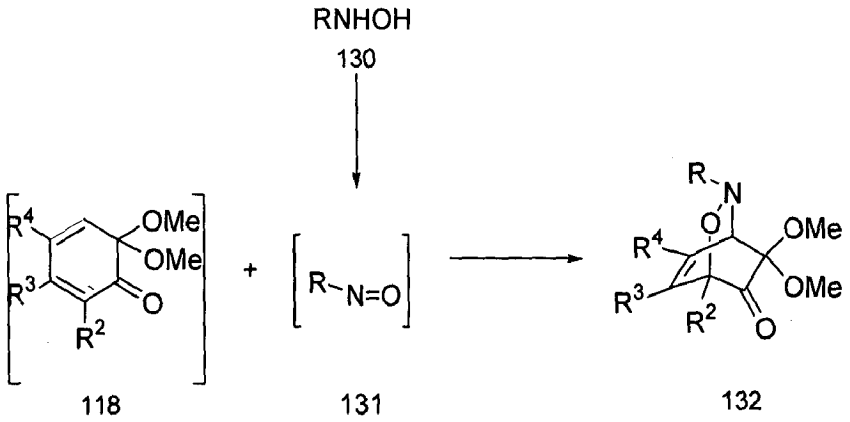
R^4= CO_2Me, COMe, CN

R= H, Me, CH_2CO_2Me

SCHEME 45

The parent indole (**127**) and 5-bromoindole on reacting with MOBs **126** produced Diels-Alder adducts **128** at room temperature and aromatized Michael adducts **129** in refluxing methanol.

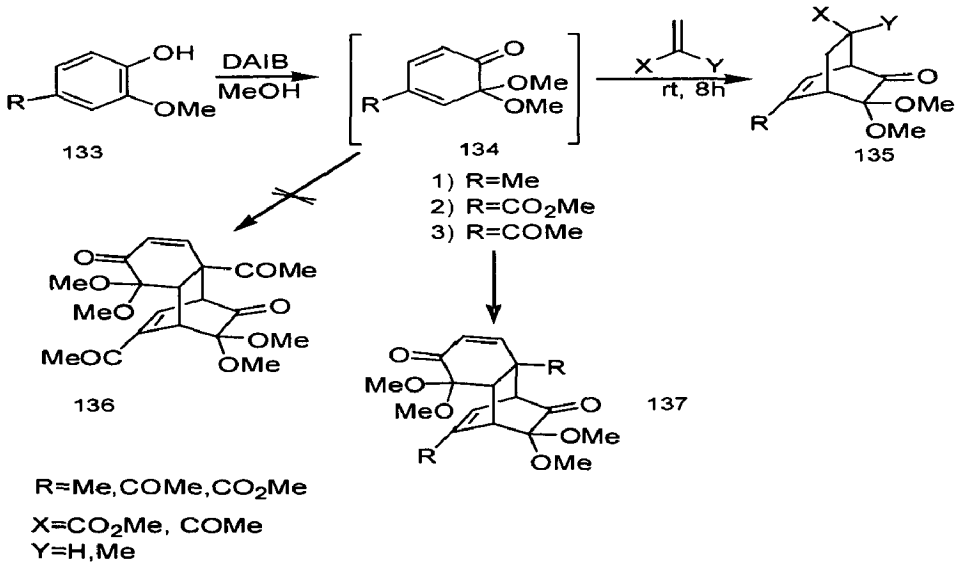
An obvious extension to the carbo-Diels-Alder reaction is the hetero-Diels-Alder reaction. The MOBs derived from guaiacol and several of its derivatives (EWGs, ERGs) were treated with nitroso compounds **131** in Liao's lab to produce highly functionalized heterocycles **132** in good to excellent yields via facile hetero-Diels-Alder reactions of transiently generated MOBs **118** and nitroso dienophiles **131** (Scheme 46) [118].



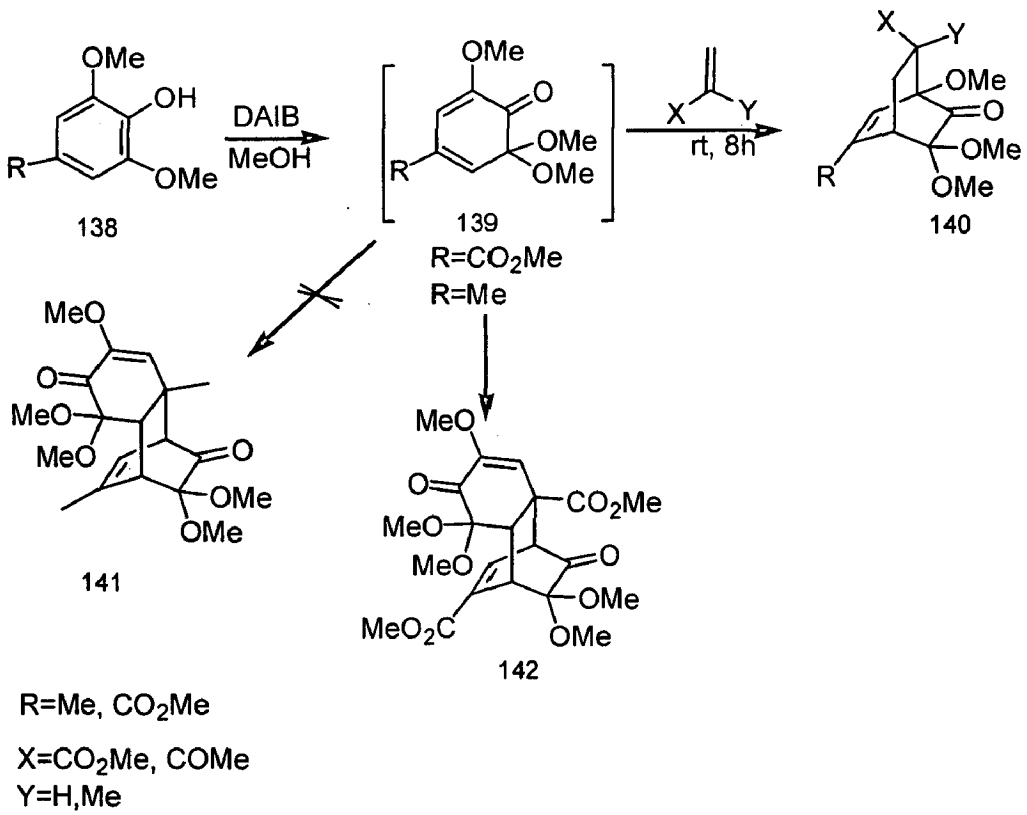
SCHEME 46

Liao et al. have developed an efficient and reliable one-pot method for the preparation of highly functionalized bicyclo[2.2.2]octenones from Diels-Alder reactions of labile and readily dimerizing masked o-benzoquinones, i.e., substituted 6,6-dimethoxy-2,4-cyclohexadienones with electron-deficient dienophiles. Oxidation of substituted 2-methoxyphenols (R= Me, CO_2Me) with (diacetoxy)iodobenzene in methanol afforded the corresponding masked o-benzoquinones which are not stable enough to be isolated and are found to dimerize under reaction conditions in a highly regio- and stereoselective manner to provide the corresponding Diels-Alder dimers. On the other hand, masked o-benzoquinones (134; R= COMe, 139; R= Me), were found to be quite labile and provided a complex mixture of products. However, masked *o*-benzoquinones when generated in

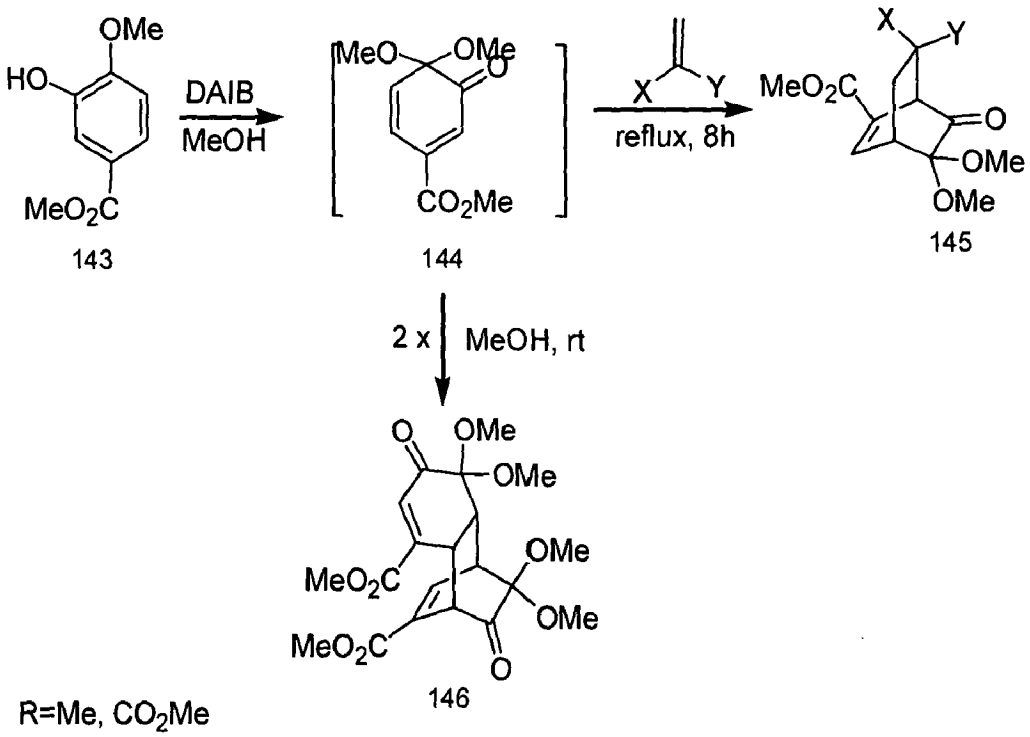
the presence of dienophiles such as methyl acrylate, methyl methacrylate, and methyl vinyl ketone, underwent highly regioand stereoselective intermolecular Diels-Alder reactions to furnish variously substituted bicyclo[2.2.2]octenones (Scheme 47-49) [84-90].



SCHEME 47

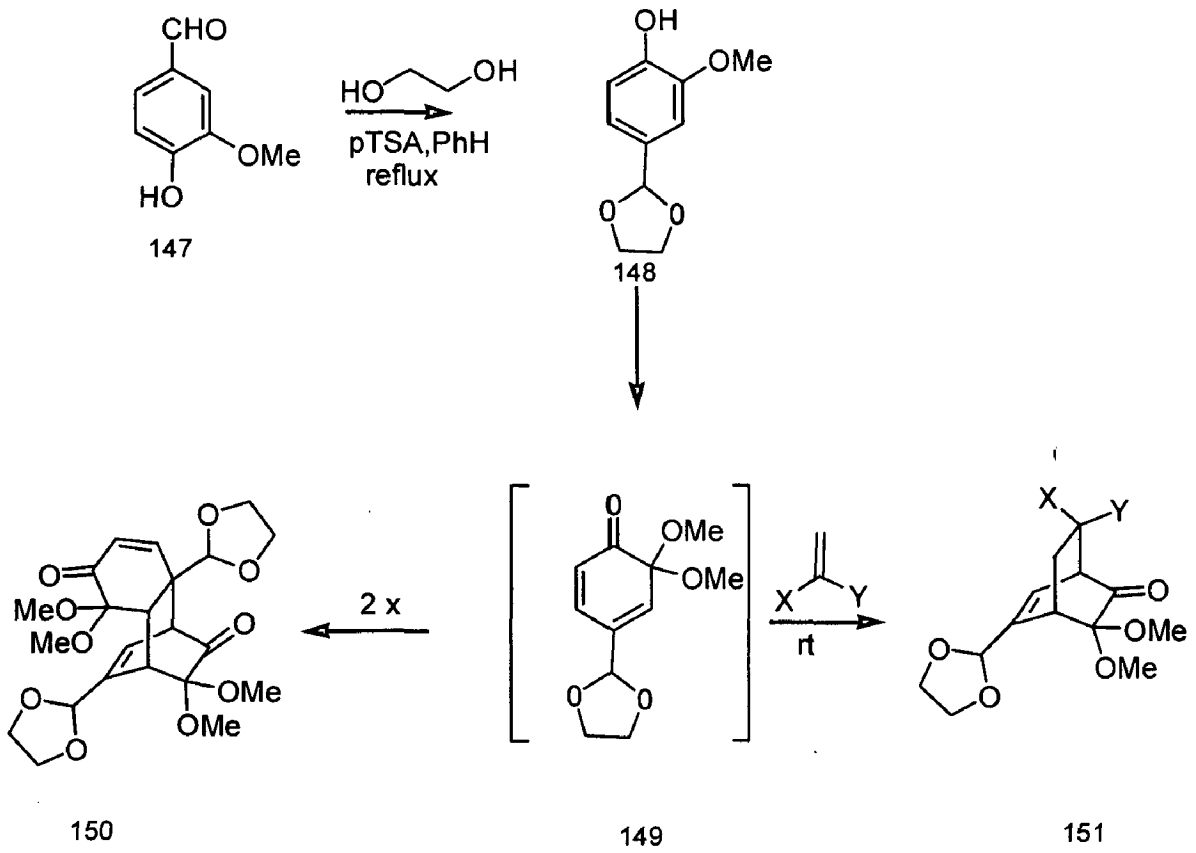


SCHEME 48



SCHEME 49

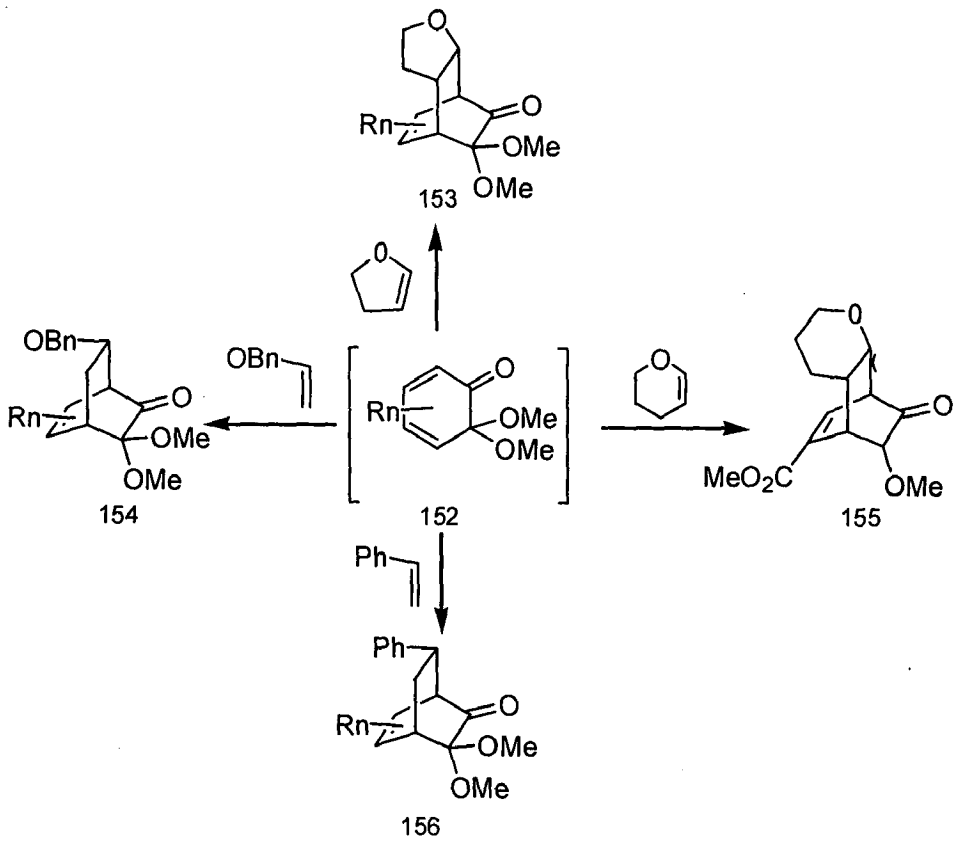
Oxidation of vanillin in the presence of MA at room temperature resulted in the production of a complex reaction mixture. Consequently, the aldehyde group was protected as an acetal, [119] and generated MOB **149** was found to be less reactive and quite stable at room temperature in methanol (Scheme 50). No trace of dimer **150** was observed in any of the reactions performed at room temperature.



SCHEME 50

To retard dimerization and to improve the yields of the requisite bicyclo[2.2.2]octenones, a detour method comprised of sequential bromination of 2-methoxyphenols [1, 120-122], oxidation and Diels-Alder reaction, and debromination has been developed by Liao's group. It is mentioned in literature that the MOBs having electron-deficient substituents undergo more facile Diels-Alder cycloadditions with benzyl ether, dihydrofurane, and styrene. The electron-rich dienophile dihydropyran is not a suitable 2π-partner for MOBs [60]. Inverse-electron-demand Diels-Alder reactions are employed predominantly by systems incorporating heteroatoms in either or both the diene and dienophile [123]. Among the purely carbon-containing diene systems, 2-pyrones [124] appear to be the most widely used electron-deficient dienes. The Diels-Alder reactions of cycloalkane-annulated dienes with electron-rich dienophiles were reported recently [125]. Nevertheless, some examples of the Diels-Alder reactions of MOBs do exist with electron-rich dienophiles [126-129]. Ethyl vinyl ether and styrene

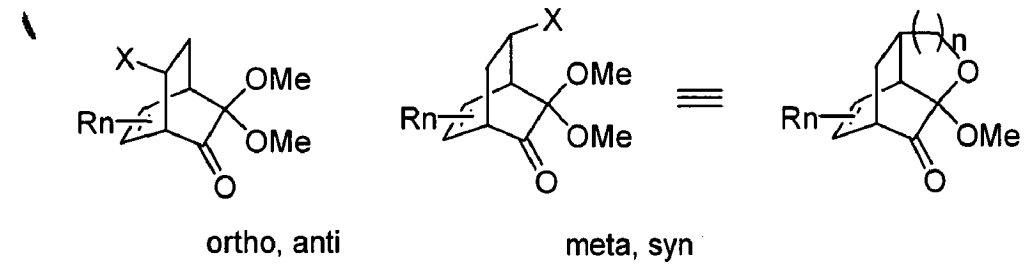
were employed as dienophiles in the reactions of MOBs having bulky substituents in Liao's laboratory [126] (Scheme 51).

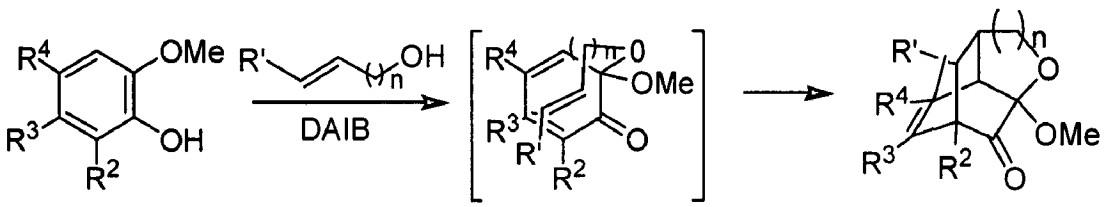


SCHEME 51

The intramolecular Diels-Alder (IMDA) reaction is a powerful tool for the rapid construction of highly substituted polycyclic carbon skeletons. When methanol is replaced by an alkenol or a dienol during the oxidation of 2-methoxyphenols, thus formed MOBs (or the MOBs bearing alkene moiety attached through a carbon tether) can undergo IMDA reaction to furnish tricyclic ring systems. Liao and Peddinti have developed an unprecedented IMDA reaction via in situ tethering of an alkene to a diene system through acetal formation [57, 63]. Several commercially available 2-methoxyphenols were oxidized by DAIB in the presence of alkenols 157 to generate MOBs **158**, which underwent IMDA reaction smoothly to furnish highly functionalized oxatricycles **159** in moderate to high yields (Scheme 52). It is worth mentioning that in

contrast to the intermolecular Diels-Alder reaction (ortho, anti-adducts), these adducts obtained via domino oxidative acetalization-IMDA process can be considered as equivalents of meta, syn-adducts (with respect to the carbonyl group).

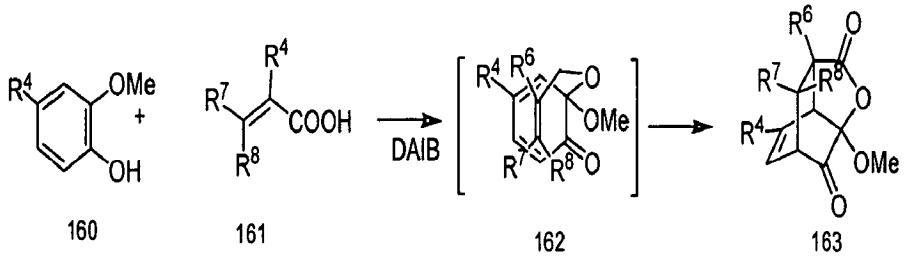




157 158 159

SCHEME 52

The reactivity of a particular MOB appears to depend on the substituents on alkene terminus and the position of substitution(s) on the dienone moiety. The alkenoic acids **161** were employed in the place of alkenols in the above process with methyl vanillate to afford tricyclic lactones **163**.

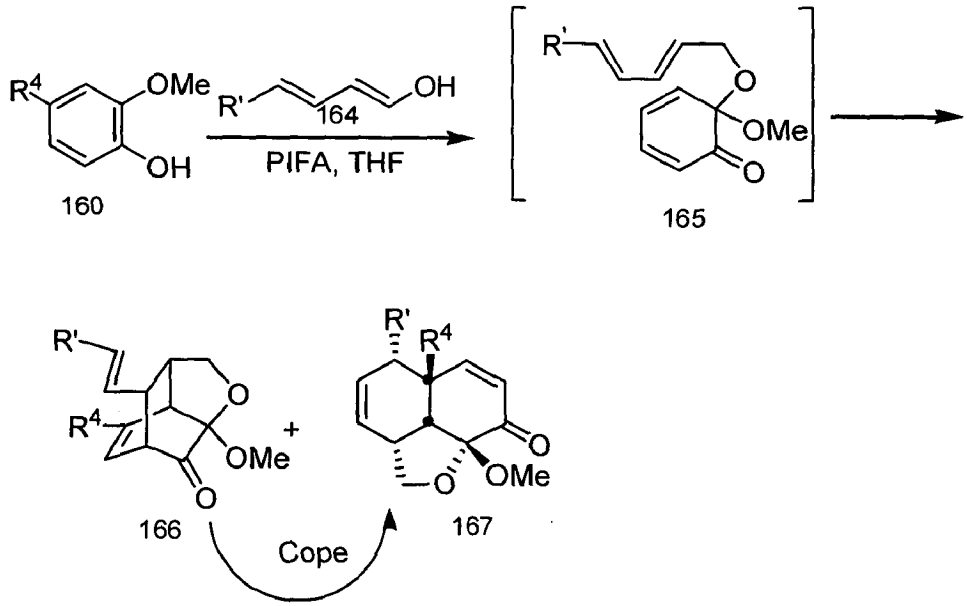


160 161 162 163

R^n= H, Me,CO_2Me

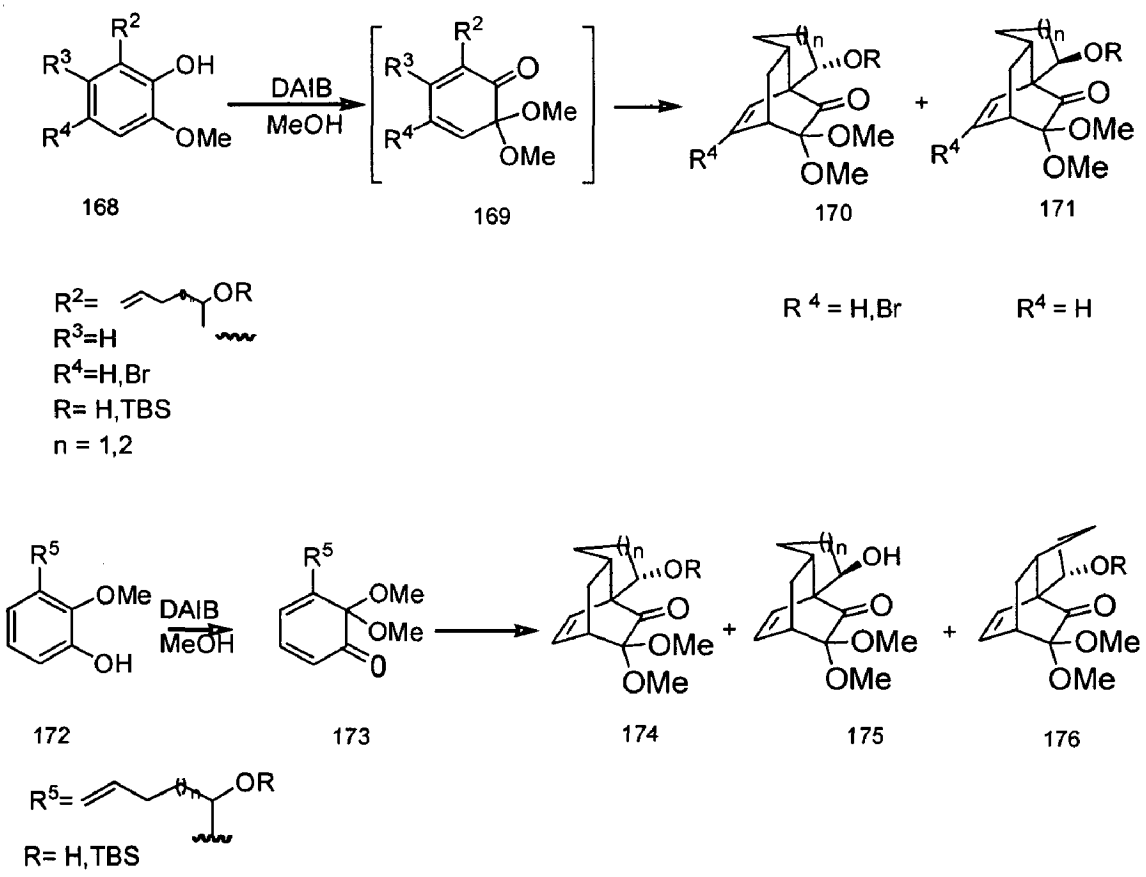
SCHEME 53

The cyclohexa-2,4-dienone moiety of MOB displayed dual behavior, i.e., both dienic and dienophilic character with 2,4-dieneol resulting in mixtures of adducts, bicyclo[2.2.2] octenones **166** and cis-decalins **167**, following the endo rule (Scheme 54) [130].



SCHEME 54

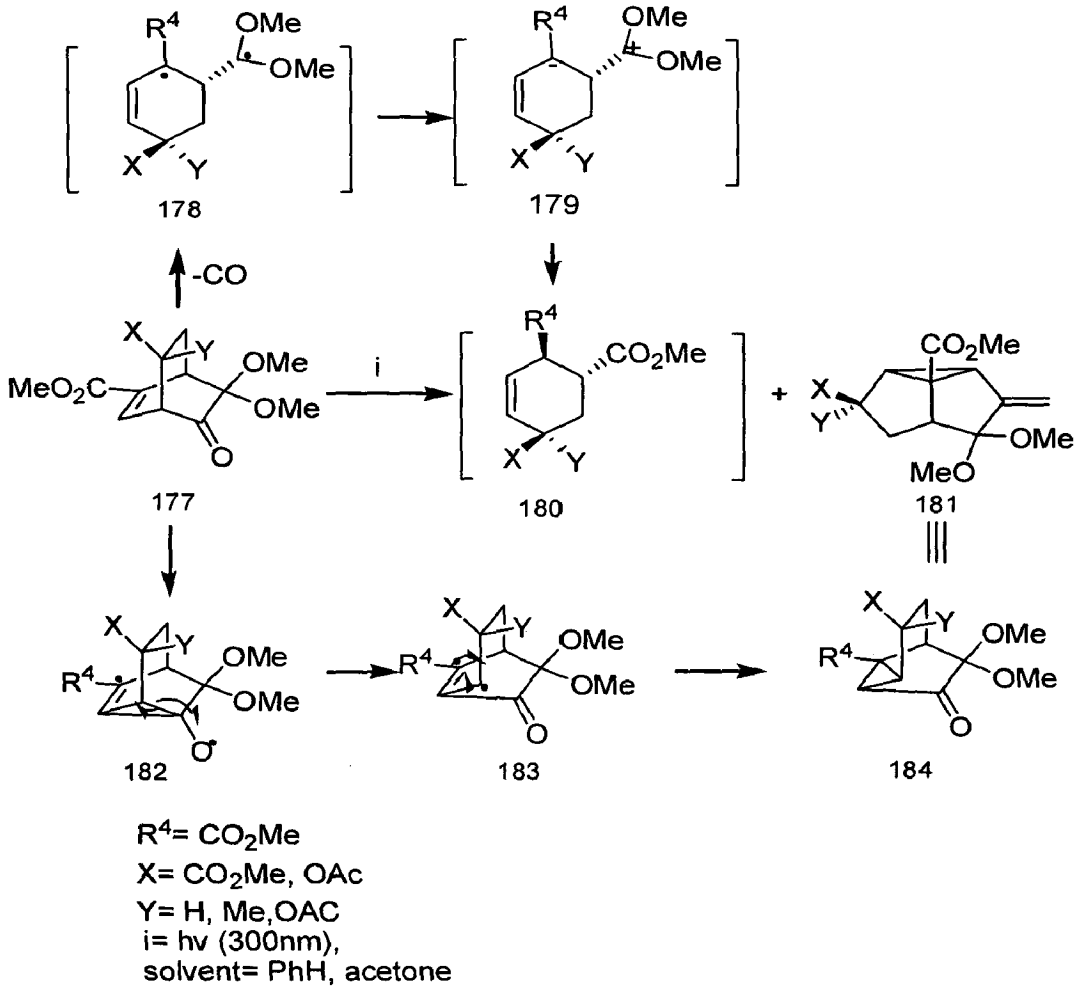
Liao et al. have reported [130] diastereoselective IMDA reactions of various MOBs **169** and **173** bearing a chiral center in the alkenyl carbon tether to provide densely substituted tricyclic[m.2.2.0] ring systems.



SCHEME 55

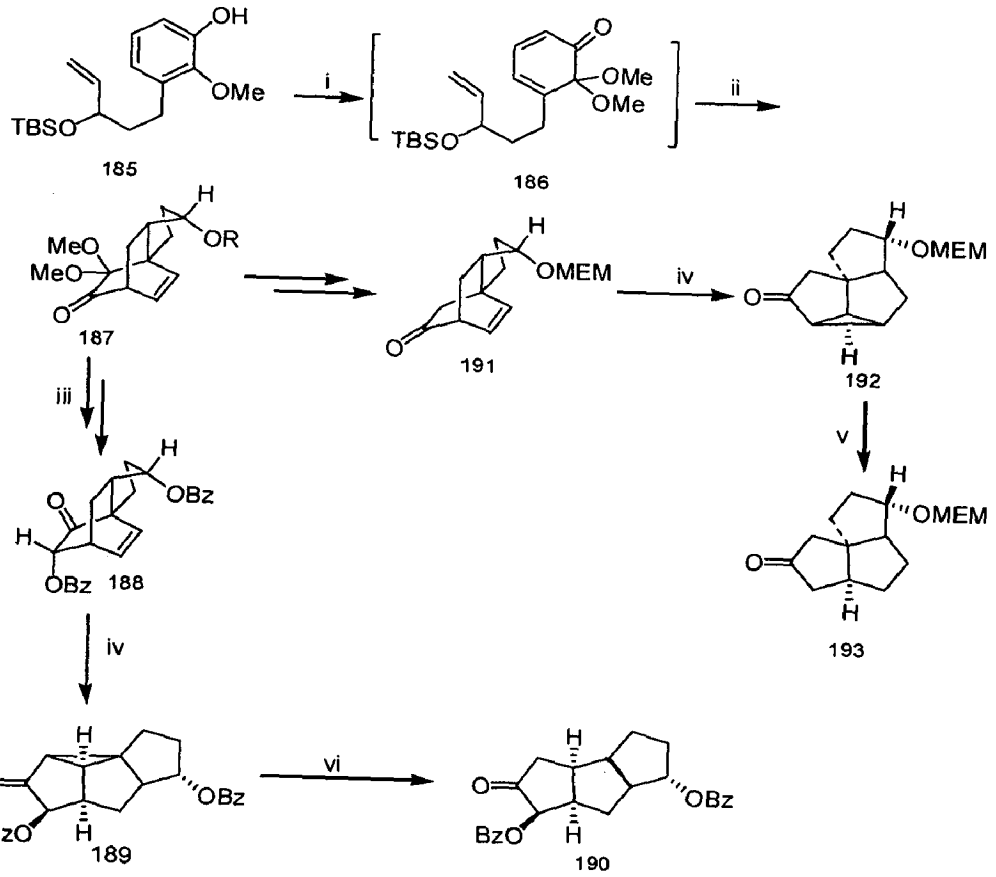
SYNTHETIC APPLICATIONS: CONSTRUCTION OF VARIOUS SKELETONS FROM 2-METHOXYPHENOL

Bicyclo[2.2.2]octenones embedded with α,β-unsaturated carbonyl chromophore are rich with photochemistry [131]. Intermolecular and intramolecular Diels-Alder adducts of MOBs offered a unique opportunity to explore their photochemical reactions. The adducts **177**, upon direct irradiation in benzene furnished cyclohexenes **180** in 41-43% and the oxa-di-π-methane (ODPM) rearrangement products **181** in minor amounts, whereas irradiation in acetone provided **181** as the major products.The plausible pathways of these photochemical transformations are depicted in Scheme 56.



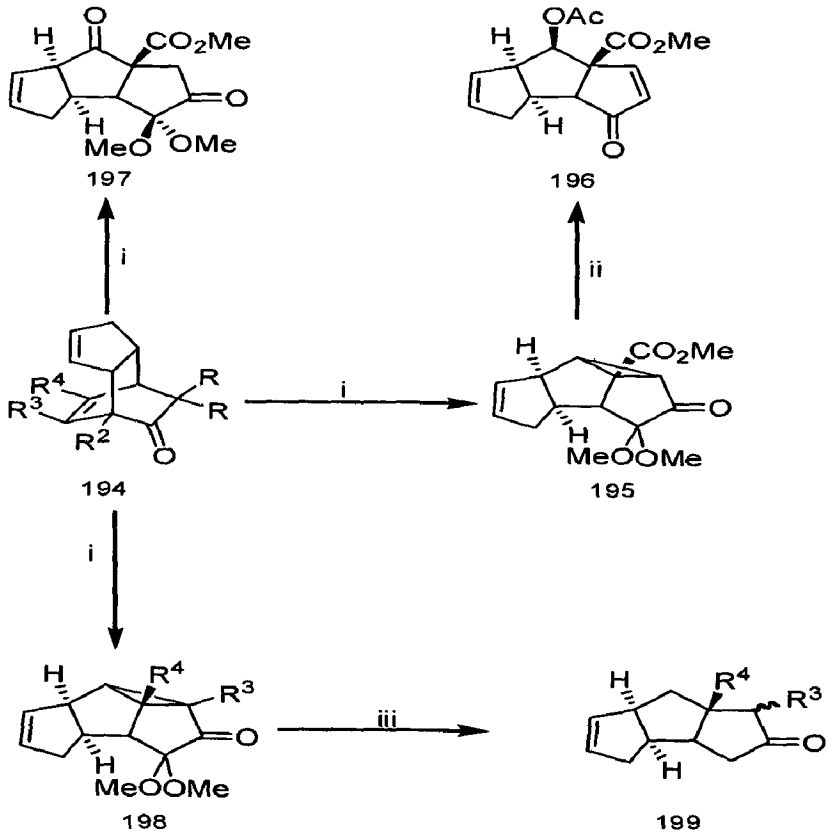
SCHEME 56

Numerous methods have been developed for the synthesis of triquinanes due to their synthetic potential toward higher polyhedra of fundamental importance. Liao and Peddinti have synthesized linearly and angularly fused triquinanes **190** and **193** (Scheme 57).



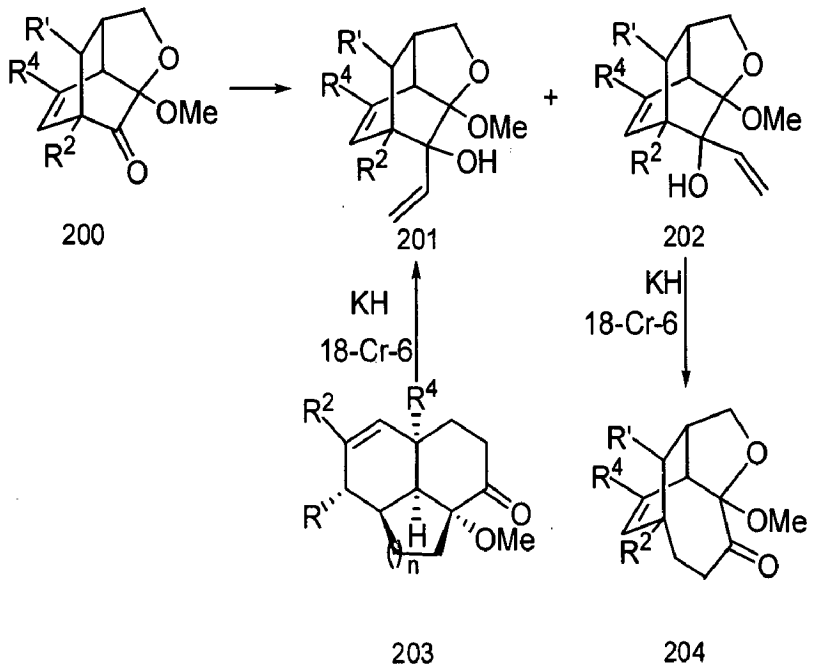
i) PIFA, MeOH-CH_3CN,
ii) mesitylene, 165 ^0C
iii) n-Bu_4NF
iv) hv, 1% in acetone
v) 2 eq. SmI_2, THF/MeOH
vi) 4 eq SmI_2, THF/MeOH

SCHEME 57



SCHEME 58

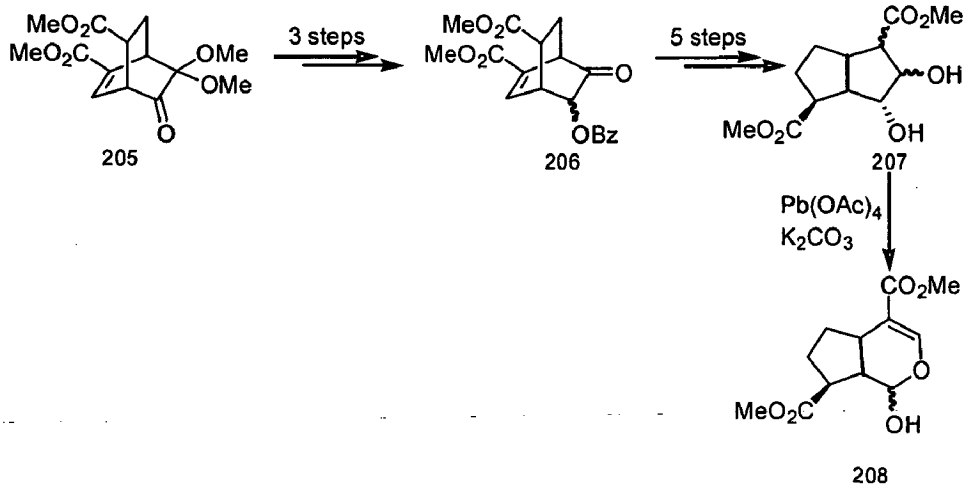
Thus, a new methodology was developed by Liao's group to synthesize appropriately oxygenated and variously substituted linear triquinanes bearing cis:anti:cis stereochemistry of naturally occurring triquinane skeletons efficiently in 3-4 steps from inexpensive and easily accessible 2-methoxyphenols [112]. The Diels-Alder protocol of MOBs serves as a powerful strategy to generate complex molecular structures with defined stereochemistry. A novel and efficient four-step methodology has been developed for the stereocontrolled synthesis of bicyclo-[4.2.2]decenones from 2-methoxyphenols by Liao et al. (Scheme 59) [65].



SCHEME 59

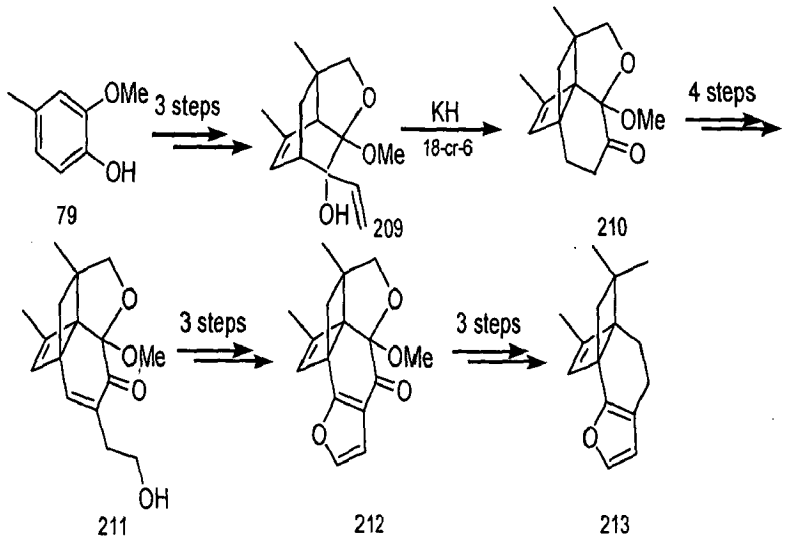
SYNTHETIC APPLICATIONS: FORMAL/ TOTAL SYNTHESIS OF NATURAL PRODUCTS

The synthesis of (+)-ryanodol by Deslongchamps' group is the earliest elegant example involving the Diels-Alder reaction of a MOB. The synthesis of iridoid (±)-forsythide aglucone dimethyl ester (122) was accomplished via MOB Diels-Alder strategy (Scheme 60) [68].



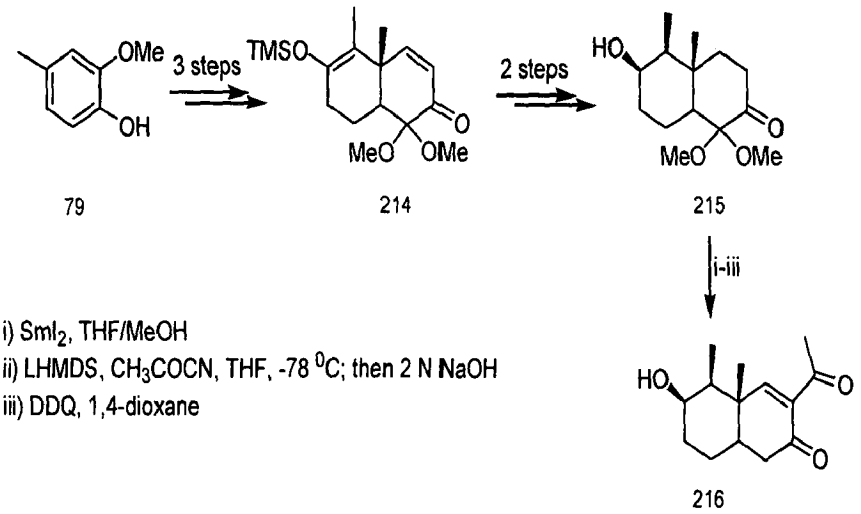
SCHEME 60

The four-step methodology developed [65] for the stereocontrolled synthesis of bicyclo[4.2.2]decenones has been utilized for the synthesis of (±)-pallescensin B **(213)** (Scheme 61) [69].



SCHEME 61

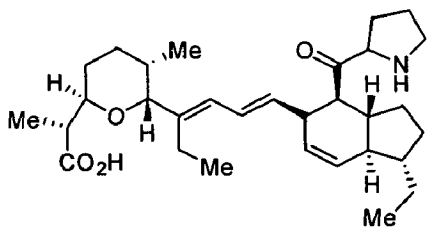
The total synthesis of (±)-eremopetasidione **(216)** was accomplished [132] by using the four-step stereocontrolled synthesis of cis-decalins (Scheme 62) [95].



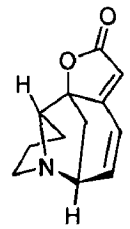
SCHEME 62

The numerous total syntheses delineated in literature appropriately define the remarkable potential of the Diels-Alder reaction to construct overwhelming molecular

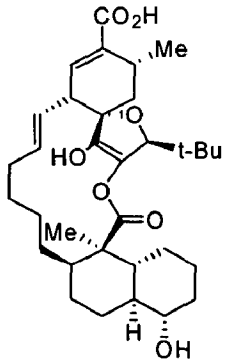
architectures. Figures 6 & 7 illustrate some examples of natural products whose total syntheses were accomplished using a Diels-Alder reaction as a key step.



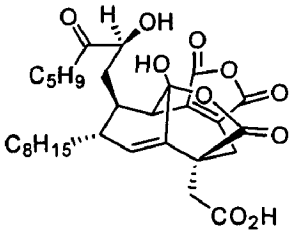
Antibiotic X-14547A
(Nicolaou et al., *JOC* **1985** *50*, 1440-1456)
IMDA



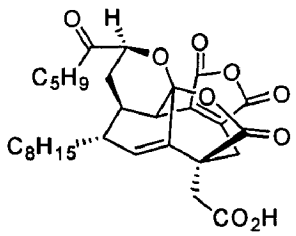
(-)-Norsecurinine
(Jacobi et al., *TL* **1989** *30*, 7173-7176)
HDA followed by rDA



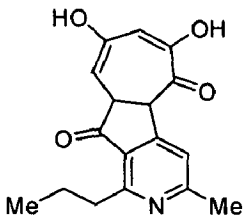
(-)-Chlorothricolide
(Roush and Sciotti *JACS* 1994 *116*, 6457-6458)
inter-/intramolecular DA cascade



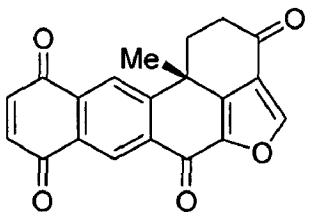
and



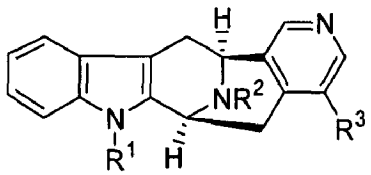
(-)-CP-225,917 (+)-CP-263,114
(Nicolaou et al. *Angew. Chem. Int. Ed.* **1999** *111*, 1774-1781)
Lewis-Acid catalyzed DA



Rubrolone aglycon
(Boger et al. *JACS* **2000** *122*, 12169-12173)
HDA and a intermolecular DA



Halenaquinone
(Rodrigo et al. *JOC* **2001** *66*, 3639-3641)
tandem oxidative ketalization, a DA and a Cope rearrangement



Suaveoline (R^1 = Me, R^2 = H, R^3 = Et)
Norsuaveoline (R^1 = R^2 = H, R^3 = Et)
(Ohba, M. et al. *TL* **2004**, *45*, 6471)

FIGURE 6

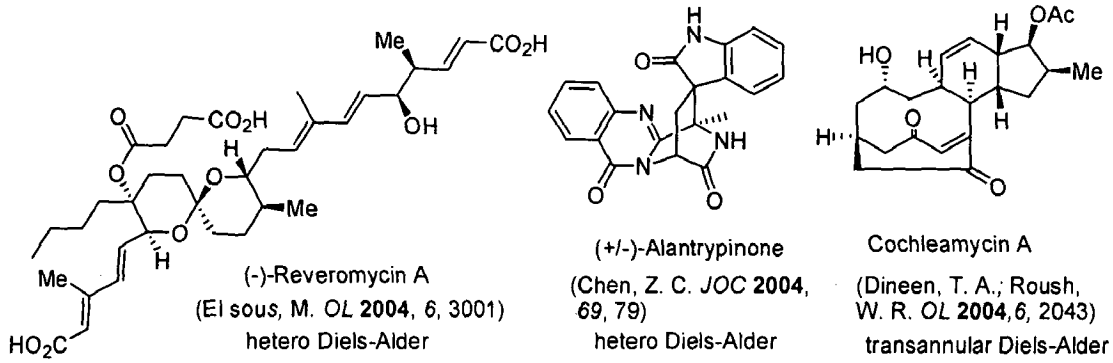


FIGURE 7

The versatility of MOBs was also exemplified by other research groups in the syntheses of the following: (±)-kadsurenone, (±)-denudatin B, (±)-liliflol B (±)-*o*-methyllliliflodione, [133] asatone, (±)-xestoquinone [134] (Figure 8).

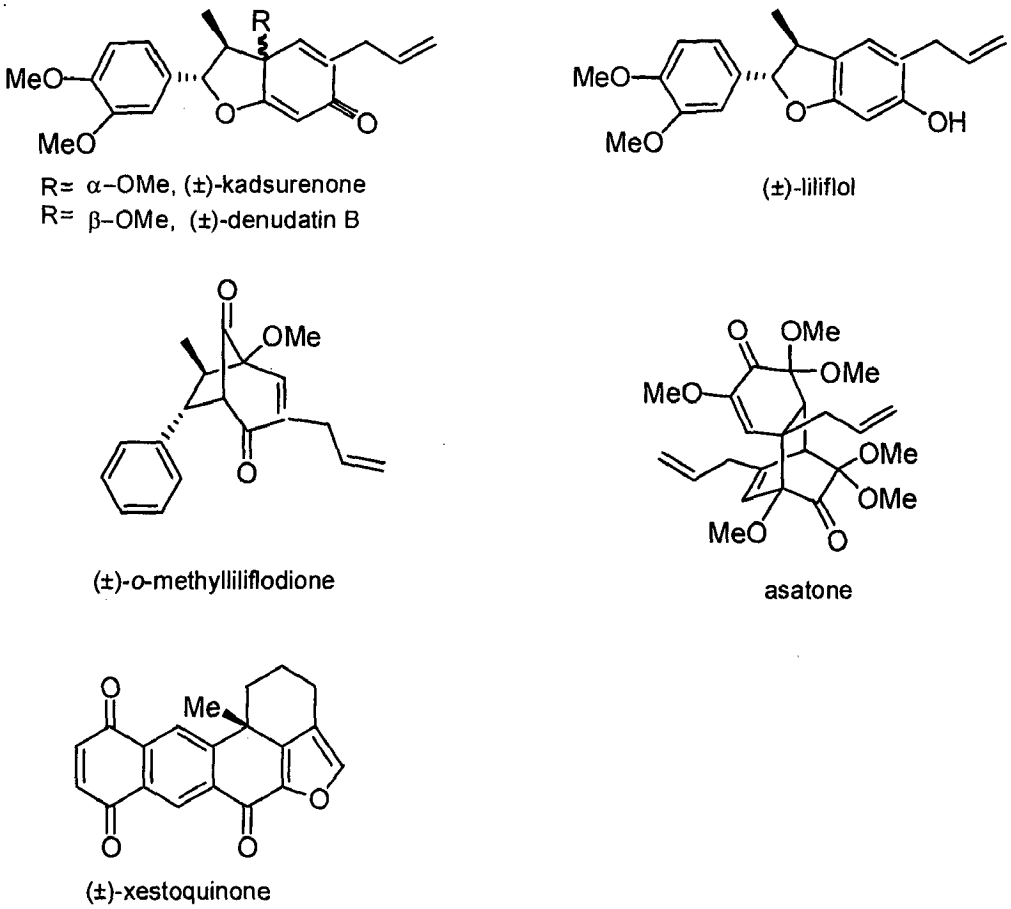
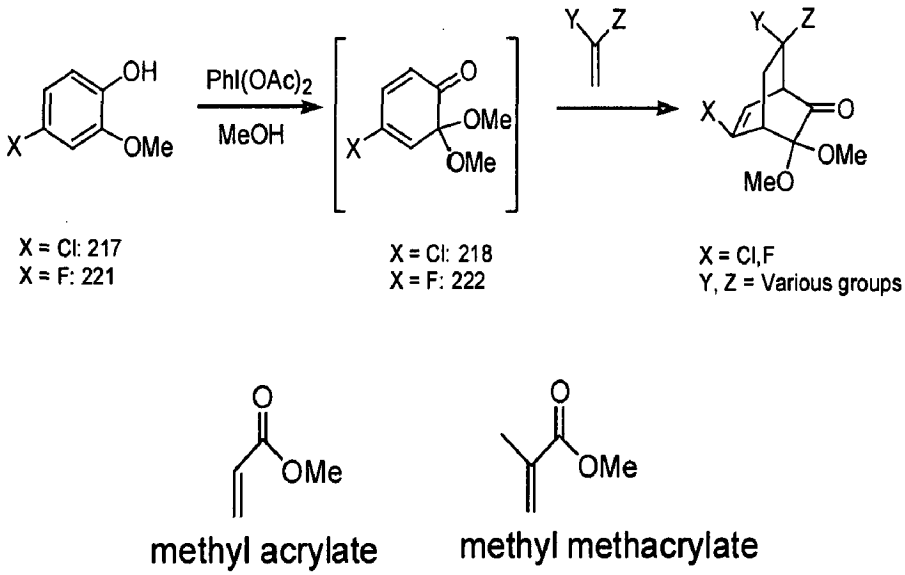


FIGURE 8

1.3 *AIM AND SCOPE OF THE PRESENT WORK*

One of the exciting challenges in modern organic synthesis is the development of simple processes for the rapid construction of multifaced molecules with definite srereochemistry from easily available starting materials. From the above survey, it is quite clear that *o*-benzoquinons and their derivatives have vast synthetic potential for the creation of molecular complixity. Simple *o*-benzoquinons are usually unstable and they undergo notorious reaction in addition to dimerization. On the other hand, *o*-benzoquinons that are protected at one of the carbonyl functionalities named masked *o*-benzoquinons (MOBs) are relatively stable compared to the corresponding unprotected *o*-benzoquinons. The biyclo[2.2.2]octenone derivatives have a wide range of application in the synthesis of natural products. Intrigued by the reactivity and synthetic potential of the MOBs, we have taken up the study of Diels-Alder reaction of cyclohexa-2,4-dienone (218, 222) which can be easily generated from commercially available 4-chloro-2-methoxyphenol (217) and 4-fluoro-2-methoxyphenol (221) with the main aim of synthesizing biyclo[2.2.2]octenone derivatives. The reactive dienophiles such as methyl acrylate and methyl methacrylate have been chosen for this study.



SCHEME 63

EXPERIMENTAL

EXPERIMENTAL PART

2.1 *CHEMICALS AND SUPPLIER*

S.No.	CHEMICALS	SUPPLIER
1.	4-Chloro-2-methoxyphenol	Aldrich
2.	4-Fluorochloro-2-methoxyphenol	Aldrich
3.	Methyl methacrylate	Aldrich
4.	Methyl acrylate	Aldrich
5.	Diacetoxyiodobenzene	Aldrich
6.	Allyl alcohol	Aldrich
7	Cinnamyl alcohol	Aldrich
8.	Dichloromethane	S.D. Fine
9.	Methanol	S.D. Fine
10.	Ethyl acetate	RANKEM
11.	Hexane	Merck
12.	Toluene	S.D. Fine
13.	Silica gel (Column) (Mesh size 60-120)	SRL
14.	Silica gel G (TLC)	SRL

2.2 THE MAKE AND MODEL OF THE INSTRUMENT

IR spectra were recorded on a NEXUS FT-IR (THERMO NICOLET) using NaCl plates and/or KBr discs. GC-MS were recorded on a Perkin Elmer (Clarus 500) Instrument. ^{1}H NMR were recorded at Brucker 500 MHz in $CDCl_3$ and ^{13}C, DEPT spectra were recorded at Brucker 125 MHz in $CDCl_3$ and chemicals shifts are reported in δ (ppm) using solvent resonance/ TMS reference as the internal reference.

2.3 GENERAL

All the solvents used for the reactions were dried and distilled using suitable drying agents before use. All the reactions were carried out under dry conditions, unless otherwise mentioned. All the reactions were monitored by TLC on glass plates (7 x 2 cm) coated with silica gel G. The spots were visualized by short exposure to iodine vapour. The products were purified by silica gel column chromatography with ethyl acetate and hexane as eluent.

2.4 *PROCEDURE*

2.4.1 Synthesis of methyl (1*S**, 2*S**, 4*R**)-5-chloro-8,8-dimethoxy-7-oxobicyclo[2,2,2]oct-5-ene-2-carboxylate (219).

Method A: Reaction at room temperature

To a solution of 4-chloro-2-methoxyphenol (0.158 g, 1 mmol) and methyl acrylate (2.15 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 30 min. at 0 °C under nitrogen atmosphere. After 10 min. the ice-bath was removed, the contents were allowed to stir at room temperature and the stirring was continued for 24 h. After the reaction was completed, the reaction mixture was concentrated by rotatory

evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **219**.

Yield: 210 mg (77 %)

Method B: Reaction at 50 °C

To a solution of 4-chloro-2-methoxyphenol (0.158 g, 1 mmol) and methyl acrylate (2.15 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 1 h. at 50 °C under nitrogen atmosphere, after it the contents were allowed to stir at same temperature and the stirring was continued for 1 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **219.**

Yield: 252 mg (92 %)

IR (neat) ν_{max}: 2952, 1734, 1623, 1446, 1325, 1298, 1206, 1104, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02 (ddd, J = 2.5, 5.5, 13.5 Hz, 1 H), 2.34 (ddd, J = 3, 13.5, 16.5 Hz, 1H), 3.04 (ddd, J = 6, 8, 11 Hz), 3.24 (dd, J = 2.75, 5.75 Hz, 1H), 3.34 (s, 3H), 3.39 (s, 3H), 3.57 (dd, J = 2, 7 Hz, 1H), 3.71(s, 3H), 6.055(dd, J = 2.75, 6.75 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 24.59 (C-3), 38.91 (C-1), 47.26 (C-4), 49.91 (C-2), 50.49 (C-8 methoxy carbon), 50.68 (C-8, methoxy carbon), 52.25 (methyl carbon of ester), 93.35 (C-8), 120.23 (C-6), 136.93 (C-5), 172.48 (carbonyl carbon of ester), 198.97 (C-7).

2.4.2 Synthesis of methyl (1*S**, 2*S**, 4*R**)-5-chloro-8,8-dimethoxy-2-methyl-7-oxobicyclo[2,2,2]oct-5-ene-2-carboxylate (220).

Method A: Reaction at room temperature

To a solution of 4-chloro-2-methoxyphenol (0.158 g, 1 mmol) and methyl methacrylate (2.5 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 30 min. at 0 °C under nitrogen atmosphere. After 10 min. the ice-bath was removed, the contents were allowed to stir at room temperature and the stirring was continued for 24 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **220**.

Yield: 183 mg (64%)

Method B: Reaction at 50 °C

To a solution of 4-chloro-2-methoxyphenol (0.158 g, 1 mmol) and methyl methacrylate (2.5 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 1 h. at 50 °C under nitrogen atmosphere, after it the contents were allowed to stir at same temperature and the stirring was continued for 1 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **220**.

Yield: 206 mg (72 %)

IR (neat) ν_{max}: 2964, 1737, 1623, 1456, 1378, 1291, 1120, 769 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.92 (dd, J = 2.5, 14 Hz, 1H), 2.54 (dd, J = 3.75, 13.75 Hz, 1H), 3.18 (dd, J = 2.75, 5.75 Hz, 1H),

3.38 (s, 3H), 3.41 (s, 3H), 3.43 (m, 1H), 3.72 (s, 3H), 6.09 (dd, J = 2.75, 6.75 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.28 (CH_3), 31.94 (C-3), 46.72 (C-2), 47.64 (C-4), 49.84 (C-8 methoxy carbon), 50.68 (C-8 methoxy carbon), 52.64 (methyl carbon of ester), 57.29 (C-1), 93.79 (C-8), 122.27 (C-6), 137.10 (C-5), 175.69 (carbonyl carbon of ester), 200.38 (C-7)

2.4.3 Synthesis of methyl (1*S**, 2*S**, 4*R**)-5-fluoro-8,8-dimethoxy-7-oxobicyclo[2,2,2]oct-5-ene-2-carboxylate (223).

Method A: Reaction at room temperature

To a solution of 4-fluoro-2-methoxyphenol (0.142 g, 1 mmol) and methyl acrylate (2.15 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 30 min. at 0 °C under nitrogen atmosphere. After 10 min. the ice-bath was removed, the contents were allowed to stir at room temperature and the stirring was continued for 24 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **223**.

Yield: 131 mg (51 %)

Method B: Reaction at 50 °C

To a solution of 4-fluoro-2-methoxyphenol (0.142 g, 1 mmol) and methyl acrylate (2.15 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 1 h. at 50 °C under nitrogen atmosphere, after it the contents were allowed to stir at same temperature and the stirring was continued for 1 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced

pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **223**.

Yield: 160 mg (62 %)

IR (neat) ν_{max}: 2958, 1739, 1670, 1448, 1361, 1205, 1163, 1073, 791cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10 (ddd, J = 3, 6, 16.5 Hz, 1H), 2.29 (ddd, J = 2.5, 4.5, 15.5 Hz, 1H), 3.002-3.007 (m, 1H), 3.16 (dd, J = 2.5, 14.5, 1 H), 3.34 (s, 3H), 3.37 (s, 3H), 3.52 (dd, J = 3.5, 5.5 Hz, 1 H), 3.70 (s, 3H), 5.31-5.33(m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 24.36 (C-3), 39.16 (C-1), 41.56 (C-4), 48.26 (C-8 methoxy carbon), 49.95 (C-8 methoxy carbon), 50.62 (C-2), 52.40 (methyl carbon of ester), 93.67 (C-8), 97.15 (C-6), 165.19 (C-5), 172.68 (carbonyl carbon of ester), 199.61 (C-7).

2.4.4 Synthesis of methyl (1*S**, 2*S**, 4*R**)-5-fluoro-8,8-dimethoxy-2-methyl-7-oxobicyclo[2,2,2]oct-5-ene-2-carboxylate (224).

Method A: Reaction at room temperature

To a solution of 4-fluoro-2-methoxyphenol (0.142 g, 1 mmol) and methyl methacrylate (2.5 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 30 min. at 0 °C under nitrogen atmosphere. After 10 min. the ice-bath was removed, contents were allowed to stir at room temperature and the stirring was continued for 24 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **224**.

Yield: 108 mg (40 %)

Method B: Reaction at 50 °C

To a solution of 4-fluoro-2-methoxyphenol (0.142 g, 1 mmol) and methyl methacrylate (2.5 g, 25 mmol) in anhydrous methanol (4 mL) was added a solution of diacetoxyiodobenzene (0.354 g, 1.1 mmol) in anhydrous methanol (6 mL) over a period of 1 h. at 50 °C under nitrogen atmosphere, after it the contents were allowed to stir at same temperature and the stirring was continued for 1 h. After the reaction was completed, the reaction mixture was concentrated by rotatory evaporator under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate/ hexanes as elutent to furnish the cycloadduct **224.**

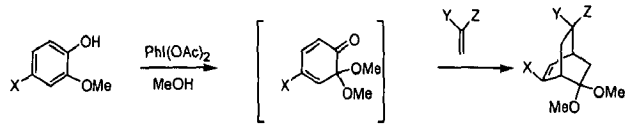
Yield: 122 mg (45 %)

IR (neat) ν_{max}: 2953, 1736, 1673, 1455, 1367, 1292, 1120, 788 cm-1

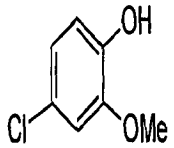
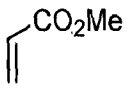
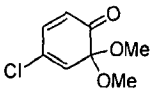
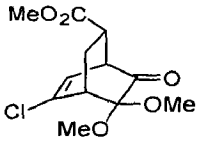
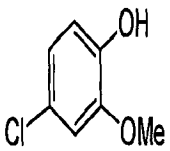
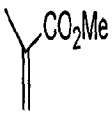
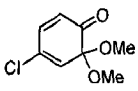
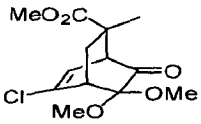
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.84 (dd, J = 3, 14 Hz, 1 H), 2.61 (dd, J = 3.5, 14 Hz, 1 H), 3.09 (dd, J = 2.5, 14 Hz, 1 H), 3.34 (dd, J = 4, 7 Hz, 1 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.70 (s, 3 H), 5.33-5.36 (m, 1 H)

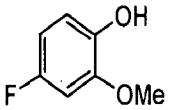
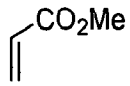
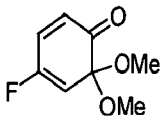
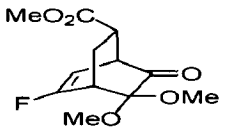
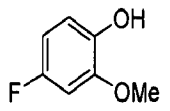
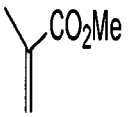
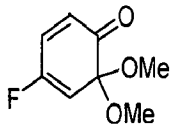
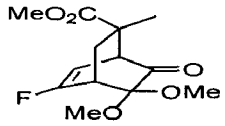
^{13}C NMR (125 MHz, $CDCl_3$): δ 25.22 (-CH_3), 30.58 (C-3), 41.63 (C-1), 46.84 (C-2), 49.73 (C-4), 50.58 (C-8 methoxy carbon), 52.30 (C-8 methoxy carbon), 54.34 (methyl carbon of ester), 93.91 (C-8), 98.87 (C-6), 165.41 (C-5), 175.73 (carbonyl carbon of ester), 200.84 (C-7)

Table 1: Intermolecular Diels-Alder reaction of 4-halo-2-methoxyphenol with methyl acrylate and methyl methacrylate in the presence of DAIB in methanol [a].



X = Cl,F
Y, Z = Various groups

S. N.	Phenol	Dieno -phile	MOBs	Cycloadduct	Reaction condition		Adduct/ Yield (%)
					Addition time/temp [b]	After addition time/temp [c]	
1					30 min/0 °C	24 h/rt	77.0
2					1 h/50 °C	1 h/50 °C	92.0
3					30 min/0 °C	24 h/rt	64.0
4					1 h/50 °C	1 h/50 °C	72.0

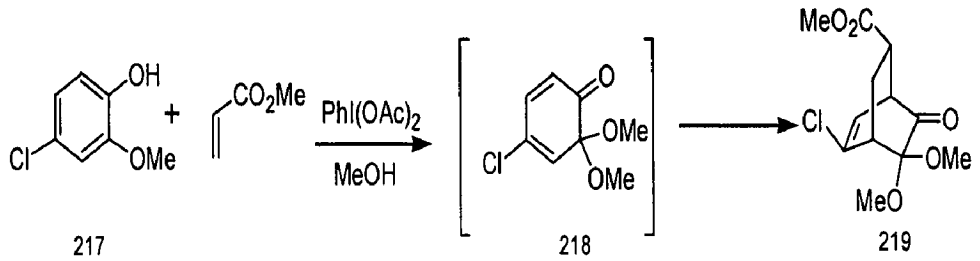
 			30 min/0 °C 1 h/50 °C	24 h/rt 1 h/50 °C	51.0 62.0
 			30 min/0 °C 1 h/50 °C	24 h/rt 1 h/50 °C	40.0 45.0

a) All reactions were carried out using 1 mmol of 4-halo-2-methoxyphenol with 25 mmol of dienophile.
b) Temperature and time during which DAIB was added to a mixture of 4-halo-2-methoxyphenoland dienophile in methanol.
c) Temperature of the reaction and the time for which the reaction mixture was stirred after the complete addition of DAIB

RESULTS AND DISCUSSION

It is known from the literature that in the absence of an external dienophile, the in situ generated reactive masked *o*-benzoquinones undergo self-dimerization to produce exclusively the dimer **103** indicating the highly unstable nature of MOBs. Consequently, high dilution techniques and a large ratio of dienophile to MOB were utilized through the course of the reaction to minimize dimerization event and to increase the yields of the desired Diels-Alder adducts.

In view of these considerations, the oxidation of 4-chloro-2-methoxyphenol (1 mmol) was carried out in the presence of large excess (25 mmol) of methyl acrylate in anhydrous methanol with diacetoxyiodobenzene under nitrogen atmosphere. Thus, to a solution of 4-chloro-2-methoxyphenol (217) and the dienophile in anhydrous methanol was added solution of DAIB in anhydrous methanol over a period of 30 min. under constant stirring with a syringe at 0 °C. After 10 min., the contents were brought to room temperature. The reaction was stirred further for 24 h at room temperature. The progress of the reaction was monitored by the TLC. After work-up and purification by column chromatography, the cycloadduct **219** was obtained in fair yield of 77 % (Scheme 64). The structure of the cycloadduct **219** was established by IR, ^{1}H and ^{13}C NMR, DEPT and GC-MS spectral analysis.



217 218 219

SCHEME 64

Encouraged by the results obtained in situ generated 4π-partner MOB **218** derived from 4-chloro-2-methoxyphenol, we were interested to improve the yield of the product. The same reaction was performed at 50 °C. In this method to a solution of 4-chloro-2-

methoxyphenol (1 eq.) and dienophile methyl acrylate (25 eq.) in anhydrous methanol was added solution of DAIB in anhydrous methanol over a period of 1 h with a syringe at 50 °C. The reaction was continued for 1 h at same temperature. The progress of the reaction was monitored by TLC. After work-up and purification by column chromatography the cycloadduct **219** was obtained in very high yield.

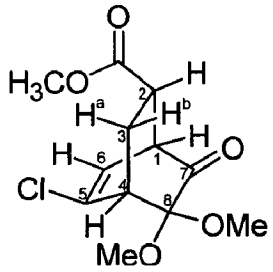


FIGURE: 9 **219**

The IR spectra of cycloadduct **219** show a strong peak at 1734 cm^{-1}, characteristic of the carbonyl group adjacent to the α,α-dimethoxy group in the functionalized cycloadduct **219**. Mass spectrum obtained from the GC-MS analysis show (M^+-28) peak but not molecular ion peak indicating the facile extrusion of CO from the molecule. Similarly further extrusion of Cl and CO_2Me also observed from the corresponding peaks at 211 and 187, respectively. The regio- and stereochemistry of the cycloadduct **219** was assigned based on the related molecules reported in the literature [72].

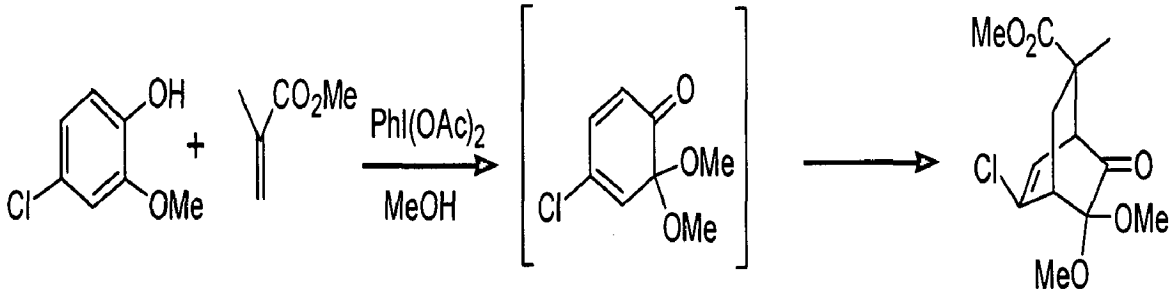
In the ^1H NMR, the chemical shifts of the bridgehead protons H^1 and H^4 are observed between δ 3.56-3.58 and δ 3.25-3.29, respectively. Due to the coupling of bridgehead proton H^1 with adjacent proton H^2 and vinylic proton H^6, a doublet of doublet (dd) pattern is observed for this proton. Similarly, a doublet of doublet (dd) pattern is observed for bridgehead proton H^4 as it couples with diastereomeric protons H^{3a} and H^{3b}. The coupling constants between H^1, H^2 and H^6 are J = 2 and 7 Hz and for H^4 and diastereomeric protons J = 2.75 and 5.75 Hz. The chemical shifts of protons H^2, H^{3a} and H^{3b} are observed at δ 3.02-3.04 and δ 2.31-2.36 & δ 1.99-2.04, respectively. The H^2 proton couples with bridgehead proton H^1 as well as diastereomeric proton H^{3a} & H^{3b}. As

a result it is splitted in "doublet of doublet of doublet (ddd)" pattern and the coupling constants are J = 6, 8 &11 Hz. The diastereomeric protons H^{3a} & H^{3b} show 2-bond geminal coupling as well as 3-bond vicinal coupling hence a "ddd" pattern is observed with coupling constant J_{3a} = 3, 13.5 & 16.5 Hz and J_{3b} = 2.5, 5.5 and 13.5 Hz, respectively. As the vinylic proton H^6 is highly deshielded, the chemical shift is observed at δ 6.04-6.06. Signals from the protons of two methoxy groups at position C-8 are resonated at δ 3.34 and δ 3.39. The signal for the protons of methoxy group of ester is observed at δ 3.71. These three signals are observed as sharp singlets (Table-2).

^{13}C NMR and DEPT-135, DEPT- 90 and DEPT- 45 also have been recorded for the cycloadduct 219. In ^{13}C NMR, 13 signals are present. Signals from quaternary carbon C-7, carbonyl carbonyl of ester group, C-5 and C-8 observed at δ 198.97, 172.48, 136.93 and 93.35, respectively. These are further confirmed by DEPT spectrum analysis in which these signals are absent. Signals from OCH3 group carbons at C-8 and methyl carbon of ester observed at δ 50.68, 50.49 and 52.25, respectively. DEPT spectrum analysis also supports these findings. In DEPT-45 (which shows the signals of all protonated carbons) these signals are present but not in DEPT-90 (which shows the signals only from C-H). Signals of C-1, C-2, C-4 and C-6 in ^{13}C NMR, observed at δ 38.91, 49.91, 47.26 and 120.23, respectively. These four signals are from C-H type carbons so they are present in DEPT-90. Signal of C-3 observed at δ 24.59.

Finally, the combined spectrum of DEPT-45 and DEPT-90 that is DEPT-135 analysed. DEPT-135 shows positive signals for carbon which is attached with odd number of protons (i.e. C-H & CH_3) and negative signals for carbon which is attached with even number of protons (i.e. -CH_2). The cycloadduct **219** has three –CH_3 groups, four –CH and one –CH_2 group. Seven positive signals (from C-H & CH_3) and one negative signal (from -CH_2) observed in DEPT-135 (Table-7).

At this juncture we turned out attention to evaluate the effect of steric bulk in Diels-Alder reaction. For this purpose, we have performed the reaction of 4-chloro-2-methoxyphenol with methyl methacrylate as dienophile. The above mentioned procedures were followed as such and the yield of the cycloadduct **220** was 64 % (reaction at room temperature) and 72 % (reaction at 50 °C).The yield in these reaction were less than reaction 1 (Scheme 65).



217 218 220

SCHEME 65

The structure of the cycloadduct **220** was established by all spectral analysis techniques. The IR spectrum of cycloadduct **220** shows a strong absorption at 1737 cm^{-1}, characteristic of the carbonyl group adjacent to a α,α–dimethoxy group in the functionalized cycloadducts **220**. Mass spetrum shows the (M^+-CO) peak at 260 and further extraction of –Cl and $-CO_2Me$. No molecular ion peak was present.

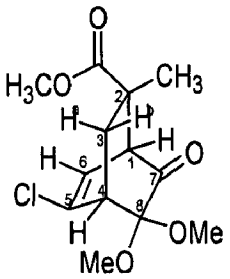


FIGURE: 10 **220**

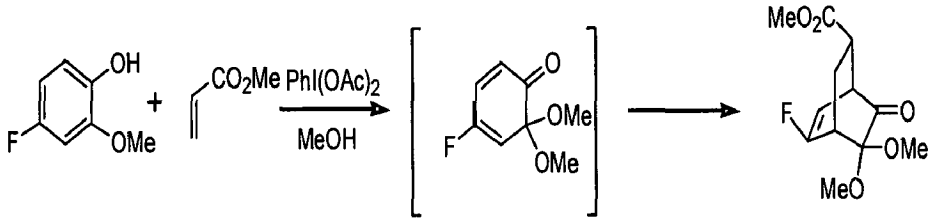
The chemical shifts of the bridgehead proton H^1 and H^4 observed at δ 3.43 and δ 3.15-3.18 respectively. The bridgehead proton H^1 couples with vinylic proton H^6 and splitted in doublet pattern. The bridgehead proton H^4 couples with diastereomeric protons H^{3a} & H^{3b} and splitted in "doublet of doublet" (dd) pattern with coupling constants 2.75 and 5.75 Hz. Chemical shifts for diastereomeric protons H^{3a} & H^{3b} observed between δ 2.52-2.56 and δ 1.90-1.94 respectively. The diastereomeric protons H^{3a} & H^{3b} are adjacent to bridge head proton H^4. "dd" pattern observed for these protons as there are

geminal as well as vicinal coupling. The J values for proton H^{3a} are 3.75 and 13.75 Hz and for H^{3b} 2.5 and 14 Hz. The chemical shift value for vinylic proton observed at its usual range δ 6.08-6.10.Coupling constant of vinylic proton observed at J = 2.75 and 6.75 Hz. There is a chance of 'W-type' long range coupling with methyl proton at position 2 as well as bridgehead proton H^4 although it is not clearly observed. Methyl proton at bridge position resonated at δ 1.33 and a sharp singlet observed for this. Similarly singlet observed for protons of two methoxy groups at position C-8 and for protons of methyl group of ester at δ 3.38, 3.41 and 3.72, respectively (Table-3).

^{13}C NMR, and DEPT-45, DEPT-90, and DEPT-135 analysis supports the above structure elucidation. Chemical shifts for quaternary carbon C-7, carbonyl carbon of ester group, C-5, C-8 and C-2 observed at δ 200.38, 175.69, 137.10, 93.79 and 46.72, respectively. These chemical shifts values are absent in DEPT spectrum. Signals from carbon of -OCH3 group at position C-8 and carbon of methyl group of ester observed at δ 50.68, 49.84 and 52.64 respectively and chemical shift value for methyl group carbon at C-2 observed at δ 25.28 in ^{13}C NMR. DEPT-45 and DEPT-90 spectrum analysis also confirmed these results. In DEPT-45 spectrum all protonated carbon signals are present but not in DEPT-90. Signals from primary carbons are absent in DEPT-90. Only C-H signals of C-1, C-4 and C-6 which observed at δ 57.29, 47.64 and 122.27 present in DEPT-90. Finally the DEPT-135 shows seven positive signals corresponding to primary and tertiary carbon and one negative signals corresponding to secondary carbon (Table-7).

Successfully preparing the chloro substituted Bicyclo[2.2.2]octenone derivatives (219 and 220) we turned our attention to other halogen compound. In this direction we worked with 4-fluoro-2-methoxyphenol and dienophiles were same that is methyl acrylate and methyl methacrylate.

Mentioning the reaction condition and concentration of dienophile exactly same as in reaction 1 we were able to produce thh cycloadduct **223**. The yield in this reaction was 51 % when reaction performed at 0 °C followed by stirring at room temperature for 24 h and 62 % when reaction temperature was 50 °C (Scheme 66)



221 222 223

SCHEME 66

In IR spectrum absorption at 1739 cm^{-1} correspondence to the carbonyl group adjacent to the α,α-dimethoxy group in the functionalized cycloadduct **223**. No molecular ion peak is present in mass spectrum but peak correspond to (M^+-28) is observed in spectrum. Further extrusion of CO_2Me is confirmed by peak at 171. Proton, ^{13}C NMR and DEPT analysis have been done to confirm to the structure and stereochemical outcome of the cycloadduct **223.**

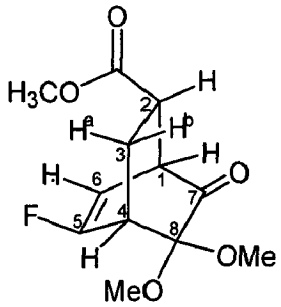


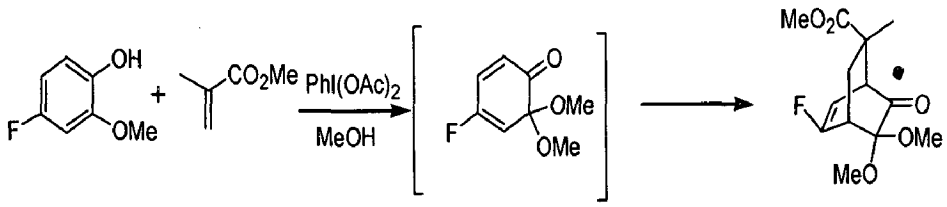
FIGURE: 11 **223**

The chemical shifts of the bridgehead proton H^1 and H^4 are observed at δ 3.50-3.53 and δ 3.15-3.18, respectively. The bridgehead proton H^1 couples with adjacent proton H^2 and vinylic proton H^6 with couling constant 3.5 and 5.5 Hz. The bridgehead proton H^4 couples with diastereomeric protons H^{3a} and H^{3b}. Typical "doublet of doublet" (dd) pattern observed for this with coupling constant values 2.5 and 14.5 Hz. Proton H^2 is adjacent to diastereomeric protons H^{3a} and H^{3b} and multiplet pattern is observed for this proton since there is chance of 'W type' long range coupling with vinylic proton H^6 and

the chemical shifts values for H^2 proton is observed at δ 3.002-3.007. Chemical shifts values for diastereomeric protons H^{3a} and H^{3b} are observed between δ 2.26-2.31 and δ 2.09-2.12, respectively. These protons are coupling with proton H^2 and bridgehead proton H^4. In addition there is a chance of geminal coupling also since there environment is not same and 'ddd' pattern is observed for these protons. The coupling constant value for H^{3a} is observed at 2.5, 4.5 and 15.5 Hz similarly for H^{3b} it is 3, 6, and 16.5 Hz. The chemical shifts for vinylic proton H^6 is observed between δ 5.31-5.33 and multiplet pattern is observed since there is vicinal coupling with protn H^1 as well as 'W type' long range coupling with proton H^2 and proton H^4. In proton NMR analysis three sharp singlets also observed and they are due to protons of methoxy group at position eight and proton of ester group with chemical shifts value at δ 3.37, 3.34 and 3.70, respectively (Table-4).

^{13}C and DEPT analysis also supports the above structure elucidation. As observed in cycloadducts **219** and **220** signals for quaternary carbons C-7, carbonyl carbon of ester, C-5 and C-8 are in downfield region and the chemical shifts values are δ 199.61, 172.68, 165.19 and 93.67, respectively. As expected these quaternary carbons signals are absent in DEPT spectrum. In addition signals from primary carbons (i.e. CH_3) of ester group and methoxy group carbon at position eight are observed at δ 52.40, 49.95 and 48.26, respectively. These signals are present in DEPT-45 also but not in DEPT-90. As DEPT-90 shows signals corresponding to tertiary carbon (C-H) so the chemical shifts of C-1, C-2, C-4, and C-6 are observed at δ 39.15, 50.62, 41.56 and 97.15, respectively. The signal corresponding to C-3 is observed at δ 24.36.The analysis of DEPT-135 shows expectd seven positive and one negative signal. Since fluorine is also NMR active having nuclear spin quantum number ½, hence there is chance of C-F coupling and it is observed in some signal as the signal lines are splitting.

Our next step was to study the effect of sterically hindered dienophile on MOBs. For this purpose the reaction of 4-fluoro-2-methoxyphenol (221) was performed with dienophile methylmethacrylate mentioning the reaction condition exactly the same as described in procedure. After work-up and purification by column chromatography the cycloadduct **224** was obtained in fair yield 40 % when reaction temperature was 0 °C/ room temperature and 45 % when reaction temperature was 50 °C. Although the yield was less then above reaction but we were able to get almost pure compound.



221 222 224

SCHEME 67

In a similar fashion the characterization has been done with the help of spectral techniques. The IR spectra of cycloadduct **224** shows a strong absorption peak at 1736 cm^{-1} characteristic to the carbonyl group adjacent to the α,α-dimethoxy group in the functionalized cycloadduct **224**. All expected peaks corresponding to C-H stretching and C-O bending etc. is observed. Similar to other three cycloadducts, no molecular ion peak is observed in mass spectrum, but the peak corresponding to (M^+-28) is observed. Further the loss of CO_2Me (59) is also observed.

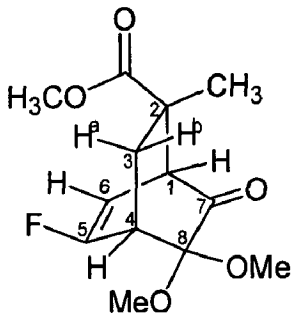


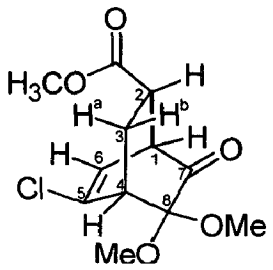
FIGURE: 12 **224**

The chemical shifts of the bridgehead protons H^1 and H^4 are observed between δ 3.33-3.34 and δ 3.07-3.11, respectively. Vicinal coupling as well as long range coupling is observed for proton H^1. Similarly the bridgehead proton H^4 couples with diastereomeric protons H^{3a} and H^{3b} and a typical 'dd' pattern is observed for this proton. Coupling constant for proton H^4 is observed at 2.5 and 14.5 Hz. The chemical shifts for diastereomeric protons H^{3a} and H^{3b} are observed between δ 2.59-2.62 and δ 1.83-1.86,

respectively. A 'dd' pattern is observed resulting from vicinal coupling as well as geminal coupling. Highly deshielded vinylic proton H^6 is observed at δ 5.33-5.36 and multiplet pattern is observed as there is chance of 3-bond vicinal coupling as well as 'W type' long range coupling with proton H^4 and methyl protons at position two with coupling constant 3, 6 and 9.5 Hz. As expected from structure of cycloadduct four sharp singlets are present and among these three are corresponding to methoxy group protons in downfield region and one is corresponding to methyl protons in upfield region. Chemical shifts for protons of ester group is observed at δ 3.70 whereas protons of methoxy groups at position eight observed at δ 3.36 and 3.38. Signals from protons of methyl at position two is observed δ 1.31(Table-5).

In addition to the ^1H NMR analysis, ^{13}C and DEPT analysis also confirms the structure of cycloadduct **224**. Signals from quaternary carbons is observed in downfield region and the chemical shifts of C-7, carbonyl carbon of ester, C-5 and C-8 at δ 200.84, 175.73, 165.41 and 93.91, respectively. As usual quaternary carbons signals are not present in DEPT spectrum. Signals from all protonated carbons are present in DEPT-45 spectrum. Chemical shifts from carbon of methoxy group of ester at position two and carbon of methoxy group at position eight are observed at δ 54.34, 52.30 and 50.58, respectively. Further the signal from methyl carbon at position two is observed at δ 25.22.These signals are present in DEPT-45 as well as in DEPT-135. The signals from ternary carbon C-1, C-4 and C-6 are observed at δ 41.63, 49.73 and 98.97, respectively. Finally the results are supported by DEPT-135 analysis which shows seven positive signals and one negative signal (Table-7).

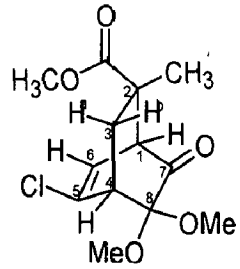
TABLE: 2 **^{1}H NMR DATA OF DIELS-ALDER ADDUCT 219**



219

Protons		Chemical Shifts(δ ppm)	Multiplicity	Coupling Constant (J Hz)
H^1		3.57	dd	2, 7
H^2		3.04	ddd	6, 8, 11
H^3	a	2.34	ddd	3, 13.5, 16.5
	b	2.02	ddd	2.5, 5.5, 13.5
H^4		3.24	dd	2.75, 5.75
H^6		6.05	dd	2.75, 6.75
OMe (C-8)		3.34	s	----
		3.39	s	----
methyl (ester)		3.71	s	----

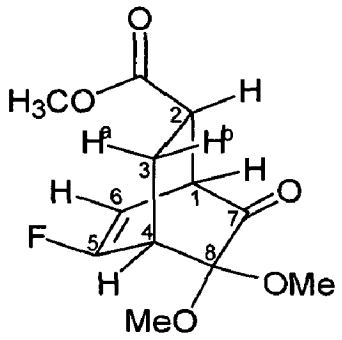
TABLE: 3 **^{1}H NMR DATA OF DIELS-ALDER ADDUCT 220**



220

Protons		Chemical Shifts(δ ppm)	Multiplicity	Coupling Constant (J Hz)
H^1		3.43	m	----
H^3	a	2.54	dd	3.75, 13.75
	b	1.92	dd	2.5, 14
H^4		3.18	dd	2.75, 5.75
H^6		6.09	dd	2.75, 6.75
OMe (C-8)		3.38	s	----
		3.41	s	----
methyl (ester)		3.72	s	----
$-CH_3$		1.33	s	----

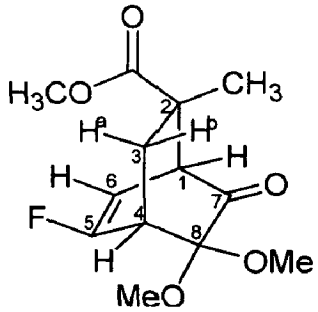
TABLE: 4 **^{1}H NMR DATA OF DIELS-ALDER ADDUCT 223**



223

Protons		Chemical Shifts(δ ppm)	Multiplicity	Coupling Constant (J Hz)
H^1		3.52	dd	3.5, 5.5
H^2		3.00	m	----
H^3	a	2.29	ddd	2.5, 4.5, 15.5
	b	2.10	ddd	3, 6, 16.5
H^4		3.16	dd	2.5, 14.5
H^6		5.31-5.33	m	----
OMe (C-8)		3.34	s	----
		3.37	s	----
methyl (ester)		3.70	s	----

TABLE: 5 **^{1}H NMR DATA OF DIELS-ALDER ADDUCT 224**

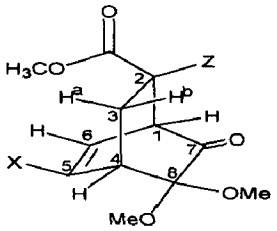


224

Protons		Chemical Shifts(δ ppm)	Multiplicity	Coupling Constant (J Hz)
H^1		3.34	dd	4, 7
H^3	a	2.61	dd	3.5, 14
	b	1.84	dd	3, 14
H^4		3.09	dd	2.5, 14
H^6		5.33-5.36	m	----
OMe (C-8)		3.36	s	----
		3.38	s	----
methyl (ester)		3.70	s	----
$-CH_3$		1.31	s	----

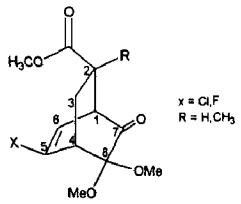
COMPARISON OF NMR DATA

TABLE: 6



δ	H^1	H^2	methyl (ester)	H^{3a}	H^{3b}	H^4	H^6	OMe (C-8)
219	3.57	3.04	3.71	2.34	2.02	3.24	6.05	3.34, 3.39
220	3.43	-	3.72	2.54	1.92	3.18	6.09	3.38, 3.41
223	3.52	3.00	3.70	2.29	2.10	3.16	5.31-5.33	3.34, 3.37
224	3.34	-	3.70	2.61	1.84	3.09	5.33-5.36	3.36, 3.38

TABLE: 7



CA[a]	NMR	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-8(OMe)	CO (ester)	methyl (ester)	CH_3
219	^{13}C	38.91	49.91	24.59	47.26	136.93	120.23	198.97	93.35	50.68 50.49	172.48	52.25	----
	DEPT-45	+	+	+	+	----	+	----	----	+	----	+	----
	DEPT-90	+	+	----	+	----	+	----	----	----	----	----	----
	DEPT-135	+	+	-	+	----	+	----	----	+	----	+	----
220	^{13}C	57.29	46.72	31.94	47.64	137.10	122.21	200.38	93.79	50.68 49.84	175.69	52.64	25.28
	DEPT-45	+	----	+	+	----	+	----	----	+	----	+	+
	DEPT-90	+	----	----	+	----	+	----	----	----	----	----	----
	DEPT-135	+	----	-	+	----	+	----	----	+	----	+	+
223	^{13}C	39.15	50.62	24.36	41.56	165.19	97.15	199.61	93.67	49.95 48.26	172.68	52.40	----
	DEPT-45	+	+	+	+	----	+	----	----	+	----	+	----
	DEPT-90	+	+	----	+	----	+	----	----	----	----	----	----
	DEPT-135	+	+	-	+	----	+	----	----	+	----	+	----
224	^{13}C	41.63	46.84	30.58	49.73	165.41	98.97	200.84	93.91	52.30 50.58	175.73	54.34	25.22
	DEPT-45	+	----	+	+	----	+	----	----	+	----	+	+
	DEPT-90	+	----	----	+	----	+	----	----	----	----	----	----
	DEPT-135	+	----	-	+	----	+	----	----	+	----	+	+

a) Cycloadduct

CONCLUSIONS

CONCLUSIONS

Our objective to utilize 4-chloro-2-methoxyphenol (217) and 4-fluoro-2-methoxyphenol (221) as an inexpensive starting material for the construction of bicyclo [2.2.2]octenone derivatives has met with considerable success. The MOBs 218 and 222 generated from 4-halo-2-methoxyphenol (217, 221) and DAIB under vent highly regio- and stereoselective intermolecular Diels-Alder reaction with electron deficient methyl acrylate and methyl mehacrylate to furnish exclusively cycloadducts (**219, 220, 223, 224).**

SPECTRA

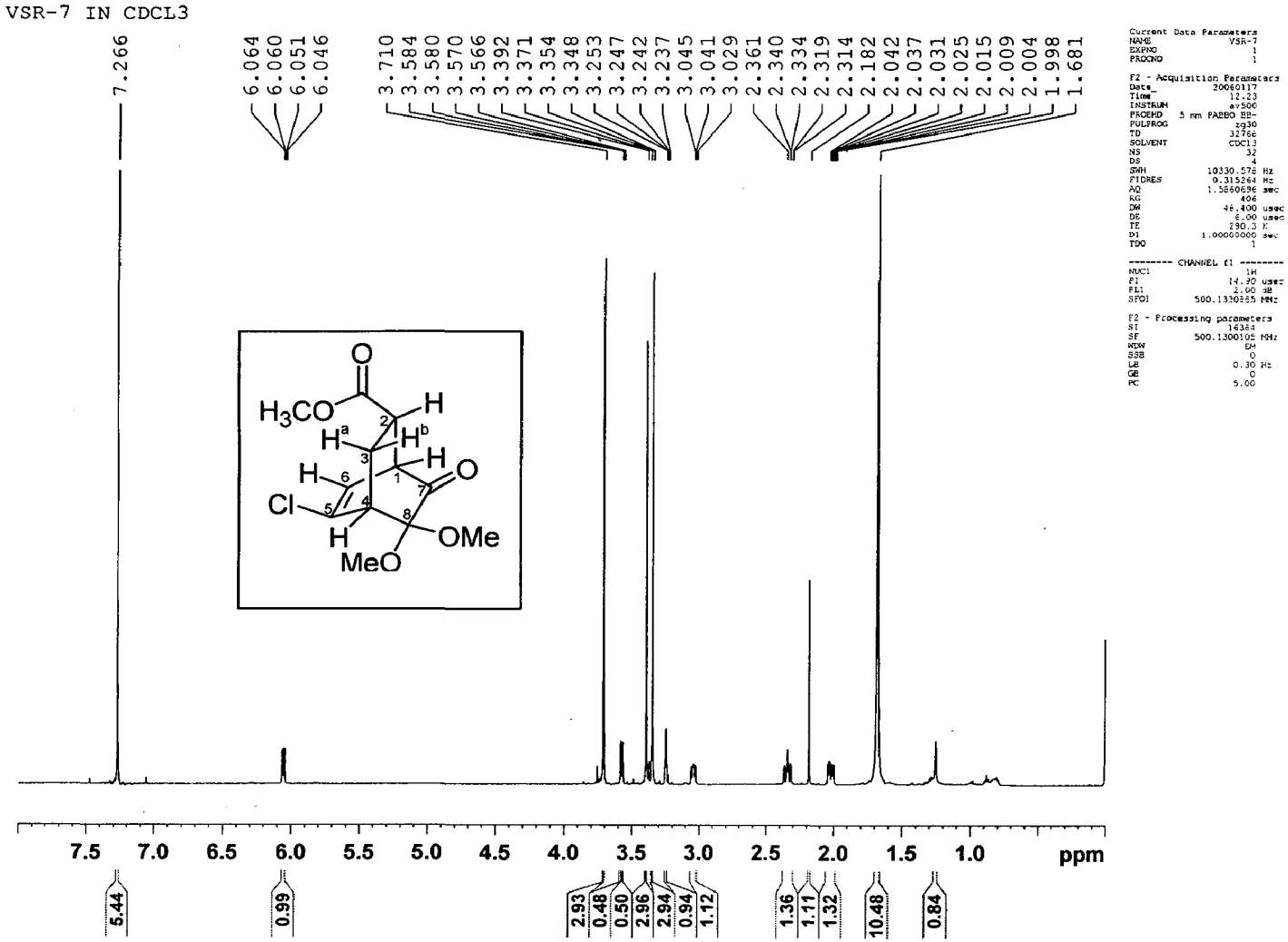


Fig 1. ^{1}H NMR Spectrum of Diels-Alder adduct 219

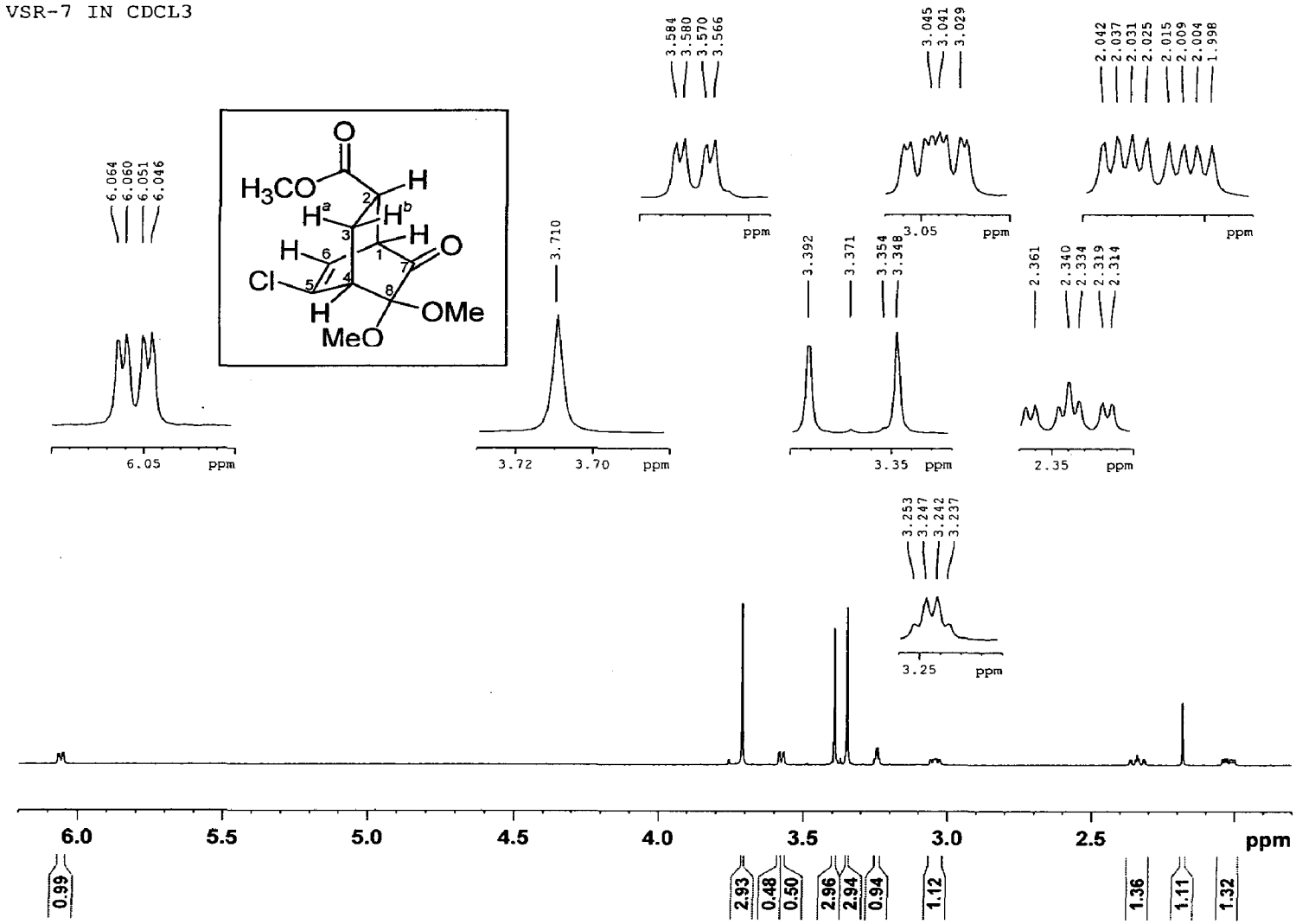


Fig 2. Expansion of ^{1}H NMR Spectrum of Diels-Alder adduct 219

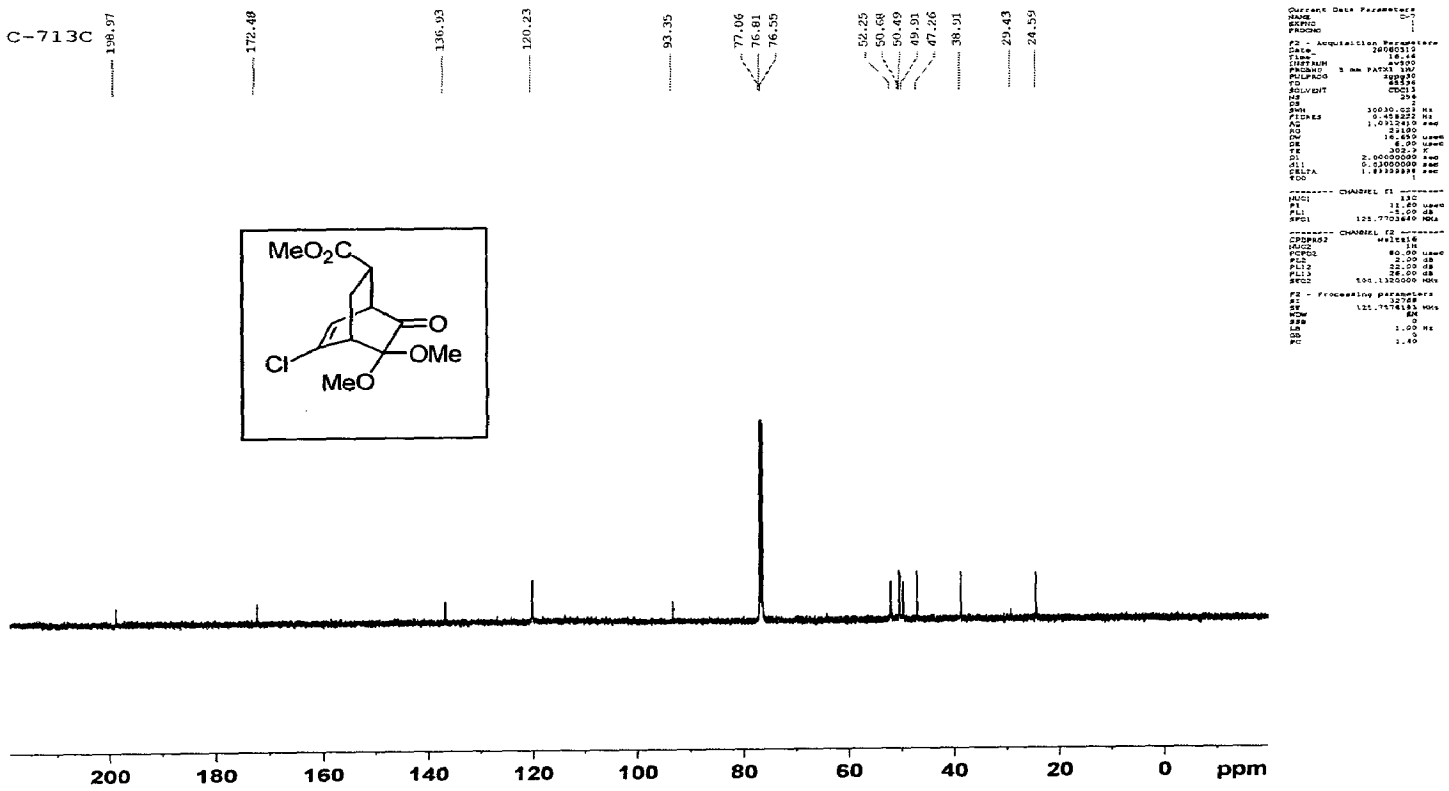


Fig 3. ^{13}C NMR Spectrum of Diels-Alder adduct 219

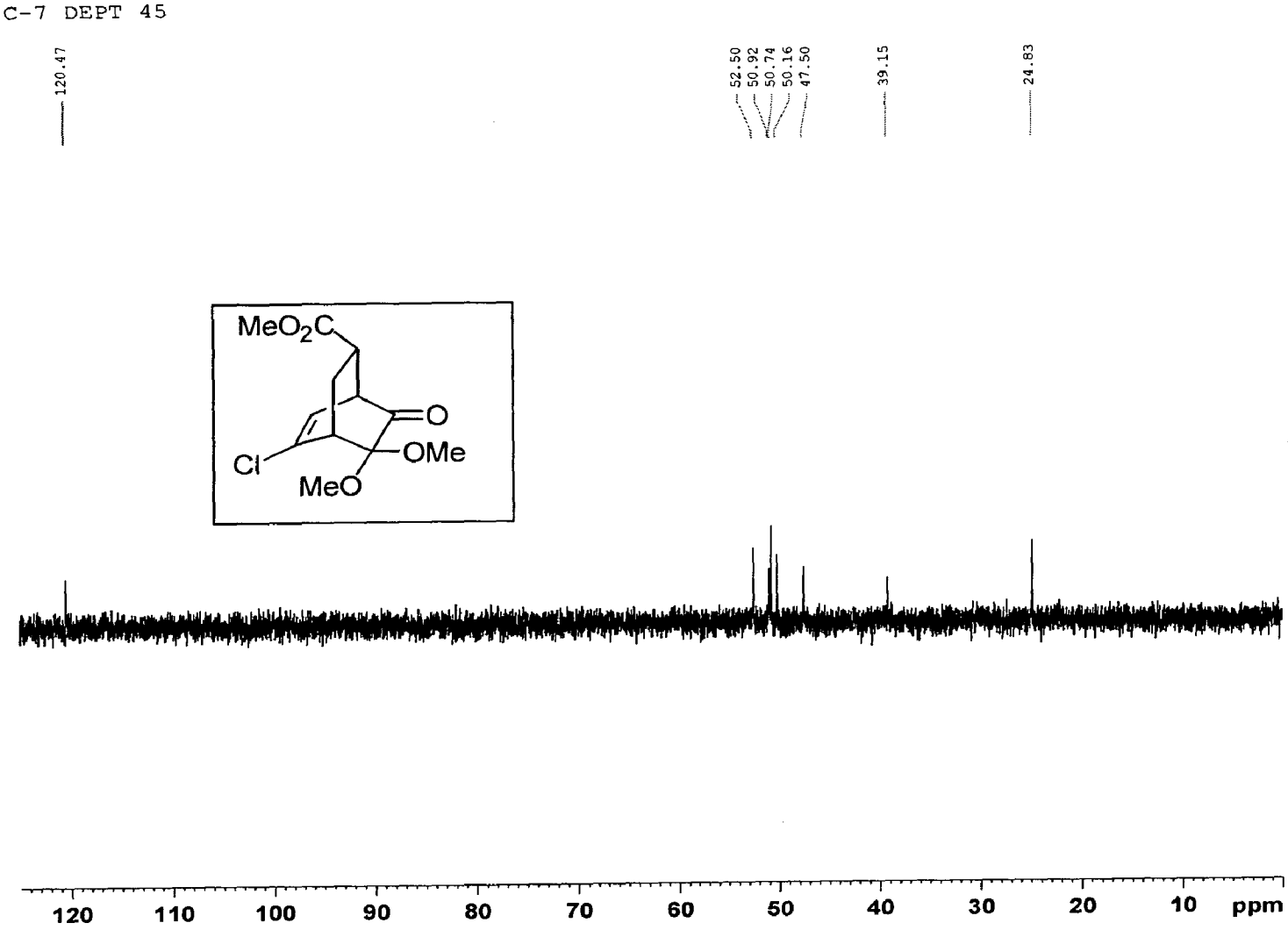


Fig 4. DEPT-45 Spectrum of Diels-Alder adduct 219

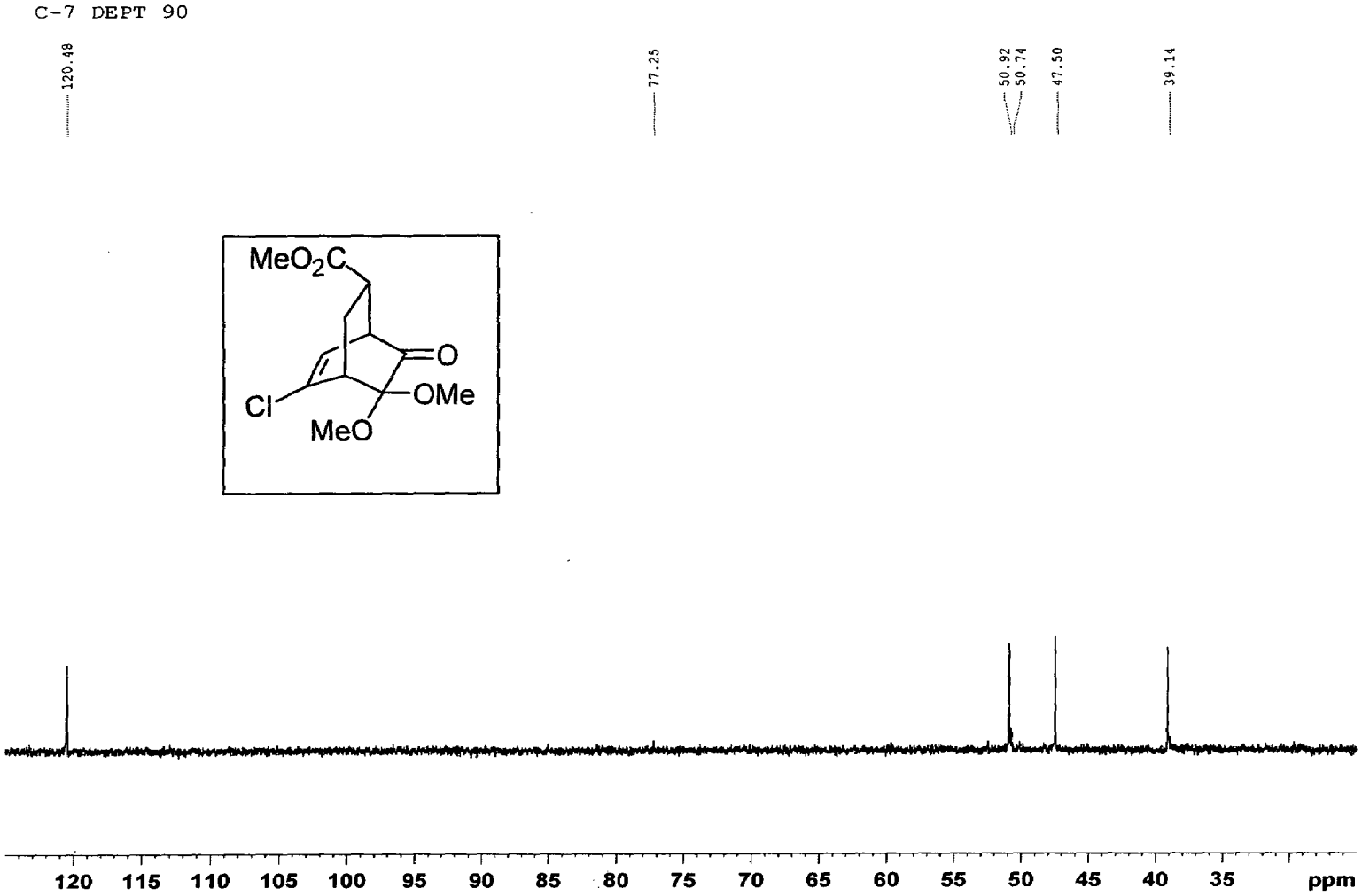


Fig 5. DEPT-90 Spectrum of Diels-Alder adduct 219

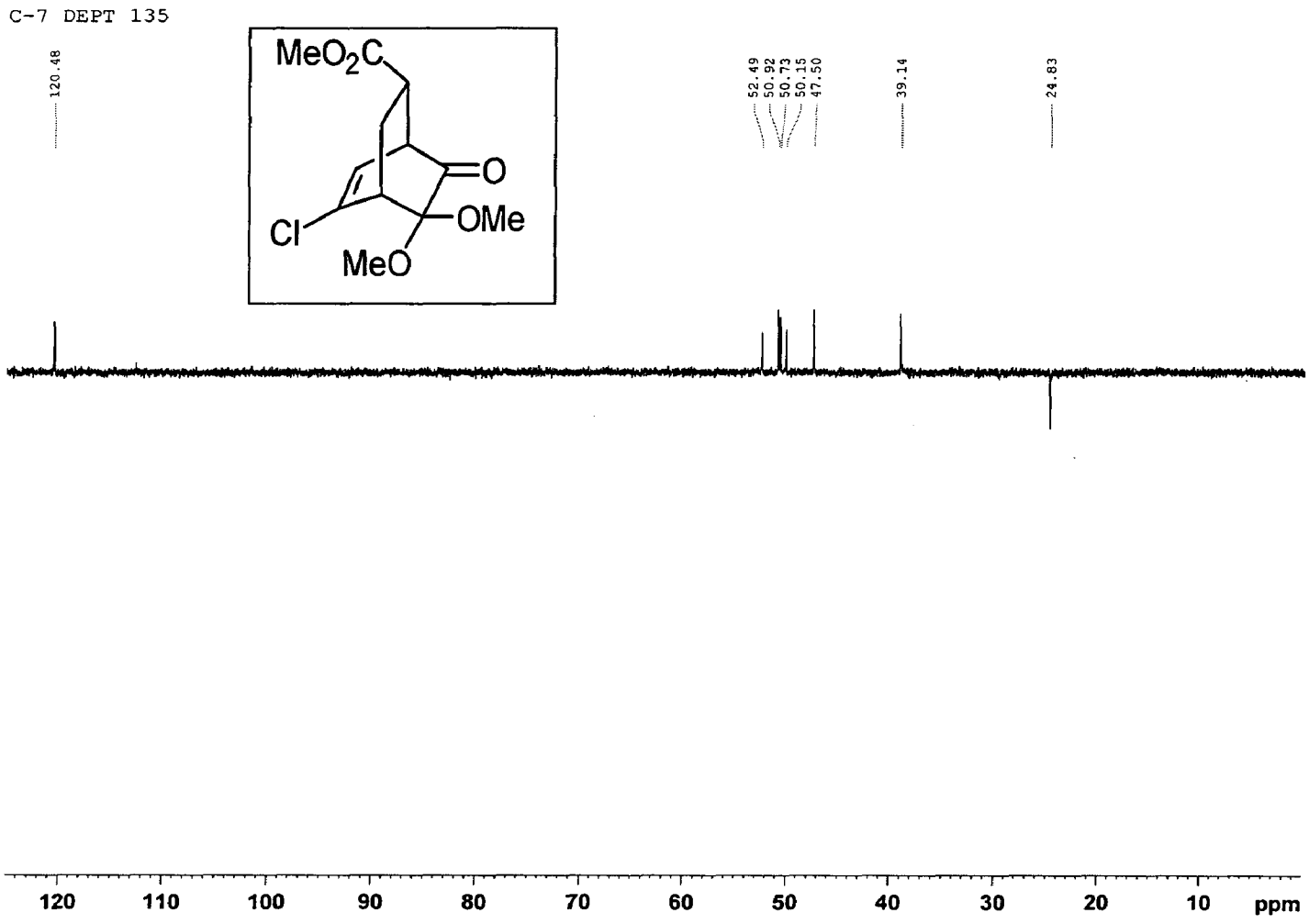


Fig 6. DEPT-135 Spectrum of Diels-Alder adduct 219

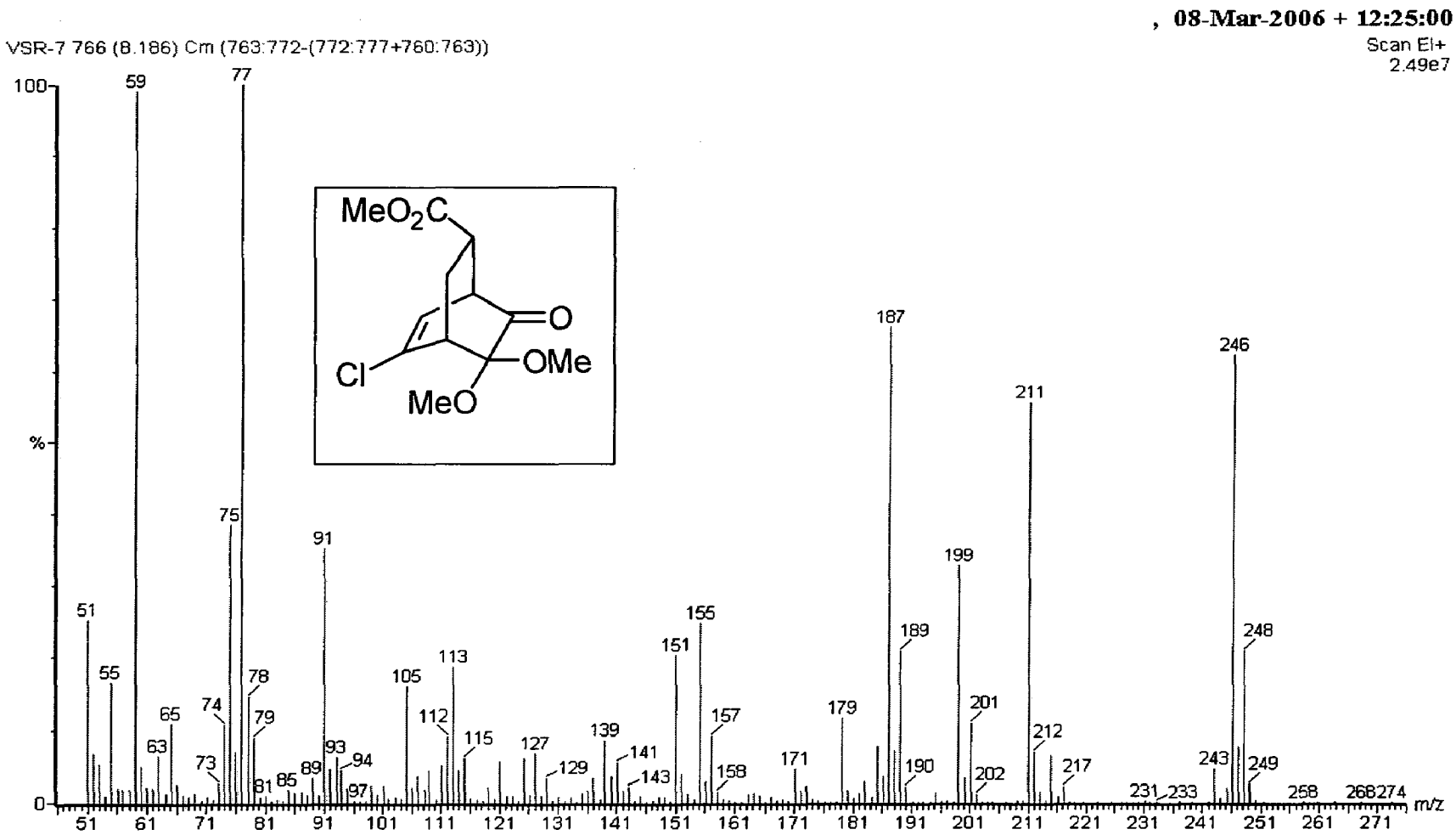


Fig 7. Mass Spectrum of Diels-Alder adduct 219

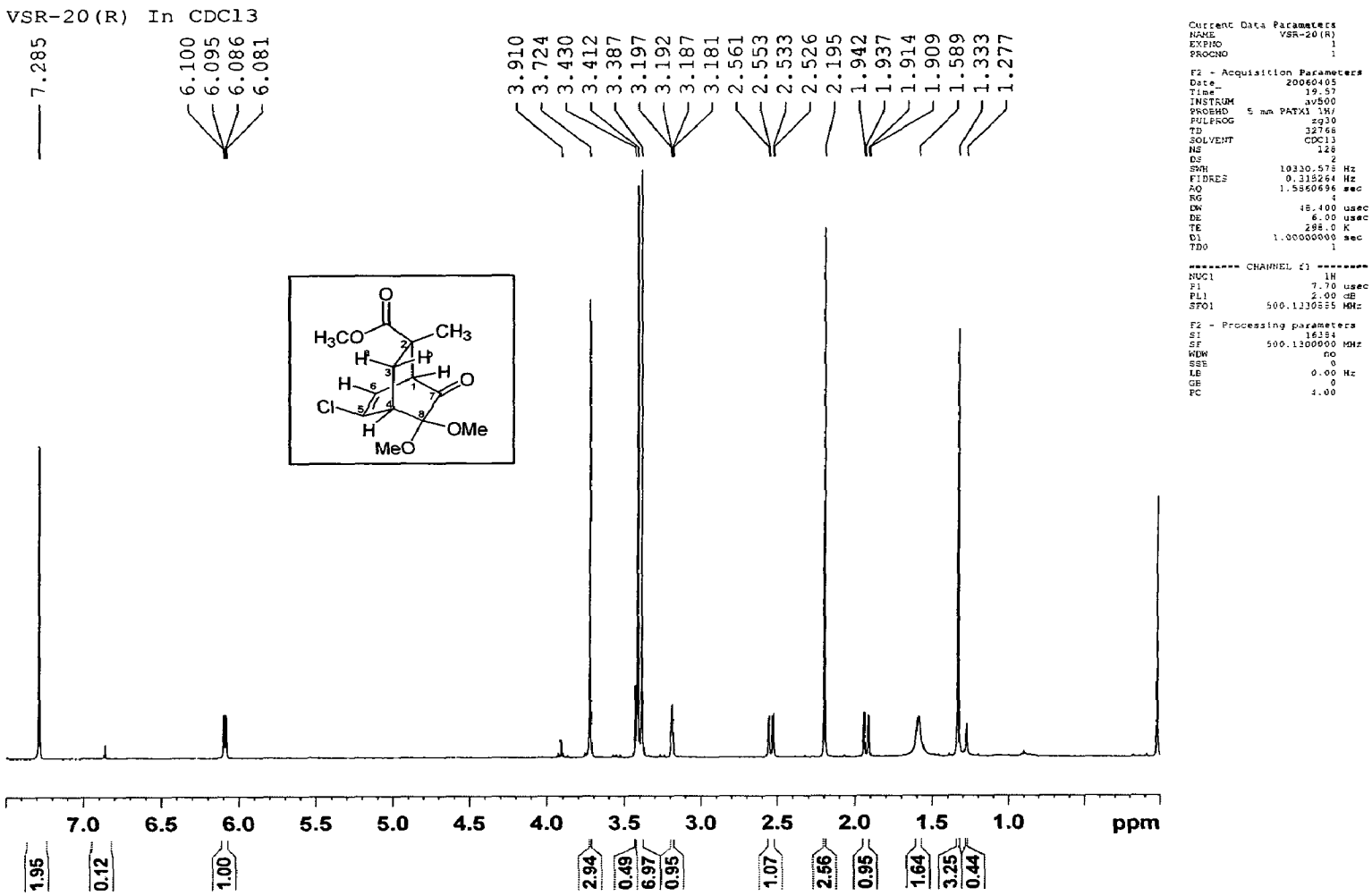


Fig 8. ^{1}H NMR Spectrum of Diels-Alder adduct 220

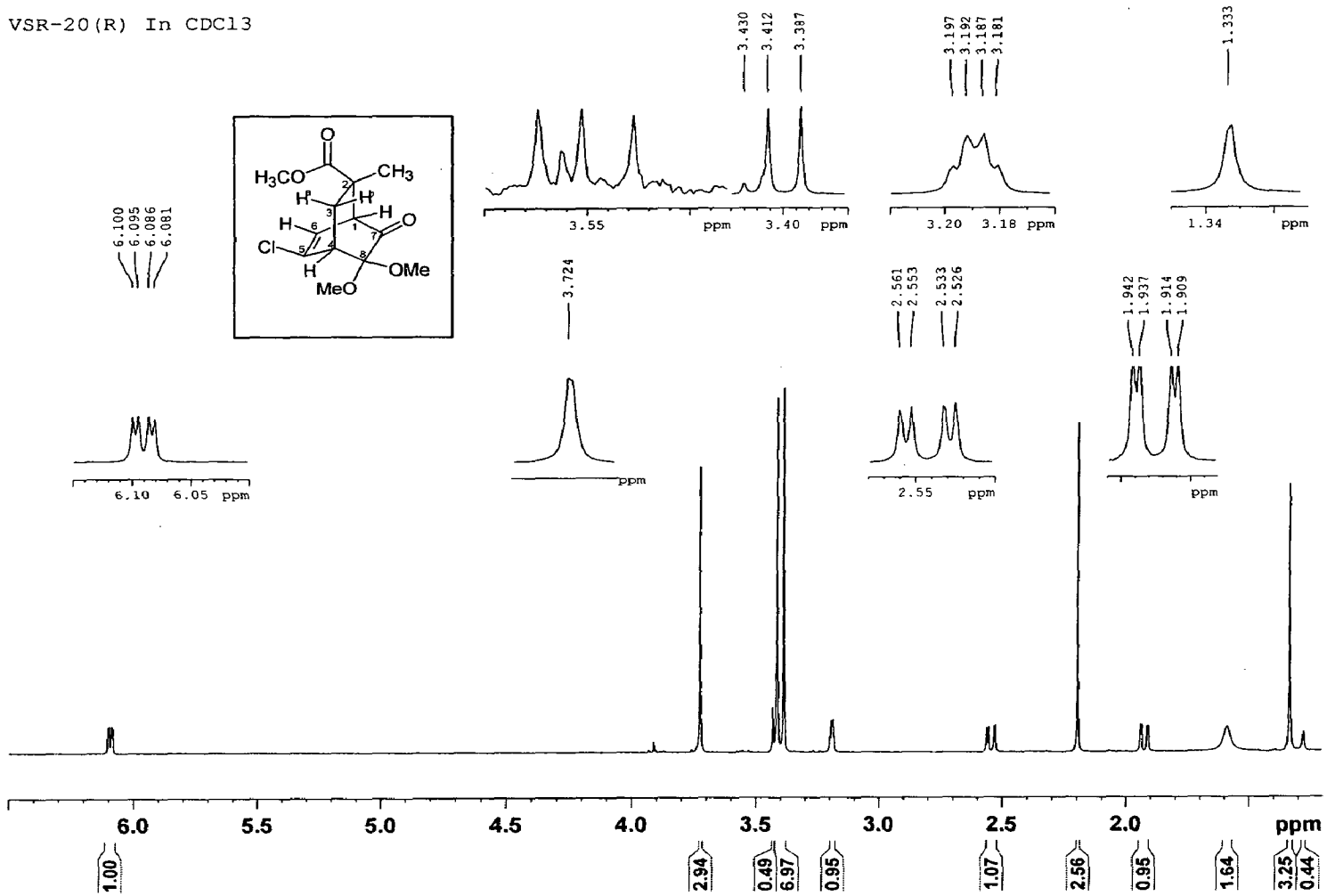


Fig 9. Expansion of ^{1}H NMR Spectrum of Diels-Alder adduct 220

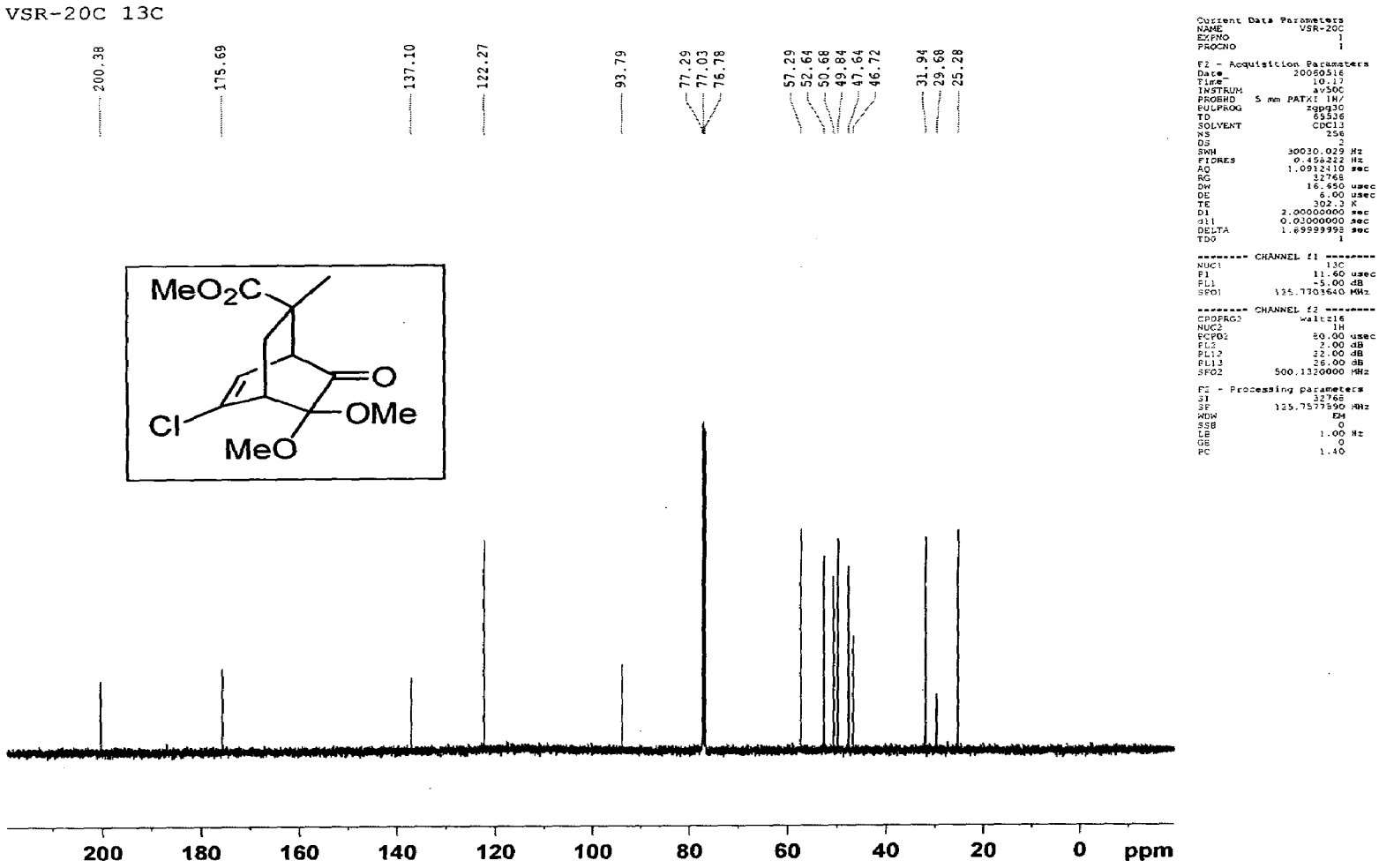


Fig 10. ^{13}C NMR Spectrum of Diels-Alder adduct 220

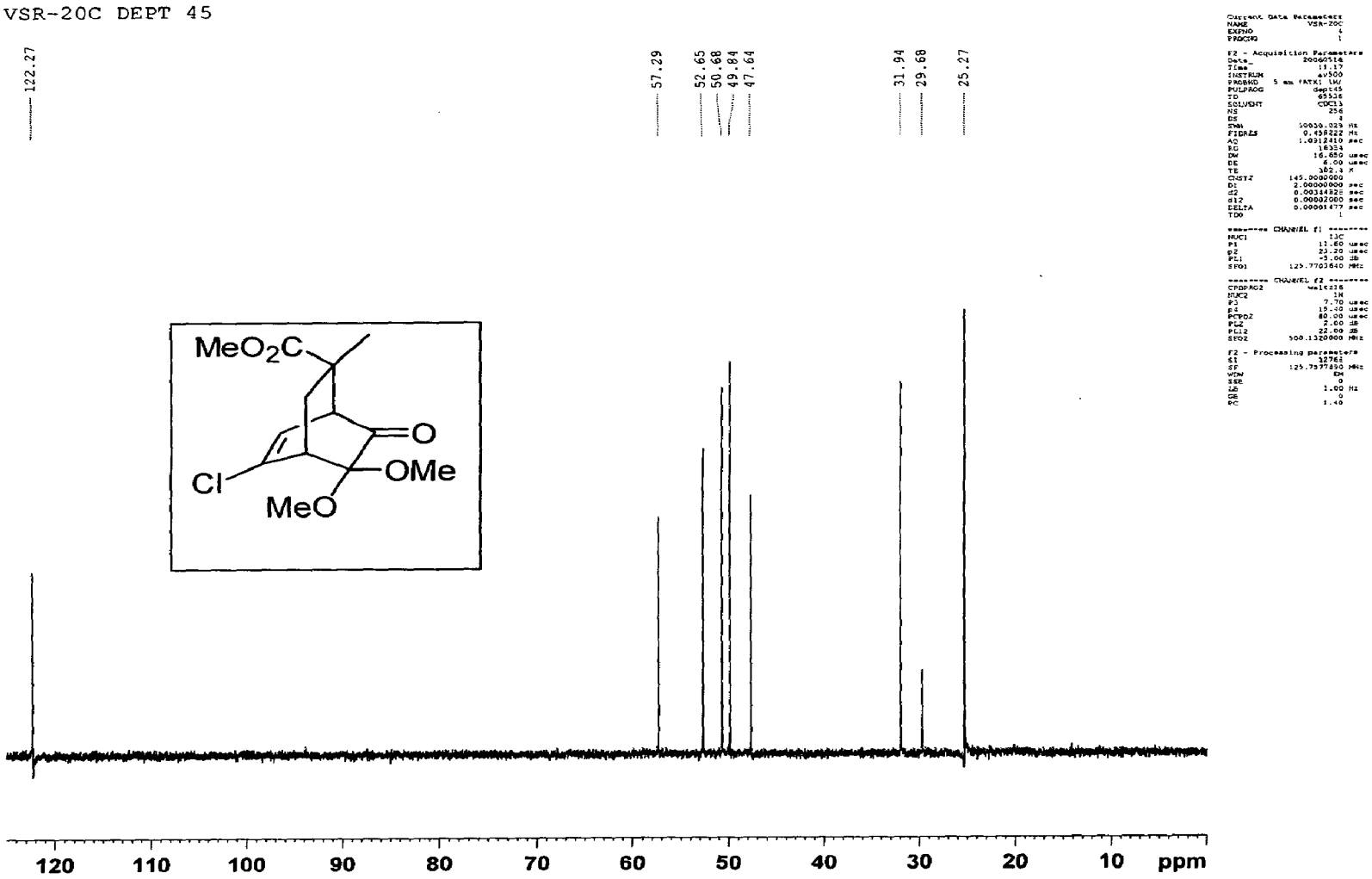


Fig 11. DEPT-45 Spectrum of Diels-Alder adduct 220

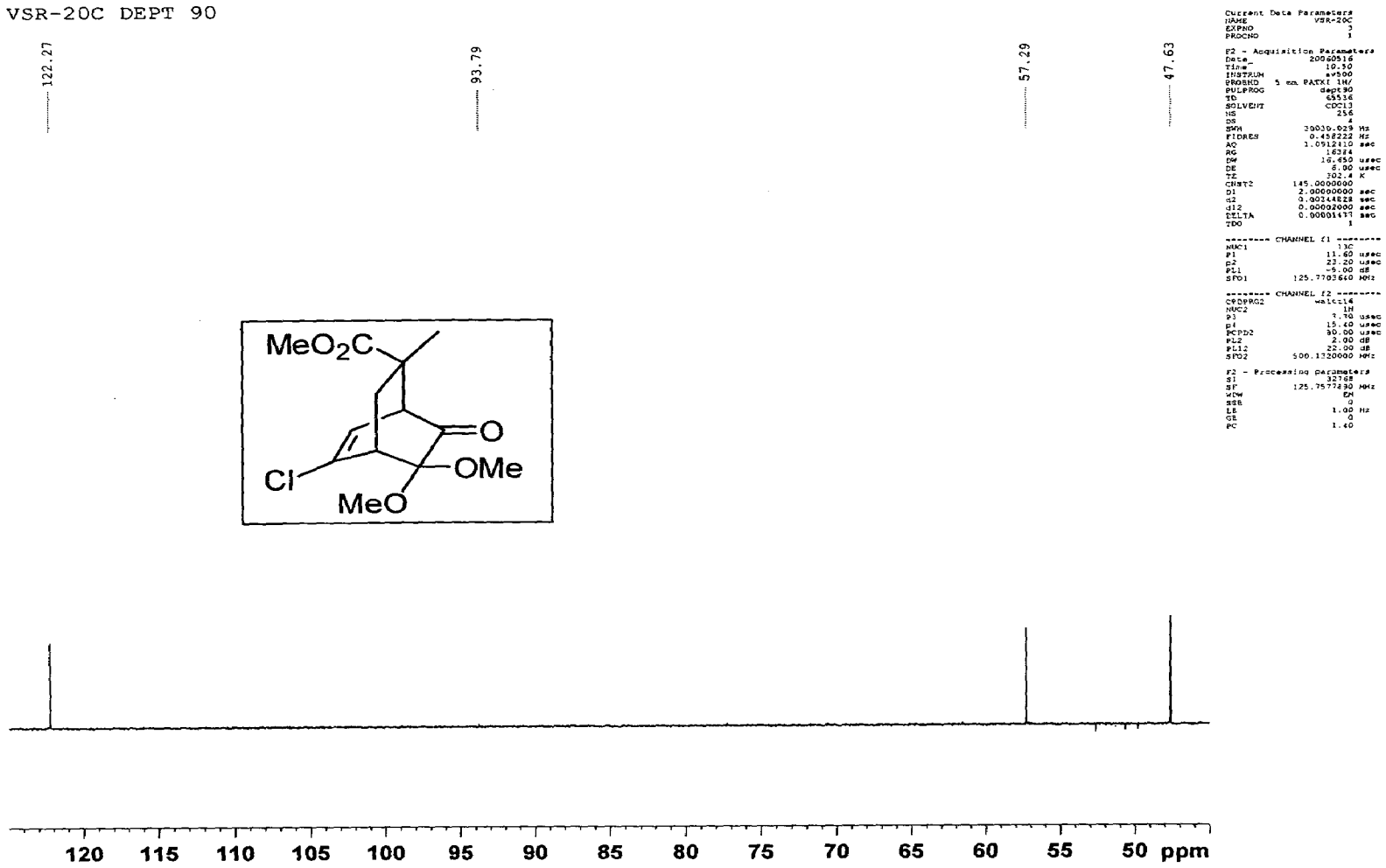


Fig 12. DEPT-90 Spectrum of Diels-Alder adduct 220

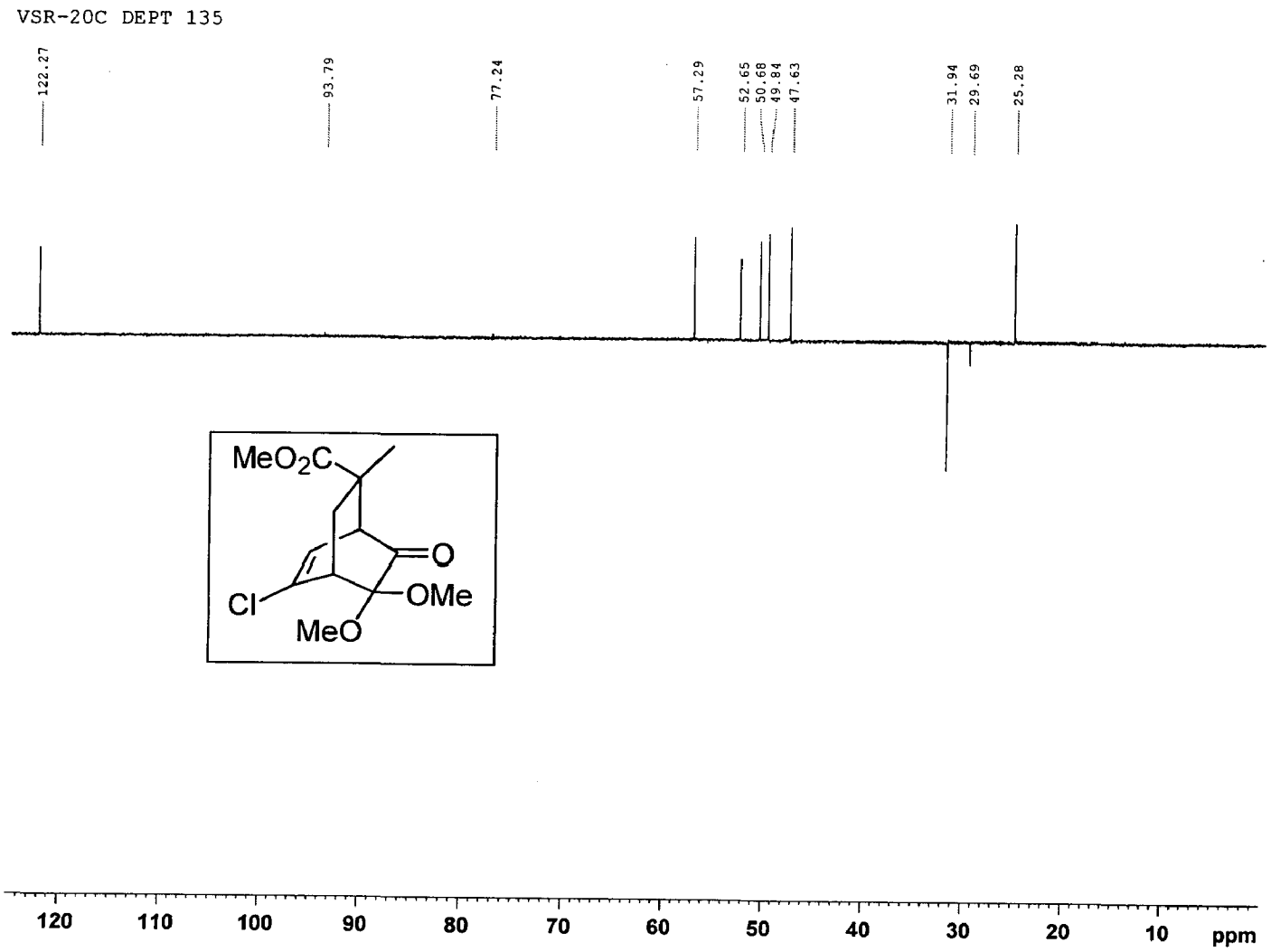


Fig 13. DEPT-135 Spectrum of Diels-Alder adduct 220

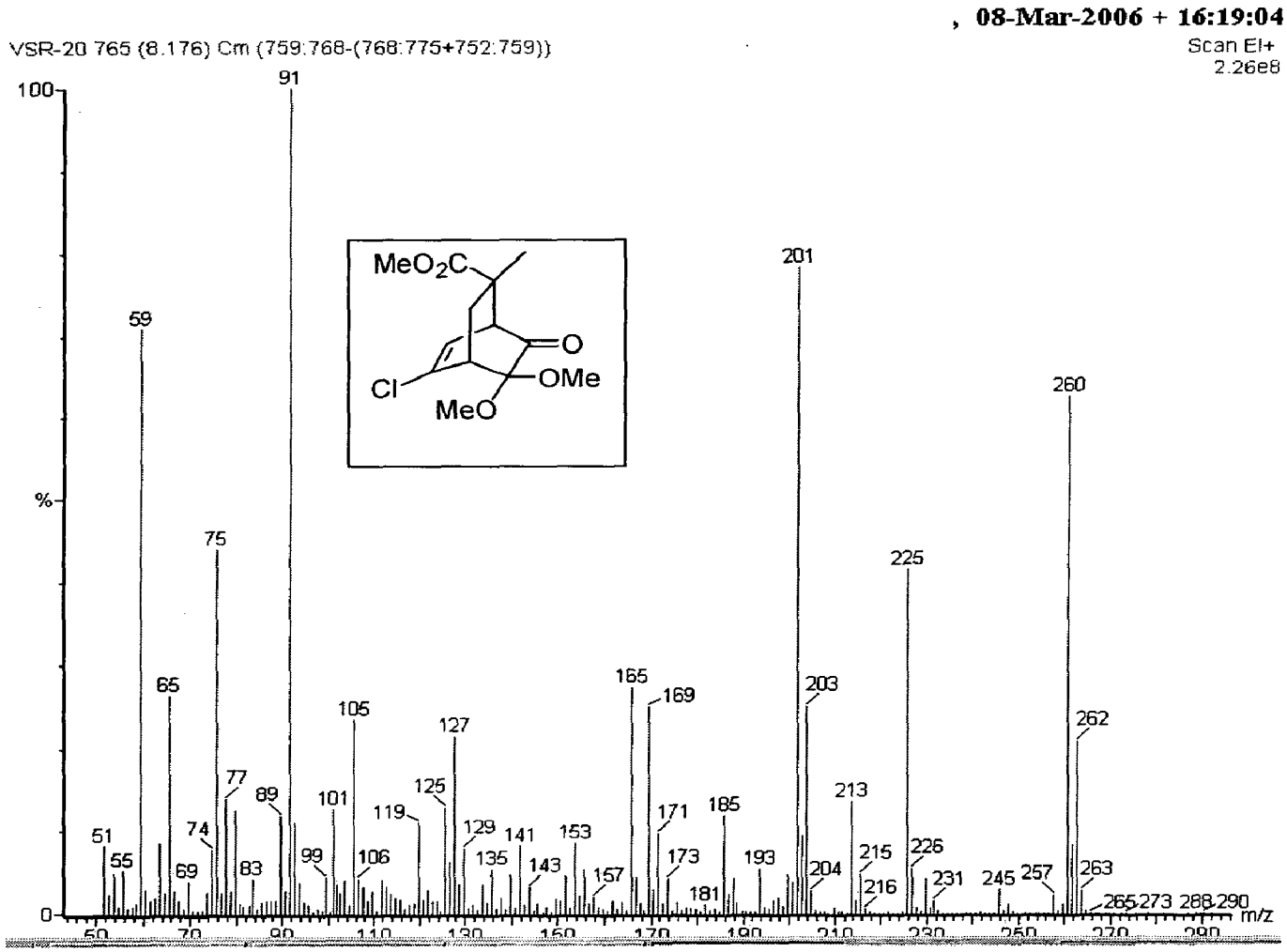


Fig 14. Mass Spectrum of Diels-Alder adduct 220

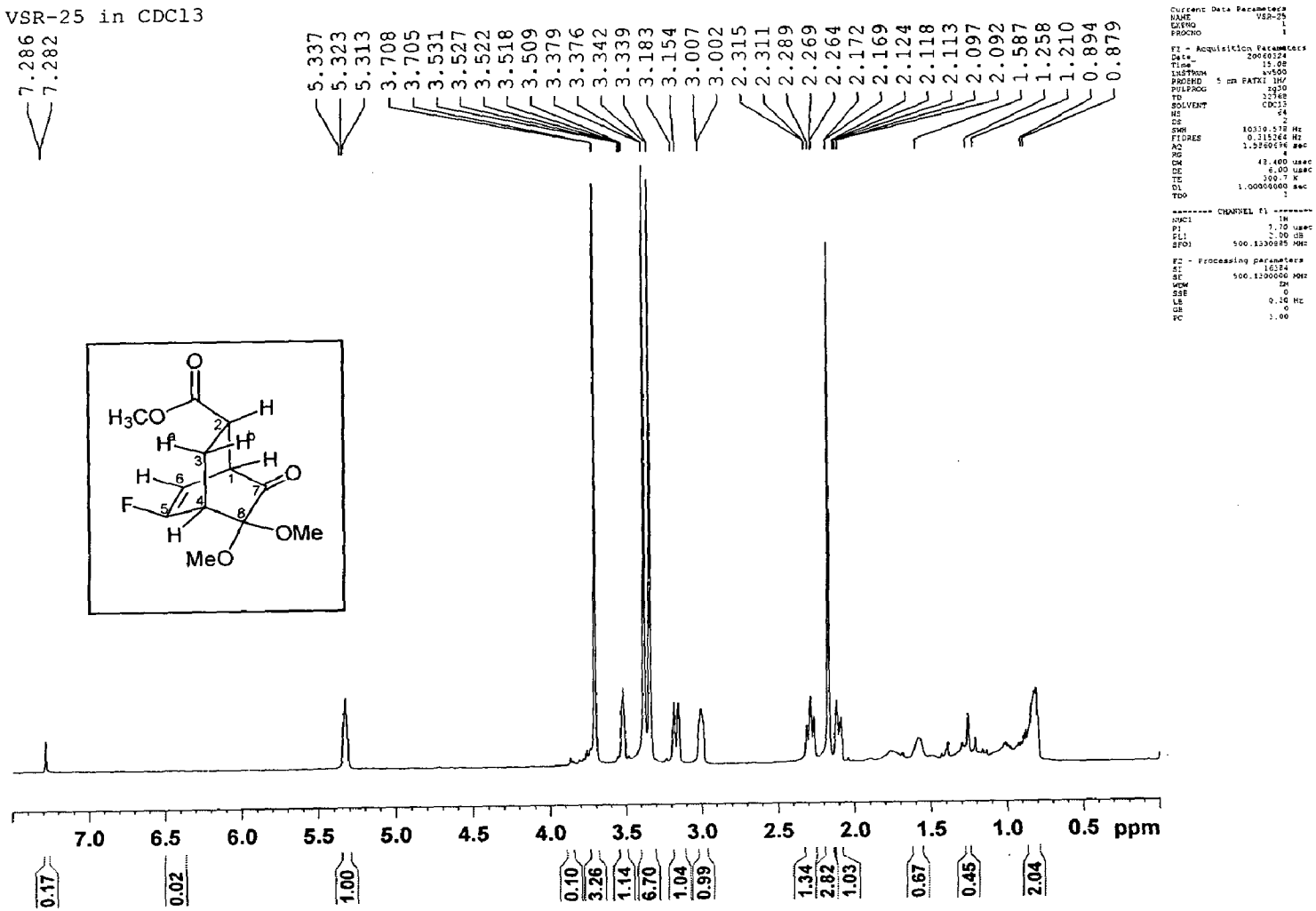


Fig 15. ^{1}H NMR Spectrum of Diels-Alder adduct 223

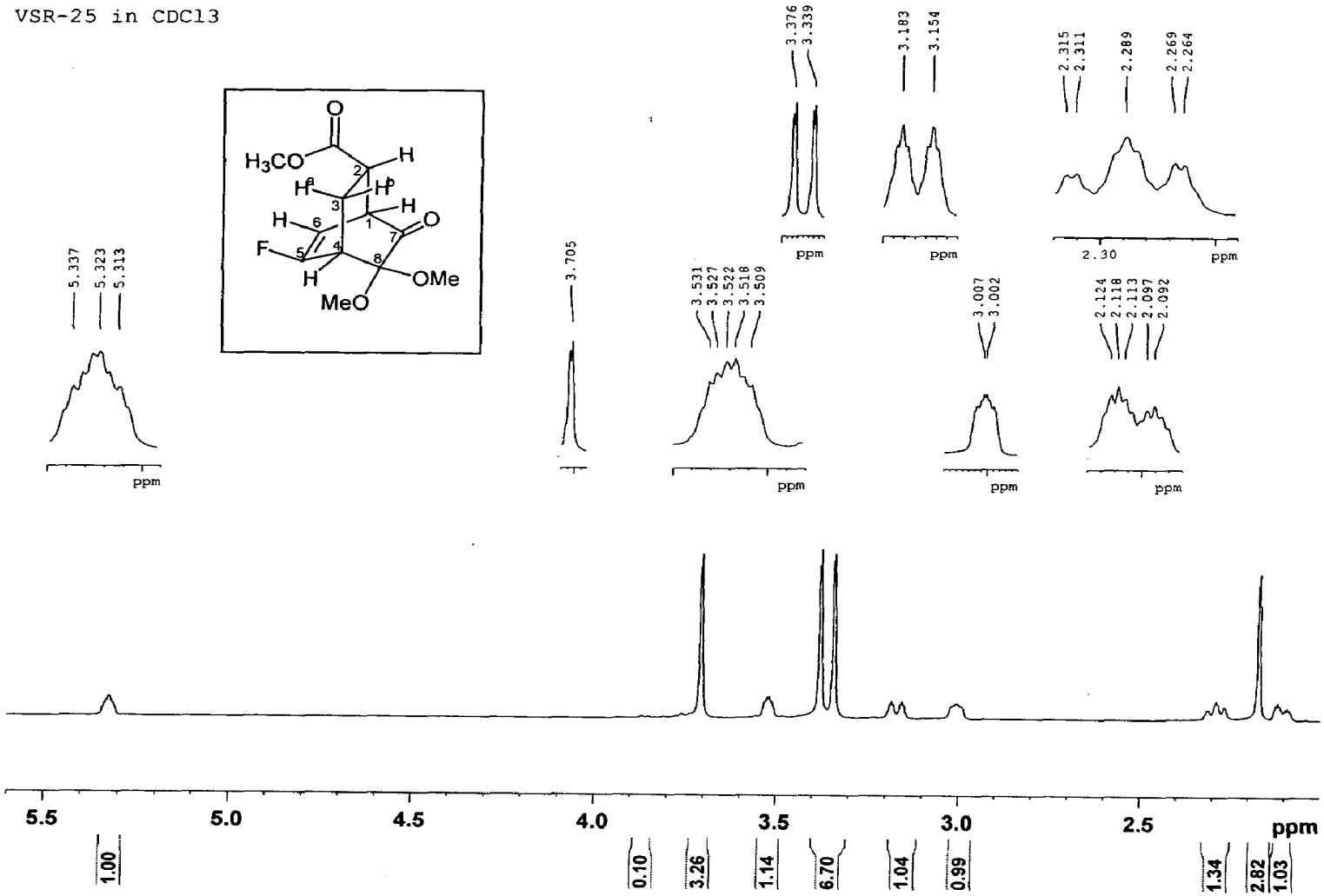


Fig 16. Expansion of ^{1}H NMR Spectrum of Diels-Alder adduct 223

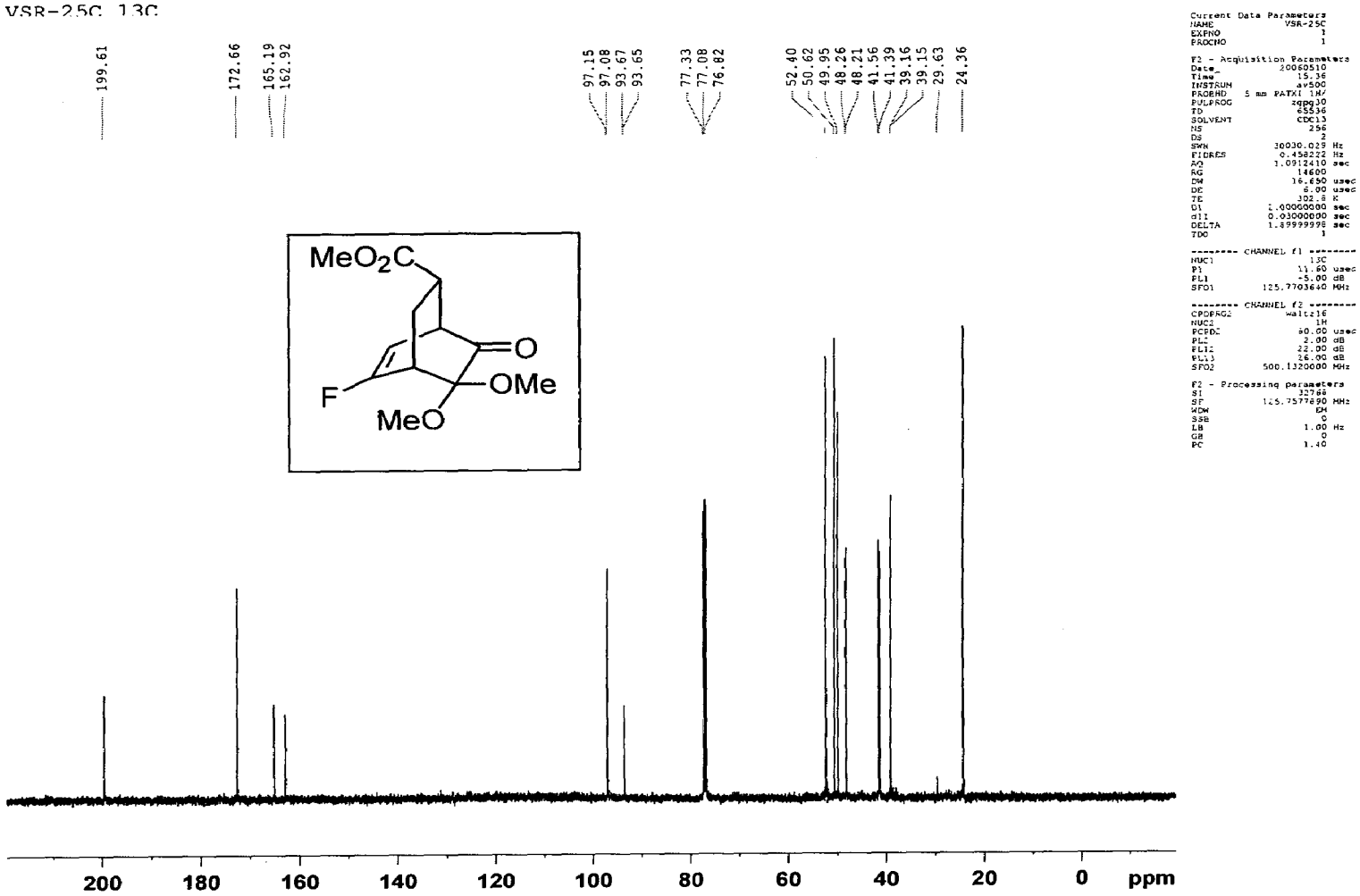


Fig 17. ^{13}C NMR Spectrum of Diels-Alder adduct 223

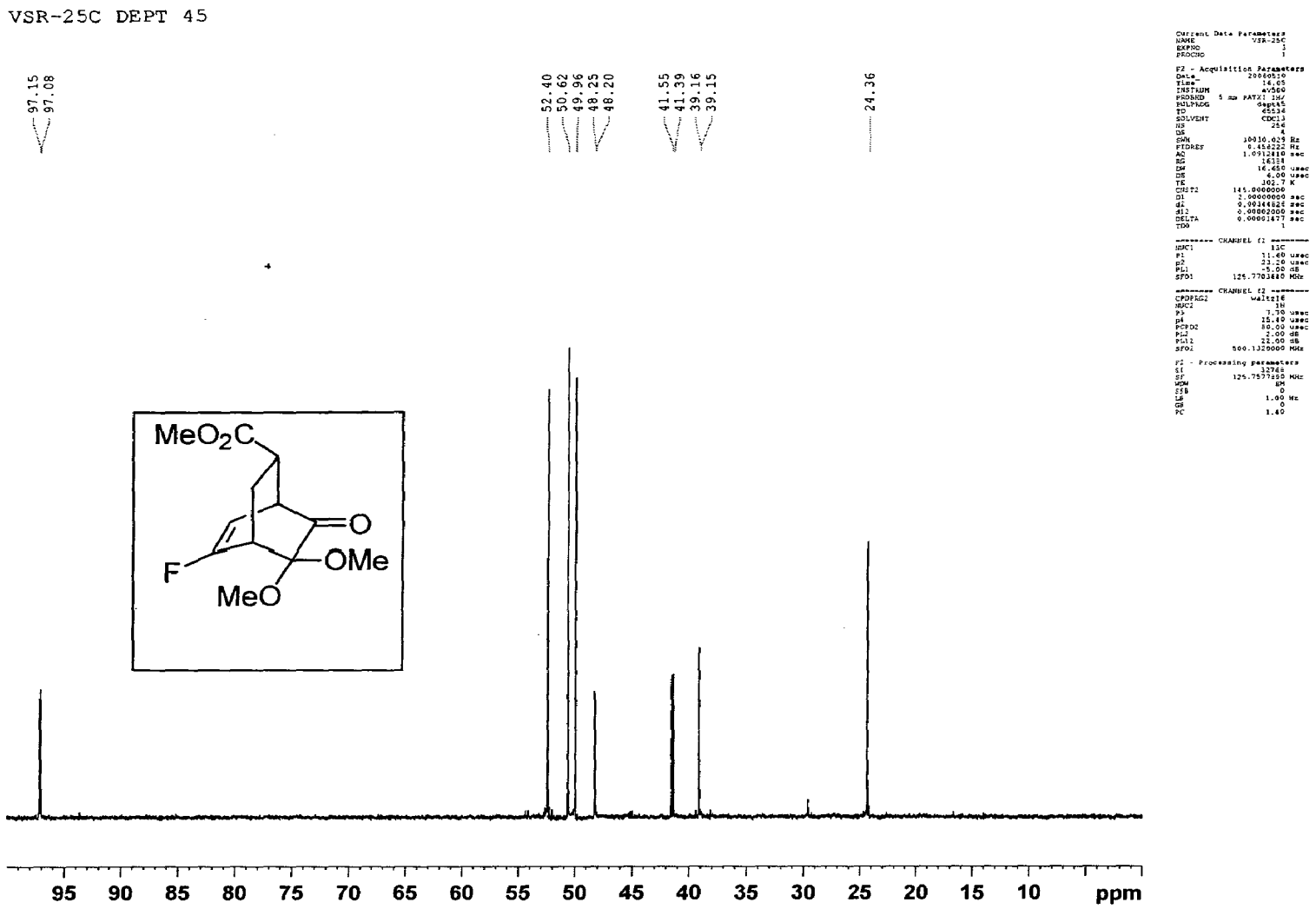


Fig 18. DEPT-45 Spectrum of Diels-Alder adduct 223

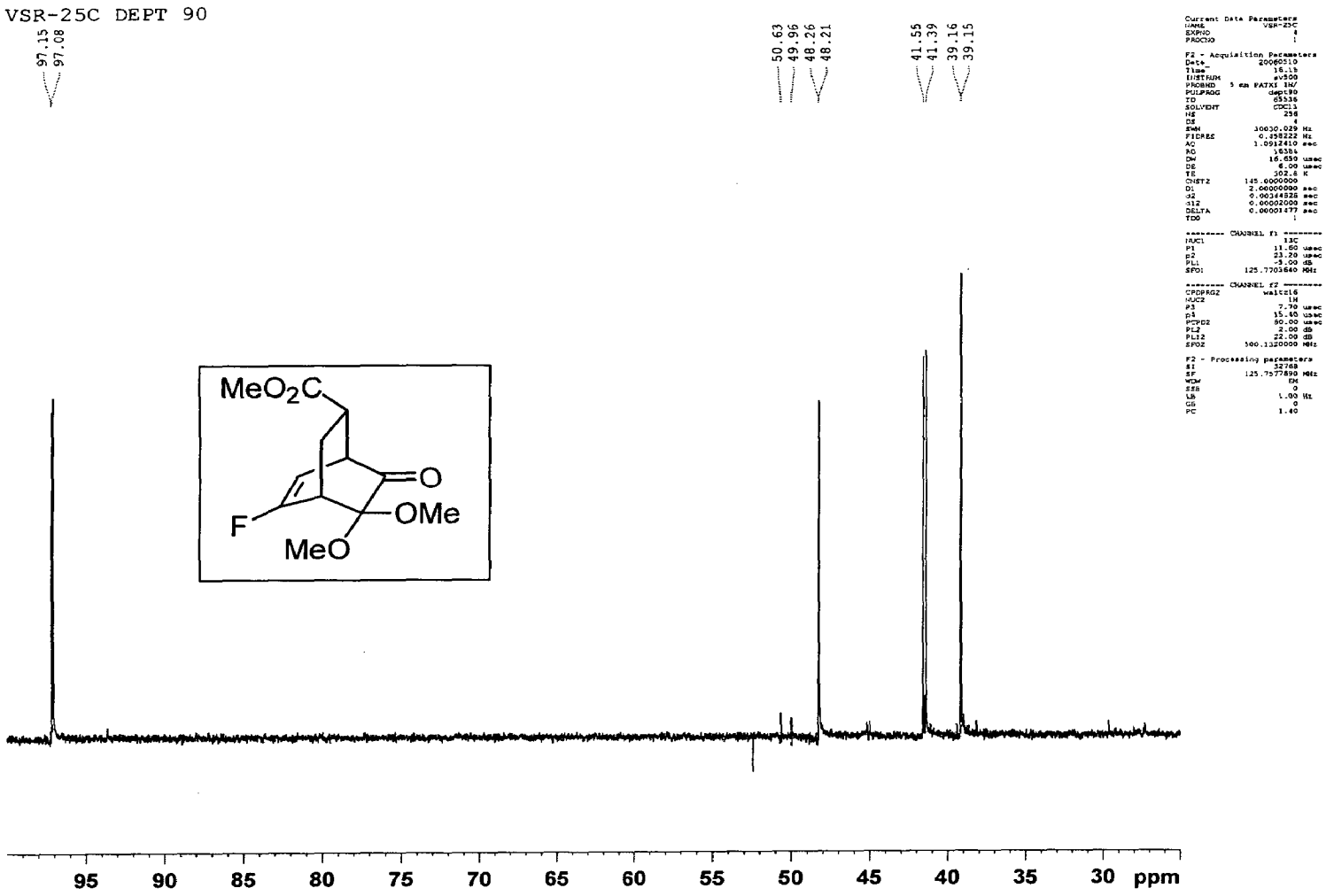


Fig 19. DEPT-90 Spectrum of Diels-Alder adduct 223

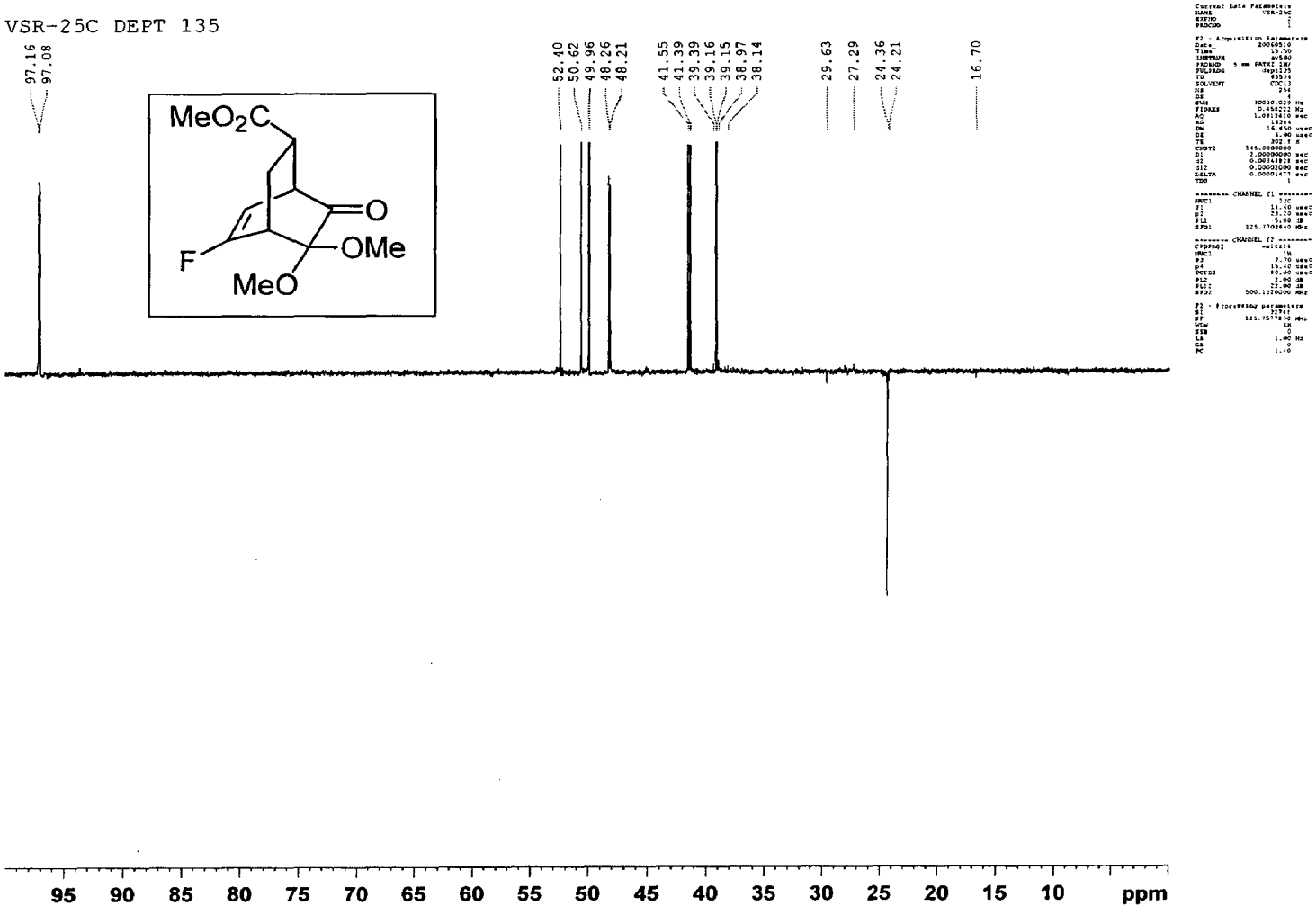


Fig 20. DEPT-135 Spectrum of Diels-Alder adduct 223

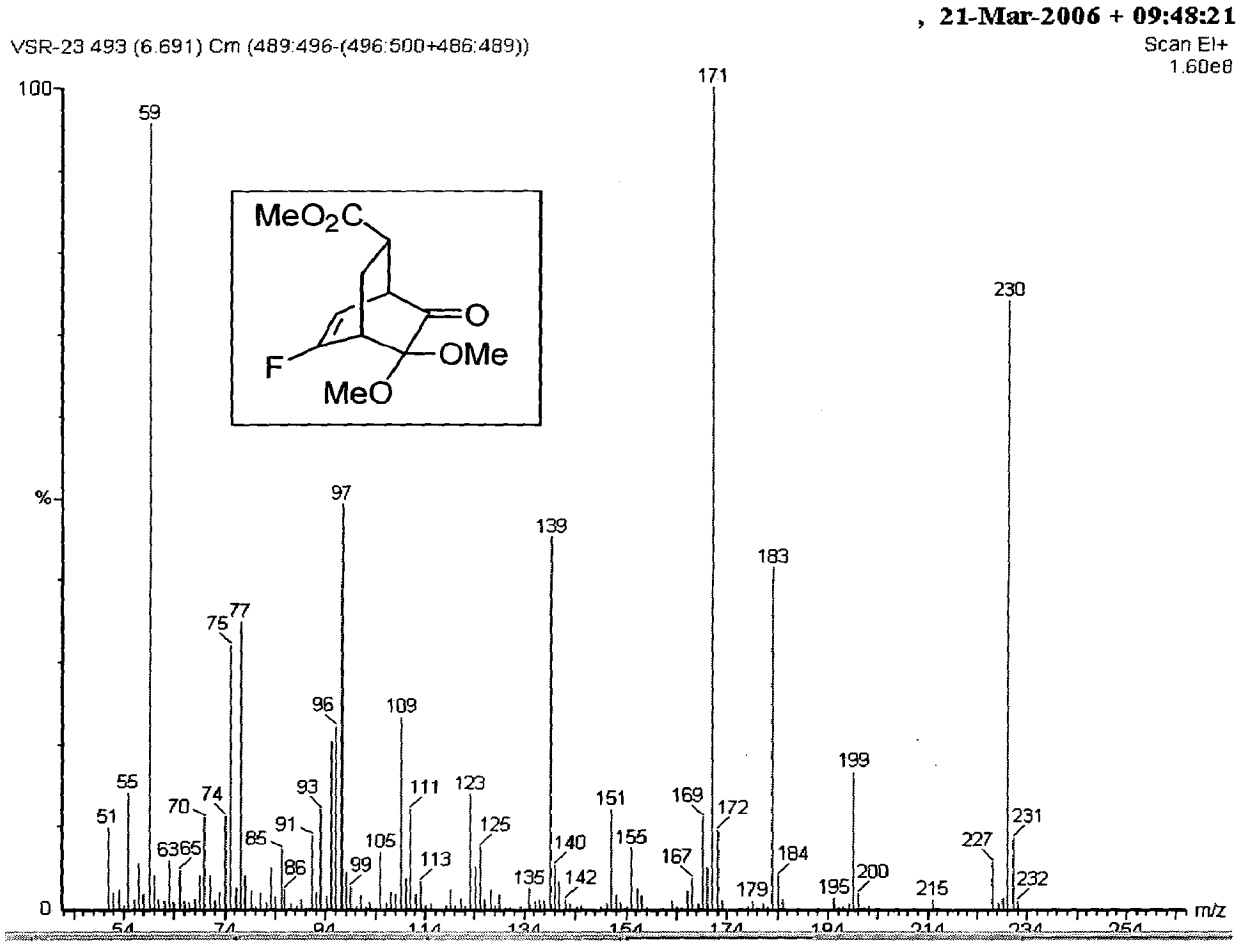


Fig 21. Mass Spectrum of Diels-Alder adduct 223

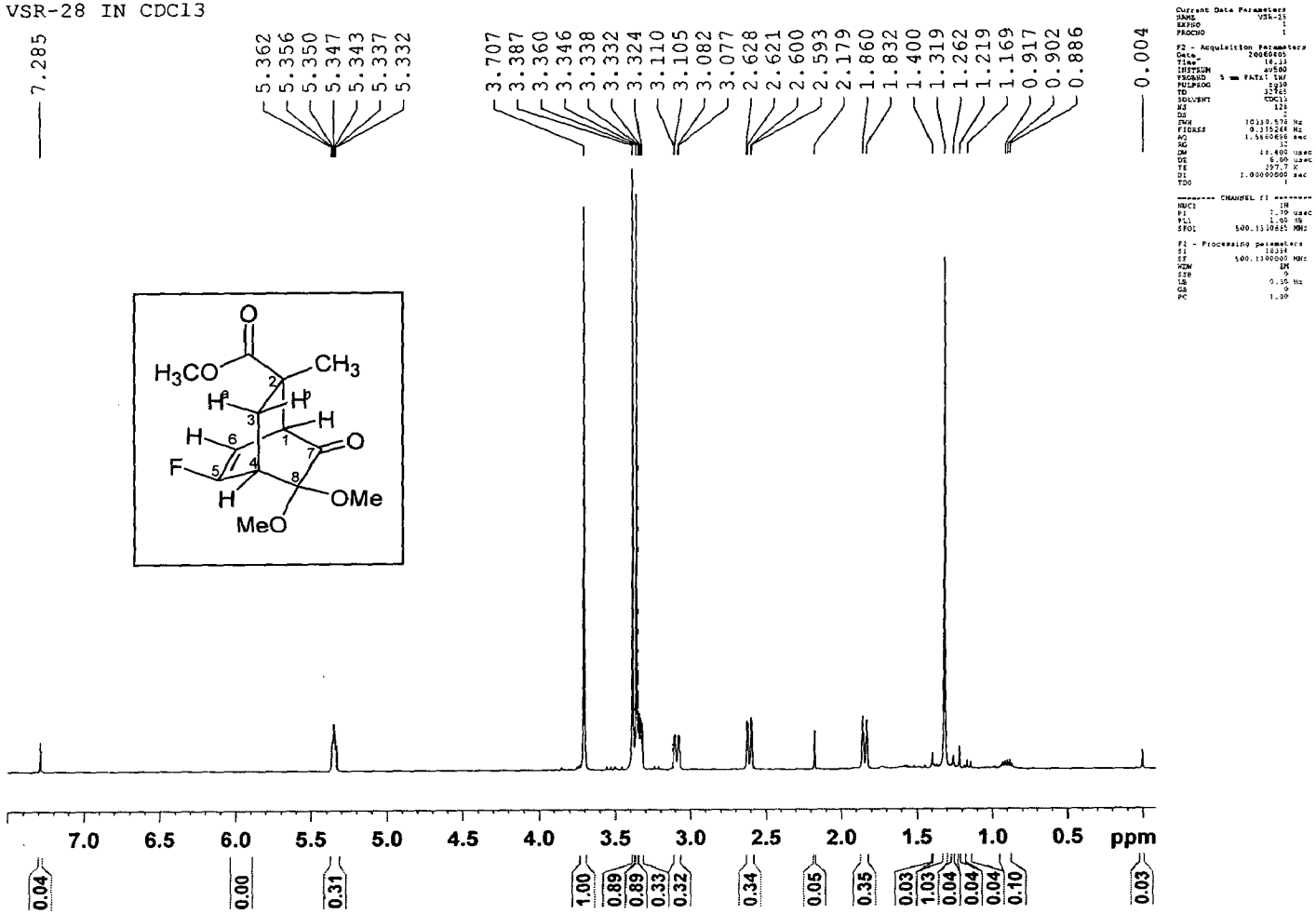


Fig 22. ^{1}H NMR Spectrum of Diels-Alder adduct 224

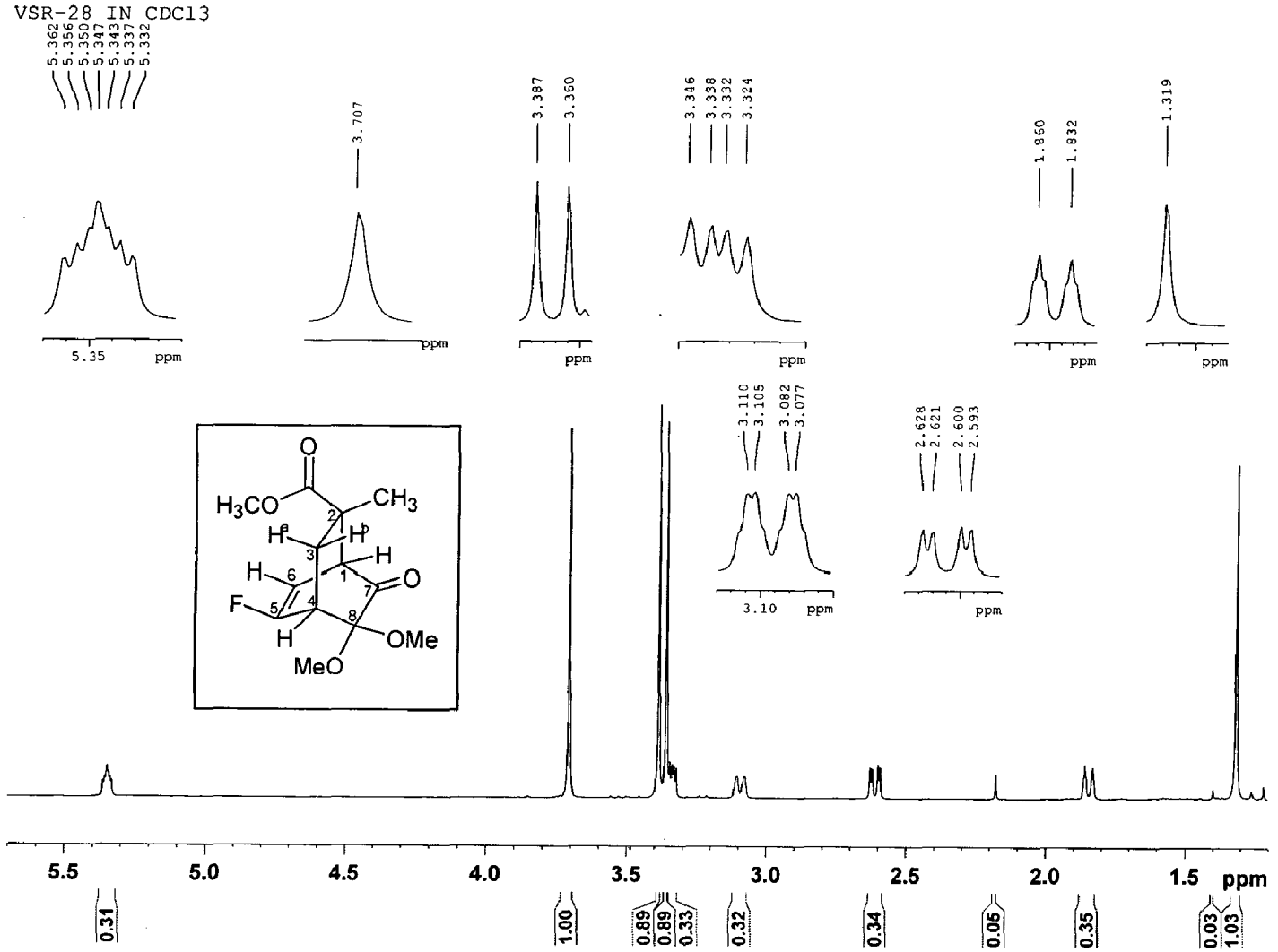


Fig 23. Expansion of ^{1}H NMR Spectrum of Diels-Alder adduct 224

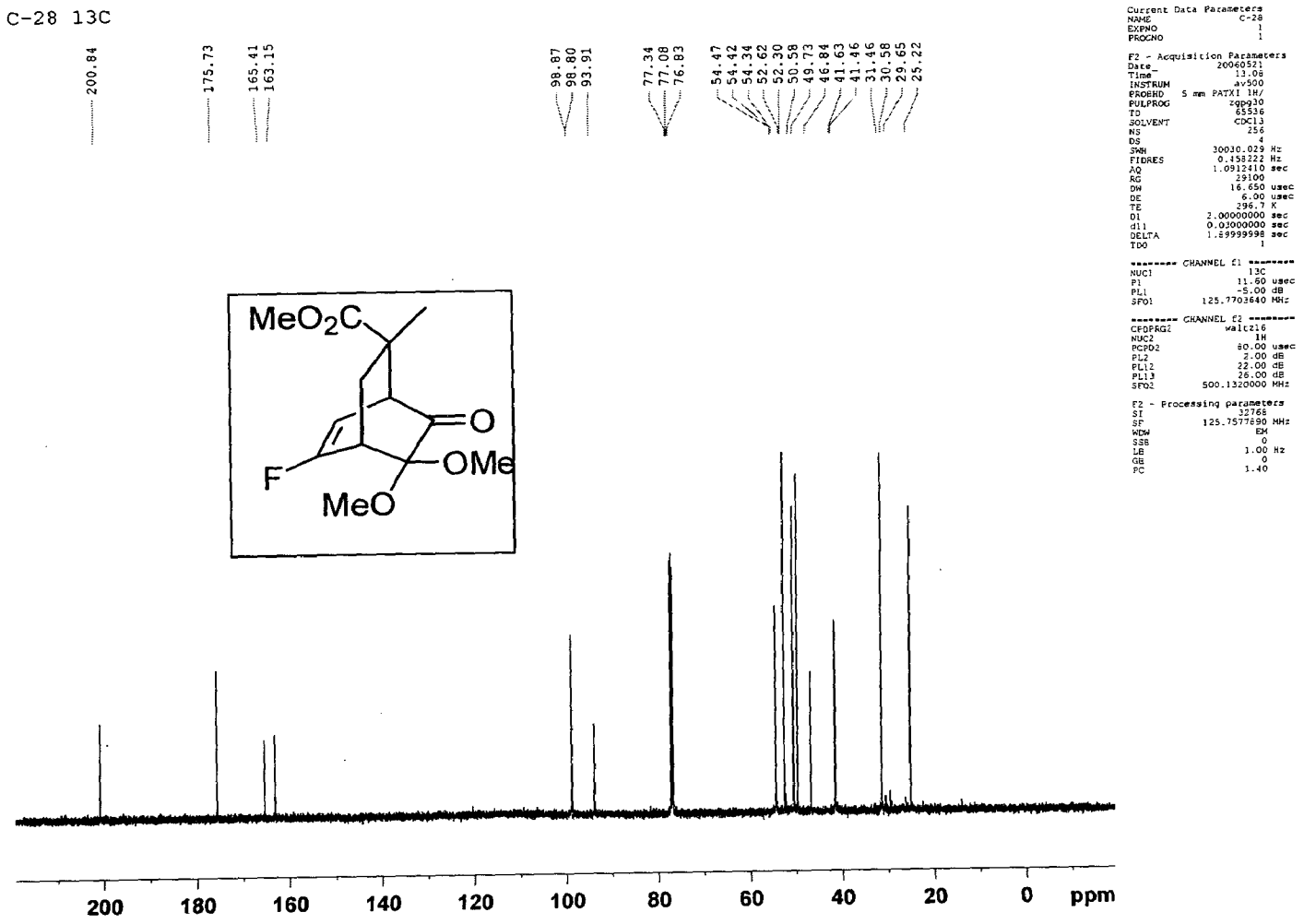


Fig 24. ^{13}C NMR Spectrum of Diels-Alder adduct 224

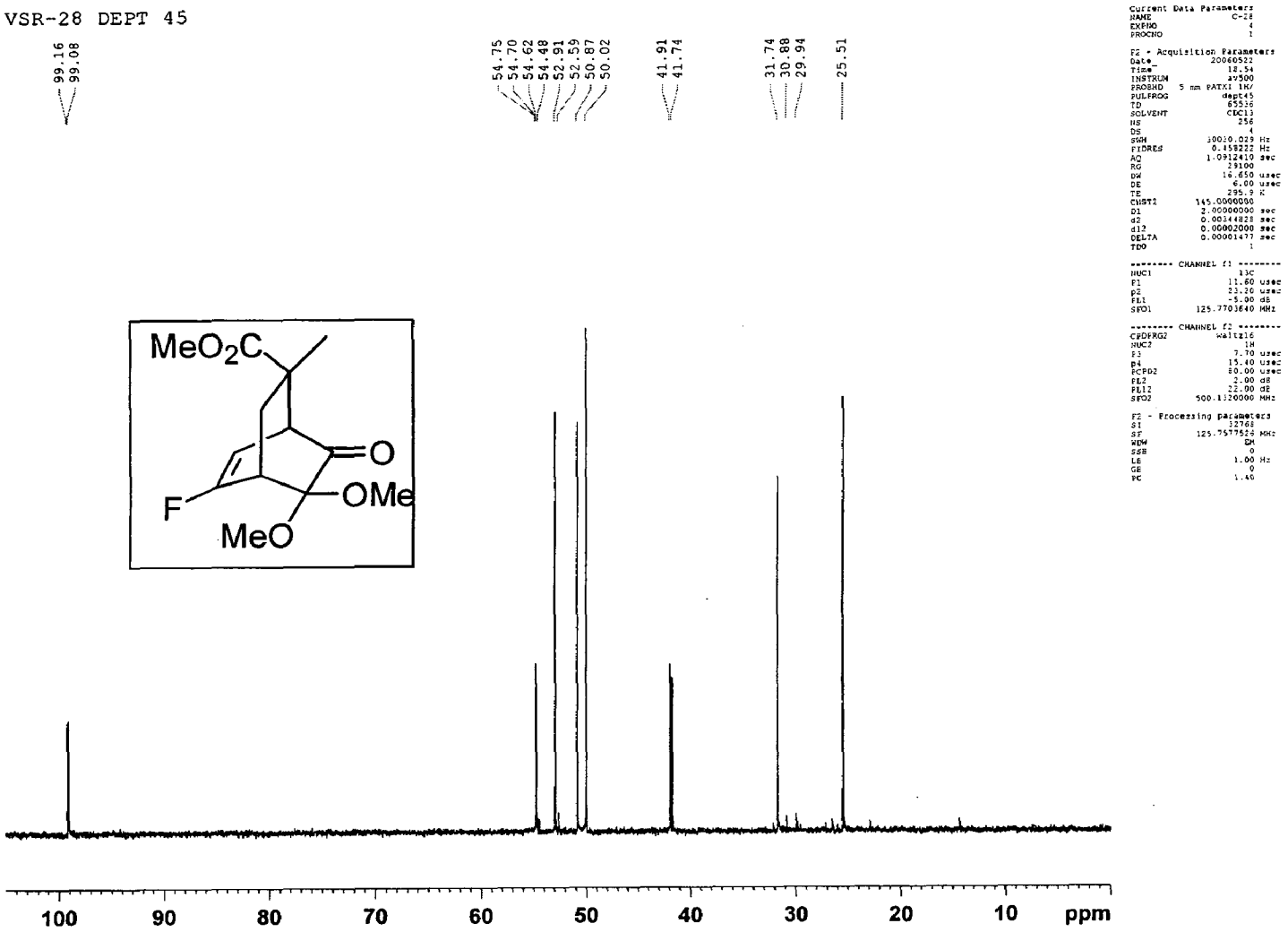


Fig 25. DEPT-45 Spectrum of Diels-Alder adduct 224

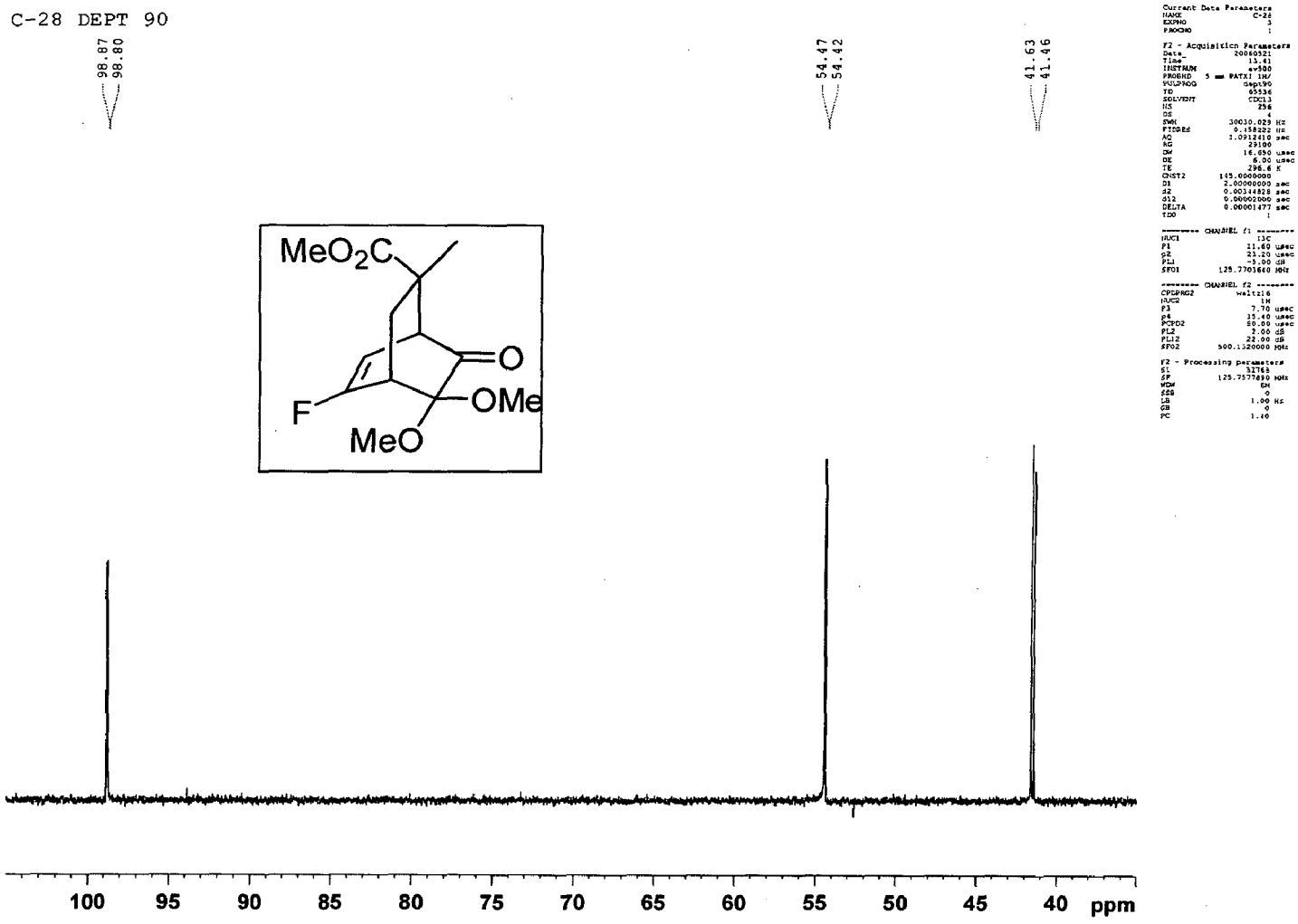


Fig 26. DEPT-90 Spectrum of Diels-Alder adduct 224

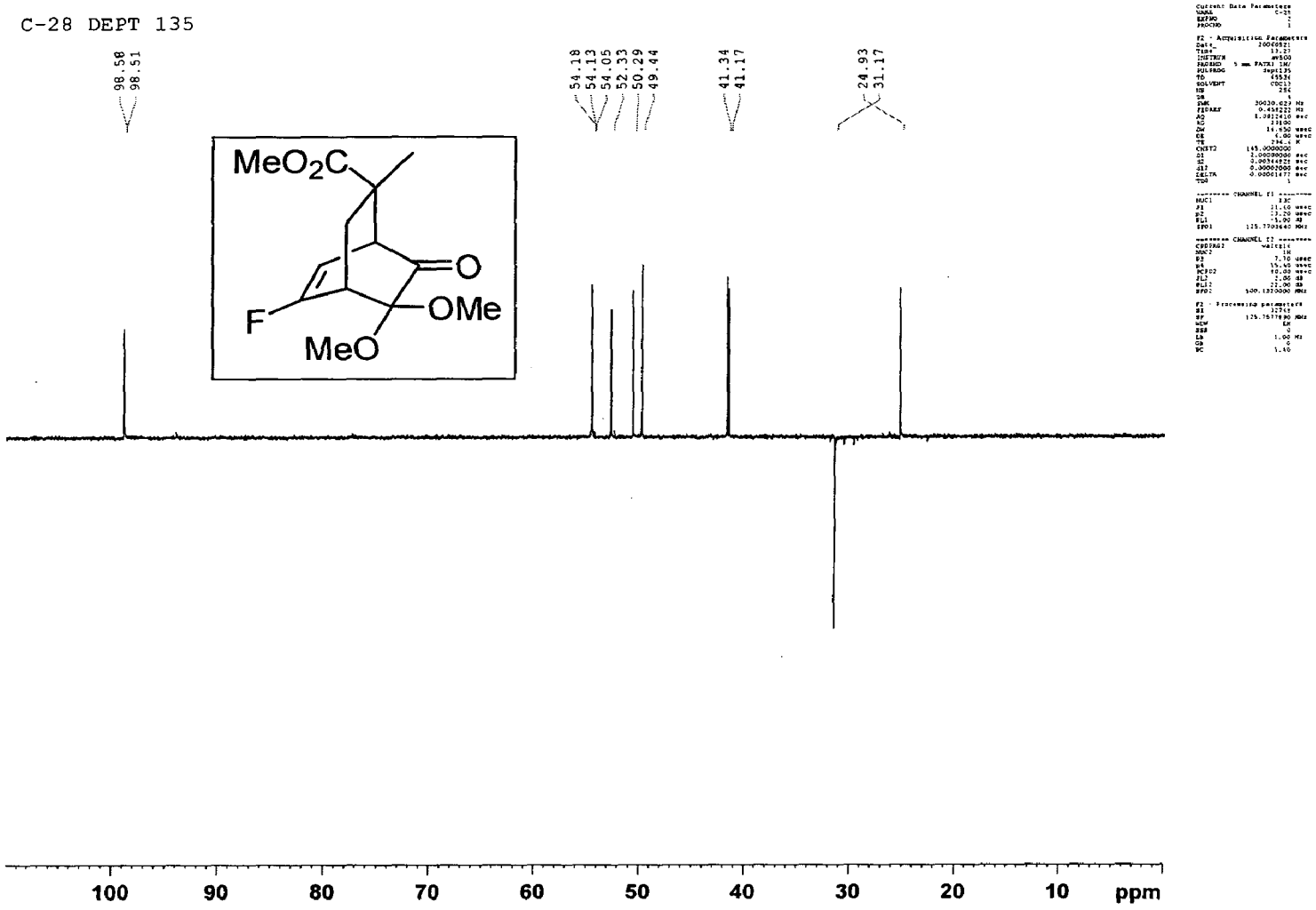


Fig 27. DEPT-135 Spectrum of Diels-Alder adduct 224

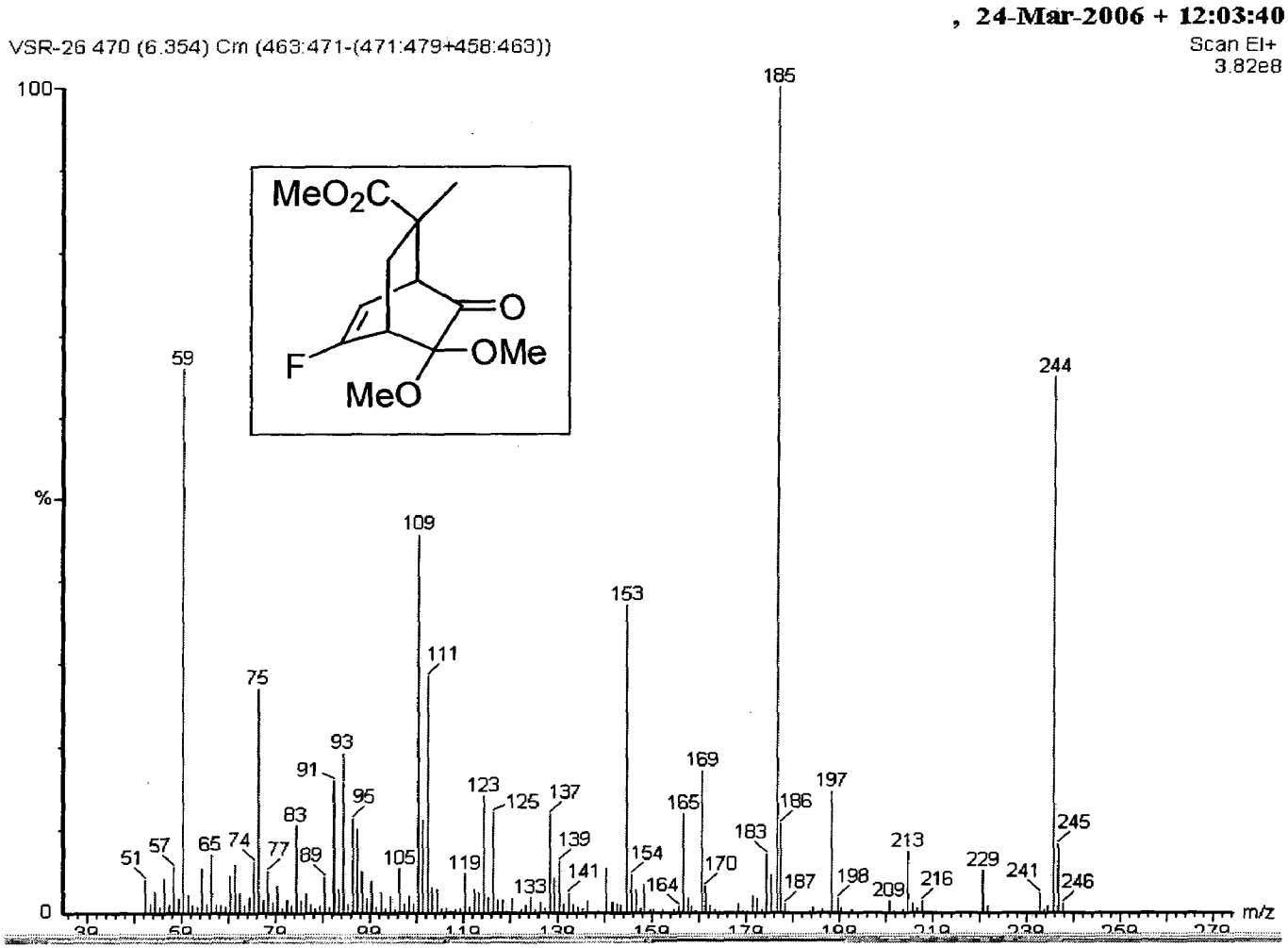


Fig 28. Mass Spectrum of Diels-Alder adduct 224

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REFERENCES

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