CYCLOAROMATIZATION REACTIONS OF ENAMINES

by

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ABSTRACT

Methyl 4-trimethylsilyl-3-dialkylaminocrotonate is synthesized by the silylation of methyl 3-dialkylaminocrotonate. It reacts with carbonyl electrophiles at its γ-position. The unusual regiochemistry of this reaction is studied and rationalized. It reacts with enamines derived from acyclic ketones or cycloketones of large ring size (of 12 and 15 membered rings) to give aromatic compounds in a 3C+3C combination and with enamines derived from cycloketones of 5-8 membered rings to give aromatic compounds in a 4C+2C combination. The mechanism of this cycloaromatization reaction is investigated.

meta-Cyclophanes with a morpholino substituent are synthesized by the above cycloaromatization reaction. These meta-cyclophanes possess planar chirality and are successfully resolved.

A number of metacyclophanes with alkyl substituents at the intraannular position are synthesized. Depending on the ring size and the steric size of the alkyl group, some of them are also resolved. The rotation process of meta-cyclophane is studied through their temperature dependent ^1H NMR.

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REACTIONS DE CYCLOAROMATISATION DES ENAMINES

Sommaire

Cette thèse décrit en premier lieu la réactivité du triméthylsilyl-4,dialkylamino-3 crotonate de méthyle vis-à-vis différents composés carbonylés. En effet, le composé silylé, obtenu à partir de la silylation du dialkylamino-3 crotonate de méthyle, réagit avec des composés carbonylés à la position γ et une étude approfondie de cette régio-acylation peu commune a été effectuée.

En second lieu, le composé silylé réagit avec des énamines acycliques et cycliques de grande taille (12 et 15 chaînons) pour donner des composés aromatiques selon une réaction de cycloaddition 3C+3C. De plus, ce même composé silylé réagit aussi avec des énamines cycliques de taille moyenne (5 à 8 chaînons) pour donner des composés aromatiques mais selon une réaction de cycloaddition 4C+2C. Les mécanismes de ces cycloaromatisations ont aussi été étudiés.

Ainsi, plusieurs métacyclophanes possédant un groupement morpholino ont été obtenus par la réaction de cycloaromatisation selon le mécanisme 3C+3C précédemment décrit. Ces métacyclophanes sont des composés optiquement actifs et ont été résolus avec succès. De plus, plusieurs métacyclophanes possédant un substituant alkyle en position intra-annulaire

ont été synthétisés et certains composés, dépendamment de la grandeur de cycle et du groupe alkyle présent, ont été résolus.

Finalement, les processus de rotation de certains métacyclophanes ont été étudiés par spectroscopie RMN ^{1}H dynamique.

ACKNOWLEDGEMENTS

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CHAPTER I INTRODUCTION

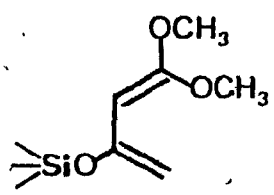
1. Synthesis of aromatic compounds from acyclic precursors

While tremendous progress has been made in the last two decades on reactions leading to the synthesis of acyclic and carbocyclic compounds, less development has occurred in the synthesis of aromatic compounds; the problem is especially acute in the synthesis of benzenoid compounds with multiple functional groups. The conventional approach of using electrophilic substitution reactions on simple aromatic precursors, with its tedious stepwise process and attendant problem of regioselection, has obvious limitations.

It is well recognized though, in nature, that condensation of poly-β-carbonyl compounds is a major pathway for the biogenesis of aromatic natural products[1,2]. Efforts to mimic this reaction in the laboratory have met, however, with limited success, mainly because of the difficulty of controlling the specificity of the direction of condensation[2]. Such control is particularly critical when the poly carbonyl precursor is compound of mixed acetate and propionate units.

One existing approach for assembling highly functionalized benzenoid compounds directly from acyclic precursors is the Diels-Alder reaction. Danishefsky and his coworkers have reported that the 1,1-dimethoxy-3-(trimethylsiloxy)-buta-1,3-diene 1, which can be considered as a synthetic equivalent of 2, reacts with a large variety of electron-deficient dienophiles to give high yields of cycloadducts which in some cases lead to aromatic compounds [3,4]. Some examples are given in scheme 1.1. Usually these

cycloadditions show high regioselectivity.



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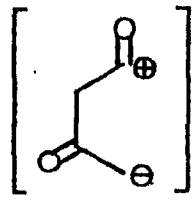

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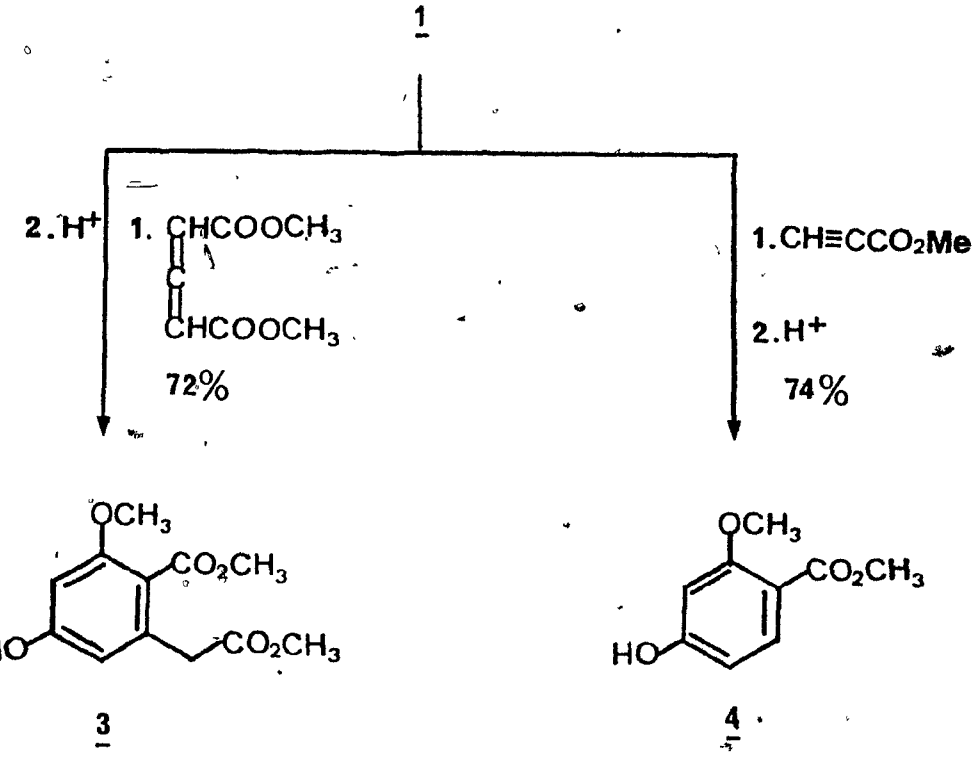
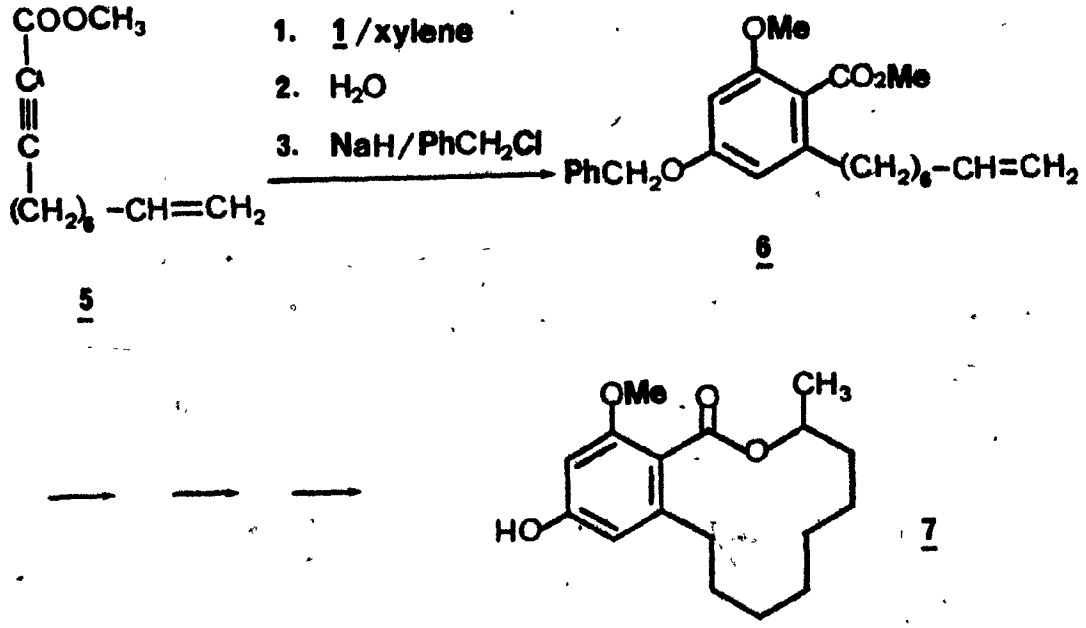


scheme 1.1

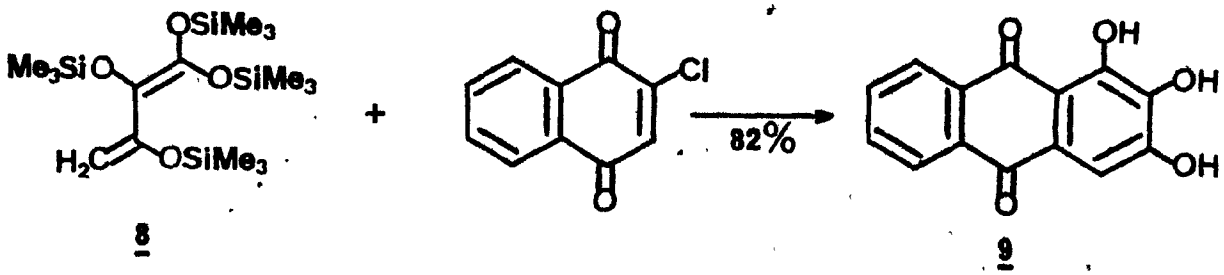
This approach has been used in an elegant total synthesis of (±)-lasiodiplodin 7 [5] (see scheme 1.2).

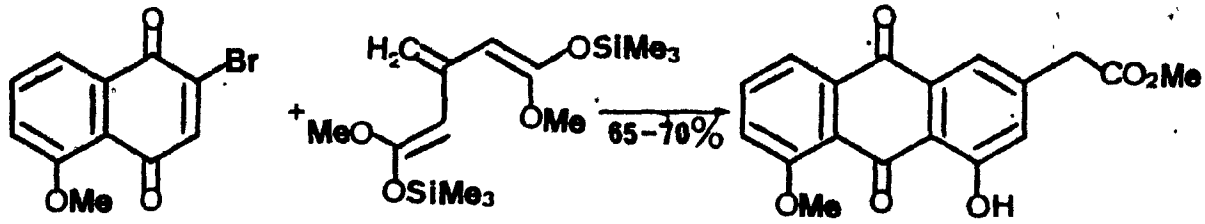
A contemporary work of **Brassard** involves the use of highly oxygenated butadienes for the synthesis of anthraquinone derivatives [6]. Two typical examples are given in scheme 1.3.

Several other silyl enol ether dienes, such as 2-(trimethylsiloxy)-furans 8 [7], 2,5-bis(trimethylsiloxy)furans 10



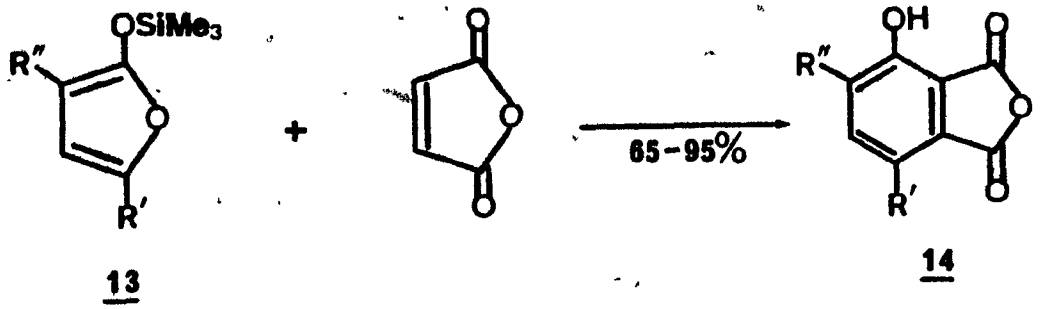
scheme 1.2





scheme 1.3

[8] and 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene 17 [9], can undergo similar reactions (scheme 1.4).



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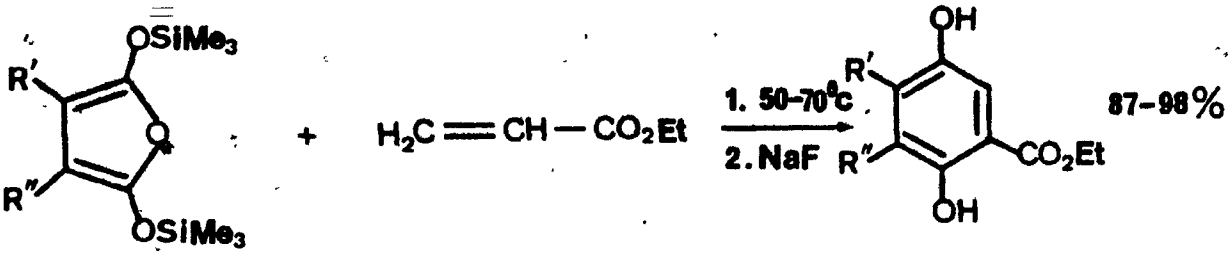

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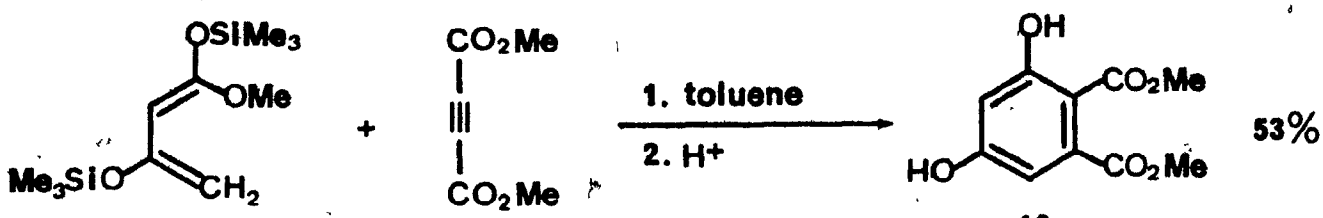
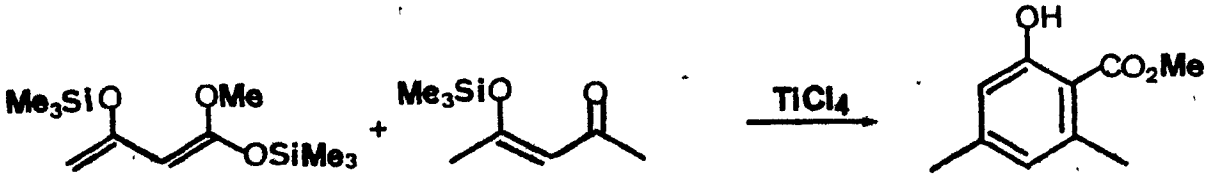


17 18

scheme 1.4

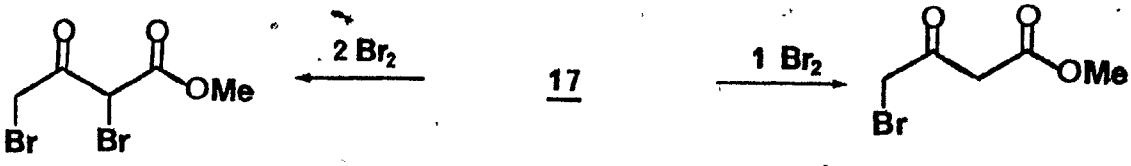
Compound 17 is a less reactive Diels-Alder diene with a pronounced tendency to form Michael adducts. However, it has tremendous power to undergo cycloaromatization reactions in a different manner, i.e. in a 3C+3C fasion [10]. Actually this approach is still being developed and studied in our group. One typical example is the reaction of 17 with compound 19 in the



17 19 20

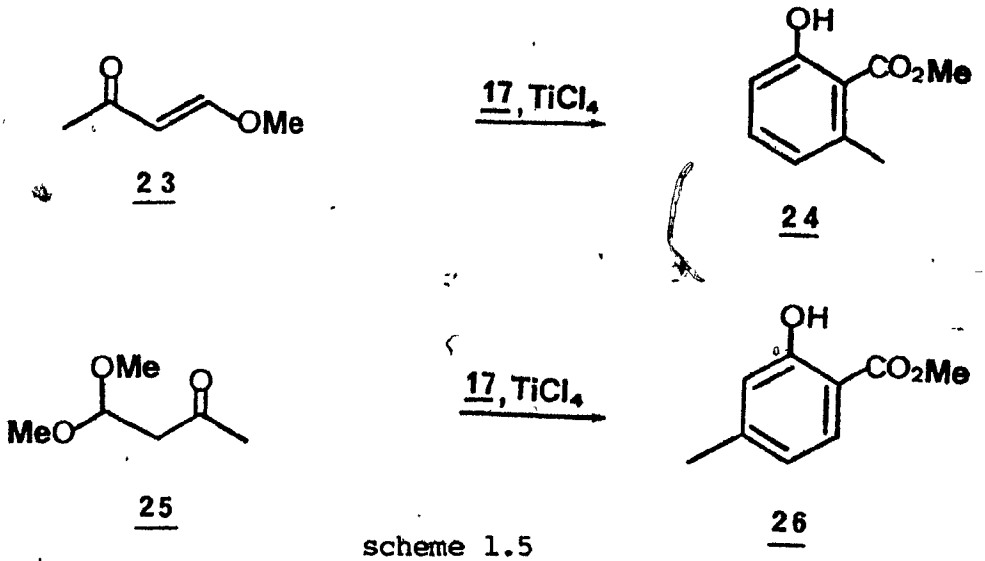
presence of titanium tetrachloride to give methyl 4,6-dimethylsalicylate 20.

Compound 17 is a 1,3-dinucleophile with C-4 being more reactive (δ^{--}) than C-2 (δ^{-}). This is illustrated by its reaction with bromine; 17 reacts with 1 mole of bromine to give 21 and with 2 moles of bromine to give 22 [11].



22 21

Because of the difference in reactivity between the C-2 and the C-4 positions, the condensation of 17 with unsymmetrical 1,3-diketone derivatives can lead to cycloaromatization products with controlled regiochemistry. Thus the reaction of 17 with 4-methoxybut-3-en-2-one 23 gave exclusively 24 on the one hand, but with 25 gave 26.



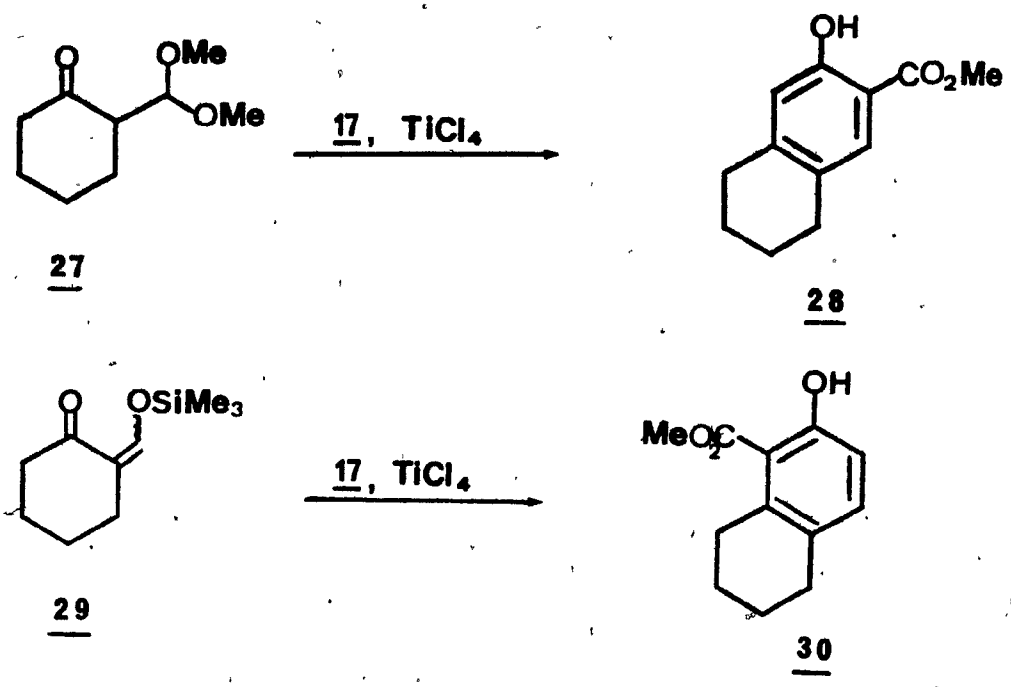
23 24

25 26

scheme 1.5

Condensation of 27 with 17 and titanium tetrachloride gave the

bicyclic aromatic compound 28. On the other hand, 29 reacted with 17 and titanium tetrachloride to give 30. Again, the reaction was perfectly regiospecific with no contamination of one isomer by the other in the product (scheme 1.6).



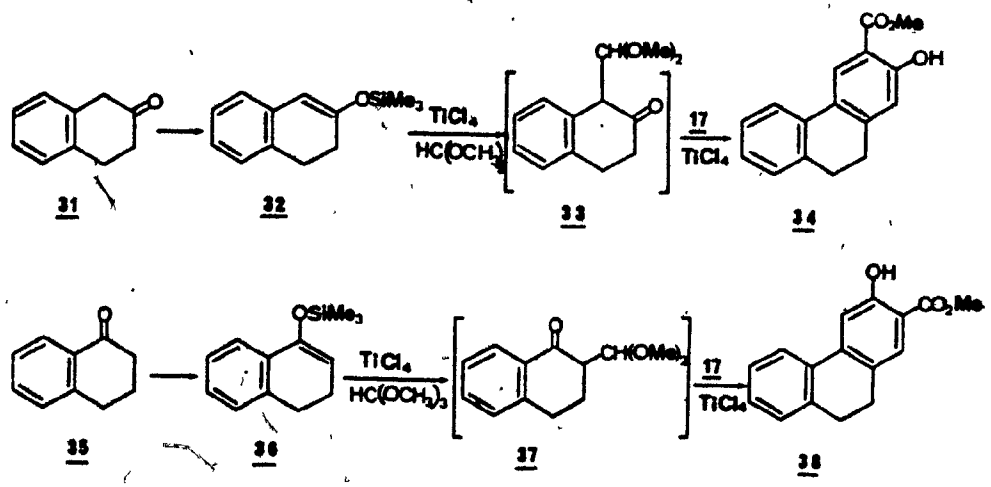
scheme 1.6

Another example of controlled regiochemistry is illustrated by the synthesis of the phenanthrene derivatives 34 and 38, starting from β- and α-tetralone, respectively (scheme 1.7).

A summary of the above observations plus a number of competitive experiments allowed us to establish the following relative reactivity order for various carbonyl functional groups in acid catalysed condensation with enol silyl ethers [12]:

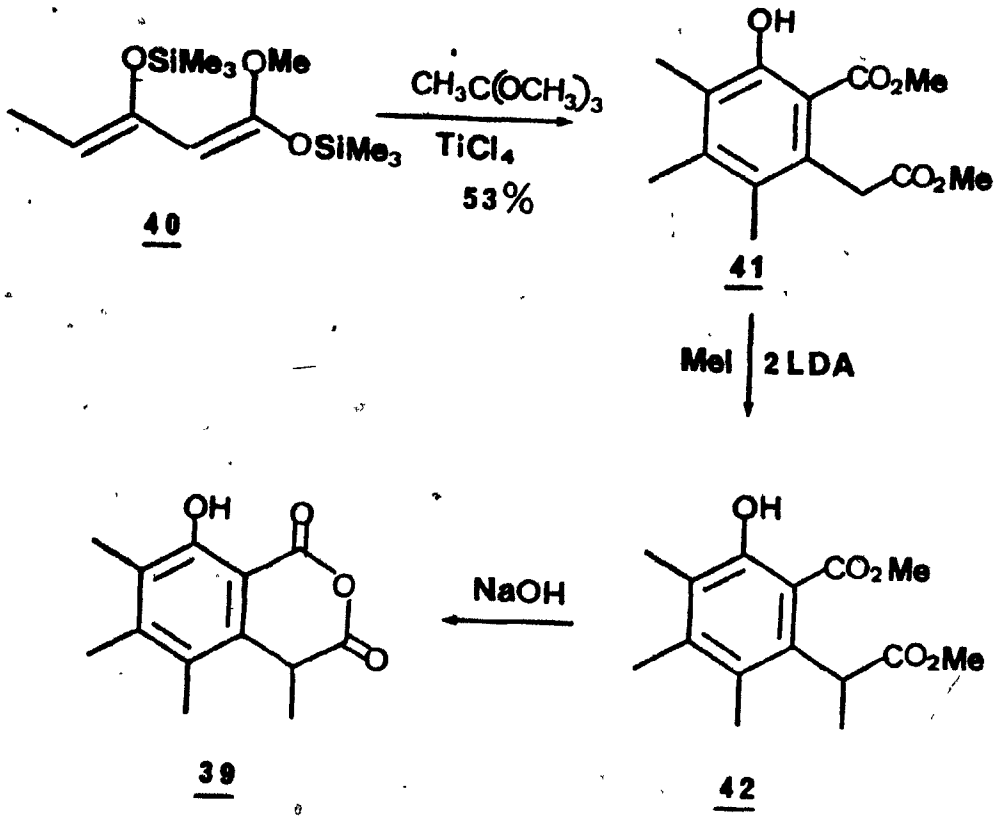
aldehydes > conjugated position of β-oxy-α,β-unsaturated ketones ~ isolated ketones > carbonyl position of β-oxy-α,β-unsaturated ketones >acetals ~ monothioacetals > conjugated

position of β-oxy-α,β-unsaturated esters or esters carbonyl.



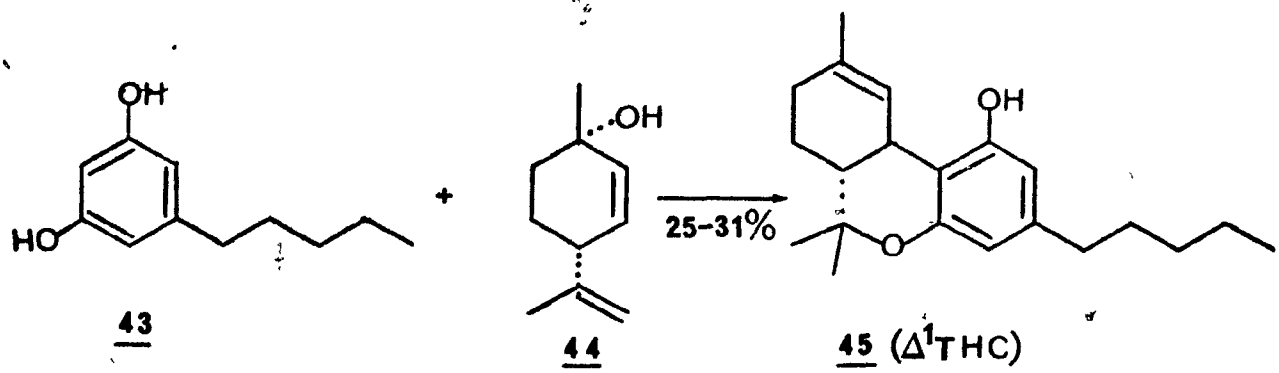
scheme 1.7

The application of this cycloaromatisation reaction is illustrated by the synthesis of Sclerin [13] and Δ^1-tetrahydrocannabinol (Δ^1-THC) [14]. Sclerin 39 is a metabolite isolated from sclerotinia fungi and possesses interesting plant growth activity. A few chemical syntheses of sclerin have previously been reported [15-17], based on the conventional aromatic chemistry, often with the inherent problem of regioselection in electrophilic aromatic substitution which leads to low overall yields. The synthetic route to sclerin using aromatization reaction is shown in scheme 1.8. Condensation of 40 (2 mole equivalents) with trimethyl orthoacetate in the presence of titanium tetrachloride gave 41 in 53% yield. Subsequent transformation of 41 to sclerin was achieved with conventional chemistry.



scheme 1.8

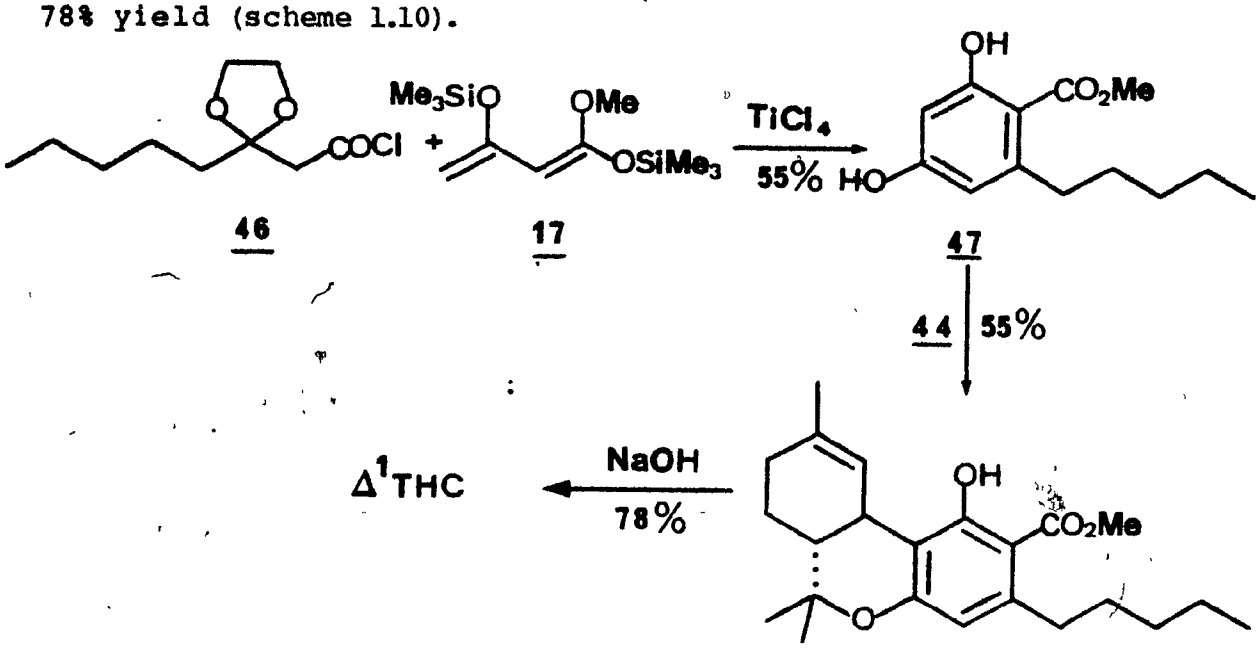
There have been several syntheses of Δ^1-THC 45 which is the active psychotomimetic component of marijuana. They have in common as the critical step that the condensation of a monoterpene with olivetol 43 (scheme 1.9) which is generally synthesized from an



scheme 1.9

aromatic precursor such as 3,5-dihydroxybenzoic acid [18]. Even with the last reported and presumably best synthesis [19], 45 can only be obtained in 25-31% isolated yield after careful chromatography of the complicated mixture from the acid-catalysed condensation of 43 with (±)-trans-p-mentha-2,8-diene-1-ol 44.

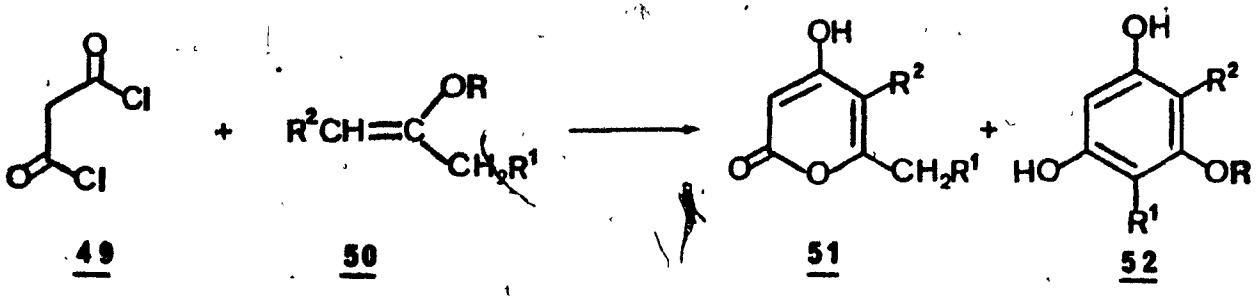
Condensation of 17 with 46 and titanium tetrachloride gave methyl olivetolate 47 in 55% yield. Condensation of 47 with 44 then gave 48 in 55% yield. Decarboxylation of 48 gave Δ^1 THC in 78% yield (scheme 1.10).



scheme 1.10

All the cycloaromatization reactions which we have discussed so far have one thing in common: they all involve the chemistry of silyl enol ethers. Cycloaromatization reactions from compounds other than silyl enol ethers have been achieved. A German group reported recently that [20] the enol ethers 50 reacted with malonic acid dichloride to give a mixture of pyranones 51 and

phloroglucinols 52 with the latter as major products. The yield of 52 can sometimes be as high as 80% (table 1).

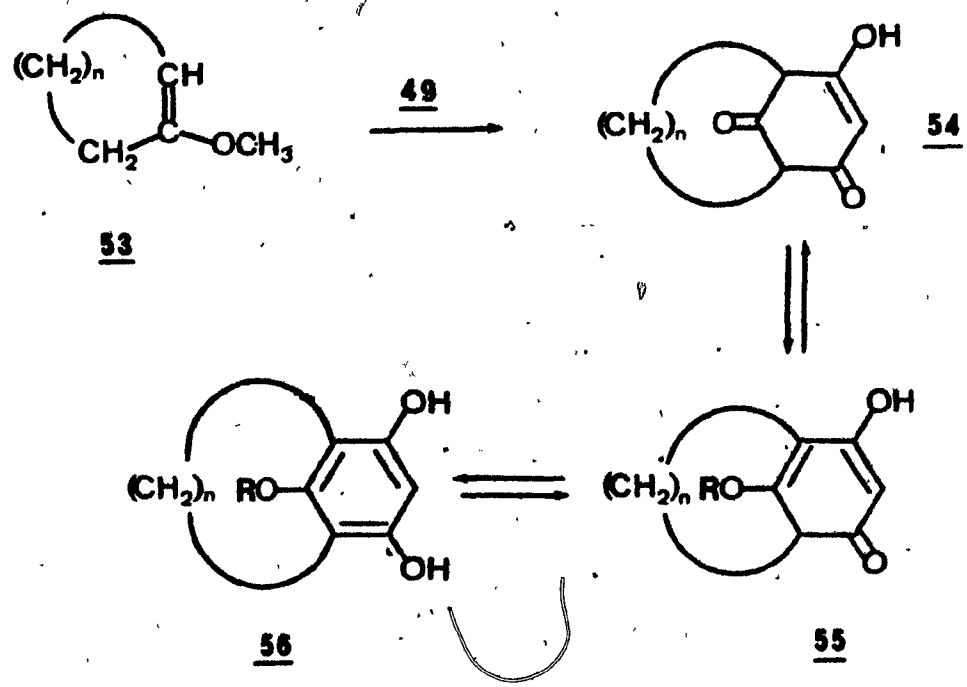


49 50 51 52

Table 1.

Compd.	R	R^1	R^2	yield(%)	
50a	CH_3	H	H	51a(43)	52a(52)
50b	C_2H_5	H	H	51a(42)	52b(43)
50c	$CH(CH_3)_2$	H	H	51a(24)	52c(65)
50d	$C(CH_3)_3$	H	H	-	52d(79)
50e	CH_3	H	C_2H_5	51b(11)	52e(80)
50f	CH_3	CH_3	CH_3	51c(30)	52f(53)
50g	CH_3	C_2H_5	H	51d(15)	52e(16)

The extension of this reaction to enol ethers of cyclic ketones 53 leads to the bicycles 54 and/or the (2,4) phloroglucinophanes 56 (scheme 1.11). With n=3,4 , 54a and 54b were obtained in 89% and 88% yield, respectively; with n=5,6, the reaction gave 55c and 55d in 70% and 31% yield, respectively. When the ring size increased to 7 or greater, metacyclophanes 56e-g were produced in 18%, 55% and 28% yield, respectively.



scheme 1.11

2. Chemistry of silyl enol ethers

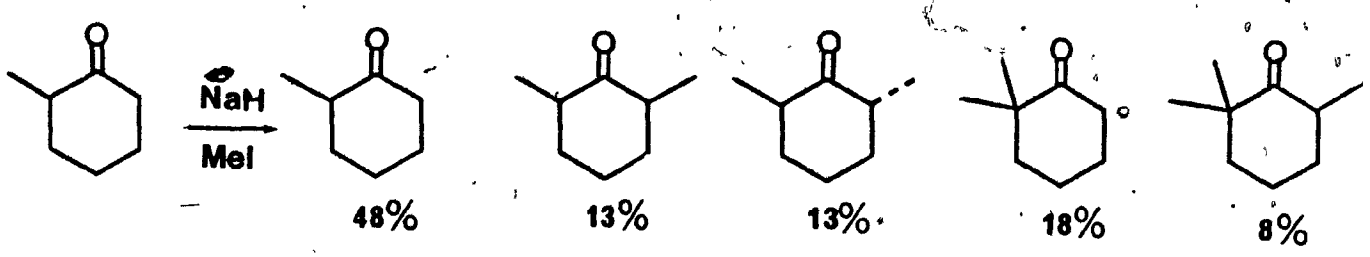
Silyl enol ethers were originally introduced as precursors of specific enolates by Stork and his coworkers in 1968 [21]. Since then, the chemistry of silyl enol ethers has so exploded and its usefulness now surpasses that of all other enol derivatives[22]. Generally speaking, their preparation is easy, their reactions are clean and require mild conditions, and they usually show high selectivities.

It is impossible to do a comprehensive review of silyl enol ether chemistry in this thesis. The readers are referred to several recent reviews. We just want to, through a brief discussion, show the reactivity and selectivity of silyl enol

ethers with electrophiles.

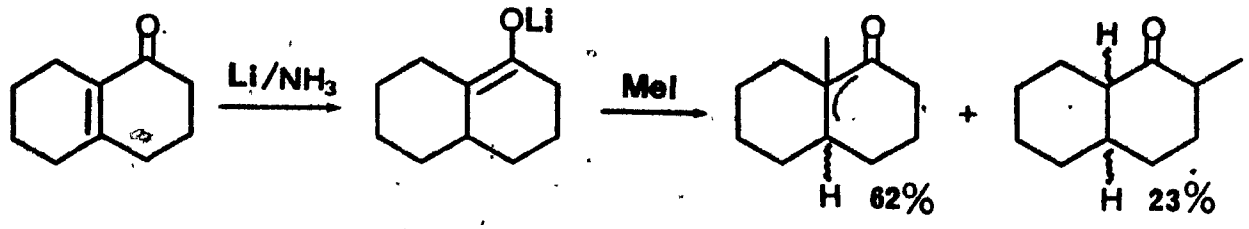
(1) Alkylation

Carbonyl compounds occupy a central place in organic synthesis because they are intrinsically electrophilic, and sometimes they can act as nucleophiles through their enolates [23]. But there are serious problems about this potential nucleophilicity for controlled alkylation. These problems include: (a) competing aldol reactions, a problem especially acute with aldehydes, (b) O-alkylation in place of C-alkylation, (c) poly-alkylation, (d) a specific enolate may not be alkylated regiospecifically and (e) alkylation is limited to primary or secondary halides [24]. 2-Methylcyclohexanone, for example, gives all the possible methylation products under NaH conditions via the sodium enolate (scheme 1.12).



scheme 1.12

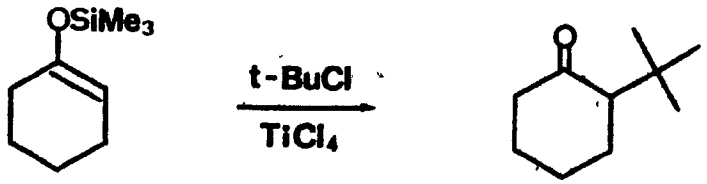
More recently, Stork discovered that lithium enolates are much better behaved than sodium or potassium enolates. For example, the specifically generated enolate 58, a particularly testing case, could be methylated to give mainly the more substituted product 59 [25] (scheme 1.13).



57 58 59 60

scheme 1.13

The α-alkylation of ketones or aldehydes through their enolate anions is limited to primary and secondary halides. When the alkyl group to be introduced is tertiary with a β-hydrogen (e.g. t-butyl), elimination predominates over substitution. This problem was solved by the use of silyl enol ether. In 1977, Chan and his coworkers reported that t-butyl group can be introduced to the α-position of ketones and aldehydes through their silyl enol ethers in the presence of Lewis acid with moderate yields [26]. Some examples are given in scheme 1.14. The application of this method was enriched independently by Reetz's work [27].

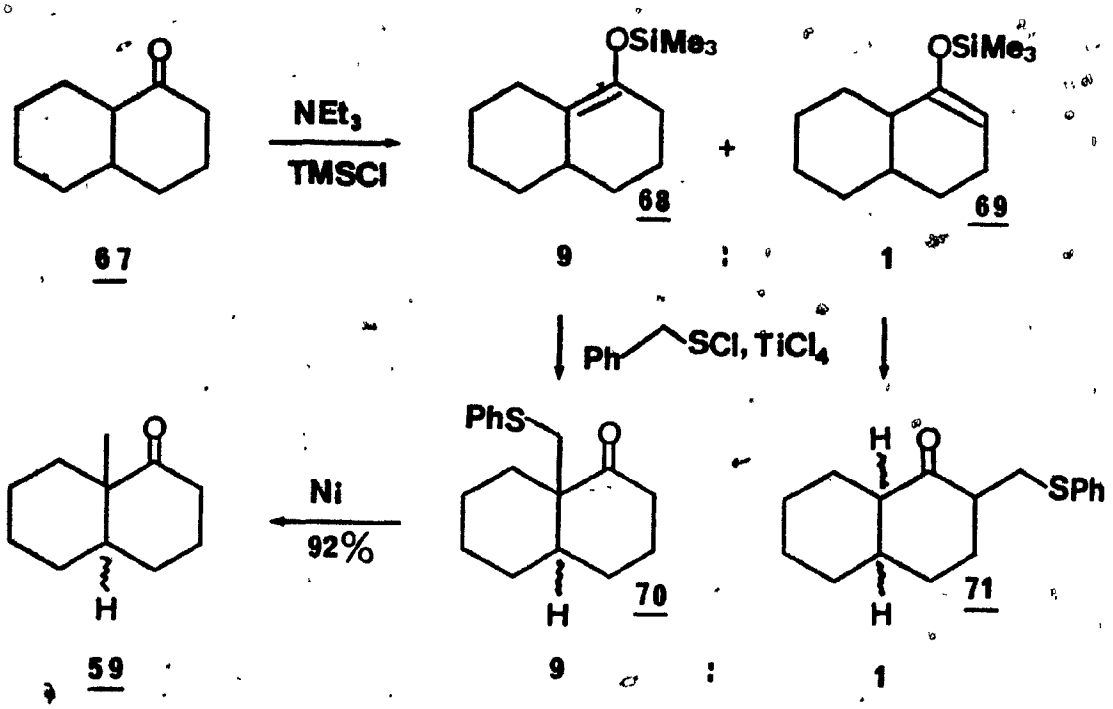


61

62 63

scheme 1.14

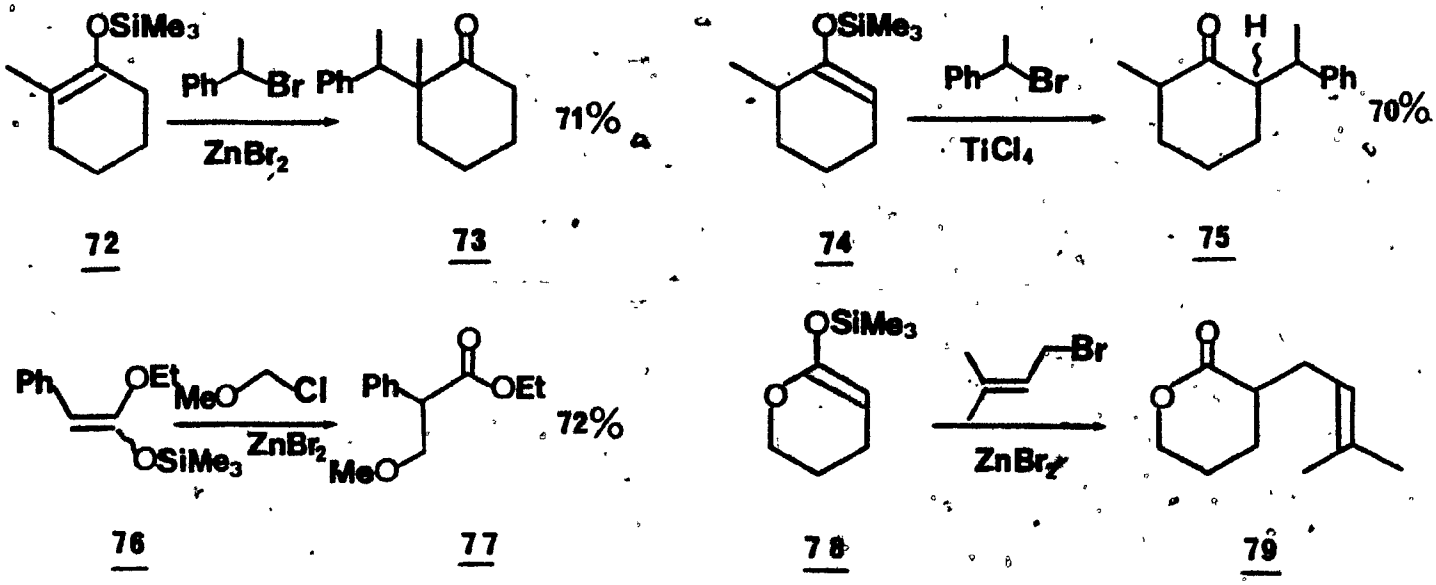
The alkylation reactions of silyl enol ethers usually show complete regioselectivity. For the methylation reaction, Fleming and Paterson reported an indirect approach which involved in the use of silyl enol ethers as an alternative of the enolate 58 [22]. It is illustrated in scheme 1.15. The silylation of 67 gave a 9:1



scheme 1.15

mixture of 68 and 69, the next phenylthioalkylation reaction is completely regioselective. The products 70 and 71 could be desulphurized with Raney nickel to give 59 in very high yield.

Direct alkylation of silyl enol ether is restricted to tertiary alkyl halides or other S_N1-type alkylating reagents, such as benzylic, secondary, allylic, and methyl halides (scheme 1.16). Again, these reactions show complete regioselectivity [28].

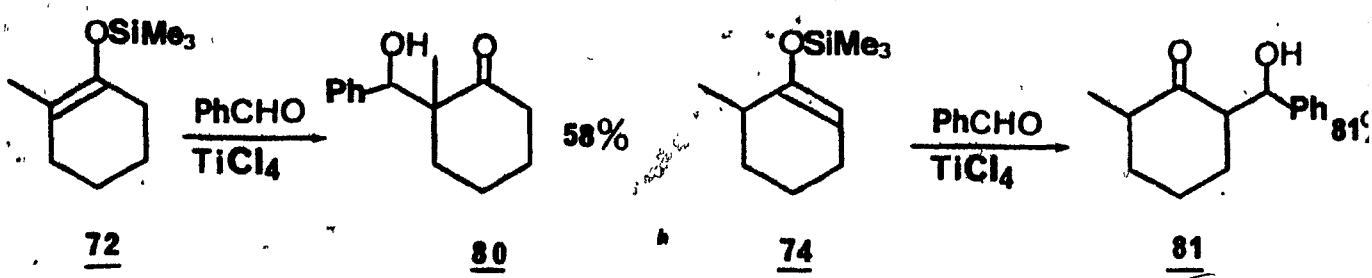


scheme 1.16

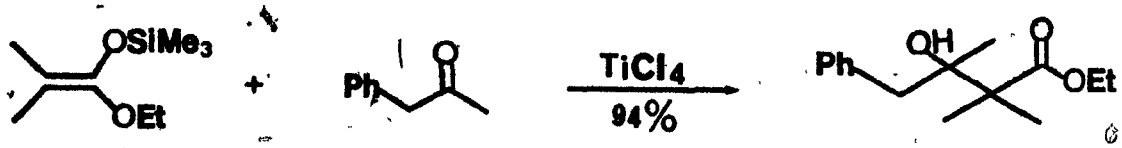
(2) Aldol condensation

The aldol condensation between two carbonyl compounds is normally carried out under basic conditions. Under these conditions, dimers, polymers, and dehydration products are often formed as by-products. More critical is the problem of ensuring specific direction in the condensation, i.e., that one particular carbonyl component will act as the nucleophile and the other as the electrophile. The Lewis acid-catalysed condensation of a silyl enol ether with an aldehyde or ketone, unlike the traditional aldol condensation, shows complete regio-and chemoselectivity, and provides high yields of the aldol products [22,29]. Some examples are given in scheme 1.17 [30].

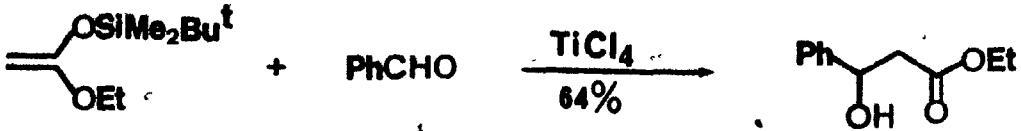
It is likely that this condensation occurs via a cyclic transition state, such as 88 [31]. The reactions often show considerable diastereoselectivity,(scheme 1.18) thus, the silyl



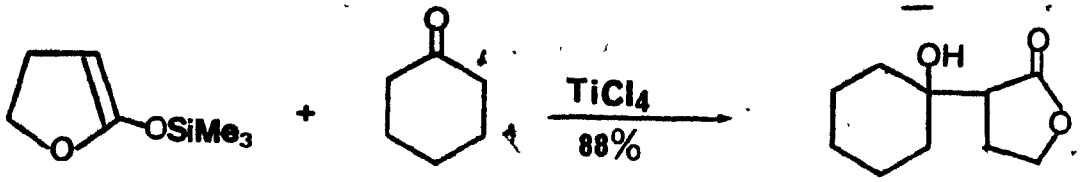
72 80 74 81



82 83

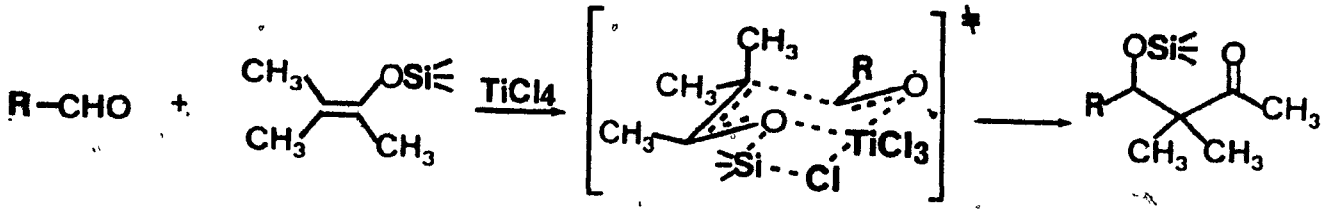


84 85

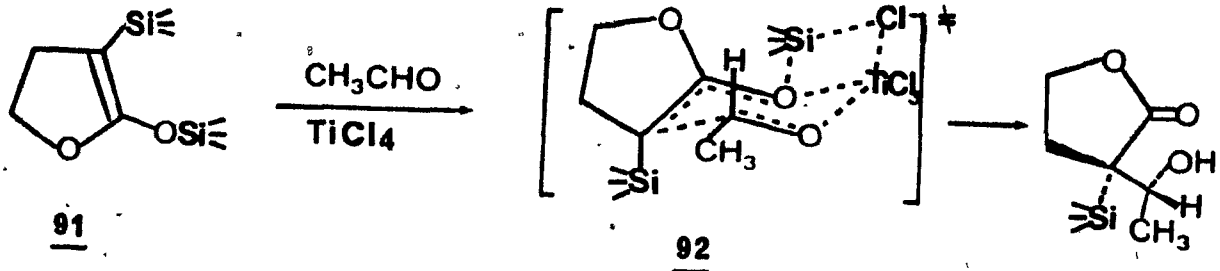


86 87

scheme 1.17



89 88 90



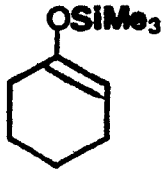
91 92 93

scheme 1.18

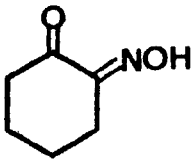
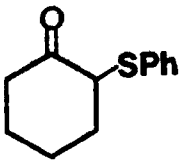
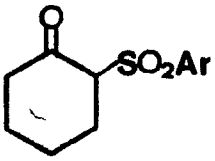
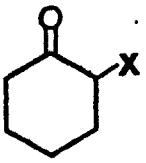
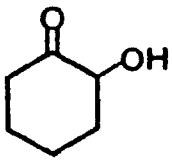
ketene acetal 91 reacts with acetaldehyde and titanium tetrachloride via the presumably preferred transition state 92 to give a single diastereoisomer of the adduct 93 in 98% yield [32].

(3) Reactions with other electrophiles

Table 2. Reactions with non-carbon electrophiles.



electrophilic reagent → Product

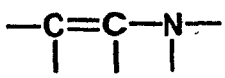
Products	reagents	references
	NOCl	33
	PhSCl	34
	$ArSO_2Cl$	35
	Br_2 or Cl_2	36
	1. MCPBA 2. $Et_3\overset{+}{N}HF^-$	37, 38

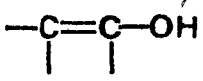
Besides aldehydes and ketones, silyl enol ethers can react with many other carbonyl derivatives, such as acid chlorides, anhydrides, isocyanates, acetals and thioacetals. They can also react with some non-carbon electrophiles. Examples are given in table 2.

3. Chemistry of enamines

Most of the ground work for enamine chemistry had been reported by Mannich and Davidson in 1936 [39]. It recaptured organic chemist's interest after a publication by Stork and his coworkers in 1954 [40] demonstrating the general utility of enamines as an alternative of enolates. Thousands of papers have been published on enamine chemistry over the next 15 years.

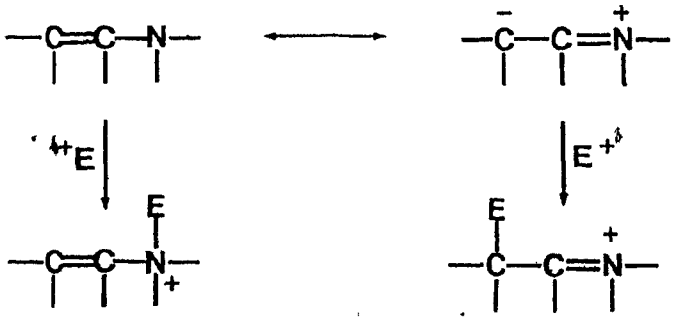
The term of "enamine" was first introduced by Wittig and Blumenthal [41] as the nitrogen analogue of "enol".





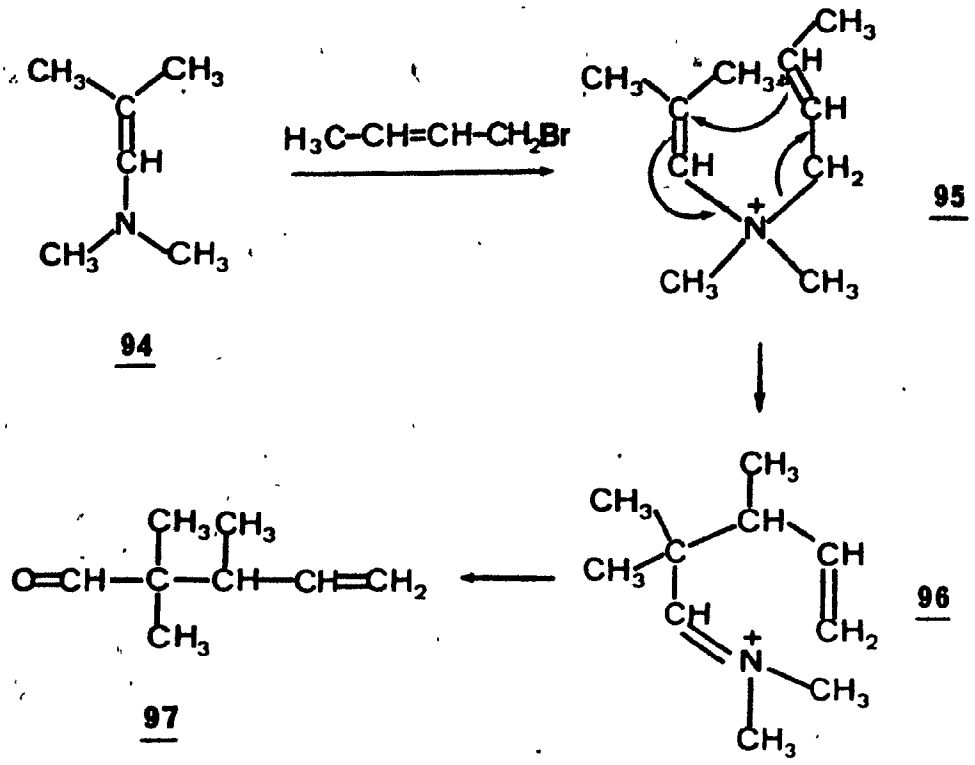
(1) Electrophilic substitution and addition reactions

Undoubtedly the most important and also best investigated aspect of enamine's chemistry is the electrophilic substitution



scheme 1.19

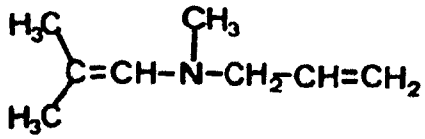
and addition reaction. Since the electron pair on the nitrogen atom can overlap with the π electrons of the double bond, enamines are capable of existing in two mesomeric forms. The electrophilic attack may take place either at the nitrogen atom to form an enammonium cation or at the β-carbon atom to form an iminium cation (scheme 1.19). This can be illustrated by the alkylation reactions of enamines with alkyl halides. Because of self-condensation under reaction conditions, enamines derived from acetaldehyde or monosubstituted acetaldehydes cannot usually be alkylated [42]. Enamines derived from aldehydes disubstituted on the β-carbon such as isobutyraldehydes , are alkylated on nitrogen by alkyl halides. Whereas with allyl or benzyl halides the C-alkylation products predominate [43,44]. The C-alkylation



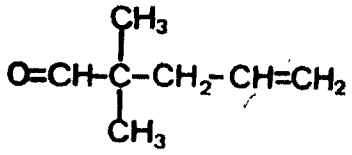
94 95 96 97

scheme 1.20

has been rationalized by the initial N-alkylation of 94, to give 95, followed by an intramolecular rearrangement which involves a six-membered cyclic transition state to the intermediate 96. Hydrolysis of 96 gave 97. This mechanism was supported by the alkylation of 98 with methyl tosylate, which on hydrolysis gave 99.

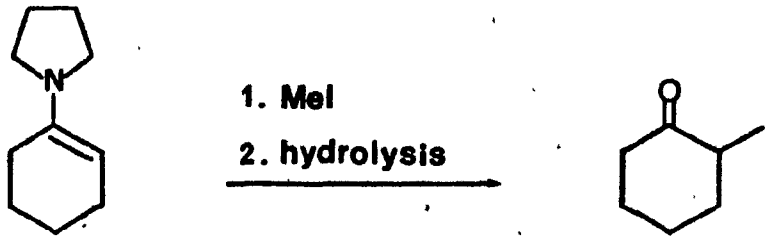


98



99

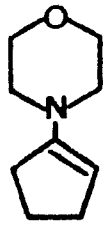
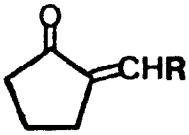
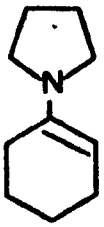
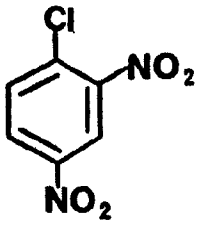
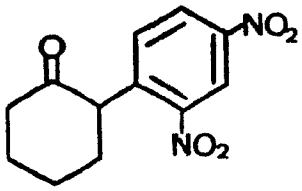
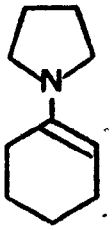
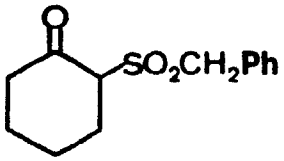
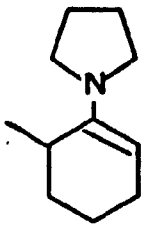
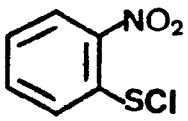
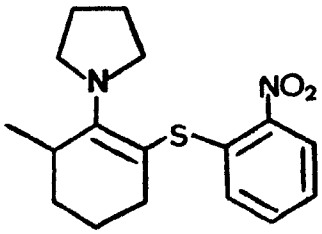
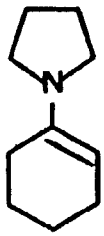
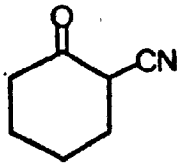
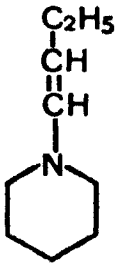
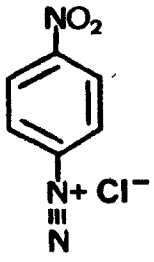
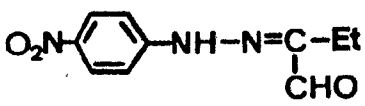
With enamines of cyclic ketones, direct C-alkylation occurs with allyl as well as alkyl halides. 2-Methyl cyclohexanone 100 could be obtained in 80% yield from the pyrrolidine enamine of cyclohexanone 101 [40].



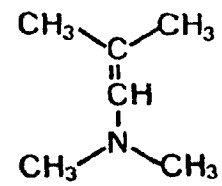
101 100

Besides the alkylation reactions, enamines can also react with many other electrophiles such as acid chlorides, anhydrides, aldehydes, activated arylhalides, sulfonyl halides, sulfenyl halides, cyanogen halides, aromatic diazonium salts, ketenes and isocyanates. Some examples are given in table 3.

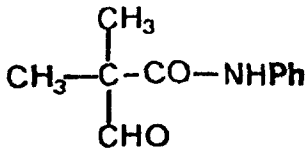
Table 3. Reactions of Enamines with Electrophiles

enamines	electrophiles	products	references
	R–CHO		46
			42
	$PhCH_2SO_2Cl$		47
			48
	ClCN		49
			50

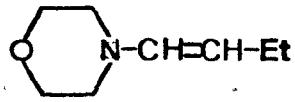
continued table



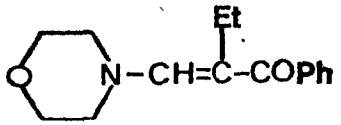
PhNCO



43



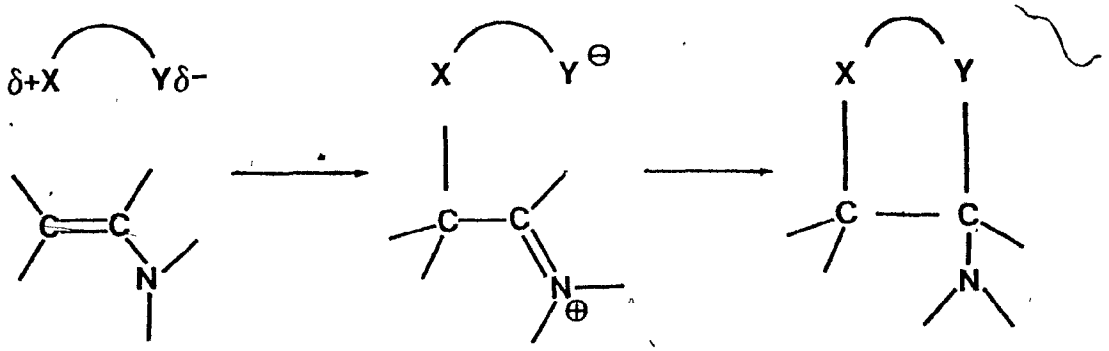
PhCOCl



45

(2) Cycloaddition reactions of enamines

One of the important areas of enamine chemistry is the cycloaddition reaction. Consider a normal condensation reaction between enamine and a electrophile which is formulated as $X^{\delta+}$ $Y^{\delta-}$. After the initial electrophilic attack at the β-carbon of enamine, a new negative charge develops on the original electrophilic part, and the enamine now becomes a iminium ion which is a very reactive electrophile. By an intramolecular nucleophilic attack, ring systems of variable sizes can be generated.

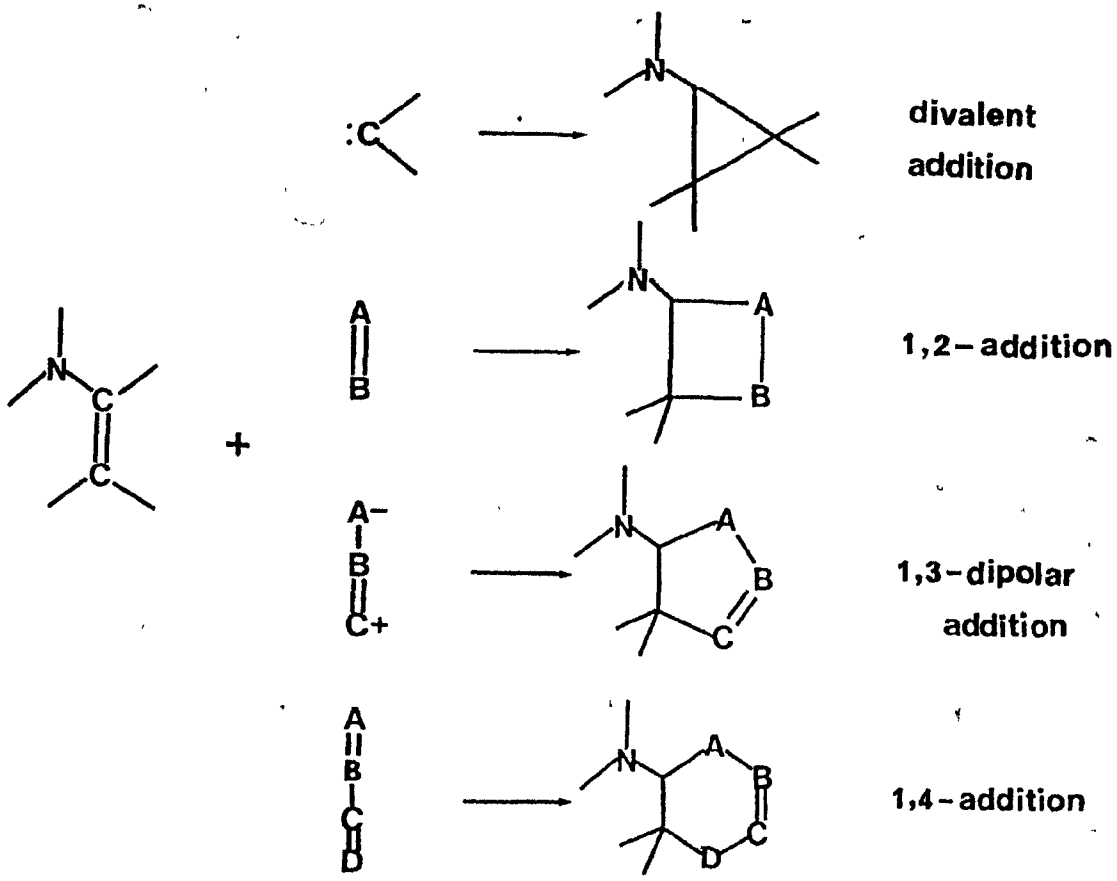


scheme 1.21

These types of cycloadditions can involve a divalent addition

to form a cyclopropane ring , a 1,2-addition with an alkene or alkyne to give a cyclobutane or cyclobutene, a 1,3-dipolar addition or a Diels-Alder reaction with enamine as dienophile.

Although in some of the reactions it has not been established whether the cycloaddition involves a concerted mechanism or a



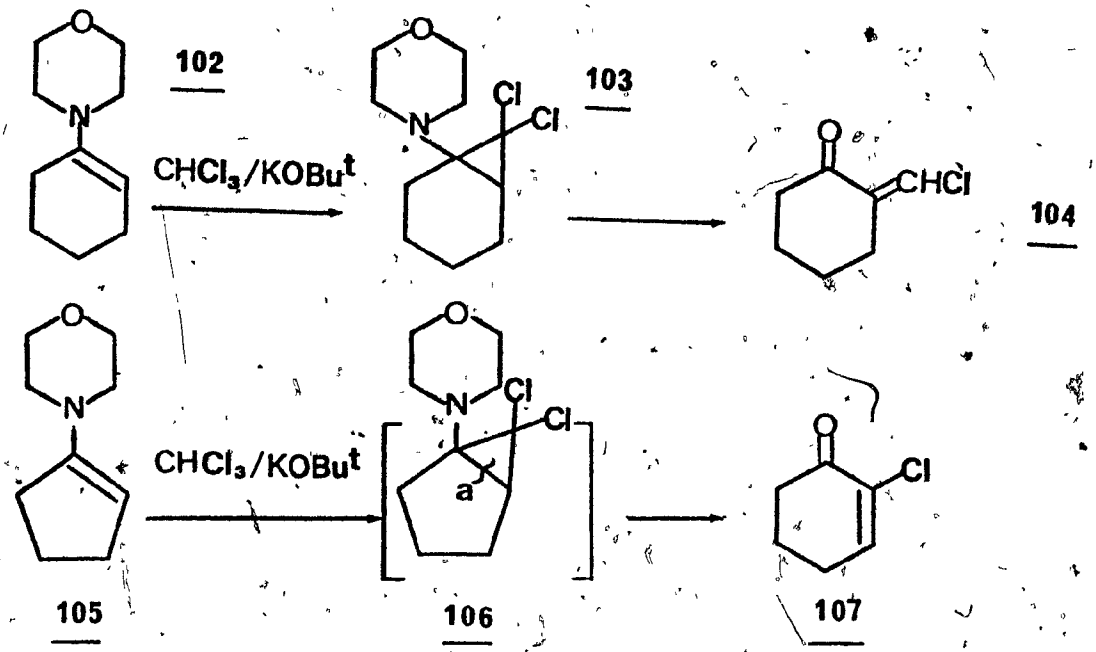
scheme 1.22

stepwise ionic mechanism, the latter seems generally the favored pathway.

(a). [2+1] cycloadditions

The reaction of enamines from cyclohexanone with dichlorocarbene gave the 1:1 adducts [51-53]. The morpholine

enamine 102 reacts with dichlorocarbene at -10° to -20°C in THF to give a stable crystalline adduct 103. Thermal decomposition of 103



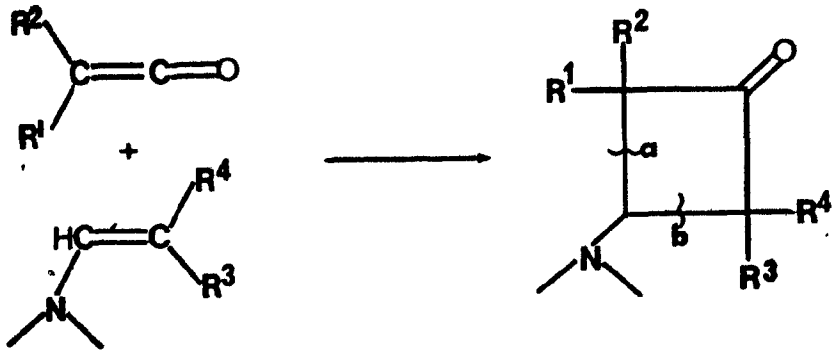
scheme 1.23

followed by aqueous workup gave an α,β-unsaturated ketone identified as compound 104. Reaction of cyclopentanone enamine 105, however, gave an unstable adduct, and the 3-membered ring opened at "a" to give the ring expanded ketone 107 on hydrolysis.

(b). [2+2] Cycloadditions

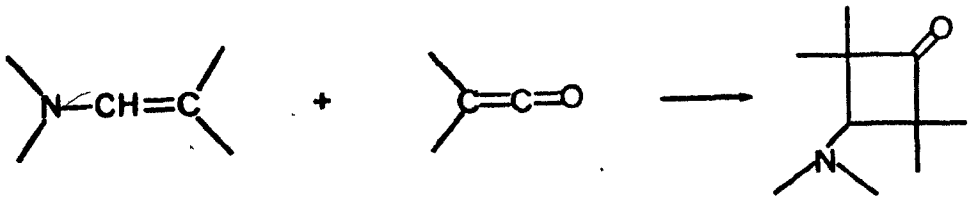
The reaction between enamines and ketenes has been actively investigated.

The first step of the reaction between a ketene and an enamine is apparently a 2C+2C cycloaddition to produce an aminocyclobutanone adduct. The thermal stability of this adduct depends on the nature of substituents R^1, R^2, R^3 and R^4.



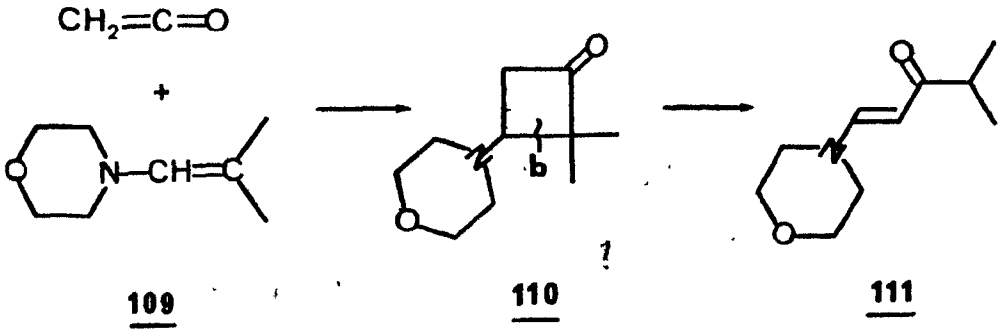
scheme 1.24

For the reaction of aldehydic enamines with no β-hydrogens and disubstituted ketenes, (e.g., R^1,R^2,R^3,R^4 are not H) the cyclobutanone adduct is thermally stable. For example the reaction of dimethyl ketene with N,N-dimethylaminoisobutene 94 produced 108 in 64% yield. Compound 108 can be distilled without decomposition [54].



94 108

The reaction between an aldehydic enamine with no β hydrogens and ketene forms a cyclobutanone adduct which is not thermally

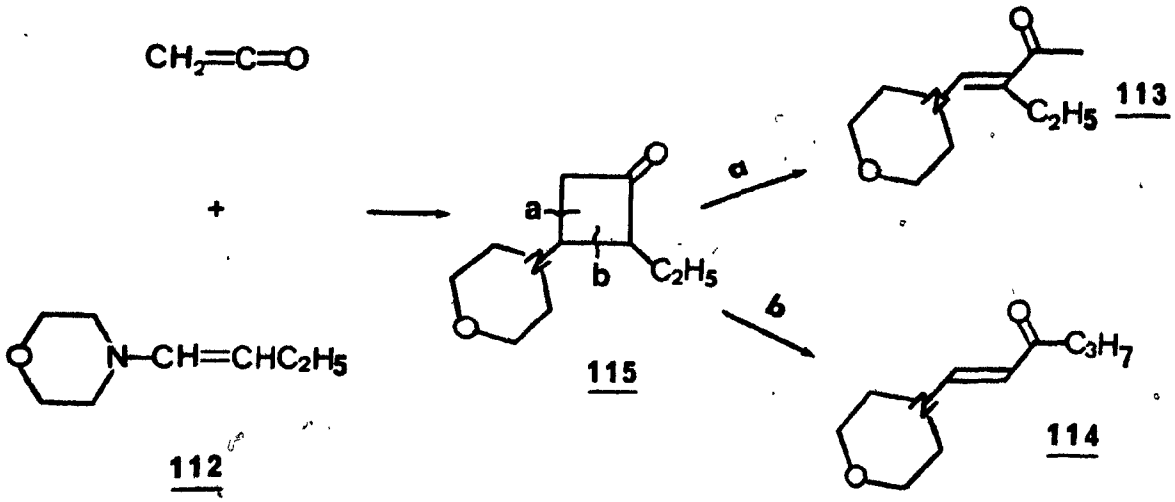


109 110 111

scheme 1.25

stable (R^3 and R^4 ≠ H, R^1=R^2=H) [45,55,56]. Thermal decomposition of the adduct gave exclusively product by the cleavage at "b" (scheme 1.25). This is illustrated by the reaction of 109 with ketene to give 110 which decomposed to 111.

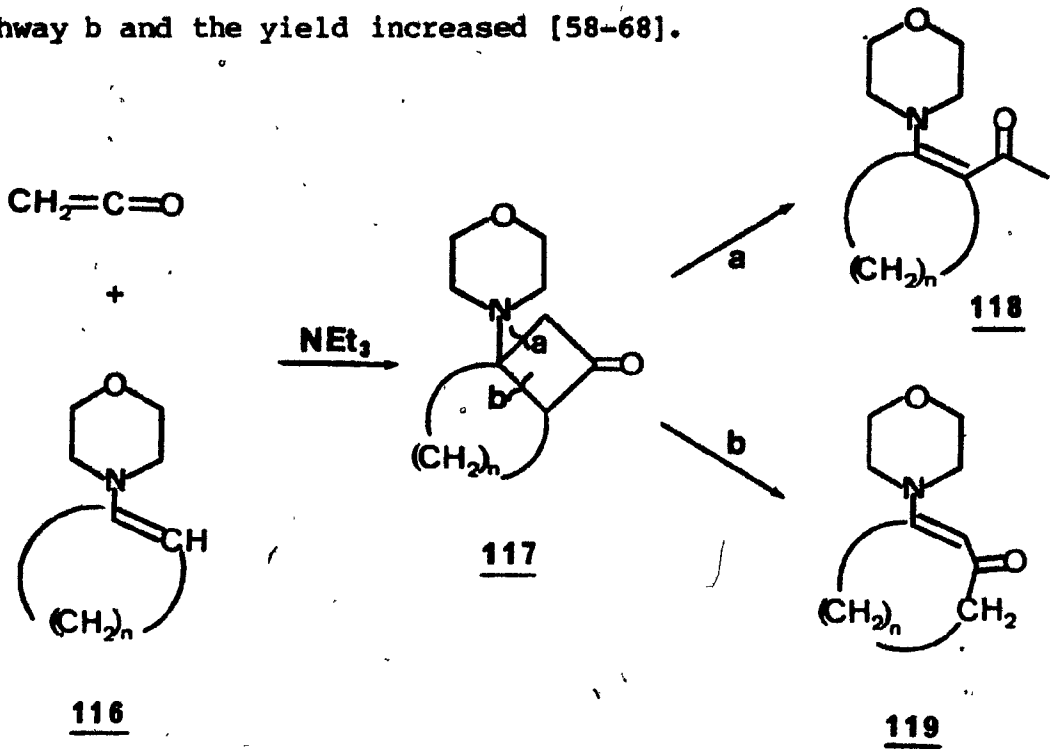
The adducts of aldehydic enamines with β-hydrogens, such as 1-(morpholino)-butene 112 and ketene are very unstable, cleavage at "a" and "b" are both possible and a mixture of 113 and 114 were obtained [57] (scheme 1.26).



scheme 1.26

Enamines derived from cyclanones react with ketene to generate first cyclobutanone followed by cleavage at "a" or "b" (scheme 1.27). The point of cleavage of the cyclobutane ring depends on the ring size of the original cyclic ketone. For adducts from five and six-membered cyclic ketone enamines (n=3 and 4), decomposition takes place at "a". The adduct from the nine membered ring enamine (n=7) was produced in very poor yield and decomposition followed both pathway a and b. As the enamine ring size increased from ten to fifteen, the cyclobutanone ring cleavage followed mainly

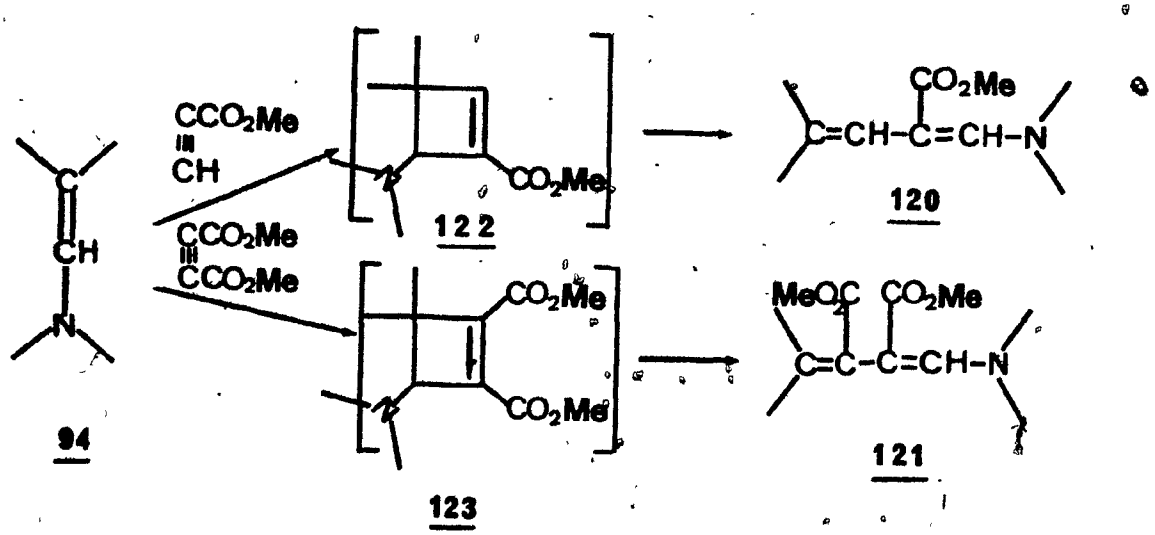
pathway b and the yield increased [58-68].



scheme 1.27

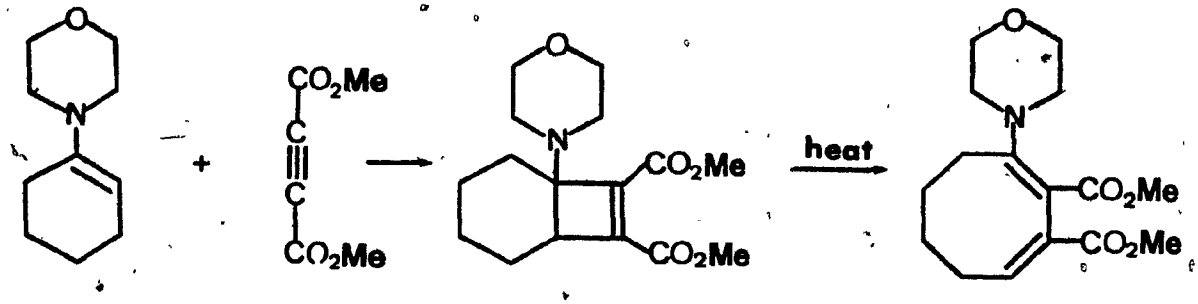
The reaction of enamines with acid chlorides was also well studied. When the acid chlorides have no β-hydrogen, such as benzoyl chloride, an acylation reaction takes place. In the case of acid chlorides possessing β-hydrogens, ketenes can be produced in situ and the reactions often involve the formation of cyclobutanone derivatives. But direct acylation was also reported [69].

Enamines can react with some electrophilic acetylenes and again the initial step was believed to be the 2C+2C cycloaddition. Compound 94 reacted with methyl propiolate to give the dienamino ester 120. Dimethyl acetylenedicarboxylate reacted similarly to give 121 [70] (scheme 1.28).



scheme 1.28

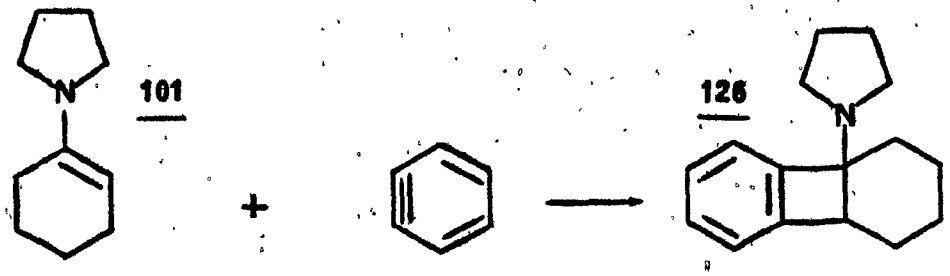
A similar sequence of reactions took place with the enamines of cyclic ketones. Six-membered ring enamines produced stable cyclobutene adducts with dimethyl acetylenedicarboxylate, which then decomposed into ring enlargement products on heating [70,71]. This is illustrated by the reaction of 102 with dimethyl acetylenedicarboxylate to form 124 which was then converted to 125 on heating (scheme 1.29).



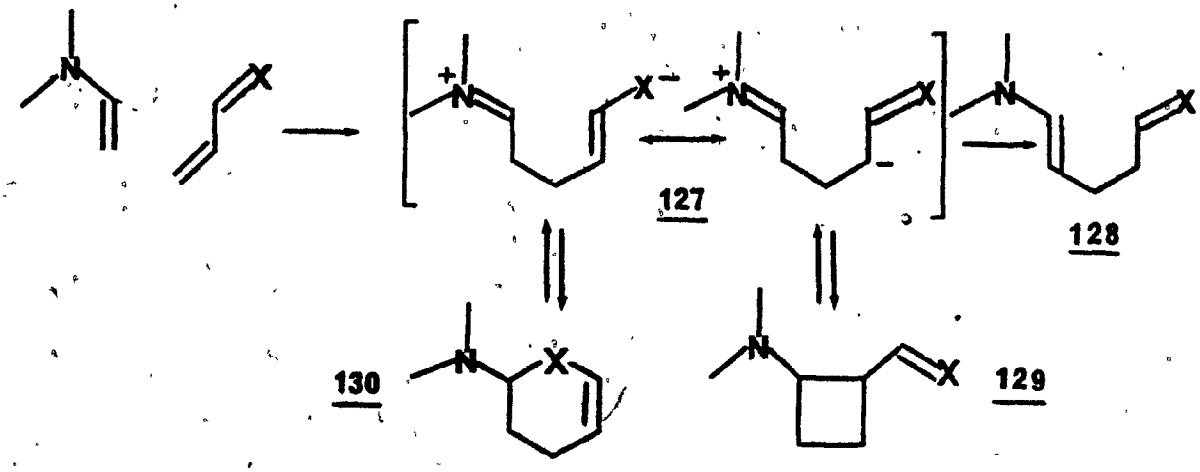
scheme 1.29

Enamines can also undergo 2C+2C cycloadditions with benzyne (obtained from fluorobenzene and butyl lithium) [72]. One example

is give below.

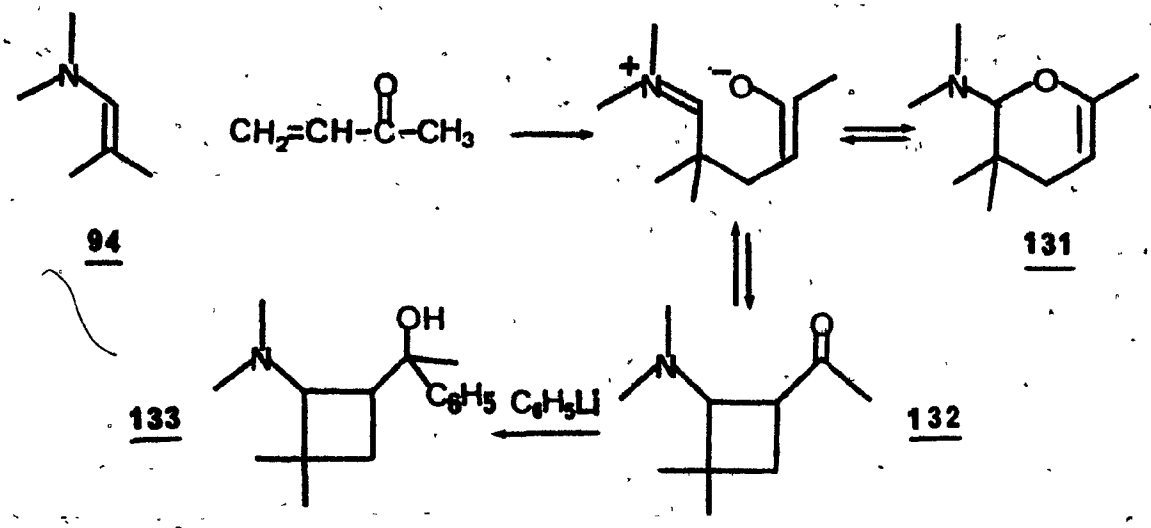


The reactions of electrophilic alkenes (alkenes attached to electron withdrawing groups) with enamines sometimes also end up as 2C+2C cycloadditions. The first step is the formation of a zwitterion intermediate 127 then followed either by one of two possible cycloadditions to give 129 (2C+2C cycloaddition) or 130 (2C+4C cycloaddition), or by proton addition to give simple alkylated product 128 (scheme 1.30).



scheme 1.30

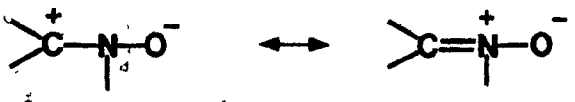
This is illustrated by the reaction of enamine 94 with methyl vinyl ketone. The initial product was dihydropyran 131 [73]. Treatment of 131 with phenyllithium gave cyclobutane 133, obviously via intermediate 132 (scheme 1.31).



scheme 1.31

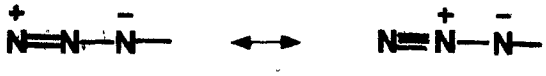
(c). 1,3-Dipolar cycloaddition

1,3-Cycloaddition across the double bond of an enamine to form an uncharged five-membered ring involves a dipolar reactant described by zwitterionic octet structures. The types of dipolar reactants which have been reported to undergo this 1,3-cycloaddition with enamines are listed below.

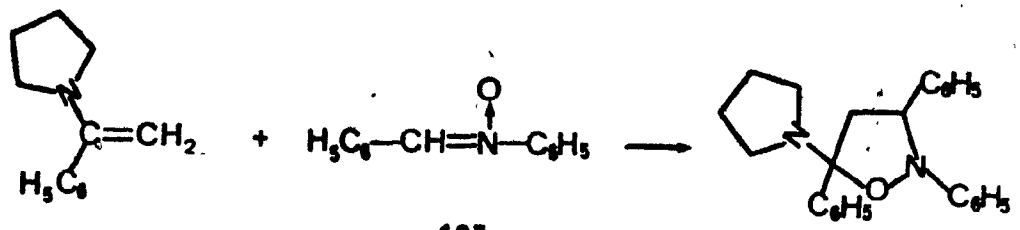
nitrones 

nitrilimines 

nitrile oxides 

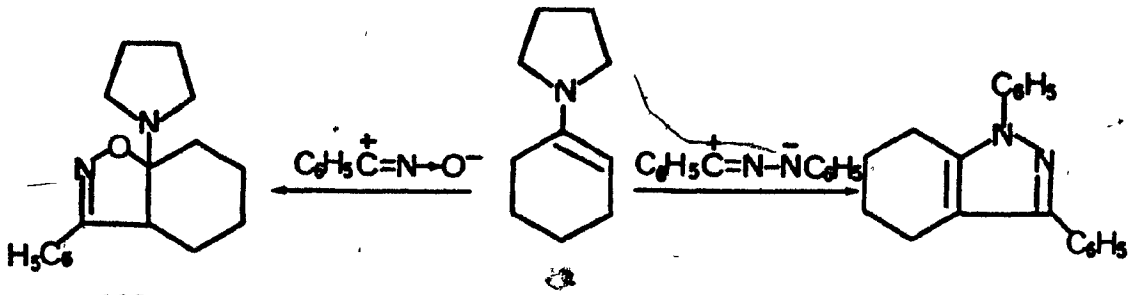
azides 

The cycloaddition of nitrone 135 to enamine 134 results in an isoxazolidine 136 [74].



134 135 136

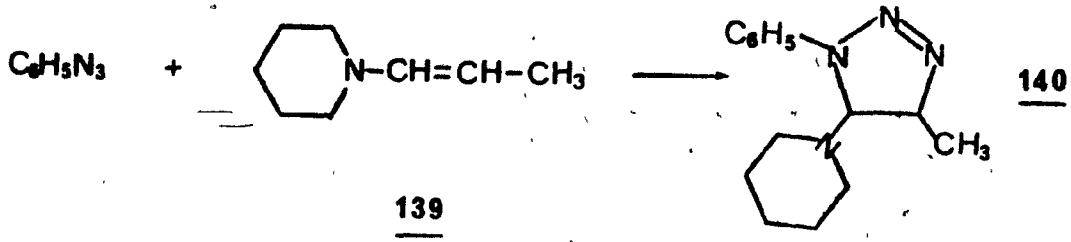
Nitrilimines undergo 1,3-cycloaddition with enamines to form pyrazoles 137 [75], and the products of the reaction between nitrile oxides and enamines are isoxazoles 138 [75].



138 101 137

scheme 1.32

Azides can also react with enamines in a 1,3-cycloaddition to form triazolines [75,76,77]. For example, the reaction between phenylazide and the piperidine enamine of propionaldehyde 139 gave 140 in 53% yield.

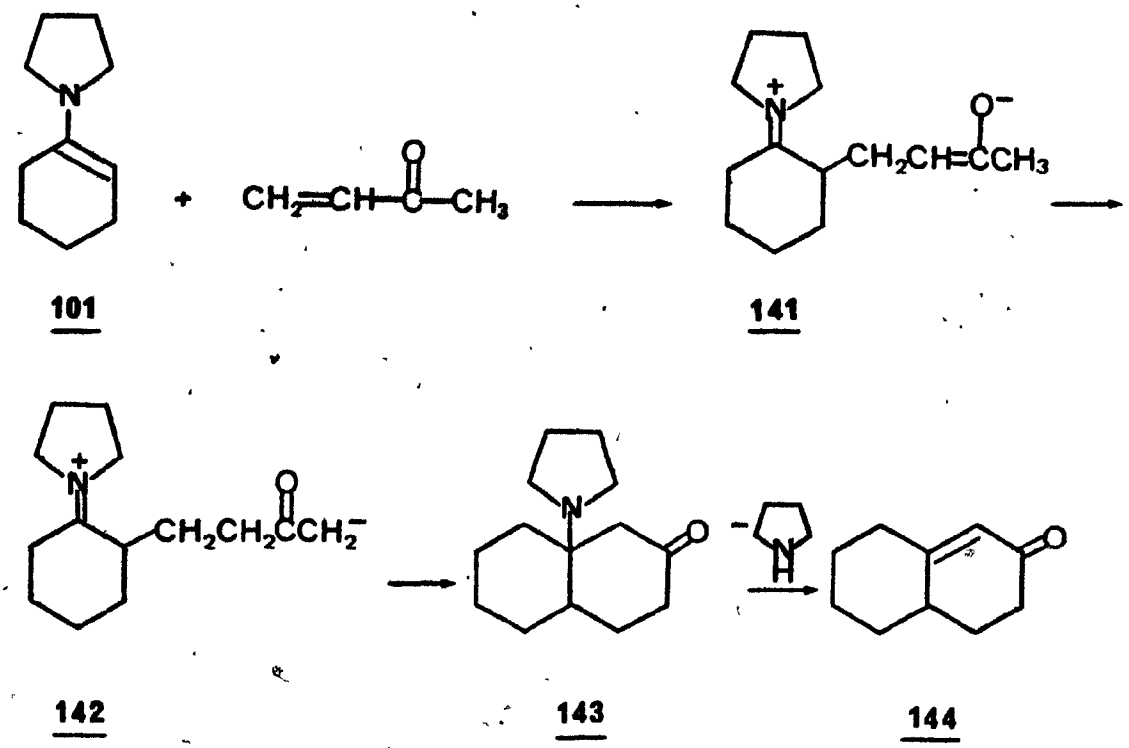


139 140

(d). 2C+4C reaction of enamines

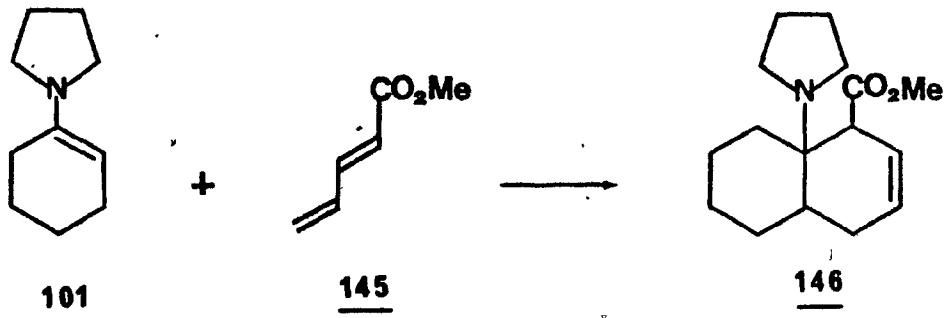
The first reported cyclization involving an enamine was the 1,4-cycloaddition of methyl vinyl ketone with enamine 101 to give,

after hydrolysis, $\Delta^{1,9}$-octol-2-one 144 [78]. It can be described by the following mechanism:



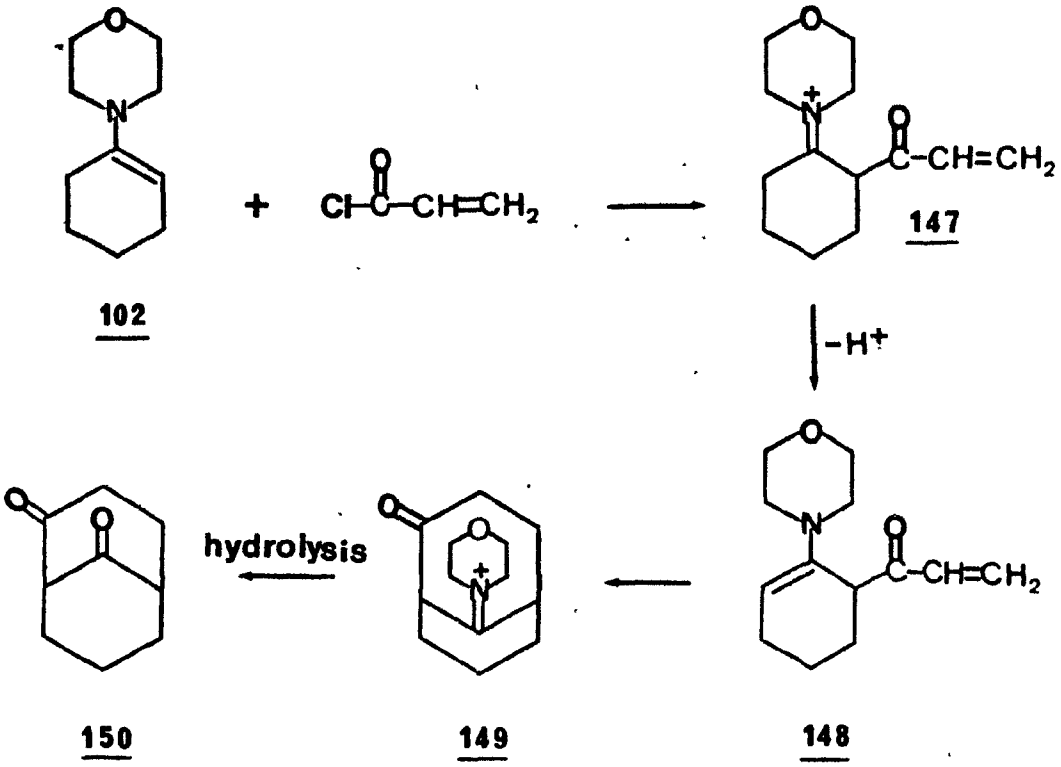
scheme 1.33

Diels-Alder reaction of enamine has also been reported. This is illustrated by the reaction between 101 and methyl trans-2,4-pentadienoate 145. Here the enamine acted as the dienophile to give the adduct 146 [79].



(e). [3+3] Cycloaddition

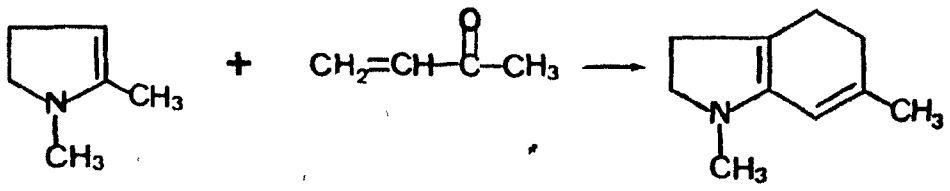
So far, in all the cycloaddition reactions we have discussed, enamines act as two carbon component. Actually enamines can also act as three carbon components in their cycloaddition reactions. The reaction of enamine 102 with acryloyl chloride followed the pathway shown in scheme 1.34 to give 150 [80].



102 147 148 149 150

scheme 1.34

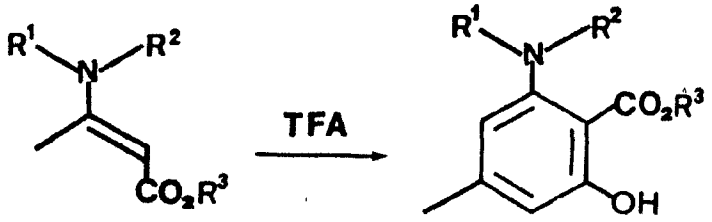
Heterocyclic enamines often undergo a similar two-step 3C+3C cycloadditions with methyl vinyl ketone. For example, enamine 151 reacted with methyl vinyl ketone to produce 152 [81].



151 152

The requirement for this type of cycloaddition reaction is that the α-position of enamine must be carbon substituted and, this carbon must carry at least one hydrogen atom. This provides the possibility of generating a new enamine by deprotonation for the second nucleophilic attack.

In 1980, Bohme et al reported that the self-condensation of 3-dialkylaminocrotonate 153 led to anilino compounds 154, sometimes in good yield [82] (table 4).



153 154

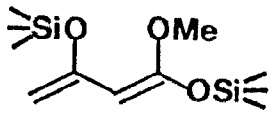
Table 4. Self-condensation reactions of compounds 153

Compd.	R^1	R^2	R^3	yield %
154a	CH_3	CH_3	CH_3	70
154b	CH_3	CH_3	C_2H_5	90
154c			CH_3	52
154d			C_2H_5	35
154e			CH_3	50
154f			C_2H_5	25
154g			CH_3	63
154h			CH_3	8
154i	C_6H_5	H	CH_3	40
154k	n-C_3H_7	H	CH_3	42

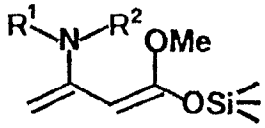
The direct application of this self-condensation reaction is limited, because no cross condensation was mentioned in their paper. This reaction is very interesting, however, because it reveals the fact that enamines can also undergo cycloaromatization reactions.

4. The proposed research

In compound 17, two nucleophilic sites are present, each is associated with a silyl enol ether. The aromatic compounds which are derived from the cycloaromatization of 17 must by necessity be limited to phenolic derivatives. It would be desirable to be able to generalize the reaction to the synthesis of other functionalized aromatic compounds. This thesis deals with the possibility of a cycloaromatization reaction leading to highly substituted anilino compounds. Our strategy is to modify 17 by replacing one of the silyl enol ether groups with an enamine group, e.g., in the form of compound 155. In 155 all of the



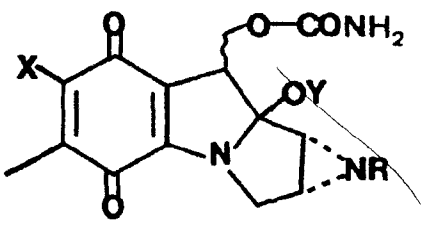
17



155

features which are required by the cycloaromatization reactions are met. Like 17, 155 is also a 1,3-dinucleophile and it is likely that C-4 will be more reactive than C-2 towards electrophiles, thus the regiochemistry of the condensation could be controlled. The reactions between 155 and β-dicarbonyl or other 1,3-dielectrophiles, if they take place, should lead to anilino compounds.

Some natural products have a substituted aniline carbon



A $X=OCH_3$, $R=H$, $Y=CH_3$

B $X=OCH_3$, $R=CH_3$, $Y=H$

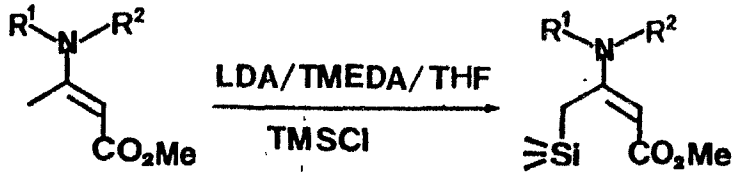
C $X=NH_2$, $R=H$, $Y=CH_3$

mitomycin

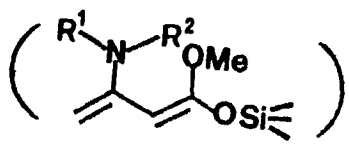
skeleton. One example is mitomycin [83] which possesses antibiotic as well as outstanding anti-cancer activities. The chemical synthesis of mitomycin A with its densely arrayed fuctionalities is a challenge which has only recently been met [84]. It may make the synthesis of these natural products much easier if a general appoach of assembling highly substituted anilino compounds can be achieved.

CHAPTER II. THE γ-REACTION OF 4-TRIMETHYLSILYL-3-DIALKYLAMINOCROTONATE ESTERS WITH CARBONYL ELECTROPHILES

Methyl 3-dialkylaminocrotonate 153 was prepared by the usual water-separator method with p-toluenesulfonic acid as the catalyst. Compound 153 was silylated by trimethylchlorosilane and LDA in THF. The result was not the expected compound 155 but the C-silyl product: methyl 4-trimethylsilyl-3-dialkylaminocrotonate 156.



153 156



155

a R^1R^2 = $-(CH_2)_4-$

b R^1R^2 = $-(CH_2CH_2\text{-}O\text{-}CH_2CH_2)-$

The structure of 156 was deduced by spectroscopic analysis. In the infrared spectra of 156, there was still the strong carbonyl absorption at 1670 cm^{-1} assigned to the ester group. The ^1H NMR spectra showed only one vinyl proton and the ^{13}C NMR showed three unsaturated carbons. Both 156a and 156b exist as one geometrical isomer. Sanchez and his coworkers studied a number of 3-dialkylaminocrotonate esters and concluded that all of them have E geometry [85]. By noting the similarity of ^1H and ^{13}C NMR between 153 and 156 (see table 1 and table 2), 156 was assigned to have E geometry as well.

Table 1. Part of ^{1}H NMR data of 153 and 156 (ppm)

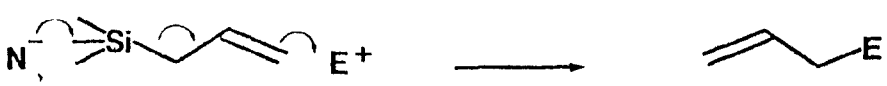
Compd.	vinyl	methoxy
153a	4.40	3.53
156a	4.47	3.60
153b	4.80	3.62
156b	4.73	3.60

Table 2. ^{13}C NMR data of 153 and 156 (ppm)

Compd.								
153a	169.2,	159.2,	82.5,	49.4,	47.5,	24.8,	16.2	-
156a	169.3,	163.0,	81.0,	49.5,	48.0,	25.0,	21.6,	-1.7
153b	169.1	161.1	87.6	66.1,	49.1,	46.1,	15.0	-
156b	169.5	165.7	86.2	66.5,	50.2,	47.1,	19.5,	-0.9

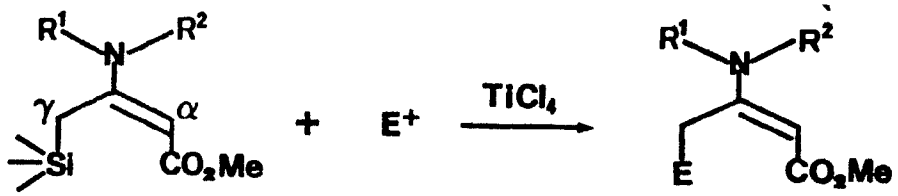
The yields of the silylation reactions are greater than 90% and the products are > 90% pure by ^{1}H NMR spectra before distillation, however, 156 is thermally stable enough to be distilled under vacuum.

In the reaction of 156 with electrophiles, one would expect that the reaction probably occurs at the α-position because of the presence of the silyl group in 156 as well as the expected reactivity of the enamine. The reactions of allylsilanes with electrophiles have been well studied and usually show high regioselectivity according to Eqn. 1 [86].



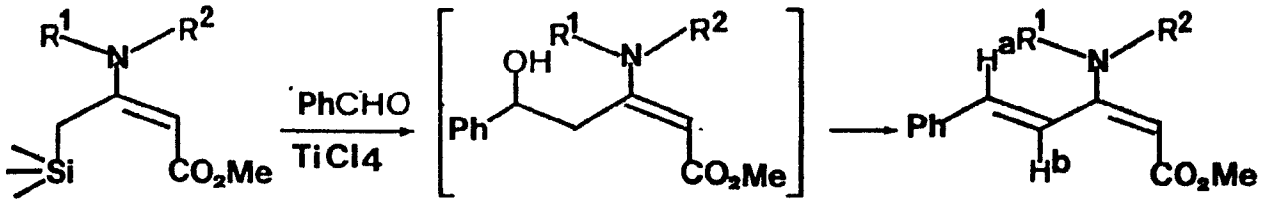
Eqn. 1

Therefore it was very surprising to us when we found that 156 reacted with a number of carbon electrophiles at the γ-position instead of the α-position [87] (Eqn. 2).



Eqn. 2

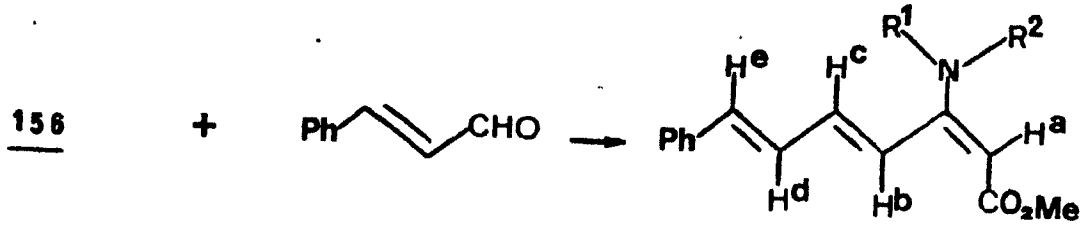
When compound 156 reacted with benzaldehyde in the presence of one mole of titanium tetrachloride in CH_2Cl_2, compound 157 was obtained in fairly good yield (see table 3). It is clear that 157 is formed from the condensation of 156 and benzaldehyde followed by the elimination of a molecule of water.



156 158 157

The ^1H NMR of 157a shows a doublet at about 6.7 ppm which was assigned to be H^a and because of the large values of coupling constant (17 Hz for 157a and 16 Hz for 157b), compound 157 has been assigned to have 2E,4E geometry.

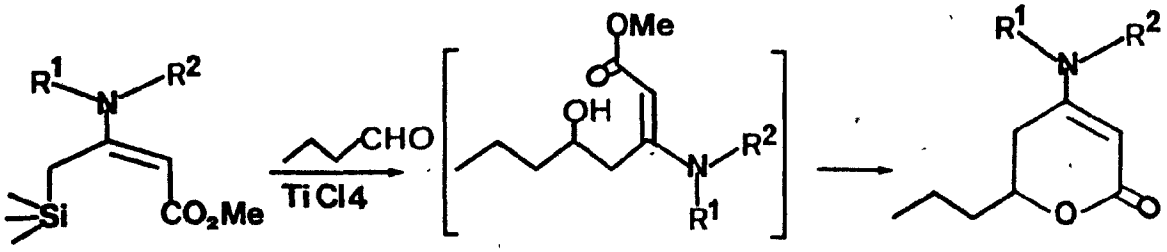
Condensation of 156 with cinnamaldehyde under the same condition gave the polyunsaturated ester 159 in good yield. In the ^1H NMR spectrum of 159a, there are five vinyl protons. One is a singlet at 4.57 ppm and obviously is H^a. Two are doublets, one at 6.54 ppm (J=16Hz), which is assigned to be H^b, the other is



156 159

at 6.86 ppm (J=16 Hz), which is assigned to be H^e. The other two vinyl signals (H^c and H^d) are both doublet of doublet (J=16 Hz and 6 Hz). From the coupling constants we assigned compound 159 to have a 2E,4E,6E configuration.

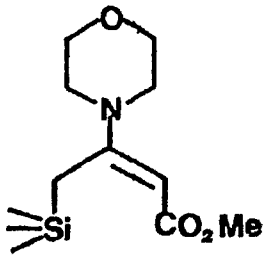
With butyraldehyde, condensation with 156 is followed by an intramolecular cyclization to give the δ-lactone 160.



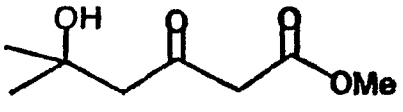
156 161 160

There are, however, differences in the reactivity between 156a and 156b. It seems that the morpholino compound 156b is more reactive than the pyrrolidino compound 156a. Thus with the less reactive ketone electrophiles, only 156b gave the corresponding products 162 and 163. Compound 162 is the hydrolized product of its enamine precursor which occurs during the aqueous workup.

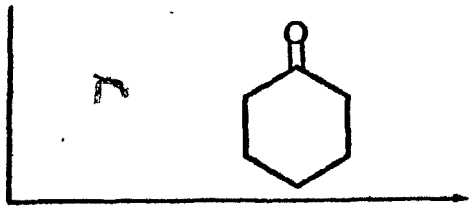
When 156a was reacted with acetone under the same conditions, only compound 153a was shown in the product, apparently from the hydrolysis of the unreacted 156a. When cyclohexanone was used, the

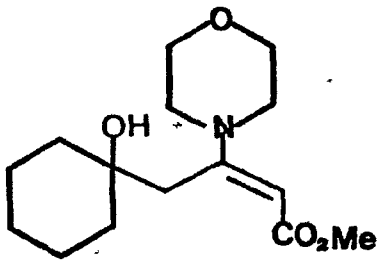


156b



162

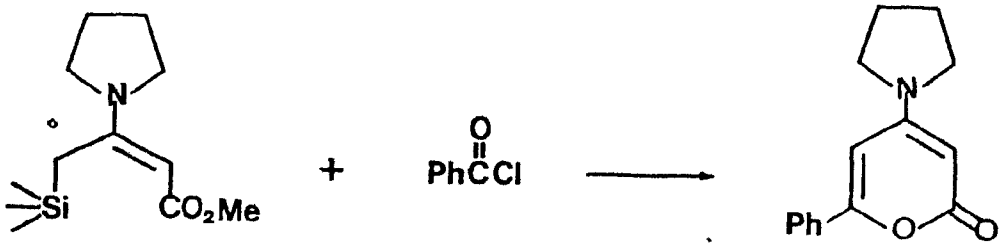




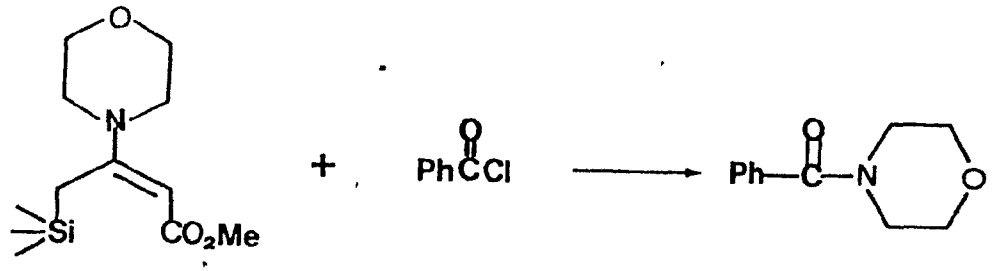
163

result was the same as the reaction of 156a with acetone. Even when dichloroethane was used as the solvent, instead of methylene chloride, and the reaction mixture was refluxed overnight, no reaction between 156a and cyclohexanone was observed.

With more reactive electrophiles, such as benzoyl chloride, only 156a gave γ-reaction product 164, while 156b gave an N-substitution product, benzamide 165.

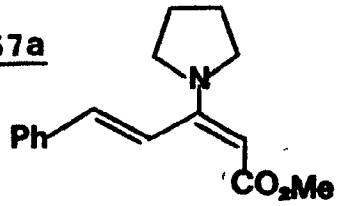
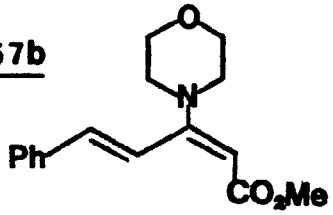
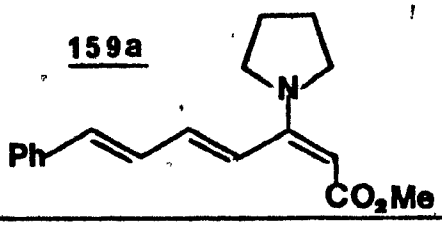
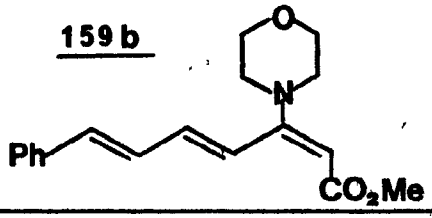
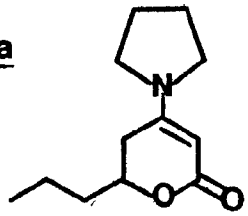
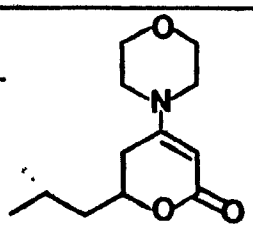
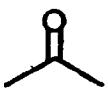
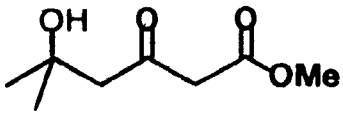


156 164

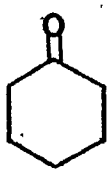
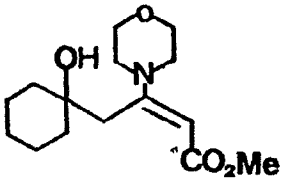
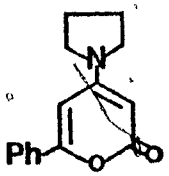
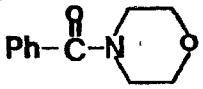


156 165

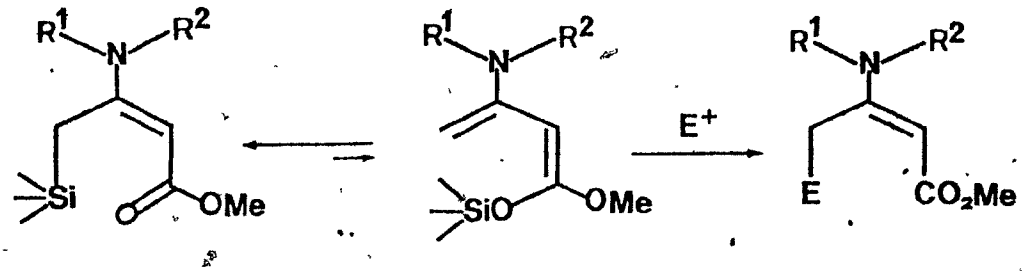
Table 3. the γ-Reactions of Compound 156 with Carbonyl Electrophile

Compd.	Electrophile	Product	Yield %
156a	PhCHO	157a 	68
156b	PhCHO	157b 	60
156a	Ph-CH=CH-CHO	159a 	81
156b	Ph-CH=CH-CHO	159b 	83
156a	CH3-CH2-CH2-CHO	160a 	53
156b	CH3-CH2-CH2-CHO	160b 	49
156b		162 	44

continued table

156b		163 	56
156a	PhCOCl	164 	44
156b	PhCOCl	165 	61

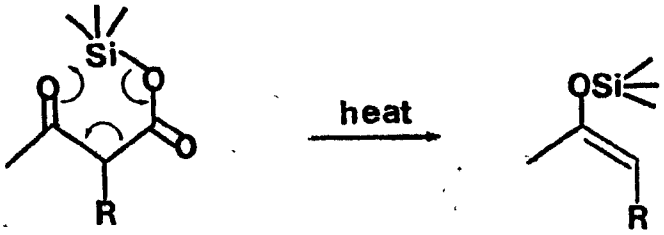
It remains to explain the regiochemistry observed in the reaction of 156 with electrophiles in Equation 2. One possibility is that there is a dynamic equilibrium between 156 and 155 and it is 155 which selectively reacts with electrophiles to give the γ-products.



156 155

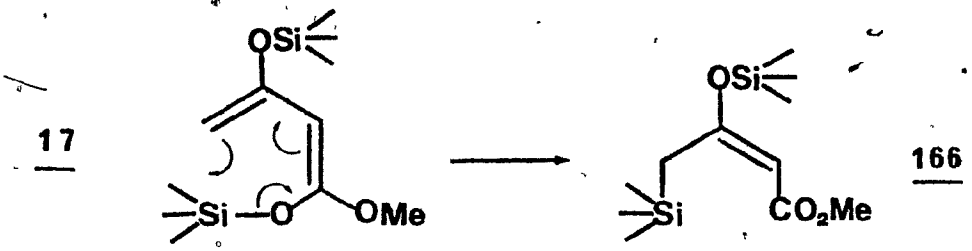
In fact, 1,5-migration of silyl groups is well known. Diketone silyl enol ethers can exhibit silyl transmission [88].

Trimethylsilyl β-keto-esters can undergo thermal silatropic rearrangement [89] to produce silyl enol ethers regiospecifically.

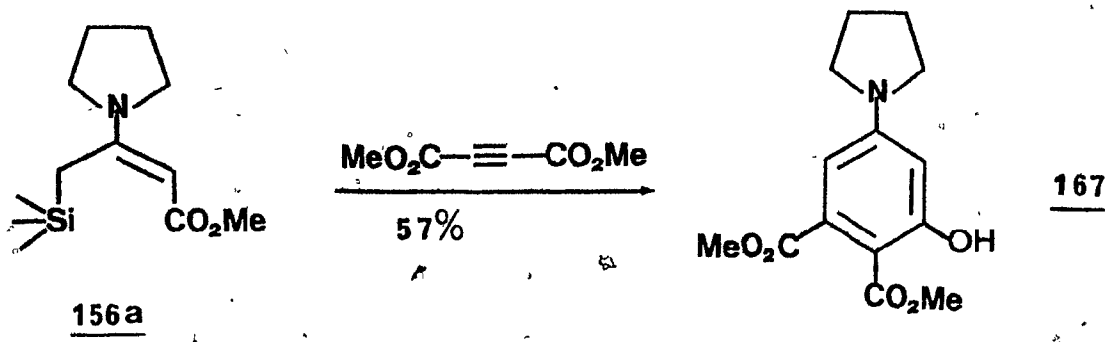


The 1,5-migration of silyl group from oxygen to carbon has also been reported [12]. It was found that at room temperature compound 17 gradually rearranges to its C-silyl isomer.

In our case, the E-geometry of compound 156 certainly renders this rearrangement process geometrically possible.



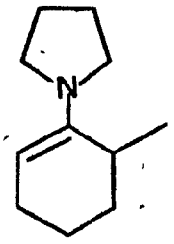
In support of this explanation, when a mixture of 156a and dimethyl acetylenedicarboxylate was heated in benzene for three days, the diene 155 was indeed trapped as the Diels-Alder adduct



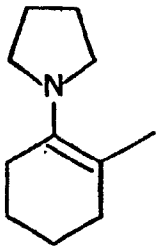
167 which was isolated in 57% yield as a crystalline compound. The ^{1}H NMR spectrum of 167 shows two aromatic protons (5.93,1H;

6.03,1H, AB quartet, J=3Hz), two methoxy groups (3.80,s,3H; 3.83,s,3H), a hydroxy group (11.03,s,1H, D_2O exchangeable, its down field chemical shift strongly indicates intramolecular hydrogen bonding), and also the corresponding pyrrolidino group (1.83-2.07,m,4H, 3.17-3.38,m,4H). The structure of 167 was also supported by IR and MS spectra.

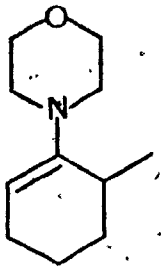
It still remains to explain the difference in reactivity of 156a and 156b. In 1965, Gurowitz and Joseph [90] found that the pyrrolidine enamine of 2-methylcyclohexanone 168 consisted predominantly of the trisubstituted isomer 168a, but the morpholine enamine of 2-methylcyclohexanone 169 was shown to be an almost 1:1 mixture of the trisubstituted isomer 169a and the tetrasubstituted isomer 169b by ^1H NMR spectroscopy.



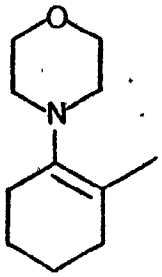
168a 90%



168b 10%



169a 52%

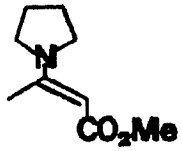
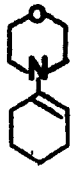
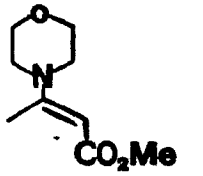
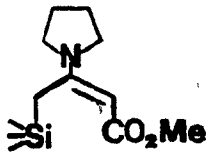
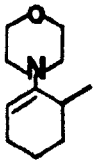
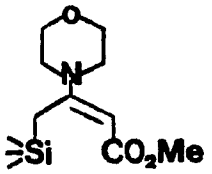


169b 48%

The authors proposed that the electron pair on nitrogen atom of pyrrolidine enamine is much more involved in the overlap with

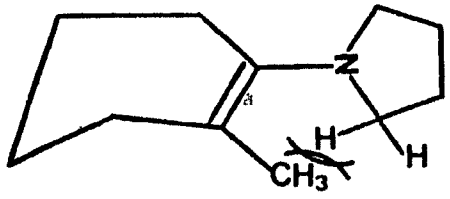
the π electrons of the double bond than that of morpholine enamine. Support for this argument was provided by the ^1H NMR spectra of these enamines. The chemical shift of the vinylic proton of the pyrrolidine enamine was at a higher field than that of the corresponding morpholine enamine by about 25 Hz. A similar difference between 156a and 156b was also observed by us (see table 4).

Table 4. The chemical shifts of vinylic protons of enamines (60 MHz)

Compd.	Hz	Compd.	Hz
	250		264
	273		288
	251		268
	276		284

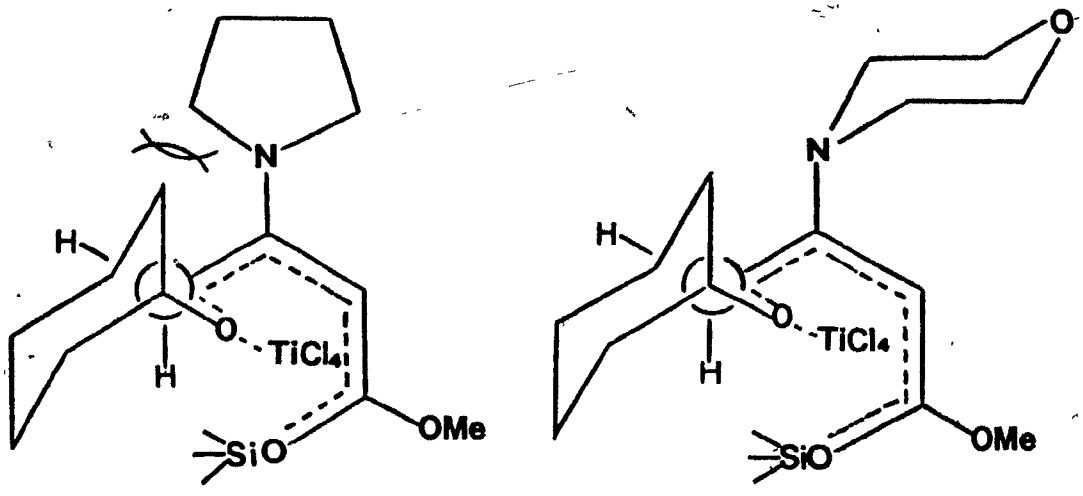
It is obvious that the more overlap between the electron pair on the nitrogen atom and the double bond, the more severe is the steric interaction between the methyl group and the methylene

group adjacent to the nitrogen atom in the tetrasubstituted isomers. That is why 169b is more favored than 168b.



168b

The different reactivity between 156a and 156b may also be due to a similar steric effect. It is well known that ketones are less reactive than aldehydes partly because the carbonyl group in ketone is more hindered than an aldehyde. In the two transition states I and II (scheme 2.1), the steric interference between the methylene group adjacent to nitrogen atom and the incoming electrophlic group is greater in I than in II. This may be the reason why 156b reacted with ketones but 156a could not under the same conditions.



a **b**

scheme 2.1

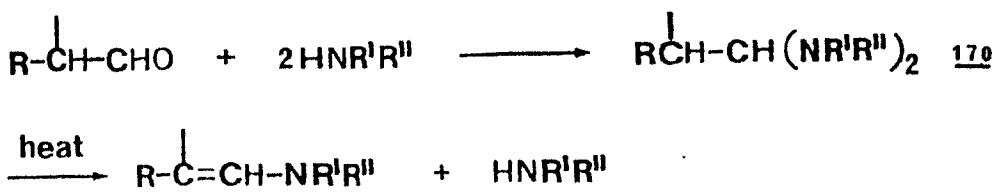
Because the electron pair on the nitrogen atom of morpholine enamine has less overlap with the double bond than that of pyrrolidine enamine, the electron density on the nitrogen atom in 156b will be greater than in 156a. It is not surprising, therefore, that 156a reacts with benzoyl chloride at the γ-position, but 156b reacts at the nitrogen position.

CHAPTER III. CYCLOAROMATIZATION REACTIONS OF ENAMINES

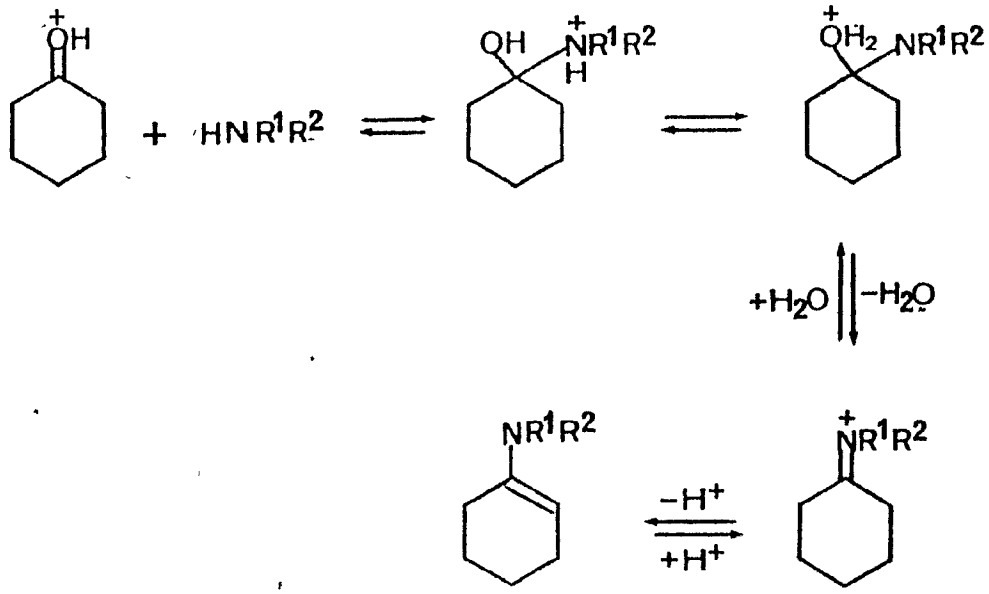
1. Preparation of enamines

The formation of enamines generally involves the condensation of aldehydes and ketones with secondary amines. With primary amines the reaction normally gives imines.

Mannich and Davidson [39] discovered that the reaction of secondary amines with aldehydes in the presence of potassium carbonate and at a temperature near 0 °C gave enamines. The reactions often involve the formation of an intermediate called aminal 170 which then decomposes to the enamine during distillation.



The intermediacy of an aminal in the formation of enamines



scheme 3.1

from ketones and secondary amines is not usually proposed. A general mechanism for the acid-catalyzed reaction has been offered [92] (scheme 3.1).

Usually the water generated by the reaction is removed from the reaction mixture by means of a water separator, or, as an alternative, it can be removed by passing the condensate through a drying agent such as molecular sieves.

Enamines can also be formed without an acid catalyst, but the rate of reaction is relatively slow. For some sterically hindered ketones, the enamine formation is very slow even when an acid catalyst is used. For example, Stork prepared the morpholine enamine of 4-heptanone using the water separator method; the reaction took 250 hrs and gave a 65% yield [93]. A versatile synthetic methodology was developed by White and Weingarter [94] using titanium tetrachloride. They found that a stoichiometric mixture of titanium tetrachloride, secondary amine and ketone produced the enamine directly and rapidly. The yields ranged from

$$2RCH_2CR^{I} + 6HNR^{II}_2 + TiCl_4 \longrightarrow 2RCH{=}C(NR^{II}_2)R^{I} + 4R^{II}NH_2Cl + TiO_2$$

55% for the mixture of enamines formed from morpholine and methylisopropyl ketone to 94% for the enamine formed from dimethylamine and methyl t-butyl ketone. The hindered ketone 2,5-dimethylcyclopentanone could be converted to an enamine, but the more hindered ketone, 2,6-di-t-butylcyclohexanone, was inert. The authors attributed the effectiveness of titanium tetrachloride in

this reaction to its ability to scavenge water and polarize the carbonyl bond.

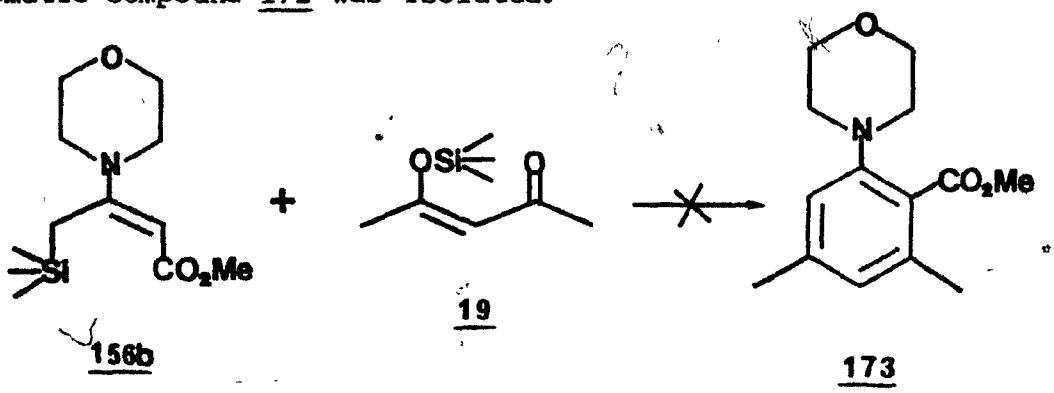
In our case, Mannich's procedure was employed to prepare the morpholine enamine of butyraldehyde. The enamines derived from acetoacetate, cyclopentanone and cyclohexanone were synthesized by the water separator procedure, with p-toluenesulfonic acid as the catalyst. All the acyclic ketone enamines as well as the enamines derived from cycloalkanones with ring size larger than 7, were prepared by the titanium tetrachloride method.

2. Cycloaromatization reactions of enamines

As we have mentioned in the introduction of this thesis, our initial strategy was to synthesize compound 155 and condense it with β-dielectrophiles to synthesize aniline derivatives. Although 155 has not been obtained directly from the silylation of methyl 3-dialkylaminocrotonate, compound 156 can be considered, in fact, as an equivalent of 155, because we have evidence that 156 exists in a dynamic equilibrium of 156 $\rightleftharpoons$ 155.

We examined, therefore, the reaction of 156 with several β-dielectrophiles. The first β-dielectrophile used by us was 4-trimethylsiloxy-3-penten-2-one 19. The reaction was carried out under similar conditions to the cycloaromatization reactions of 17 [10] with titanium tetrachloride as catalyst and CH_2Cl_2 as solvent. The reaction mixture was stirred for 3 hrs at -78°C then overnight at room temperature. It was poured into a solution of sodium bicarbonate with vigorous stirring, and extracted with ether. The extract was then concentrated to give a yellow oil which was then purified by flash chromatography. Indeed an

aromatic compound 172 was isolated.



156b 19 173

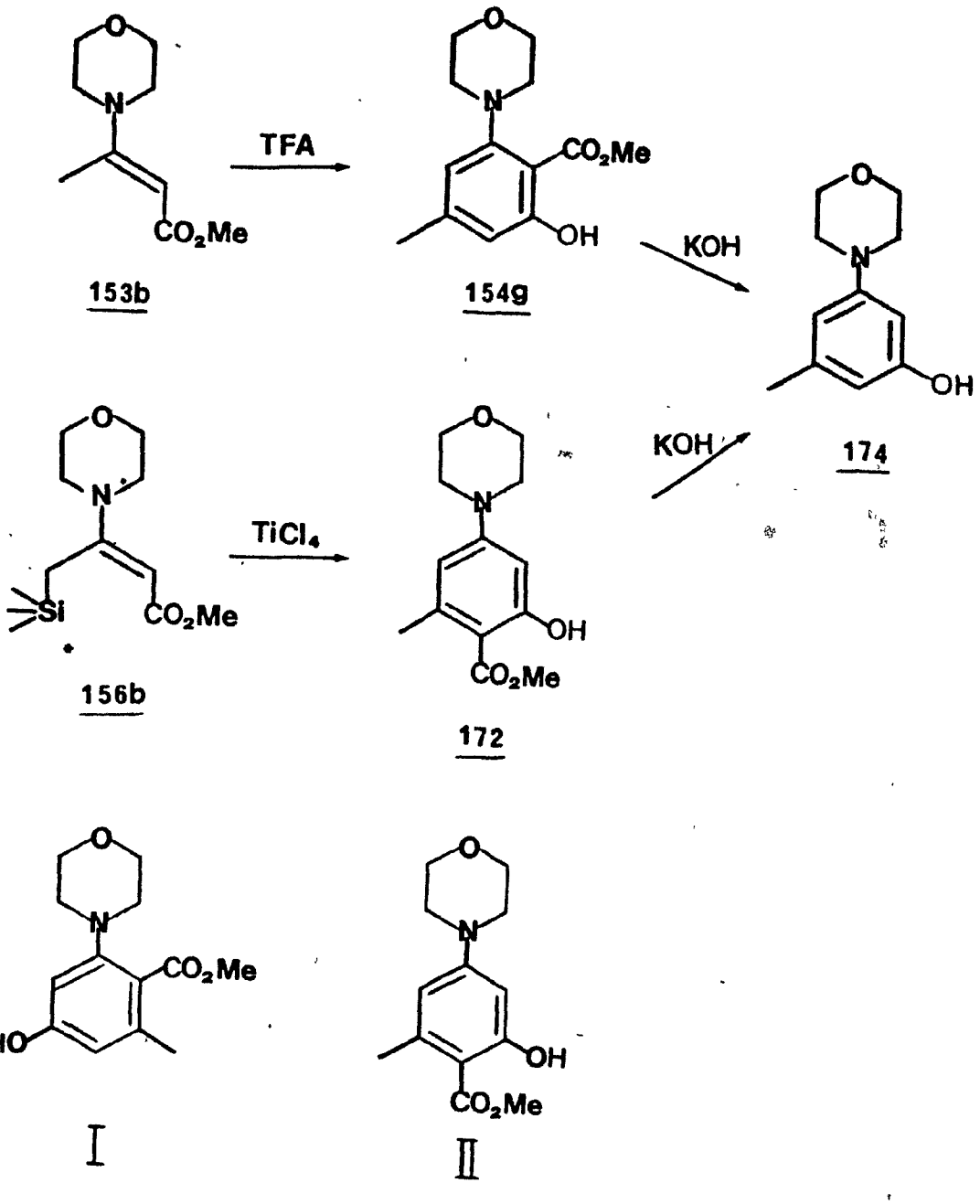
The ^1H NMR of 172 shows two aromatic protons (6.20ppm, s, 2H), one methoxy group (3.90,s,3H), one methyl group (2.53,s,3H), a hydroxy group (11.7,s,1H, D_2O exchangeble), and a morpholino group. It is definitely not the desired product 173, because in the expected ^1H NMR of 173, there should be two methyl groups and no hydroxy group. Besides, the molecular weight of 173 should be 249 and the molecular weight found for the product 172 is 251 according to mass spectrometry.

Obviously 172 was derived from the self-condensation reaction of 156b. When 156b alone was treated under the same conditions, 172 was obtained in 49% yield.

As we have mentioned previously, compound 153 can undergo self-condensation reaction to give the aniline 154 under acidic conditions [82]. But 172 was not the same as 154 because the ^1H NMR spectrum of 172 was quite different from that of 154g reported by Bohme.

Hydrolysis and decarboxylation of 172 gave 174 (scheme 3.2). We repeated Bohme's reaction and obtained 154g. It was found that the decarboxylation product of 154g was also 174. From these experiments compound 172 was deduced to have two possible

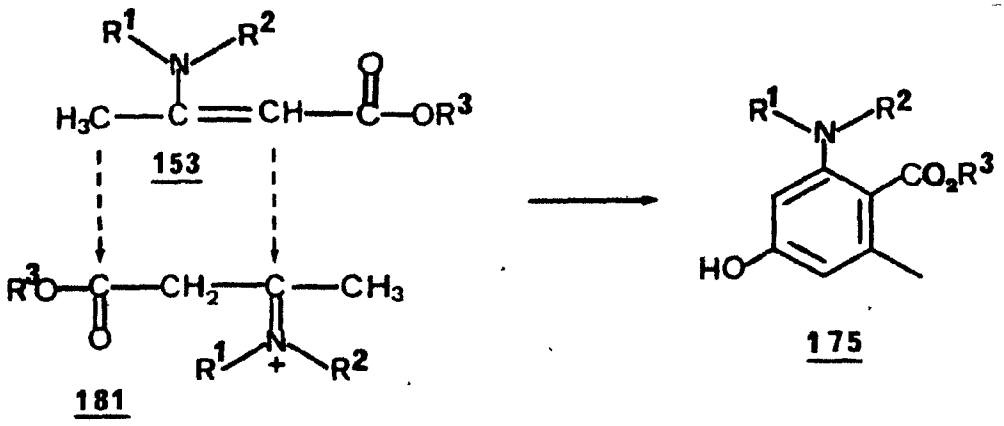
structures i.e. I and II. Since the chemical shift of the hydroxy group in 172 is 11.7 ppm, which strongly suggests the existence of the intramolecular bonding, the hydroxy group must be ortho to the ester group. Therefore, we finally assigned 172 to have the structure II.



scheme 3.2

The structure of 156 is almost the same as 153 except for the terminal trimethylsilyl group. Therefore it was not surprising to us that 156 can undergo a self-condensation reaction to give the aromatic product. But the interesting point is that 156 gave a different product. This means that the self-condensation of 156 must follow a different pathway.

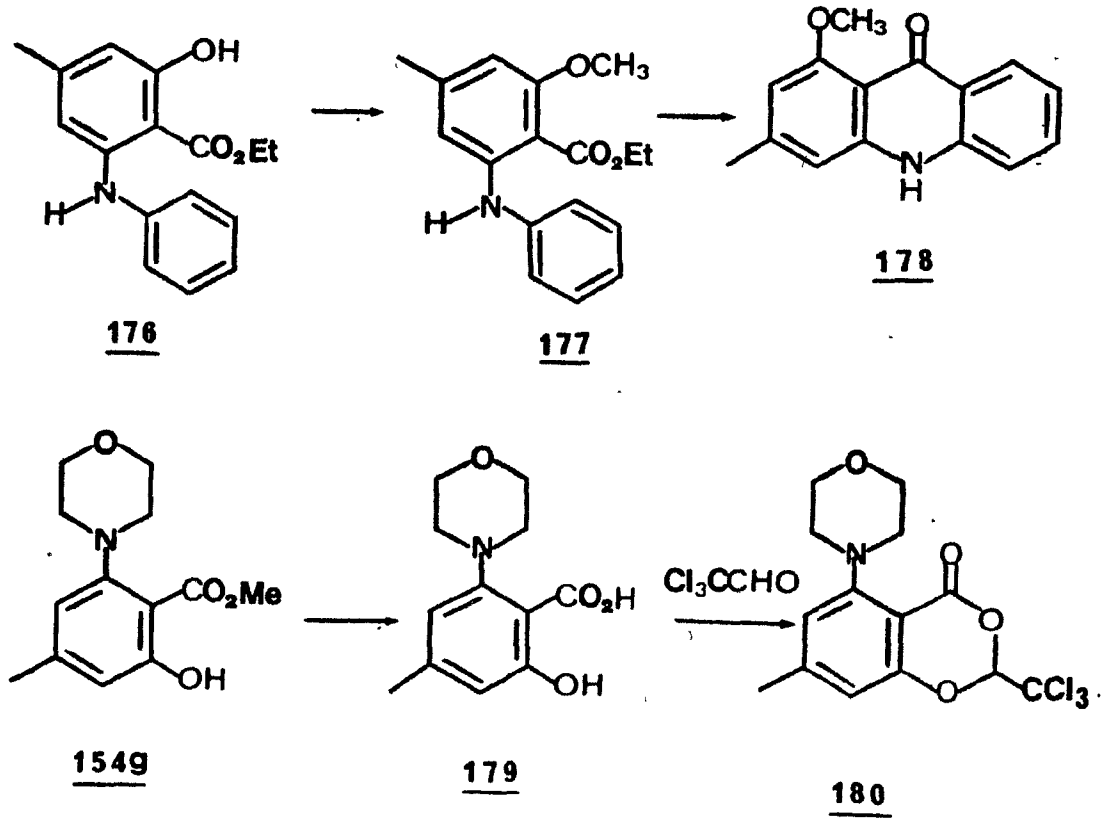
Bohme et al reported in their paper [82] that when they first obtained the self-condensation products, they assigned them as 175 because they thought that the iminium group should be more reactive than the ester group in terms of electrophilic reactivity (scheme 3.3). Anyhow, it was difficult to account for the large



scheme 3.3

chemical shift of the hydroxy proton. More than ten compounds were synthesized by different combination of R^1,R^2 and R^3 groups, and the chemical shifts of hydroxy groups for all the products were above 10 ppm.

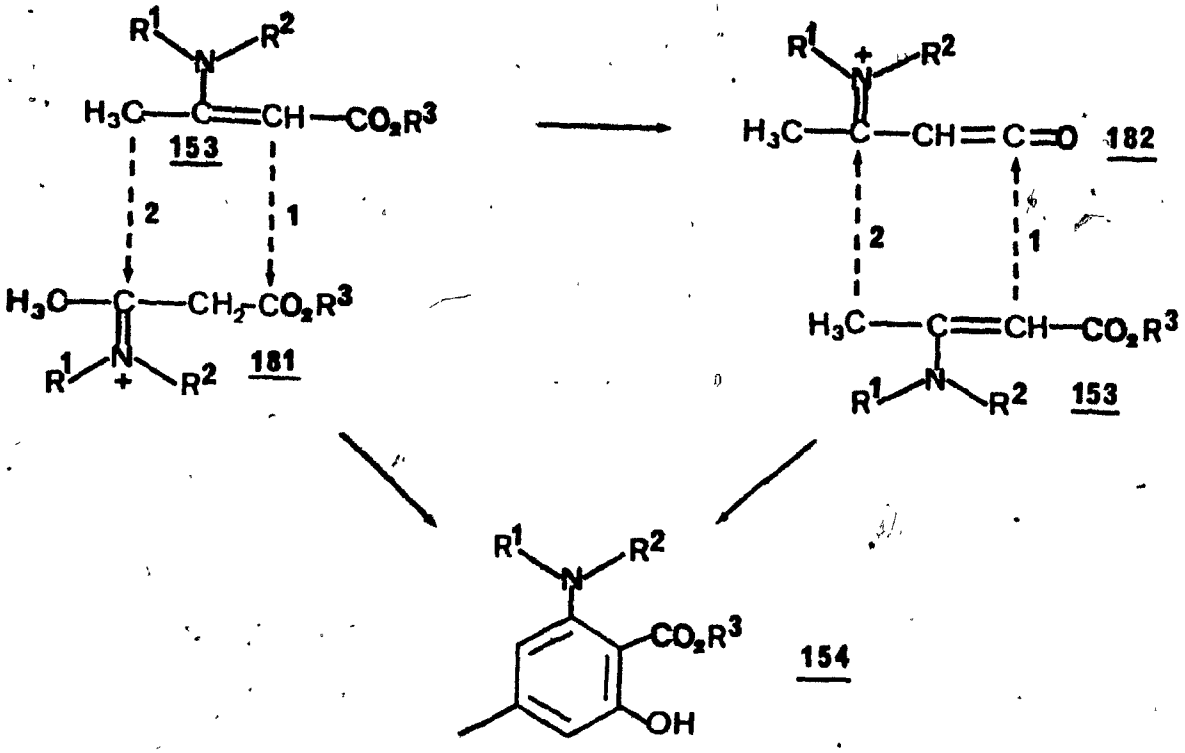
In order to make sure that the structural assignment was correct, compound 176 was prepared by them. It was then induced to undergo intramolecular cyclization leading to 178 (scheme 3.4). This established that the ester group must be ortho to the amino



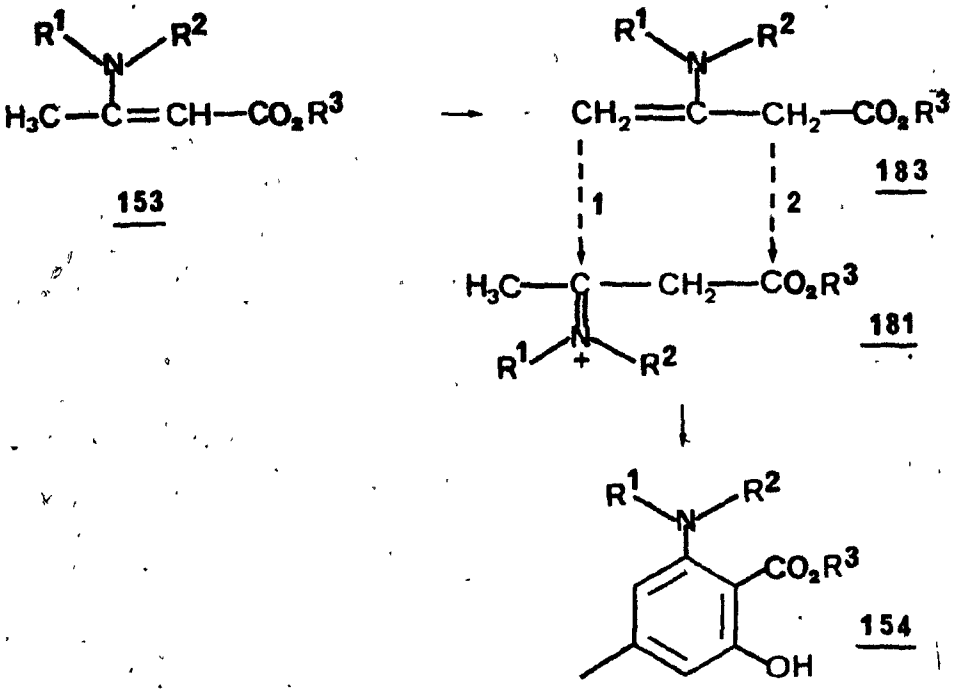
scheme 3.4

group. Compound 179, which was obtained from the hydrolysis of 154g, was reacted with trichloroacetaldehyde to give 180. This confirmed that the hydroxy group must be ortho to the ester group in 154g. By noting the similarity in ^1H NMR spectra of all their self-condensation products, Bohme assigned their structures to be 154.

With the structure firmly established, they proposed two possible pathways which will lead to the observed regiochemistry (scheme 3.5). In the first pathway, 153 was postulated to be in equilibrium with 181 under the acid catalysed conditions. This was followed by an unspecified 3C+3C cyclization to give the observed product. In the second pathway, 153 was assumed to have undergone elimination to give the iminium ketene 182. Again, an unspecified



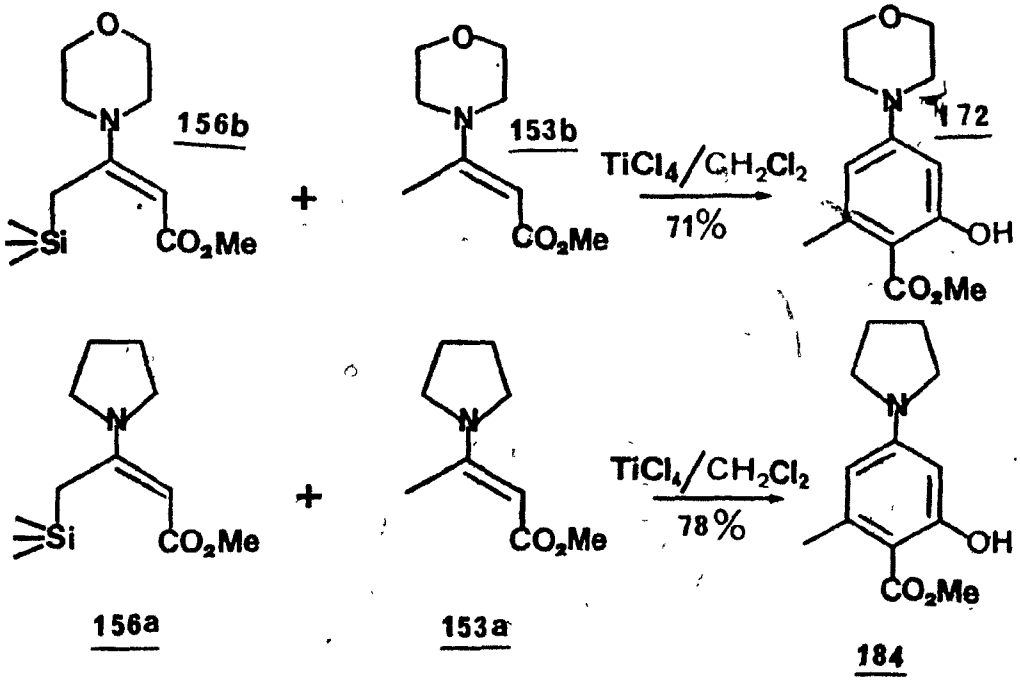
scheme 3.5



scheme 3.6

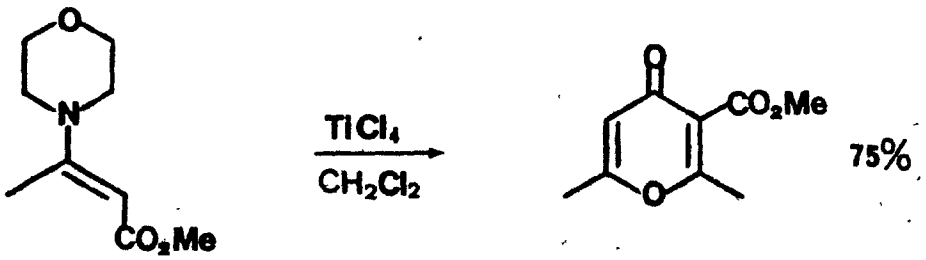
3C+3C cyclization, according to scheme 3.5 gave the observed product. In their paper they did not point out which pathway was more favored. It seems to us that they postulated these two pathways only to account for the regiochemistry of the reactions. They did not present evidence to rule out the possibility that 153 may rearrange to 183 first, and then attack on the iminium carbon of 181 as the first step of the condensation reaction (see scheme 3.6).

In order to understand further the self-condensation reaction both of 156 and 153, 156b was allowed to react with 1 equivalent of 153b in the presence of titanium tetrachloride. The mixture was stirred for 3 hrs at -78°C then overnight at room temperature, followed by the usual workup. The same compound 172, which was obtained from the self-condensation of 156b, was isolated in 71% yield. A similar reaction between 156a and 153a gave 184 in 78% yield [95].



scheme 3.7

Certainly, 172 or 184 are not derived solely from the self-condensation of 156b or 156a respectively. If that were the case, the yield could not be higher than 50%. One possibility is that, under these conditions, both 156 and 153 can undergo self-

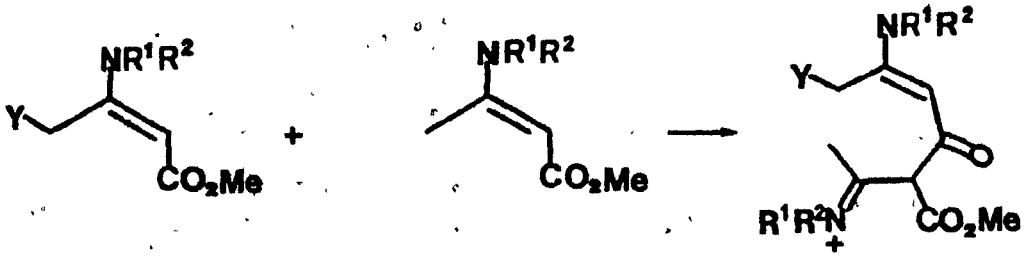


153b 185

condensation and give the same product. Alternatively, 172 or 184 are formed from the cross-condensation between 156 and 153. To test this, 153b alone was treated under identical conditions and we found that the result was not 172 but the pyrone 185. The yield of 185 was 75%. The structure of 185 was deduced by spectroscopic analysis. The ^1H NMR spectrum of 185 shows two methyl singlets at about 2 ppm and one methoxy at 3.90 ppm. There is also a vinyl proton at 6.13 ppm. There are two carbonyl absorption bands in the IR spectrum and its molecular weight is 182, given by MS.

It is clear, therefore, that 172 and 184 are indeed formed from cross-condensation. To facilitate subsequent discussion, we then proposed a working hypothesis to account for the cycloaromatization reactions observed in our case as well as in Bohme's case (scheme 3.8).

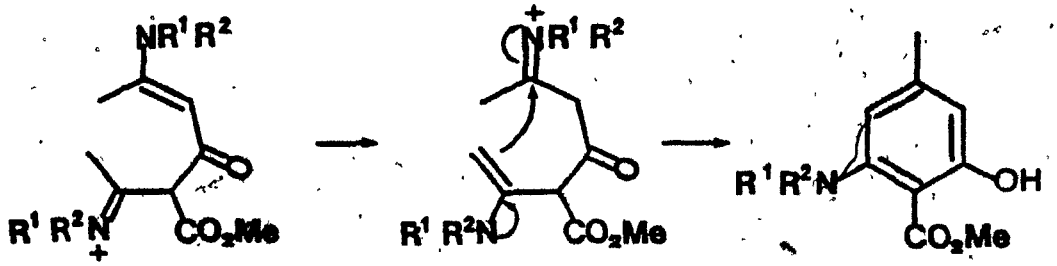
The first step (equation 1) is the condensation of the enamine with the carboxyl group of another component to give the intermediate 186. In the absence of further reaction, 186



(1)

186

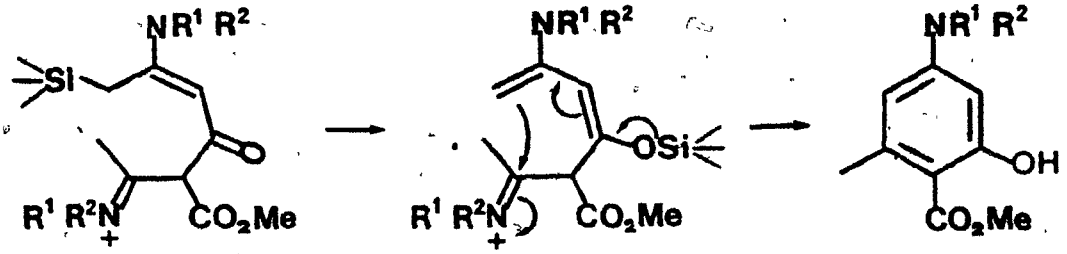
when Y=H (Bohme's case)



(2)

187 154

when $Y=Me_3Si$ (our case)

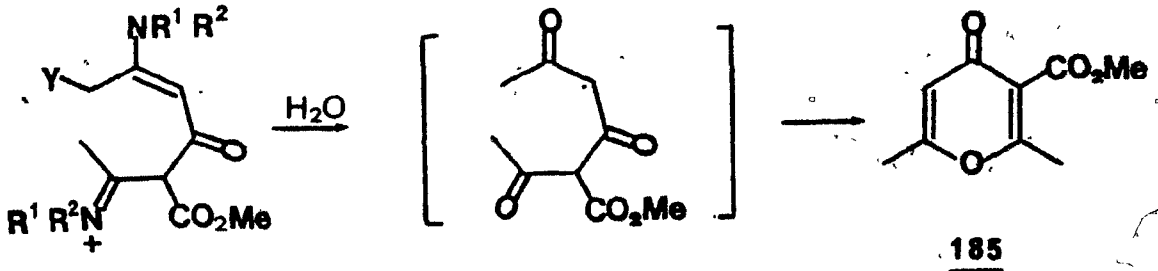


(3)

188

scheme 3.8

hydrolyses on aqueous work-up to give the pyrone 185.



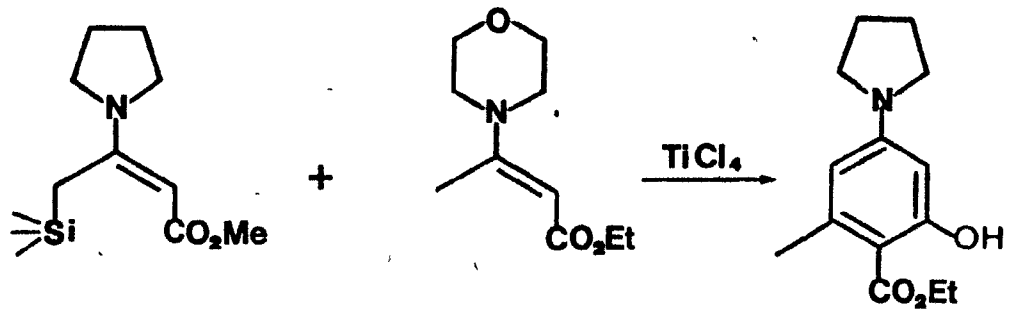
186 185

In the case of Y=H (equation 2), TFA effects the isomerization of 186 to the deconjugated enamine 187 which gives 154 by an intramolecular condensation in a 3C+3C combination.

When $Y=Me_3Si$ (equation 3), a 1,5-silyl shift causes the formation of 188 which leads to 172 or 184 by way of an intramolecular condensation in a 4C+2C combination.

The reaction of 156b with 153b was repeated. This time we took half of the reaction mixture out of the reaction flask after 3 hrs at -78°C. After the usual work-up procedure, we obtained a 1:1 mixture of 185 and 172. The other half of the reaction mixture was allowed to be stirred overnight at room temperature and then worked up. The product was found to be completely 172 with very little 185. This experiment supports the suggestion that 186 is indeed the intermediate in the cross condensation reaction. Furthermore, the first step in scheme 3.8 is faster than the second step.

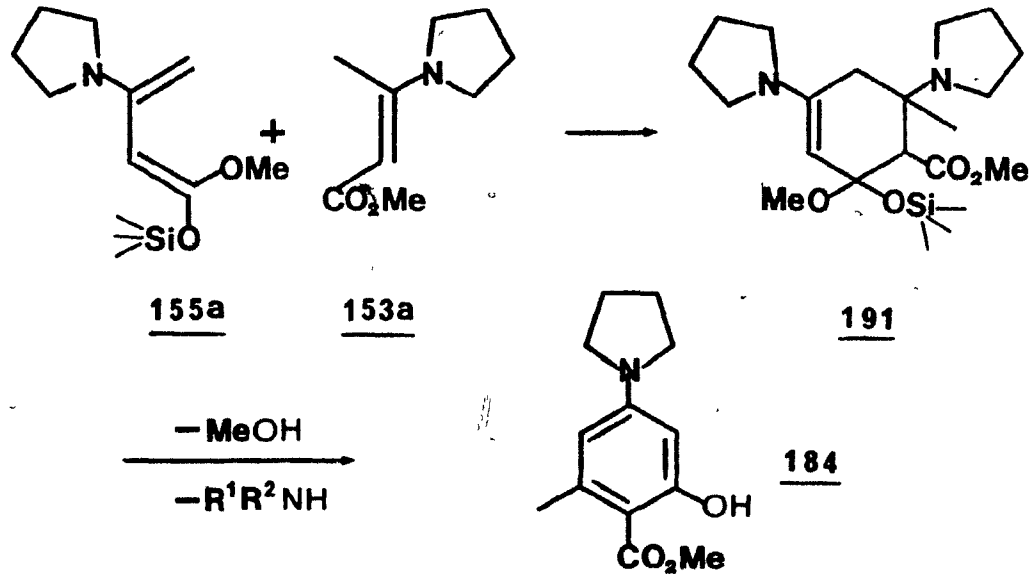
According to the mechanism postulated in scheme 3.8, in the cross condensation between 156 and 153, 156 acts as a four carbon component and 153 acts as a two carbon component. In other words, in the first step, the α-position of 153 selectively attacks the carboxyl group of 156, and in the next step the γ-position of 156 attacks the iminium carbon of 153. To verify this, we allowed methyl 4-trimethylsilyl-3-pyrrolidino-crotonate 156a to condense with ethyl 3-morpholino-crotonate 189 under $TiCl_4$. If our postulation is correct, the final product will contain pyrrolidino and ethyl groups. It was found to be the case. The product of the reaction was 190. Besides two aromatic protons (5.90,s,2H), a methyl singlet (2.50,s,3H) and the OH group (11.90,s,1H), the ^1H



156a 189 190

NMR of 190 shows a triplet at 1.36 ppm (3H, J=7Hz) and a quartet at 4.33 ppm (2H, J=7Hz), which are related to the ethyl ester group; two sets of multiple peaks (1.83-2.13, 4H, and 3.13-3.43, 4H) indicate the pyrrolidino group. The structure of 190 was also supported by the IR and MS spectra.

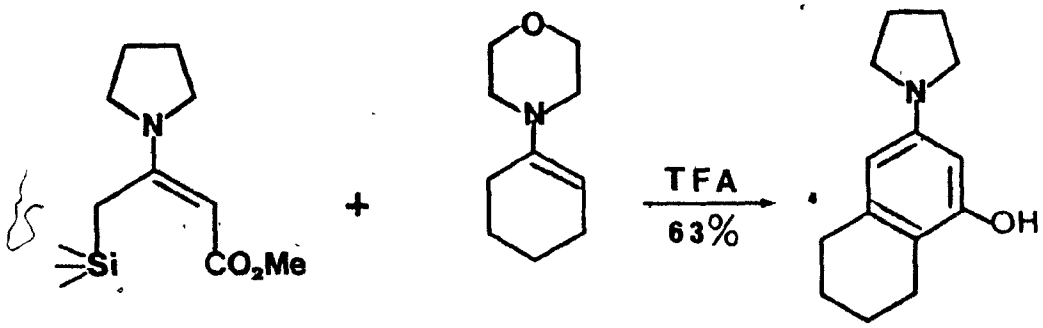
One might argue that another possible pathway for the cross condensation is the Diels-Alder reaction. For example, Diels-Alder reaction between 156a, (by way of 155a) and 153a can lead to 184 if the reaction proceeds with the regiochemistry indicated. To check this possibility, a 1:1 mixture of 156a and 153a was



scheme 3.9

refluxed in benzene for 3 days. No change was detected by ^1H NMR spectroscopy showing that it was still a 1:1 mixture of 156a and 153a. Therefore, the possibility of a Diels-Alder reaction is ruled out at least under thermal conditions.

At this stage, the following conclusion appears to be resonable: the reaction between 156 and 153 is a stepwise 4C+2C cycloaddition with 156 acting as the four carbon component and 153 as the two carbon component. As we have discussed in the introduction part of this thesis, in most of the cycloaddition reactions of enamines, the enamines act as a two carbon component. One would expect, therefore, not only compound 153 but other enamines as well have the potential to undergo the same kind of cycloaromatization reaction with 156. We proceeded to examine this possibility.



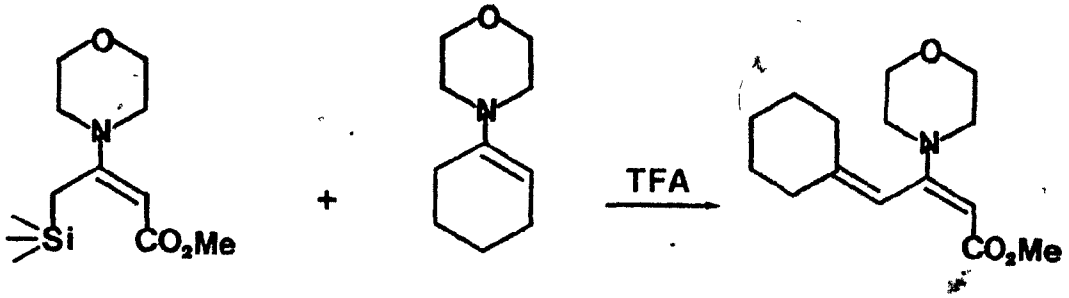
156a 102 192

A 1:1 mixture of 156a and the morpholine enamine of cyclohexanone plus two equivalents of trifluoroacetic acid was refluxed for two days in CH_2Cl_2. The reaction mixture, on workup, gave compound 192 in 63% yield. The ^1H NMR spectrum of 192 shows two aromatic protons (5.8ppm,d,J=2Hz,1H; 5.9ppm,d,J=2Hz,1H), a broad peak at 4.4ppm (-OH), a multiplet between 2.9-3.2 ppm

(4H,pyrrolidino), another multiplet between 2.34-2.8 ppm (4H,2 methylenes connected to the aromatic ring), and a broad peak between 1.6-1.85 ppm (8H). The structure of 192 is supported by IR and MS as well (3400cm^{-1} in IR and strong M^+ peak in MS).

Enamines derived from cyclopentanone, cycloheptanone, and cyclooctanone were also allowed to react with 156a under the same conditions except that the reaction mixtures were refluxed in dichloroethane instead of in dichloromethane. The yields of the corresponding cyclization products were found to be between 59%-64% (see table 1).

On the other hand, when the amino group in the silylcrotonate component is morpholine 156b, the reaction with 102 under identical conditions gave instead the γ-reaction product 199. The structure of 199 was assigned on the basis of spectroscopic analysis. The ^{1}H NMR spectrum of 199 shows two vinyl protons, both are singlets, one at 4.83, the other at 5.83 ppm; one methoxy group (3.65ppm,s,3H), 5 methylenes between 1.57 to 2.40 ppm, and also the corresponding morpholino group. The structure of 199 is supported by IR and MS as well. Since we have previousely shown that 156b undergoes γ-reaction more readily than 156a, and 102 can be easily protonated to give the corresponding immonium cation in



156b 102 199

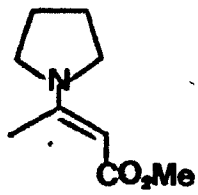
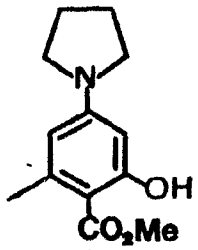
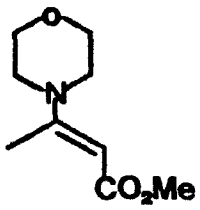
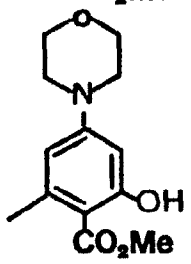
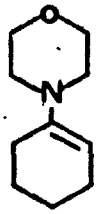
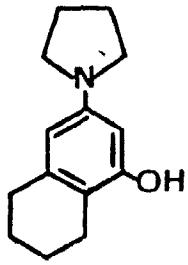
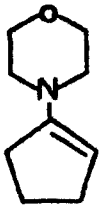
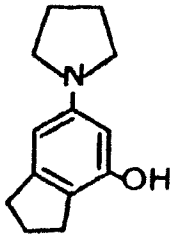
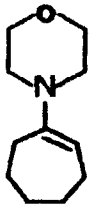
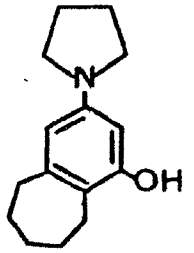
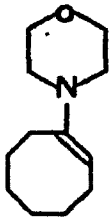
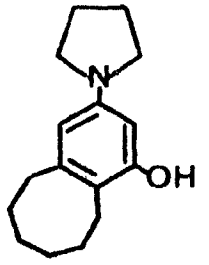
the presence of TFA, the observed γ-reaction between 156b and 102 is understandable.

There remains the 3C+3C self-condensation observed in Bohme's case. If the postulated mechanism in scheme 3.8 is correct, one would expect the same pathway to proceed between 156 and an enamine of acyclic ketones.

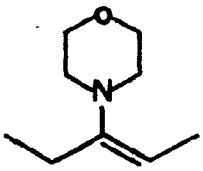
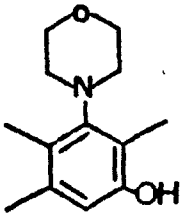
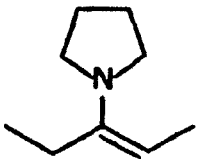
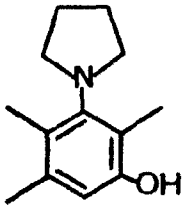
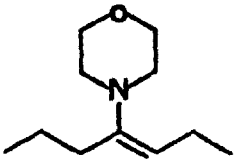
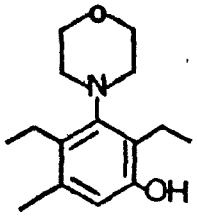
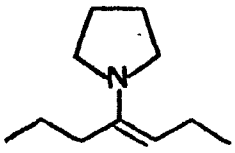
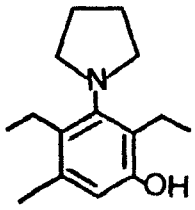
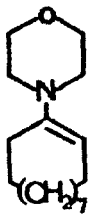
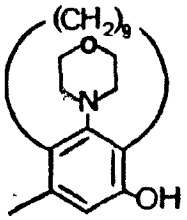
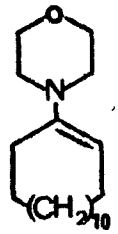
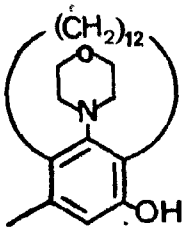
The reactions between 156a and enamines derived from acyclic ketones were therefore next examined.

The morpholine enamine of 3-pentanone was reacted with 156a in the presence of TFA. The reaction mixture was refluxed for 2 days in dichloroethane and followed by the usual workup. Compound 200 was isolated in about 30% yield. The ^1H NMR spectrum of 200 showed one aromatic proton (6.4ppm,s), a peak at 4.8 ppm assigned to the OH group, and a strong singlet at 2.23 ppm which amounted to 9 protons by integration corresponding to the three methyl groups. The presence of the morpholino group was also confirmed. There is a strong and broad absorption at 3300cm^{-1} in the IR for the -OH function and a strong [M+] ion by MS. The yield of 200 was low. The main reason for the low yield is the self-condensation of 156a. In order to improve the yield of the cross condensation product, two equivalents of 201 were used and the yield was raised to 41%. The same reaction was also carried out by using titanium tetrachloride as the catalyst instead of TFA; with two equivalents of 201, the yield of 200 was 38%. It seems that titanium tetrachloride does not show too much difference from TFA in terms of its efficacy.

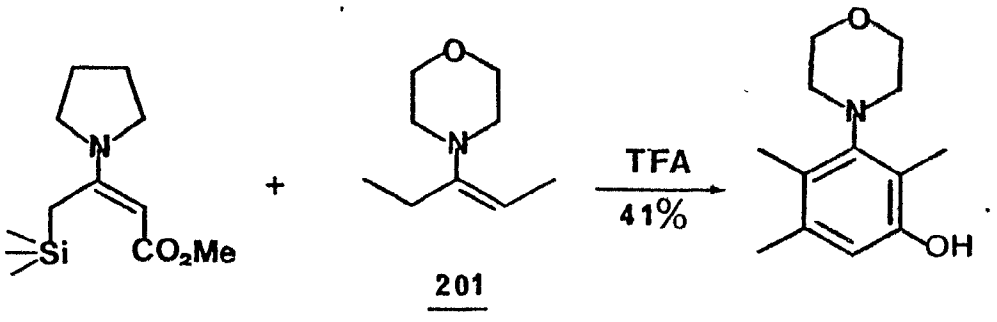
Table 1. the Cycloaromatization Reactions of 156 with enamines

compound 156	enamine	reaction conditions	product	isolated yield %
a		$TiCl_4/CH_2Cl_2$		78
b		$TiCl_4/CH_2Cl_2$		71
a		TFA/CH_2Cl_2		63
a		$TFA/ClCH_2CH_2Cl$		64
a		$TFA/ClCH_2CH_2Cl$		59
a		$TFA/ClCH_2CH_2Cl$		67

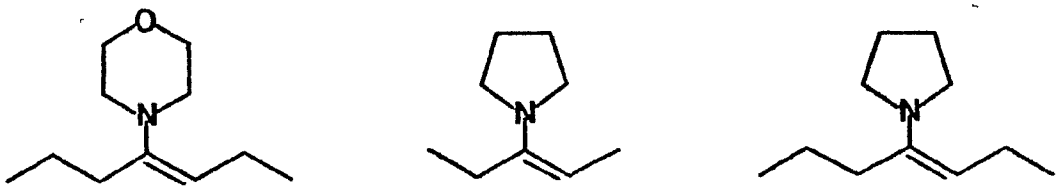
Continued table

a		TFA/CH_2Cl_2		41
a		TFA/CH_2Cl_2		42
a		TFA/CH_2Cl_2		37
a		TFA/CH_2Cl_2		36
a		TFA		51
a		TFA		25

Several similar reactions were carried out by reacting 156a with 202, 203, and 204 respectively in the presence of TFA. In all cases, the 3C+3C cyclization products were observed. The yields ranged from 36% for 207 to 42% for 205 (see Table 1).



156a 201 200

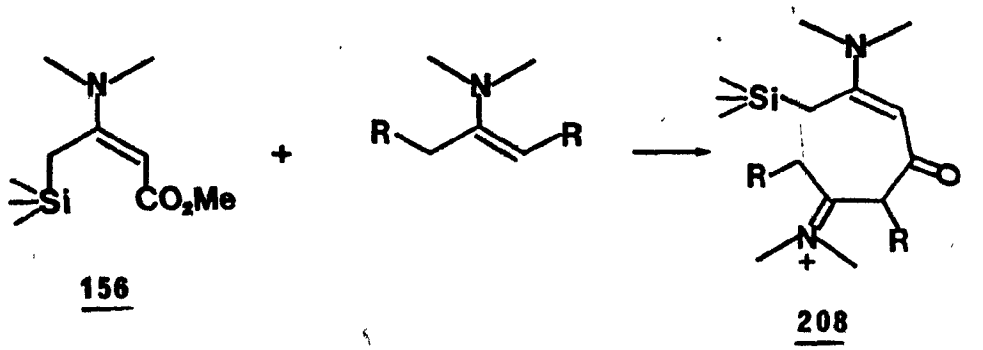


203 202 204

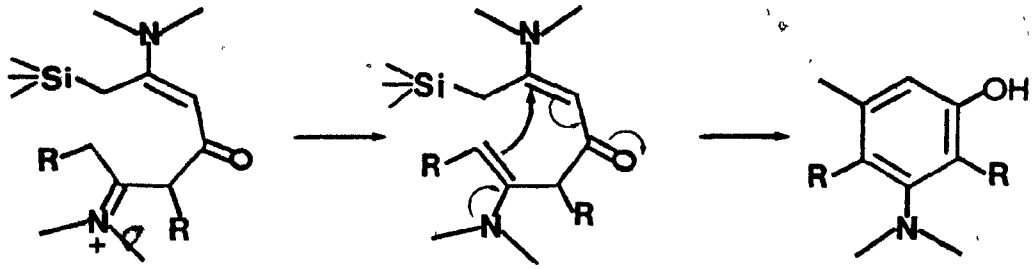
So far, only the enamines derived from symmetrical acyclic ketones have been used in reactions with 156a. This is because in the case of unsymmetrical ketones, a mixture of isomeric enamines is possible. The product of cycloaromatization reaction will also likely be a mixture of isomers which will be difficult to separate.

Now we can summarize that enamines derived from cyclic ketones favor 4C+2C annelation with the enamines acting as the 2C component, whereas enamines derived from acyclic ketones prefer a 3C+3C annelation. A mechanism in analogy to scheme 3.8, which is consistent with the above observation is presented in the

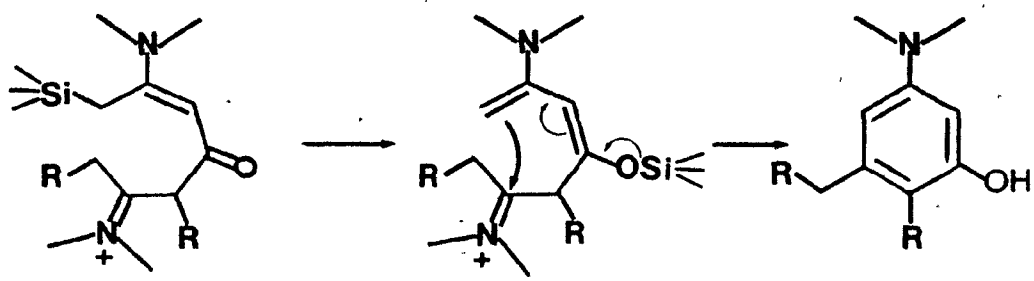
following scheme.



156 208



208 209



208 210

scheme 3.10

The first step is the condensation of the enamine with the carbonyl group of the ester in 156 to give the intermediate 208. Isomerization of 208 to 209 followed by an intramolecular Michael condensation lead to aromatization in a 3C+3C combination. The

silyl group is then protodesilylated under the reaction conditions [86]. For cyclic ketones (of 5-8 membered rings), the isomerization step dose not lead to aromatization due to the strain in forming the final meta-cyclophanes. Thus the isomerization of 208 to 210 by a 1,5 silyl shift occurs. This is followed by an intramolecular Mannich reaction in a 4C+2C combination giving the aromatic product.

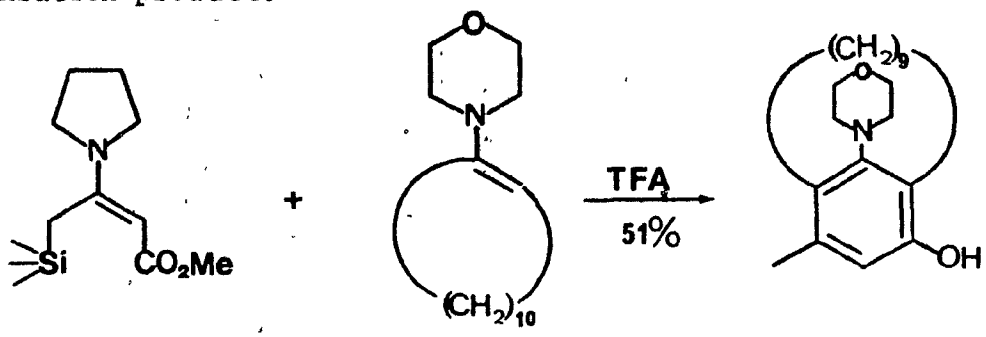
According to this mechanism, one would expect enamines derived from aldehydes to follow the 4C+2C pathway. We therefore tried the reaction of the morpholine enamine of butyraldehyde 112 with 156a in TFA. The reaction mixture was stirred overnight under N_2 in dichloromethane, diluted with ether and then washed with a saturated solution of sodium bicarbonate. After the solvent was removed, a black sticky oil was left. Its ^1H NMR spectrum showed no aromatic compound and nothing was isolated from column chromatography. Presumably 112 polymerized under the reaction conditions. Optiz and Mildenberger have reported that enamines derived from linear aldehydes and monosubstituted acetaldehydes could not be alkylated because of the self-condensation under the reaction conditions [42].

This reaction was repeated using titanium tetrachloride as catalyst instead of TFA. A brown oil was obtained which was then purified by flash column chromatography. Only the self-condensation product of 156a was isolated.

Considering the reactions between 156a and enamines derived from acyclic ketones, in principle, both 3C+3C and 4C+2C condensations should be possible. Since no 4C+2C cross-

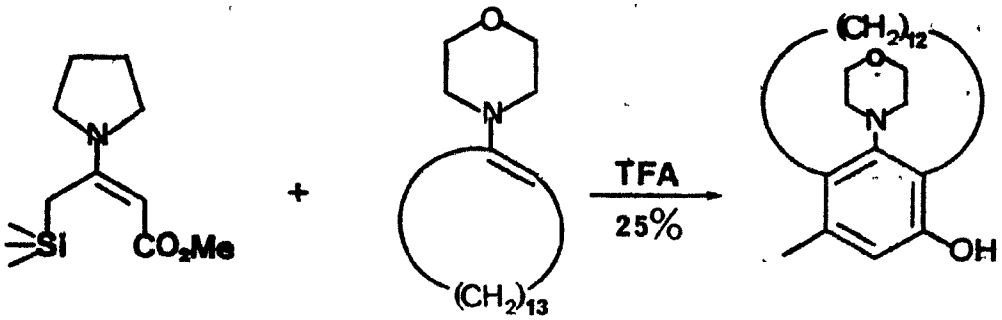
condensation product was observed, it seems that the 3C+3C pathway is more favored than the 4C+2C condensation.

The fact that reactions of enamines derived from cyclic ketones (5-8 membered rings) actually followed the 4C+2C pathway exclusively, is believed to be due to the strain in forming the final meta-cyclophanes. If this is the case, and a large enough cyclic ketone enamine is used in the reaction, one would expect the 3C+3C pathway to dominate again. To test this, the morpholine enamine of cyclododecanone 211 was synthesized and then reacted with 156a in the presence of TFA. The reaction mixture was heated for 3 days at 80°C, then diluted with ether, and washed with a sodium bicarbonate solution. The organic solution was dried with $MgSO_4$ and was concentrated by rotary evaporator to give a brown oil. It was purified by TLC mesh chromatography and compound 212 was isolated in 51% yield. Compound 212 is indeed the 3C+3C condensation product.



156a 211 212

The ^1H NMR spectrum of 212, like all other 3C+3C products, shows only one aromatic proton (s,6.52ppm,1H), and a -OH group (s,4.80,1H,D_2O exchangeble), a methyl peak (s,2.14,3H) plus the corresponding morpholino peaks and proton signals of the hydrocarbon chain.



156a 213 214

The reaction between 156a and 213, the morpholine enamine of cyclopentadecanone, gave 214 in 25% yield. This reaction has been repeated several times and no improvement in yield was achieved.

Compound 212 seems to be not very stable., It is slightly yellow even after two recrystalization from hexane. It gradually becomes red on standing in the air. This change is faster in chloroform solution. Compound 214 also turns red in chloroform but at a much slower rate than 212. Compound 214 is a colorless crystalline solid after recrystalzation. In the solid state it shows no color change on standing.

From the ^{1}H NMR spectra of 212 and 214, and also from the molecular model of these compounds, it is clear that these meta-cyclophanes possess interesting stereochemical properties. This will form the subject of investigation in the next chapter of the thesis.

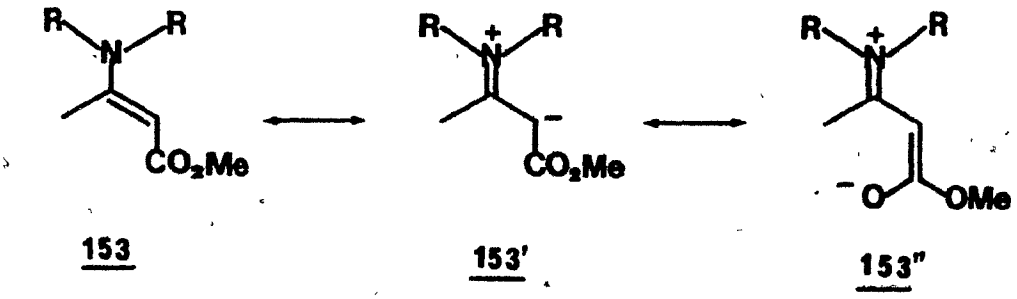
To return to the mechanism of the cycloaromatization reaction, although the only difference between 156 and 153 is the silyl group, they behave quite differently. Therefore, the silyl group of 156 must play an important role in the cycloaromatization reactions. This seems quite obvious in the 4C+2C reactions between

156 and cyclic ketone enamines. Following the attack of the ester group of 156 by the enamine, it is the 1,5-silyl shift that activates the terminal carbon of 156 in the subsquent intramolecular cyclization leading to the 4C+2C combination. However it seems not so clear for the 3C+3C reactions between 156 and enamines derived from acyclic ketones. The trimethylsilyl group appears not to have an important role according to the mechanism we propose in scheme 3.10. The silyl group was simply removed during the workup. Actually it is not the case. When compound 153a was allowed to react with 201 and 211, respectively, under the identical conditions as those used for 156a, we found that the only aromatic compound obtained was the self-condensation product of 153a. There was no product derived from cross-condensation. It seems clear that the silyl group does play an indispensable part even in the 3C+3C cycloaromatization reactions.

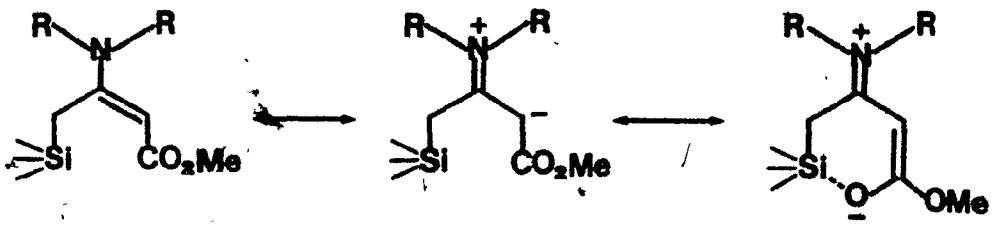
Further functions of the silyl group in our cross-condensation reactions are postulated as follows:

1, The silyl group discourage compound 156 from undergoing the self-condensation reaction thus increasing the possibility of cross-condensation by lowering the reactivity of its own enamine position to reduce the chance of its acting as the nucleophilic component. In compound 153 the interaction between nitrogen and the ester group can be expressed by the three resonance structures 153, 153', 153''. Any factor which enhances the contribution of 153'' will diminish the reactivity of the α-position towards electrophiles (scheme 3.11). In compound 156, the situation is similar but the negative charge at the oxygen atom in 156'' is

partially shared by the silicon atom therefore enhancing its contribution.



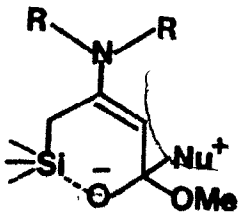
153 153' 153"



156 156' 156"

scheme 3.11

2, In the reaction between 153 and 156, the enamine in 153 exclusively attacks the ester carbonyl of 156 and no self-condensation has been detected. We have said that the enamine position in 153 is more reactive than that of 156, but this alone is insufficient. The ester carbonyl in 156 must also be more easily attacked than that in 153, otherwise, the self-condensation of 153 could not be avoided. The effect of the silyl group to



215

stabilize the tetrahedral intermediate 215 may account for the activation of the ester carbonyl in 156.

CHAPTER IV STEREOCHEMISTRY OF META-CYCLOPHANES

In 1848, Pasteur successfully separated two different types of sodium ammonium tartrate crystals. One type of crystal showed a mirror image relationship to the other. This first resolution of a racemic compound introduced to the chemical world a particularly important form of isomerism, viz., enantiomerism. Thirty years later, Le Bel and van't Hoff introduced the concept of tetrahedral carbon by pointing out the existence of optical isomers in compounds which have carbon atom bonded to four different substituents. Since then, tremendous progress has been made in the understanding of enantiomerism, which forms the basis of stereochemistry. It is now well established that those molecules, which are chiral,(those with asymmetric carbon atoms,as well as those without symmetry elements of reflection: S_n axes or plane) can in principle give rise to enantiomerism. In the previous chapter, we have prepared compounds 212 and 214, examination of the molecular models shows that the hydrocarbon chain and the morpholine group are located in different faces of the aromatic plane. Since the aromatic ring is further substituted by two different groups (-OH and $-CH_3$), compounds 212 and 214 meet the above definition of chirality, namely, there is no symmetry element of reflection in them. Thus both 212 and 214 exist as two enantiomers (Figure 1).

Such chiral meta-cyclophanes belong to a group in which the optical isomerism is caused by restricted rotation. A very important feature of this type of enantiomerism is the energy factor. The energy barrier of the rotation must be high enough to

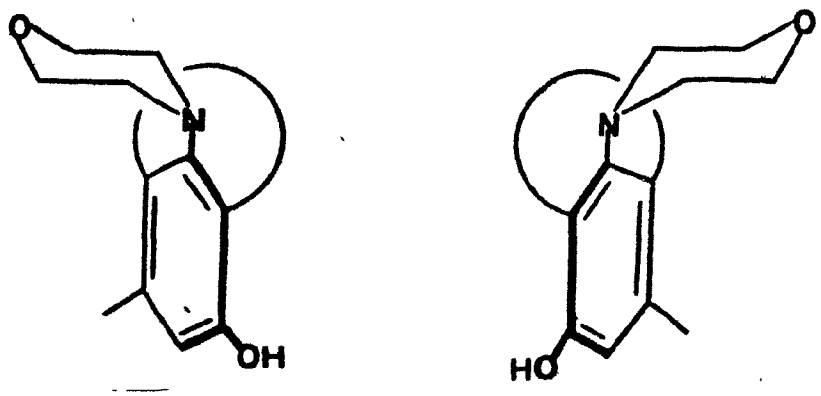
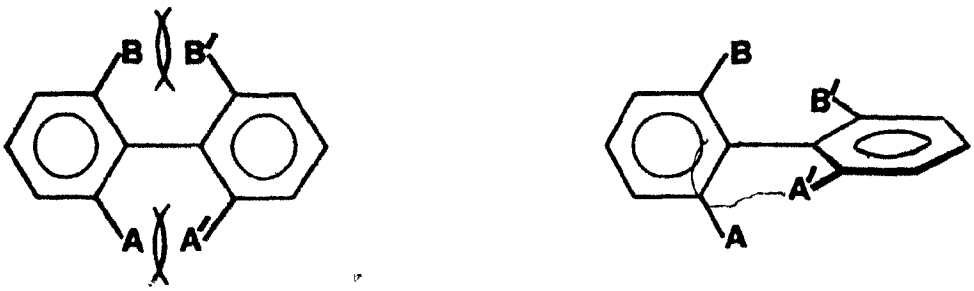


figure 1

permit enantiomers to be resolvable. Some well known examples of enantiomerism due to restricted rotation are the biphenyls. ortho-Disubstituted biphenyls have a preferred non-planar conformation (Figure 2) because of the steric interaction between the ortho



disfavored planar conformation

favored non-planar conformation

figure 2

groups. When A≠B and A'≠B' (in figure 2), there is no plane of symmetry in the molecule, enantiomers exist. The transition state of the interconversion of enantiomers involves a planar conformation (see figure 3). In the case described, there are two such planar transition states and the rotation takes place via the transition state I in which the unequal sized groups pass each other (this requires lower energy). The racemization of biphenyl

atropisomers depends on the size of the ortho-substituents. The

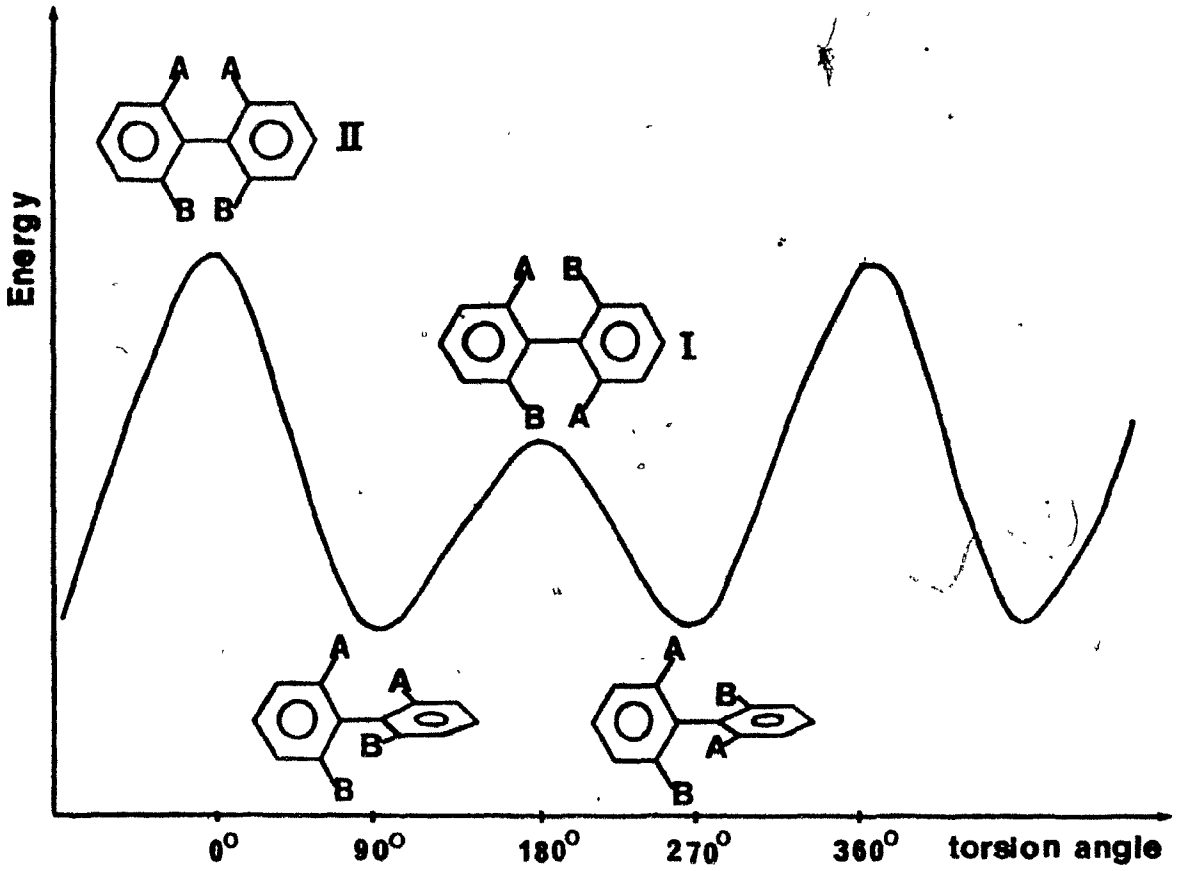
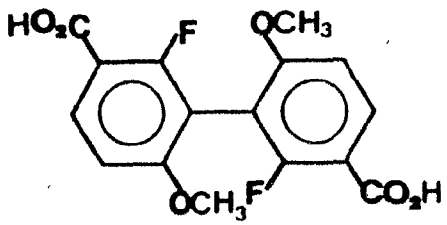


figure 3. Energy diagram for racemization of biphenyls

larger the substituents, the more difficult is the racemization. Methoxy and fluoro groups are both considered small, therefore compound 216 racemizes so fast that it cannot be resolved at room temperature. Compound 217 is resolvable but easily racemized on heating whereas compound 218 shows optical stability.



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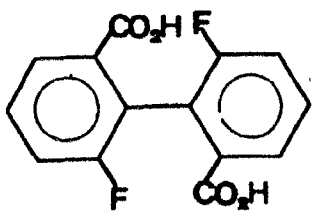

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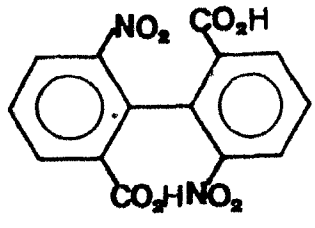
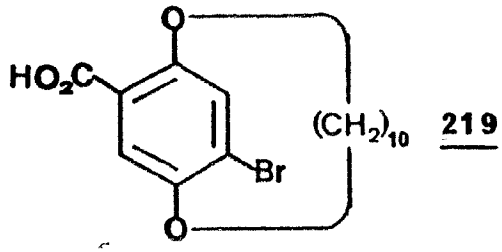


218

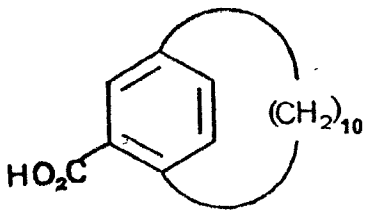
The stereochemistry of para-cyclophanes has been well investigated since the first successfull resolution of compound 219 by Lüttringhaus and his coworkers in 1941 [96]. Compound 219



219

was treated with strychnine to give a crystalline salt which was separated by recrystallization. Acidic decomposition of one diastereomeric salt gave an optically active acid, mp 154°C, $[\alpha]_D^{17}$ =-37.2° (acetone). The other enantiomer, mp 154°C, $[\alpha]_D^{17}$=+37.5° was obtained by the same treatment on the other diastereomeric salt.

The oxygen-containing para-cyclophanes are not the only system which have been resolved. The carbocyclic analog 220 was resolved by Blomquist and Smith [97]. The resolution of [2,2]-para-cyclophane 221 was reported by Cram and Allinger [98]. In 1968, Gerlach and Huber prepared a series of para-pyridinophanes 222 and found that the compound with m=9 was resolvable [99].



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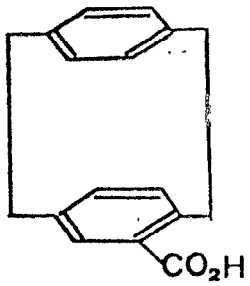

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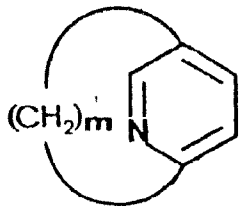
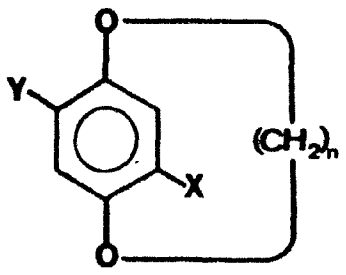


222

The racemization of para-cyclophanes depends on the size of the substituents on the aromatic ring and on the length of the side chain. This is illustrated by the study on some ansa

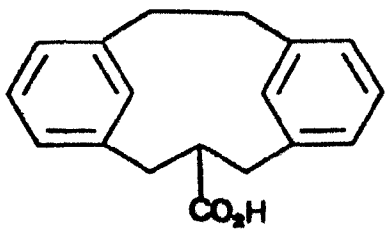
derivatives [100]. Compounds 223 and 224 with two ortho substituents and a 10-membered methylene bridge are optically



223	$X=CO_2H$,	Y=Br,	n=10
224	X=Y=Br,		n=10
225	$X=CO_2H$,	Y=H,	n=10
226	$X=CO_2H$,	Y=H,	n= 9
227	$X=CO_2H$,	Y=H,	n= 8

stable. In the case where there is only one substituent, such as compound 225, it is not resolvable. But compound 227, with an eight-carbon chain, can be resolved and is optically stable. Compound 226 with its nine-carbon bridge shows intermediate optical stability. It was resolvable but racemized on heating. ($t^1/_2$=444 min at 95.5°C).

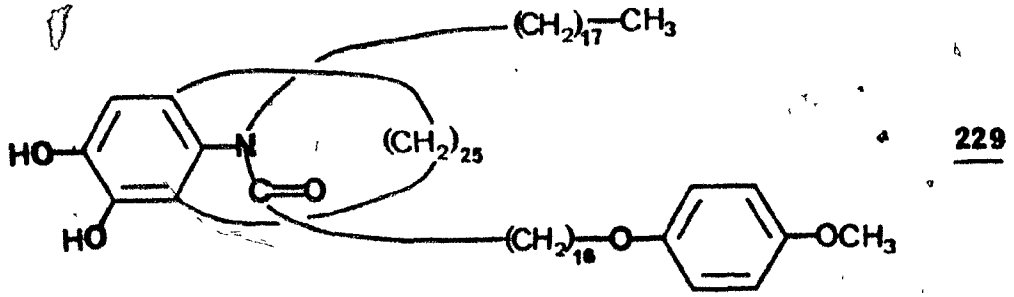
The enantiomerism of meta-cyclophanes was recognized as early as that of para-cyclophanes by Lüttringhaus. Most of the work on para-cyclophanes was contributed by Lüttringhaus and his co-workers but no special effort was made to resolve the enantiomers of meta-cyclophanes. This is perhaps due to the fact that there was not a suitable compound available then. The existance of this type of enantiomerism was demonstrated by Griggin and Coburn in 1963 through the study of temperature dependent NMR spectroscopy



228

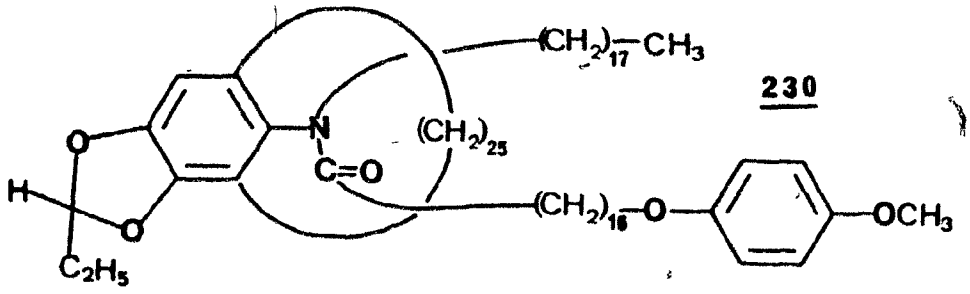
on compound 228 [101], but the resolution of this compound was not successful.

This challenge was taken up again by G. Schill in 1966. In the attempt to synthesize catenanes, they obtained compound 229 which

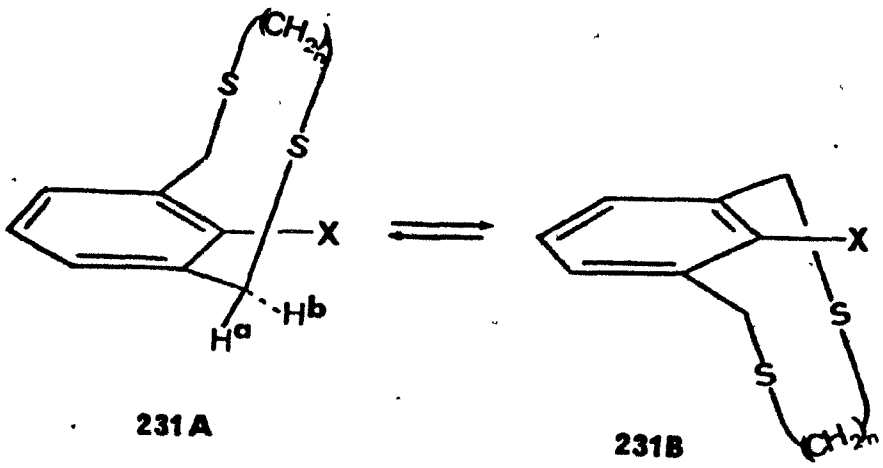


229

met the conditions for enantiomerism. Compound 229 was chromatographed on cellulose-2,5-acetate but no optical activity was observed in the compound after chromatography. After this failure, the diastereomer 230 was prepared and again subjected to chromatography on cellulose-2,5-acetate. No optical activity of the chromatographed material was detected [102].



In order to study the size of different substituents, a number of meta-cyclophanes of 231 type were synthesized by Forster and Vögtle [103]. When the rotation process is restricted, H^a and H^b appear as AB quartet in the ^1H NMR spectra. Because if either of them is replaced by another group, it not only creates a chiral carbon, but also ruins the planar symmetry of the original

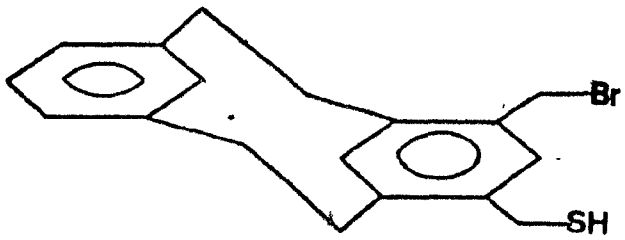


231A 231B

molecule. In other words, the benzyl methylene protons are diastereomeric in 231. The enantiomerism of meta-cyclophanes was shown by 231, but 231 itself is not chiral.

Up to 1979, a number of books had been published on stereochemistry and as far as we are aware, none of them mentioned meta-cyclophanes.

A successful resolution of [2,2]metacyclophane 232 was reported very recently (1983) by Anet and Mislow [104] after the completion of our work.



232

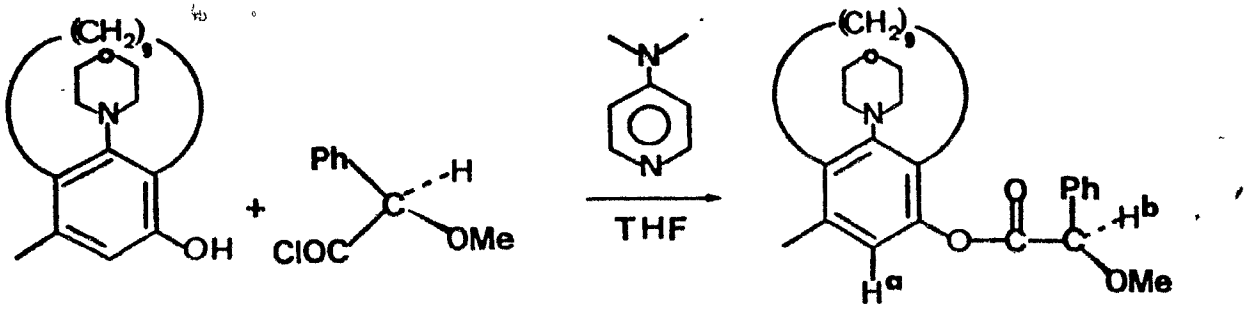
In view of the lack of success in the resolution of m-cyclophanes, we began to examine the stereochemistry of the m-cyclophanes prepared by us in the previous chapter.

Various methods of resolution have been employed. The very first resolution of a racemic mixture was perfomed by Pasteur by mechanical sorting of crystals. This method has no practical

importance because very few racemic compounds can be separated this way. Partial resolution can sometimes be achieved by chromatography on optically active adsorbents such as cellulose-2,5-acetate, or by crystallization from optically active solvents. But the most general technique has until now been the formation of diastereoisomers. The principle of this method is to introduce a new center of asymmetry into the molecule by means of reaction with an auxiliary optically active compound. The two diastereomers so obtained usually show different physical properties and thus can be separated by crystallization or chromatography. After the separation of the diastereomers, the auxiliary compound is removed and the initial compound regenerated in optically active form.

Compound 212 possesses a hydroxy group and should be readily converted into diastereomeric compounds. R-(+)-α-Methyl benzyl isocyanate 171 was used first as the auxiliary component. It has been successfully used for the resolution of amines and alcohols. Unfortunately, the reaction did not take place. A mixture of 212 and 171 was refluxed for 3 hrs in ether and nothing happened according to ^1H NMR. Compound 212 was allowed to react with R-(-)-methoxyphenylacetic acid chloride which was generated *in situ* from the corresponding acid with thionyl chloride. When pyridine was used as the catalyst, no reaction took place. Finally, dimethylaminopyridine was employed, and the expected diastereomeric ester 234 was obtained in 81% yield.

In the ^1H NMR spectrum, the two diastereomers are clearly distinguishable. The aromatic proton (H^a) of the two diastereomers (α and β) differed by 16 Hz. Two methoxy signals are observed, as



212 233 234 α+β

well, separated by 5 Hz (see table 1). The ratio of α-234 to β-234 is about 1:2 by ^{1}H NMR.

The mixture of α-234 and β-234 is a colorless oil, and attempts at crystallization failed. They were finally separated by careful chromatography on a silica gel column using a combination solvent of pentane, ethyl acetate and acetonitrile (20:1:1) as the eluant (discussed later in detail). 200MHz ^{1}H NMR showed that both α-234 and β-234 are more than 90% pure.

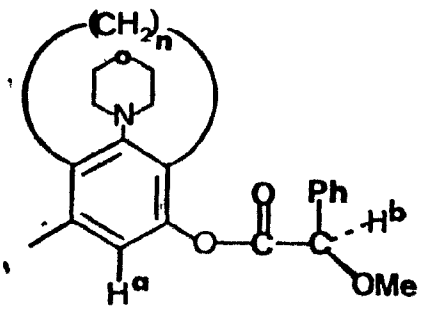
Reduction of α-234 with lithiun aluminum hydride gave (-)-212 with $[\alpha]_D^{20}=-30^\circ$ (acetone). The ^{1}H NMR and IR of (-)-212 are identical to the racemic compound 212. Similar reduction of β-234 with LAH gave (+)-212, $[\alpha]_D^{20}=+26.4^\circ$ (acetone).

Successful resolution has also been achieved with compound 214. The yield of the esterification reaction is 87%. In the ^{1}H NMR spectrum of 235, H^a was separated by 24 Hz and the methoxy by 8 Hz for the two diastereomers, respectively. The ratio of the two isomers is also 1:2. Similar chromatography of 235(α+β) led to the separation of the two diastereomers. Both isomers are more than 95% pure as judged by ^{1}H NMR spectra (200MHz).

Compounds α-235 and β-235 were each reduced with LAH. It was

found that the α-diastereomer gave (-)-214, $[\alpha]_D^{20}=-17^\circ$ (THF), and the β-diastereomer gave (+)-214, $[\alpha]_D^{20}=+11^\circ$ (THF). Again, their ^1H NMR and IR spectra are identical to those of the racemic compound 214.

Table 1. partial ^1H NMR data for the ester diastereomers*



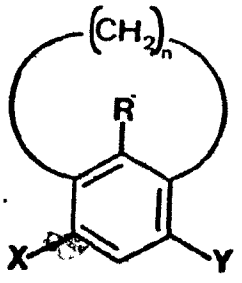
234 n= 9

235 n=12

Compd.	H^a	-OMe	CH_3	H^b
α-234	6.45	3.51	2.15	4.96
β-234	6.62	3.48	2.15	4.96
α-235	6.54	3.50	2.23	4.94
β-235	6.66	3.46	2.23	4.94

* chemical shift (δ) in $CDCl_3$ (200 MHz)

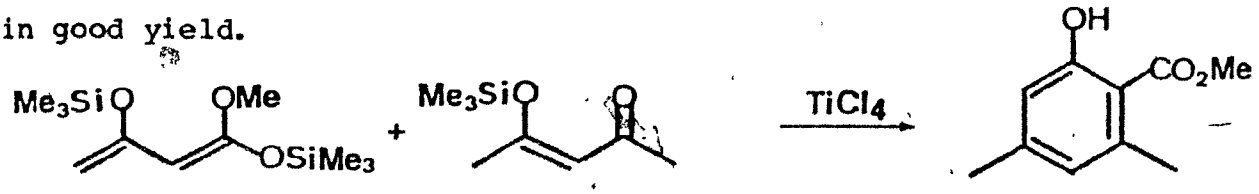
The cycloaromatization reactions of enamines will only allow us to synthesize those meta-cyclophanes with an amino group inside the hydrocarbon chain. However, the enantiomerism of the meta-



236

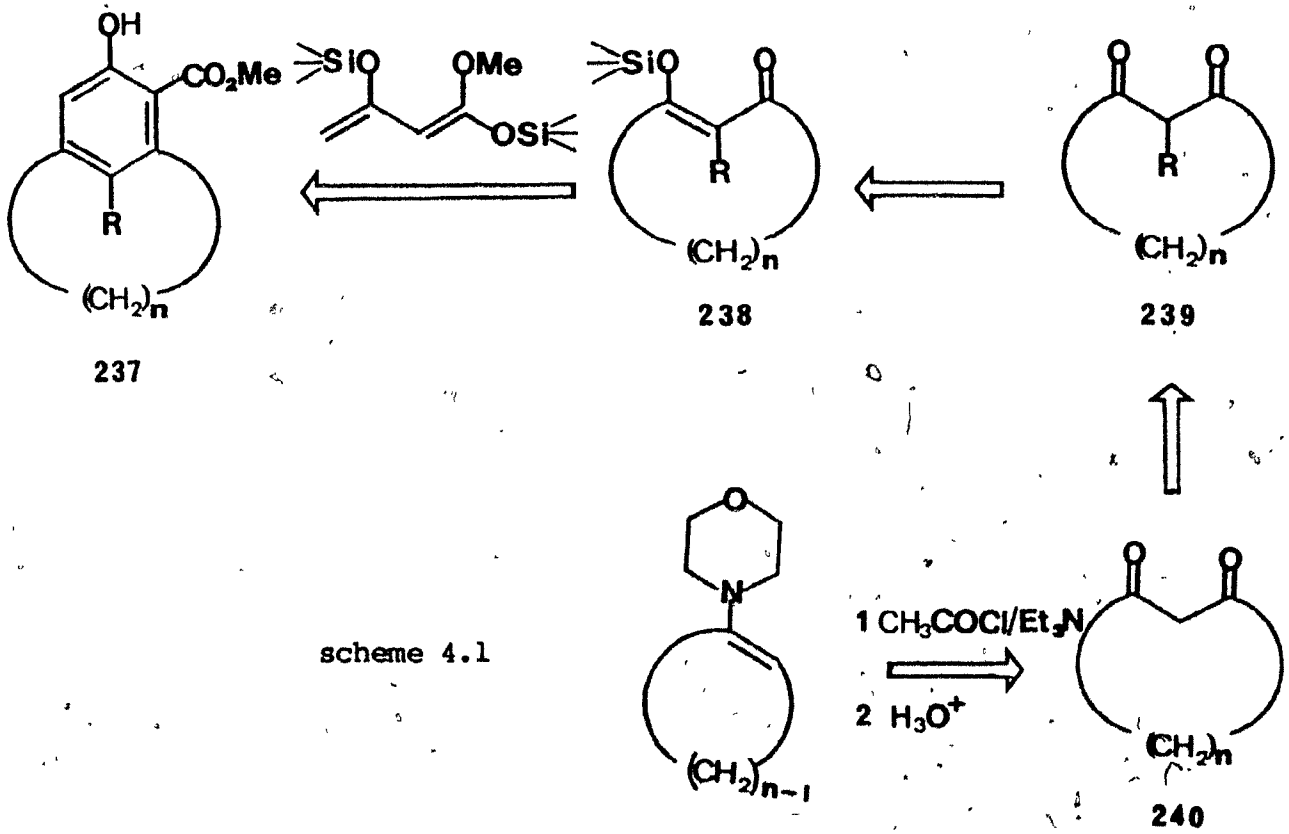
cyclophanes certainly is not limited to the aniline derivatives. In principle, any molecules of type 236, even when R is H, as long as the side chain is small enough, will be chiral.

As we have already mentioned, the condensation of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene 17 with 4-trimethylsiloxypent-3-ene-2-one 19 gives the aromatic compound 20 in good yield.



17 19 20

If we can synthesize the cyclic analogs of 19, we would have in hand a way to synthesize 237 (scheme 4.1). This approach will also allow us to vary the R substitution.

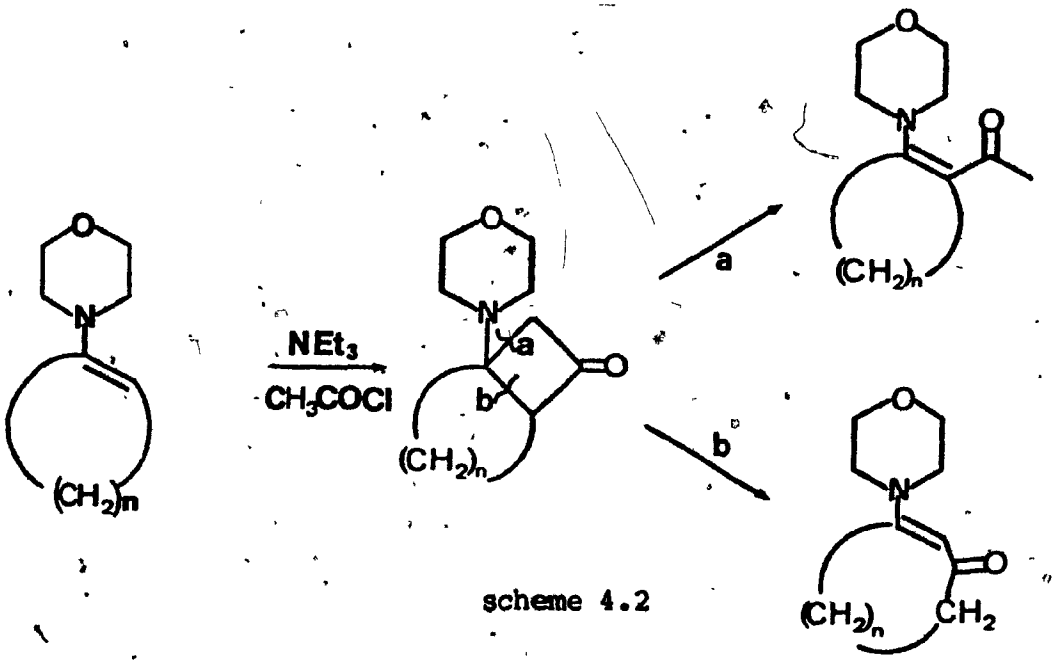


237 238 239 240

scheme 4.1

Compound 237 possesses conformational chirality and as long as the R group is large enough relative to the ring size, it will be resolvable.

The first step in scheme 4.1 is the reaction of cyclic enamines with acetyl chloride. This is a 2C+2C cycloaddition. It is well known that the point of cleavage of the cyclobutane ring (in scheme 4.2) depends on the ring size ofthe originalcyclic ketone. For adducts from five and six-membered cyclic ketone enamines (n=3 and 4), decomposition takes place at a. The adduct



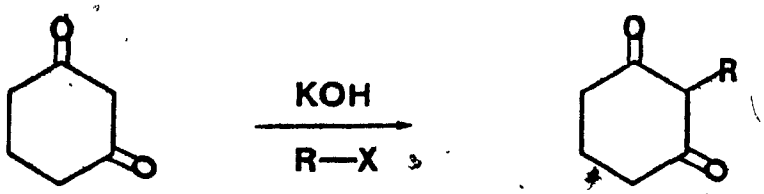
scheme 4.2

from the nine-membered ring enamine (n=7) is produced in very poor yield and decomposition follows both pathway a and b. As the enamine ring size increases from ten to fifteen, the cyclobutane ring cleavage follows mainly pathway b and the yields increase. Since thirteen and fourteen-membered ring cycloketones are not commercially available, but cyclododecanone is quite inexpensive, we decided to choose cyclododecanone as the starting material for

the synthesis of 237.

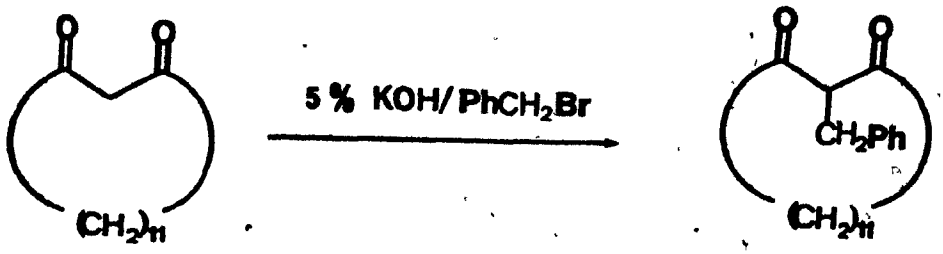
Compound 241 was prepared following the method of Kirrmann and Wakselman [68] except for the purification of the product. In their case, $Cu(OAc)_2$ was used to form a chelate with the β-diketone. Two crystallization of this chelate gave pure 241 in 25-38% yield. We purified 241 by flash chromatography (28% yield).

Hermann and Stetter reported [105] that 1,3-cyclohexanedione was rapidly alkylated with alkyl halides in the presence of potassium hydroxide. Certainly, we can use this method for our



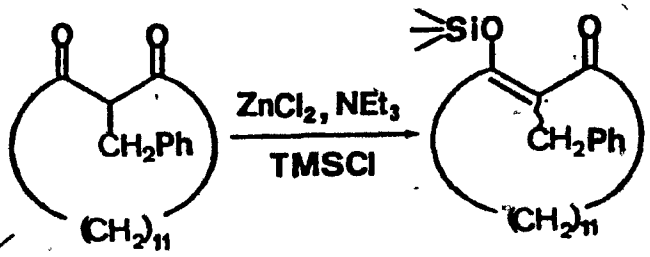
alkylation reaction. We examined the alkylation of 241 with benzyl bromide, because the benzyl group is definitely large enough to guarantee that the final aromatic product 237 will be resolvable.

The benzylation reaction of 241 was performed by Hermann's method. To 1.12g 241 (5 mmol) in 2 ml 20% potassium hydroxide was added 0.86g benzyl bromide (5 mmol) at room temterature, it was stirred for 15 minutes at room temperature, then warmed up to 60°C and stirred for 3 hrs. After workup, in addition to the desired product, a significant amount of double alkylated product was observed by ^1H NMR. The reaction was attempted a second time and the reaction mixture was only stirred for 1 hr at room temperature. The product still had a considerable amount of the double alkylated compound. Finally, 5% potassium hydroxide was used in the reaction and 241 was quantitively converted to 242.



241 242

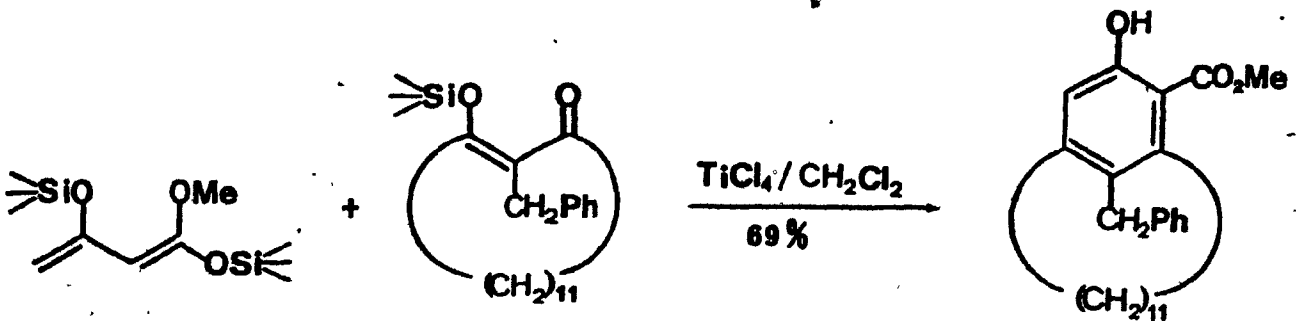
Thesilylation of 242 was done by the literature method [106] with quantitive yield. Compound 243 was directly used to react with 17 without distillation. The ^1H NMR spectrum of 243 showed the presence of a 2:1 mixture of two geometrical isomers.



242 243

The condensation reaction of 243 with 17 was carried out in methylene chloride with titanium tetrachloride as catalyst. A quantity of 1.5 equivalants of 17 was used, because we found that in the case when 1 equivalent of 17 was used, the yield of condensation was low. More importantly, there was a significant amount of 242 remaining in the crude product, and it was extremely difficult to remove 242 from the product by chromatography. Another point worth mentioning is that long reaction times (8 hrs) under low temperature (-23°C) appear to be necessary. The rate of this condensation is much slower than that of the condensation

between 17 and 19. In the latter case, the reaction was completed in 3 hrs at -78°C. In the present case, after 3 hrs at -78°C, ^1H NMR spectrum showed that only small amount of aromatic product was generated. When the reaction mixture was stirred for further 12 hrs at room temperature, the yield of 244 was found to be 53%. This reaction was finally performed under the following conditions: 8 hrs at -23°C and then overnight at room temperature. The isolated yield of 244 was increased to 69%.



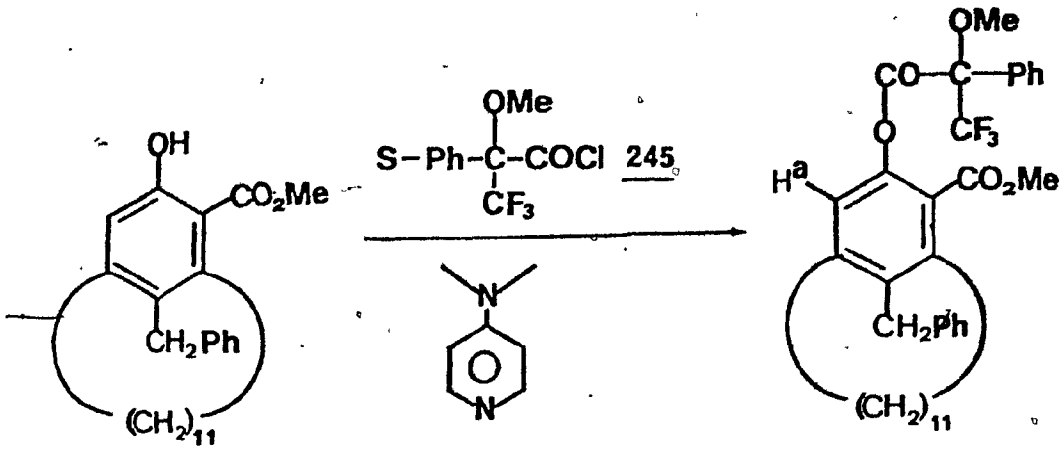
17 243 244

The ^1H NMR spectrum of 244 shows one aromatic proton (6.63ppm, s, 1H), a methylene group (4.17 ppm, s, 2H, $-CH_2-Ph$), a methyl ester group (3.85ppm, s, 3H) and a broad peak at 10.90 ppm indicating the hydroxy group (s, 1H) as well as other signals corresponding to the structure. In its IR spectrum, there is an absorption band at 3420 cm^{-1} and a strong band at 1655 cm^{-1} indicating the hydroxy and the ester groups, respectively.

When R-(-)-α-methoxyphenylacetic acid was used in the resolution of 212 and 214, it was found that the ratio of the two diastereomeric esters was 2:1 for both 234 and 235. Although it is normal that two enantiomers behave differently towards another chiral molecule, in this particular case we could not eliminate

the possibility that there might be some racemization during the esterification reaction. The hydrogen at the position both in the acid chloride and in the product ester is quite acidic. Since dimethylaminopyridine is a reasonably strong base, racemization by proton abstraction is possible. In the case of 235, after separation by column, both the α and β-diastereomers were greater than 95% pure by 200MHz ^1H NMR spectra. Yet, the specific rotations of the two reduced enantiomers of 214 were found to be quite different: one is -17^o and the other is $+11^o$. We therefore looked for anothor resolving agent where such racemization is not possible.

Optically pure α-trifluoromethyl-α-methoxyphenylacetic acid chloride 245 has also often been used to resolve racemic alcohols and amines or to determine their optical purities [107]. With 245, one does not have to worry about racemization, at least under our reaction conditions. Another advantage of 245 is that it can be kept in a refrigerator for several month without apparent decomposition whereas 234 is unstable and must be prepared immediately prior to its use.



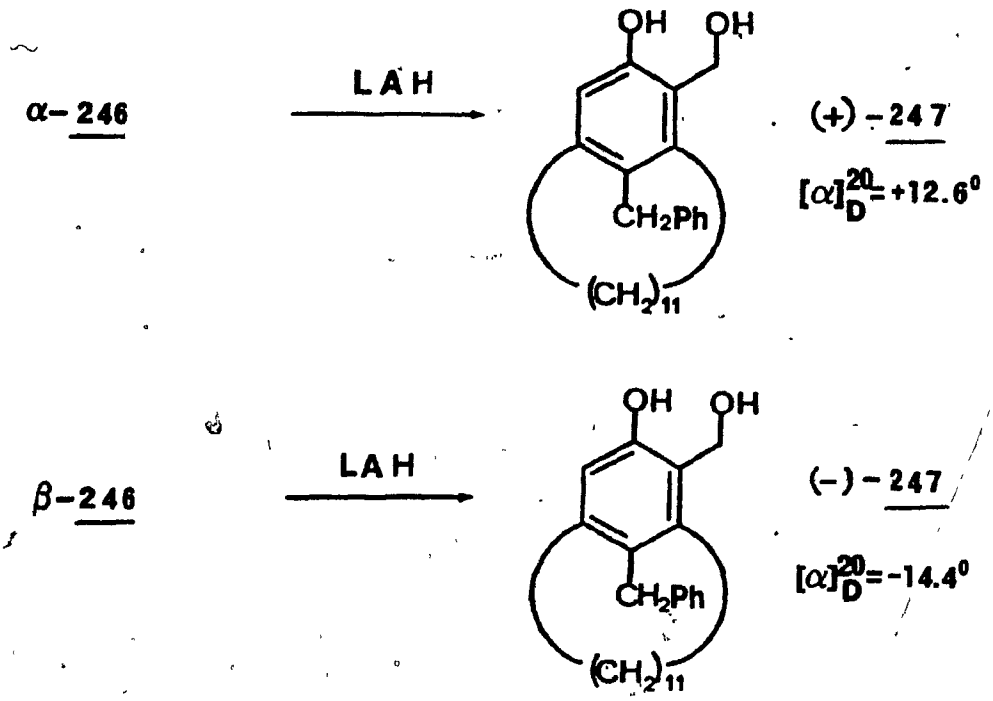
244 246 $\alpha+\beta$

The esterification of 244 with 245 was perfomed in the same manner as using dimethylaminopyridine. A 1:1 mixture of diastereomeric esters α-246 and β-246 was obtained in essentially quantitive yield.

The ^1H NMR spectra of these two diastereomers are clearly distinguishable, the aromatic proton H^a is separated by 6Hz and the methoxy of the methyl ester group is separated by 16Hz.

The mixture of α-246 and β-246 was separated by chromatography on silica gel eluted with petroleum ether and ethyl acetate (35:1). From 180 mg of the mixture there was obtained 66 mg of the α-isomer and 75 mg of the β-isomer. They are both more than 90% pure by ^1H NMR spectra (200 MHz).

Both α-246 and β-246 were reduced by lithium aluminum hydride in ether. Compound (+)-247 was obtained from the α-diastereomer, which has $[\alpha]_D^{20}=+12.6^\circ$ in acetone. Isomer (-)-247 was obtained from the β-diastereomer, which has $[\alpha]_D^{20}=-14.4^\circ$ in acetone.



When either (+)-247 or (-)-247 were refluxed in hexane, no change in their specific rotations was observed.

By examining the molecular models of 212 and 214, one would conclude that the morpholine group is simply too large to pass through the cavity of the m-cyclophane ring. If one wants to study the racemization process of the meta-cyclophane compounds, one would have to either enlarge the ring size or to reduce the size of the amino group. In compound 214 we have already used cyclopentadecanone which is the largest cycloketone conveniently available. On the other hand, even the smallest dialkylamino group i.e. dimethylamino group (ammonia and primary amines do not favor the formation of enamines but imines) does not seem to be small enough to pass through the cyclopentadecanyl ring.

The successful synthesis and resolution of 244 not only provide us one more example of the enantiomerism of meta-cyclophanes, it also showed us that the synthetic route which we proposed in scheme 4.1 was practical and feasible. Since the R group in 237 can be modified easily, we were ready for the study on the rotation process of meta-cyclophanes. The ^{1}H NMR spectra of the two diastereomeric esters of 246 were clearly distinguishable, and it is expected that its analogs with other R substituents will have the same feature. With a proper R group in 237, the rotation process can be studied by the temperature dependent ^{1}H NMR of the corresponding diastereomeric esters. The study of this rotation process is significant not only because it will give us information about the racemization of the chiral meta-cyclophanes, but also the information about the sizes both of the cavity of the

side chain and the intraannular substituents.

The significant influence of steric interactions on reactions has been well recognized and the amount of information about sterically influenced reactions increased very fast. But attempts at empirical quantitative description were relatively less made. Van der Waals radii of substituents can be determined by several methods [108], but their results differ considerably. The measured size parameters are compromises between several effects and therefore have different values under different conditions. This problem is even greater in the case of polyatomic substituents. Furthermore, geometric data do not offer experimental chemist an immediate insight into the energetic significance of steric interactions between the groups in a given molecule. It is desirable to represent the size of a substituent by an energy contribution to the steric interaction in various systems.

Steric interaction is such a common phenomenon in organic chemistry that it is involved in most the organic reactions, more or less. However the investigation must be carried out on those processes in which the steric factor predominates. The rotation processes of ortho-disubstituented biphenyls, para-cyclophanes and meta-cyclophanes meet this requirement.

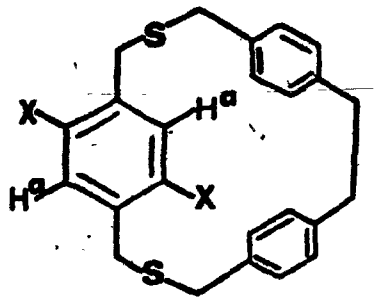
The following order of size for some groups was deduced based on the study on the racemization of biphenyl systems [109].

$$Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F > H$$

Tabushi et al compared the chemical shift of the H^a proton in

248 with that of H^a proton in the dithiol starting material [110]. They found that as the steric interaction between X and the side chain increased, the shielding effect of the benzene rings in the side chain on H^a decreased. The following sequence was obtained:

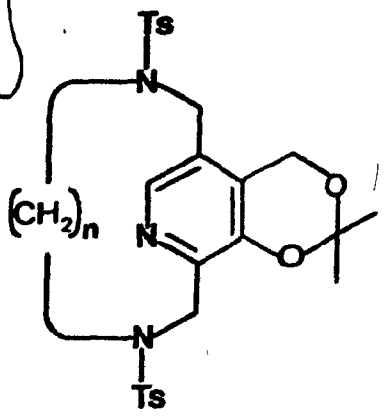
$$Cl > CH_3 > OCH_3 > F > H$$



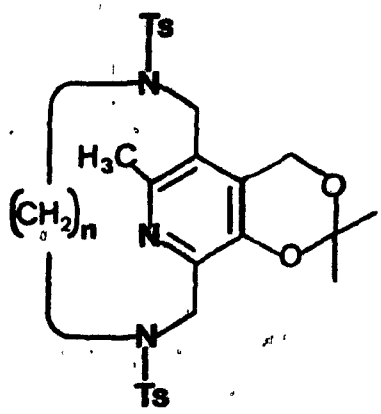
248

It is consistent with the one obtained from biphenyl systems except for Cl > CH_3.

The rotation of the paracyclophane in a number of pyridine analogs have been reported very recently by a Japanese group [111]. A series of diaza(2,5)-pyridinophanes 249 and 250 was synthesized. The activation free energy for the rotation process of 249d was calculated to be 11.9 Kcal/mol from its temperature dependent ^1H NMR spectra.



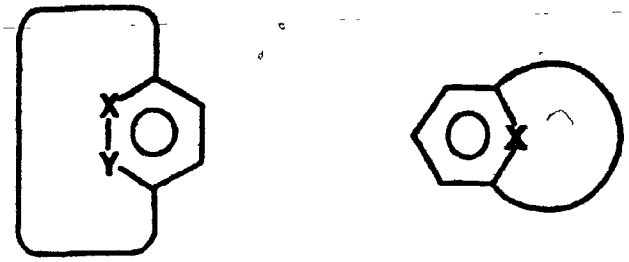
249



250

a n=5, e n=9
b n=6, f n=10
c n=7, g n=12
d n=8

The meta-cyclophane system probably is better than the para-cyclophane system in terms of the study of the size of the substituent. In para-cyclophanes the rotation is affected by both X and Y (there may be substituents on them), whereas only by X for the meta-cyclophanes.



The study on the rotation of meta-cyclophanes was mainly developed by Vögtle and his co-workers. As we already mentioned, a series of dithioderivatives of meta-cyclophane 231 has been synthesized by varying the X group and the length of the side chain. A number of activation free energies for the rotation process of 231A ⇌ 231B were calculated from the temperature dependent ^1H NMR. Some of them are presented in table 2 [103].

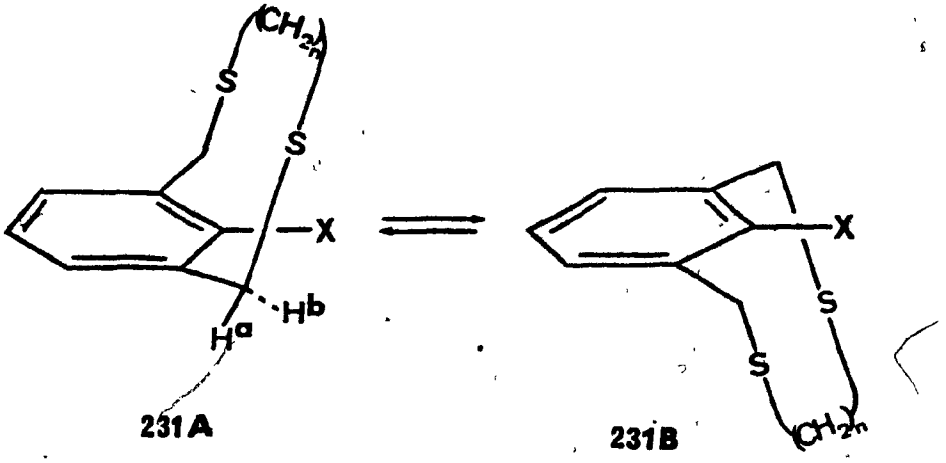


Table 2. Activation free energies at the coalescence temperature ($\Delta G^{\ddagger}$) for the rotation process 231A $\rightleftharpoons$ 231B (kcal/mol).

X \ n	4	5	6	7	8	9	10
-F	23.5	15.3	10.5				
$-NO_2$					15.2		
-Cl				23.5	15.4	11.6	
$-CH_3$				25.8	16.6	12.0	
-CN					23.6	14.5	
-Br					22.5	15.4	9.5
$-OCH_3$					23.2	17.9	10.5

The analysis of the data in table 2 can provide us a similar sequence as that from the biphenyl system. The only outstanding difference is the position of $-OCH_3$. However this is easy to understand. In the case of biphenyl compounds, the interaction of the methoxy group occurs mainly via the oxygen atom; whereas for the rotation of meta-cyclophanes, the side chain has to pass around the whole methoxy group.

An apparent difference between 231 and the meta-cyclophanes that we have synthesized is the side chain. In our case it consists of a pure polymethylene chain whereas it has sulfur atoms in 231. An advantage we have with our compound is that the aromatic proton in the ^1H NMR spectra of the diastereomeric ester

$$k_r = \pi \Delta \nu / \sqrt{2} \qquad \text{Eqn. 1}$$

$$k_r = \pi \left(\Delta \nu^2 + 6J^2 \right)^{1/2} / \sqrt{2} \qquad \text{Eqn. 2}$$

appears as a doublet (one peak for each isomer) and k_r can be calculated by simple equation (Eqn. 1) [112]. Whereas for 231, H^a and H^b appear as an AB quartet and more complicated equation (Eqn. 2) is necessary [113]. Besides, $\Delta\nu$ value may be measured with less error in the uncoupled AB case than that of AB quartet case.

The smallest alkyl group is methyl, according to the data in table 2 it seems to be a proper sized group for the eleven-membered side chain in 237. Therefore the next thing we did was to synthesize the methyl analog of 237.

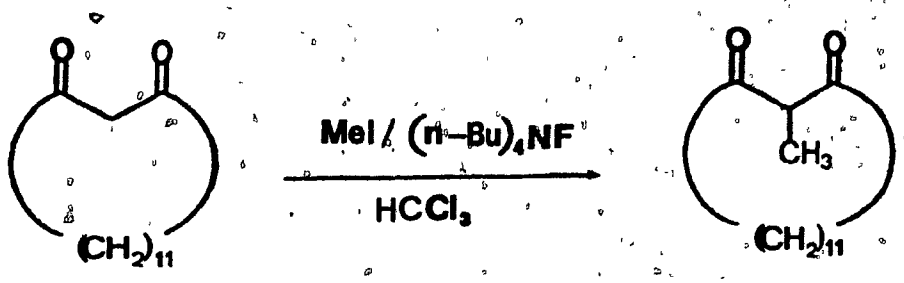
The methylation reaction of 241 was first carried out by the same method used for its benzylation, i.e. with methyl iodide and 5% potassium hydroxide. The ^1H NMR spectrum showed that the product was an almost equal amount of C-alkylated and O-alkylated compounds. The R_f values of these two components on TLC are too close (almost one spot) to be separated by chromatography.

Table 3. Alkylation reactions of acetylacetone

Base	Alkyl agent	%C	%O	reference
NaH	CH_3I	97	3	[114]
	CH_3CH_2I	83	17	
	$(CH3)_2CHI$	48	52	
	$CH_3(CH2)_3I$	76	24	
$(n\text{-}Bu)_4NF$	CH_3I	all C-alkylation product		[115]
	CH_3CH_2I			
	$(CH_3)_2CHI$			
	$CH_3(CH_2)_3I$			

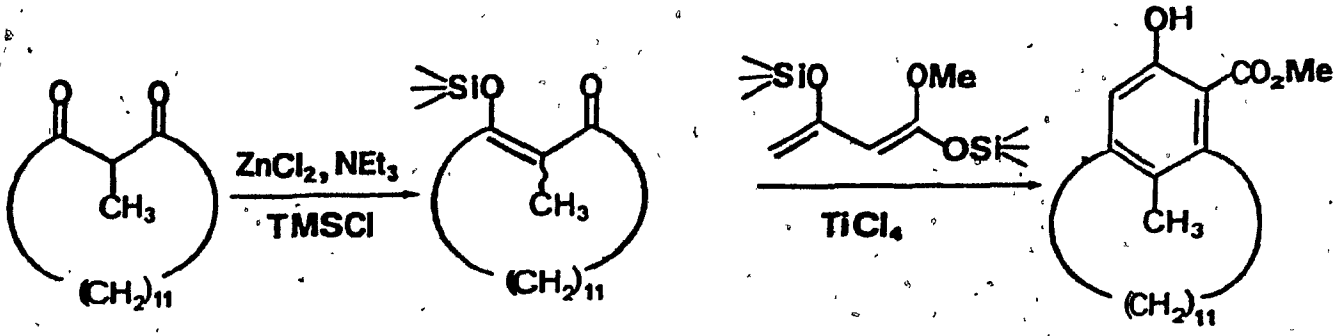
The C- versus O-alkylation reactions of acetylacetone have been well investigated. The C-alkylation (usually the desired one) was often accompanied by O-alkylation when NaH was used as the base (see table 3).

In 1977 Clark and Miller reported that with tetra-n-butylammonium fluoride [115], the product was exclusively due to C-alkylation. The idea is that the bulky ammonium cation shields the oxygen atom and therefore minimizes O-alkylation. Following the method of Clark and Miller, 2-methylcyclotetradecane-1,3-dione 251 was obtained in 87% yield from 241.



241 251

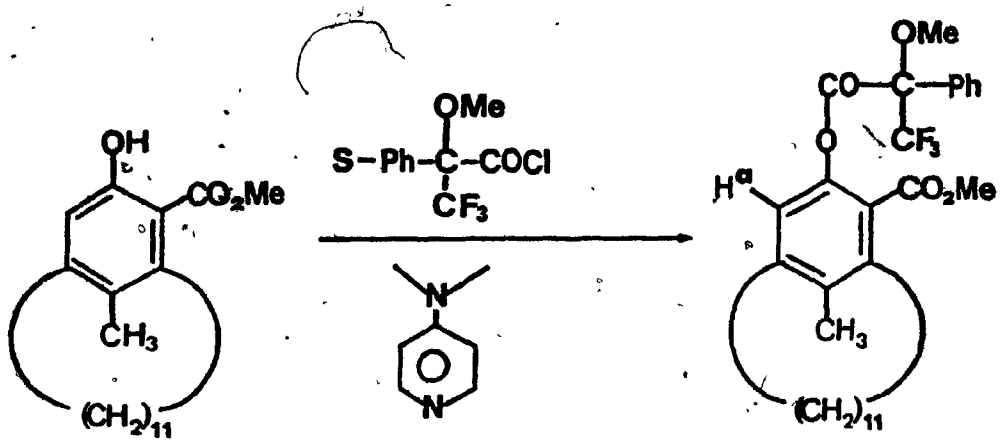
Compound 253 was obtained following the route shown in scheme 4.3 in 63% yield. It then was converted to the corresponding



251 252 253

scheme 4.3

diastereomeric esters 254 with trifluoromethyl-α-methoxy-α-phenylacetic chloride. Similar to 246, the ^1H NMR spectrum of this ester showed two clearly distinguishable diastereomers (table 4).



253 254 α+β

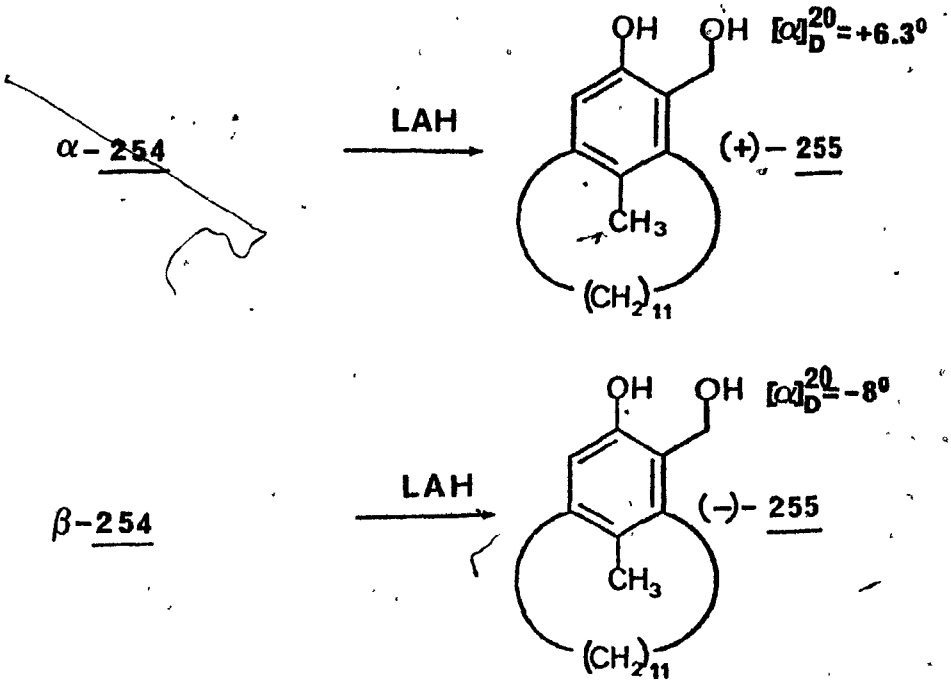
Table 4. ^1H NMR data of diastereomeric ester 254 ($CDCl_3$, 200MHz)

Compd.	H^a	$-CO_2Me$	-OMe	$-CH_3$
α-254	6.76	3.67	3.66	2.32
β-254	6.80	3.58	3.66	2.32

Two diastereomers were shown in the ^1H NMR spectrum of 254. However, it did not mean that 253 was necessarily resolvable. It could be that the rotation was completely restricted at room temperature or that the two diastereomers interconverted at a rate slower than the NMR time scale. The resolution of 253 thus was tried.

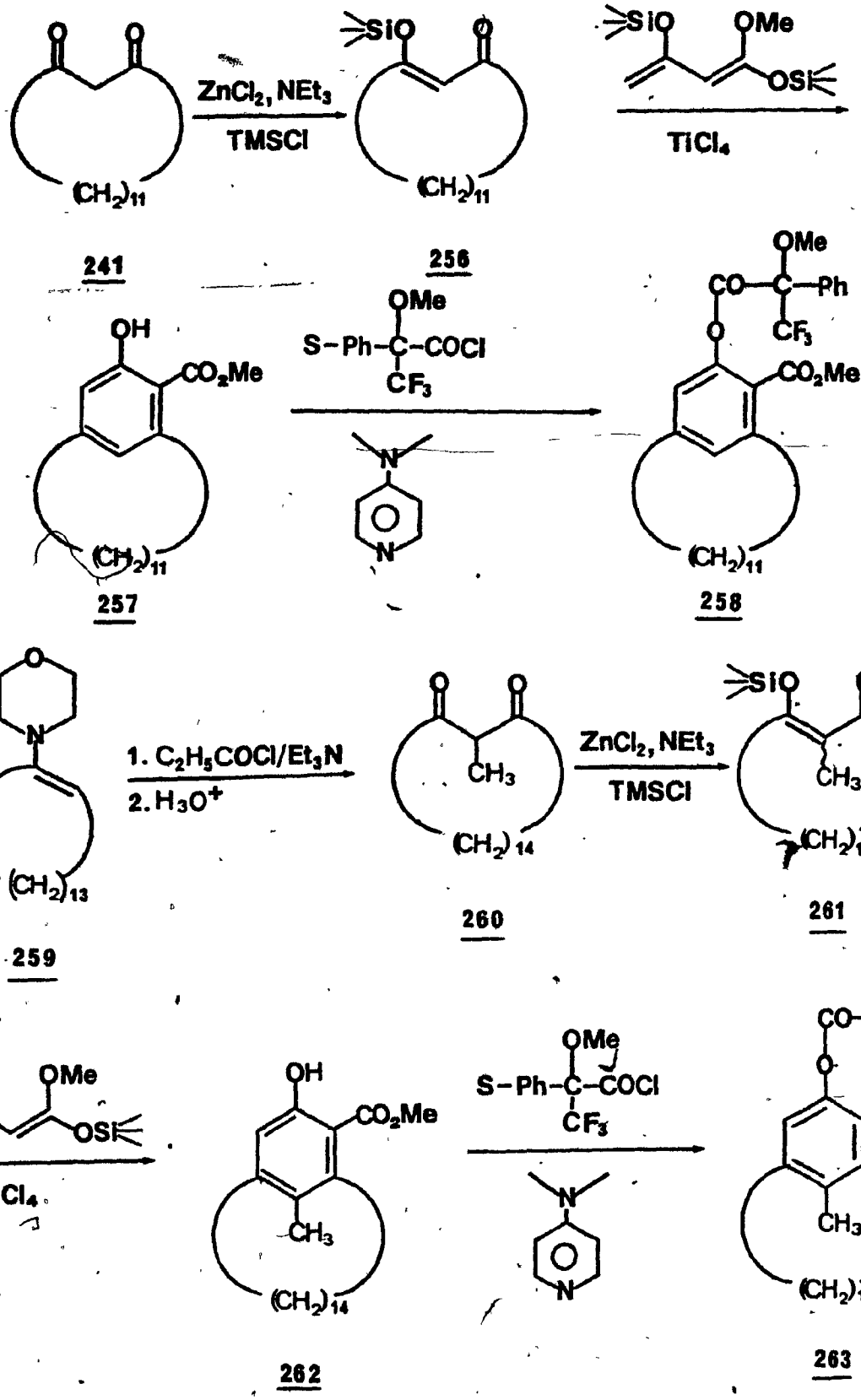
The diastereomeric mixture of 254 was separated with similar column chromatography as that used for the separation of 246. The result of this separation is even better than the benzyl one. Both isomers are more than 95% pure by ^1H NMR spectra. After standing

in deuterated chloroform for 3 days at room temperature, their ^1H NMR were checked again and no change was observed at all. This means that there is no racemization at room temperature.



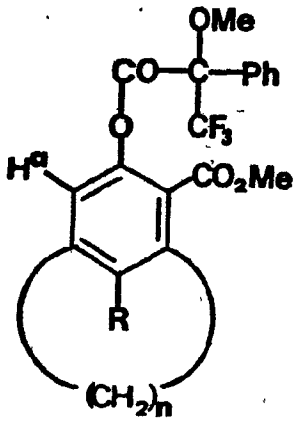
The reduction of these two diastereomers gave (+)-255 and (-)-255, respectively. Specific rotation for (+)-255 is $[\alpha]_D^{20}=+6.3^o$ (acetone) and for (-)-255 $[\alpha]_D^{20}=-8.0^o$ (acetone). After (+)-255 was refluxed in hexane for about 5 minutes, its optical activity totally disappeared.

Before we proceeded to the dynamic NMR study, two more analogs of 254 were prepared by us following the routes shown in scheme 4.4. The ^1H NMR spectra of 258 and 263 showed only one set of signals for each case at room temperature (see table 5). In other words, the two diastereomers interconverted by rotation of the side chain at a rate faster than the NMR time scale.


ZnCl2, NEt3
TMSCl
TiCl4
241
256
257
258
1. C2H5COCl/Et3N
2. H3O+
259
260
261
262
263

scheme 4.4

Table 5. ^1H NMR spectra of 258 and 263 at room temperature in CD_2Cl_2



258 R=H, n=11

263 R=CH_3, n=14

Compd.	H^a	R	$-CO_2Me$	OMe
258	6.81*	7.15*	3.66	3.63
263	6.83	2.31	3.62	3.62

* The assignment of the these two aromatic protons might be reversed.

The temperature dependent ^1H NMR of 258 was studied in CD_2Cl_2. Even at -70°C the aromatic protons remained as distinct singlets. The chemical shift of the methyl ester group was shifted considerably and also broadened but nevertheless it remained a singlet (figure 4).

The variable temperature ^1H NMR of 263 was performed in a range of temperature from 20°C to -90°C by about 10°C intervals in CD_2Cl_2. It is shown in figure 5. At 20°C, H^a appears as a singlet and the methoxy A (of the methyl ester) overlaps with methoxy B (from the mandelic part).

The H^a started to broaden at lower temperature. At -70°C and

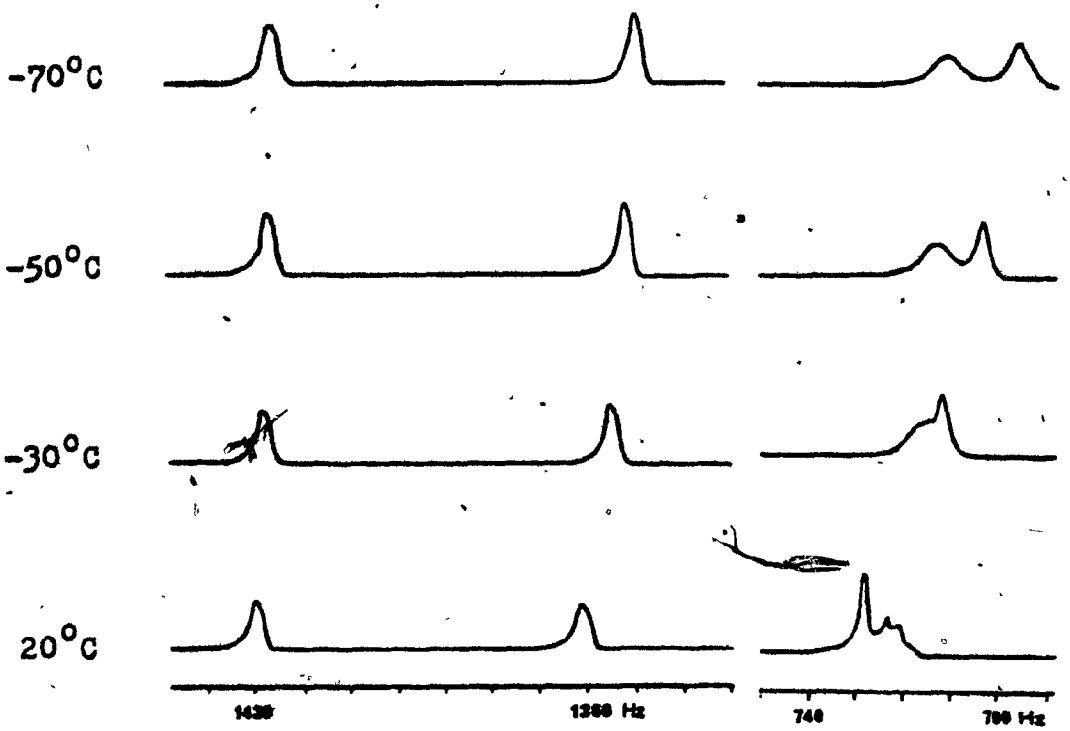


Figure 4. Temperature dependent ^1H NMR spectra of 258 in CD_2Cl_2 (200 MHz).

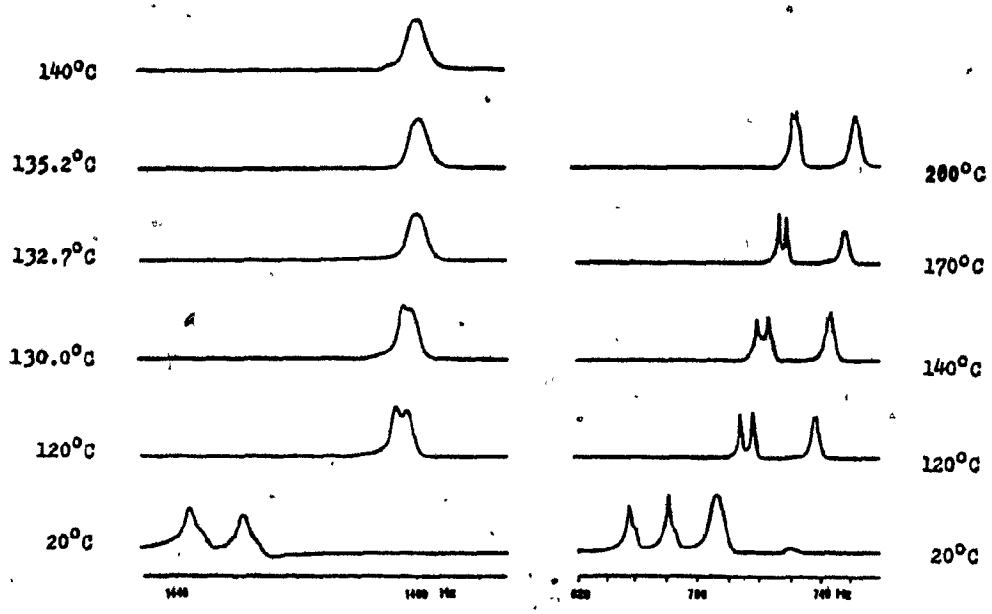


Figure 6. Temperature dependent ^1H NMR spectra of 254 in $C_6D_5NO_2$ (200 MHz)

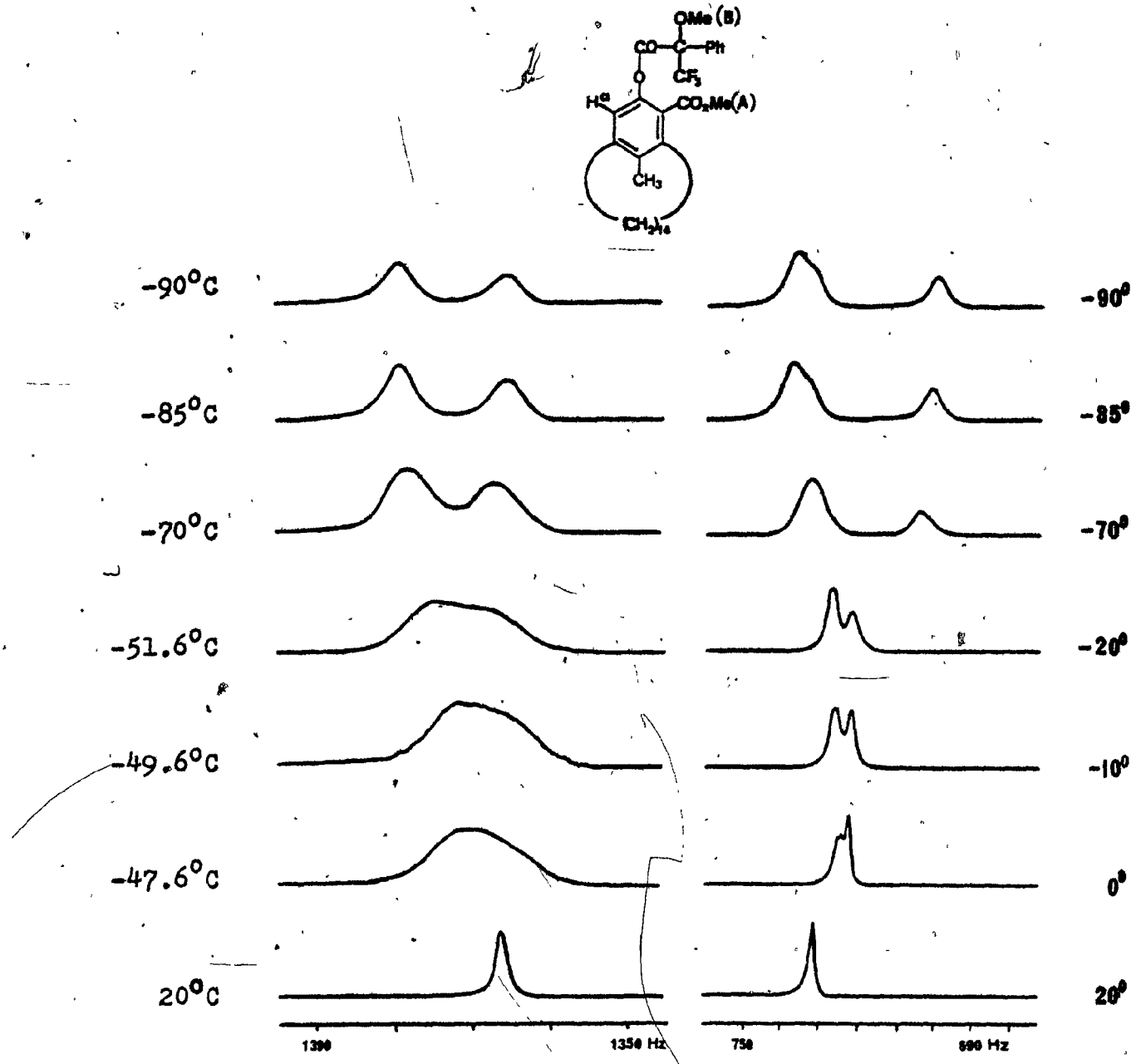


Figure 5. Temperature dependent ^1H NMR spectra of 263 in CD_2Cl_2 (200 MHz)

lower temperatures, it appeared as two signals. The coalescing temperature was determined to be at -49.6°C. The activation energy of the rotation process for 263 has been calculated to be 11.4 kcal/mol (47.9kJ/mol) by equation 3 [116].

$$\Delta G^{\ddagger} = RT(\ln kKT - \ln k_r h) \qquad \text{Eqn. 3}$$

where T: coalescence temperature

k: Boltzman constant

K: transmission coefficient (in this case K=1)

k_r: rate constant for the rotation. $k_r = \pi \nu_{AB}/\sqrt{2}$

$\nu_{AB}(\Delta\nu)$ was found to be 13.8Hz for H^a at -85°C.

At 0°C, methoxy A shifted away from methoxy B and showed up as a singlet. At -10°C, it became a doublet but with the right component being stronger than the left one. This indicated that methoxy A had started coalescing and the signal of one diastereomer's methoxy A still overlapped with methoxy B. The difference in intensity and also the distance of the two components (right and left) became larger and larger as the temperature was lowered, and at -85°C, a shoulder can be seen from the left peak. The changing of relative intensity of the two components indicated that at the beginning of coalescing, the populations of the two diastereomers were not the same, (or they have different lifetimes) but were very close to 1:1 at -85°C. The shape of the peaks at -90°C is almost the same as that at -85°C, and we believe that at -85°C it has reached the unchangable point. However, it is hard to tell the coalescing temperature of the methoxy A because the signal of one isomer overlaps with that of methoxy B.

The temperature dependent ^1H NMR of 254 was performed in a range of temperature from 20°C to 200°C in deuterated nitrobenzene ($C_6D_5NO_2$) (see figure 6). The aromatic proton coalesced at 132.7°C, whereas the methyl ester still remained as two separate signals though with considerable broadening. A rotation barrier of $\Delta G^{\ddagger}$ =21.4 kcal/mol (89.9 kJ/mol) has been calculated for 254 using equation 3.

When X is methyl and n is equal to 7 (the total length of the side chain is 11-membered), 231 has $\Delta G^{\ddagger}$=25.8 kcal/mol according to Vögtle's result (see table 2). It is expected that replacement of -S- by $-CH_2-$ will shorten the length of the side chain and slow the rate of the rotation. Contrary to expectation, 254 has a $\Delta G^{\ddagger}$ value 4.4 kcal/mol smaller than 231. Besides the side chain, there are still other difference between 254 and 231, i.e., the substitution on the aromatic nucleus. In 231 there is no extra substituent except for the methyl group, but 254 has two more substituents. The effect of the substituents on the rotation process of the meta-cyclophanes was also investigated by Vögtle and his co-workers. They found that electron-releasing groups retard, whereas electron-withdrawing groups accelerate, ring inversion [117]. The ester group in 254 may then account for the observed small $\Delta G^{\ddagger}$.

ORD and CD study of m-cyclophanes

ORD and CD curves of all our resolved enantiomers have been obtained. They are presented in figure 7-12. Both ORD and CD show quantitatively a mirror image relationship for every enantiomeric pair.

The experiments were performed in methanolic solution on a JASCO ORD//UV-5 instrument. $[\phi]$ Value was calculated by equation 4. $\Delta\epsilon$ Value was calculated by equation 5 which comes from the Japan Spectroscopic Company instruction manual for the above instrument with CD attachment.

$$[\phi] = \frac{\alpha \cdot M}{c \cdot l \cdot 100} \qquad \text{Eqn. 4}$$

where α = observed rotation (degrees)

M = molecular weight

c = concentration (g/ml)

l = length of the sample tube (dm)

$$\Delta\epsilon = \frac{1}{l \cdot c} \times \text{"CD scale reading"} \times \text{"chart reading"} \qquad \text{Eqn. 5}$$

where l = length of the sample tube (cm)

c = concentration (mols/l)

In figure 11, the maximum of the CD curve of 212 is located at about 10 nm longer wavelength than that of 214. But no such difference is shown between 247 and 255 (see figure 12).

The position of the CD curve depends on the position of uv absorption and the latter depends on the difference in energy

levels between π and π^* of the benzene ring. The more strain in the molecule, the higher the energy level of the HOMO (π), but the strain should affect less the LUMO (π^*). Compound 212 with a nine membered methylene side chain must possess more strain than compound 214 which has a twelve membered methylene side chain.

212 scheme 4.5 214

This may lead to a greater deviation in planarity for the benzene ring in compound 212, thus effectively raising the energy level of the HOMO orbital of 212. Therefore, $\Delta E_1 < \Delta E_2$ (see scheme 4.5) and consequently the uv absorption of 212 should appear at longer wavelength than that of 214.

In the case of 247 and 255, they have the side chains of the same length, although the benzyl group in 247 is larger than the methyl group in 255, compound 247 must adopt the conformation in which the benzene ring of the benzyl keeps away from the side chain, consequently there is not too much difference in strain between 247 and 255.

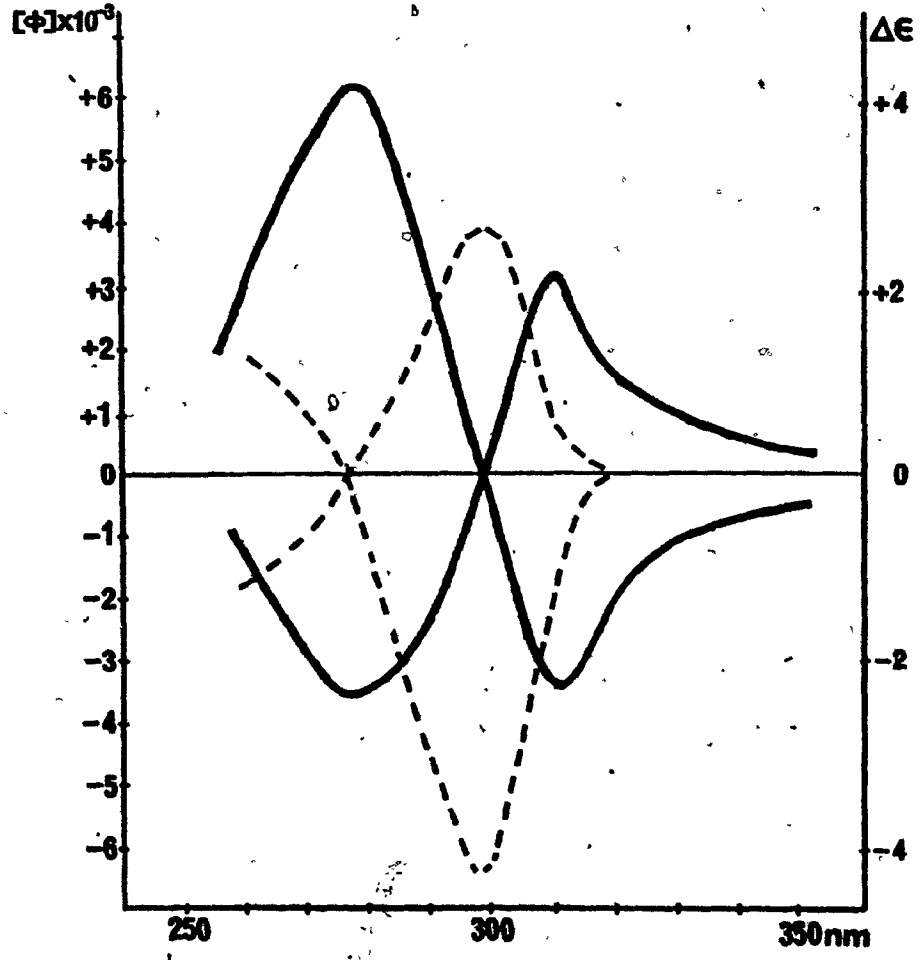


Figure 7. ORD and CD of 212 (MeOH)

——— ORD ----- CD

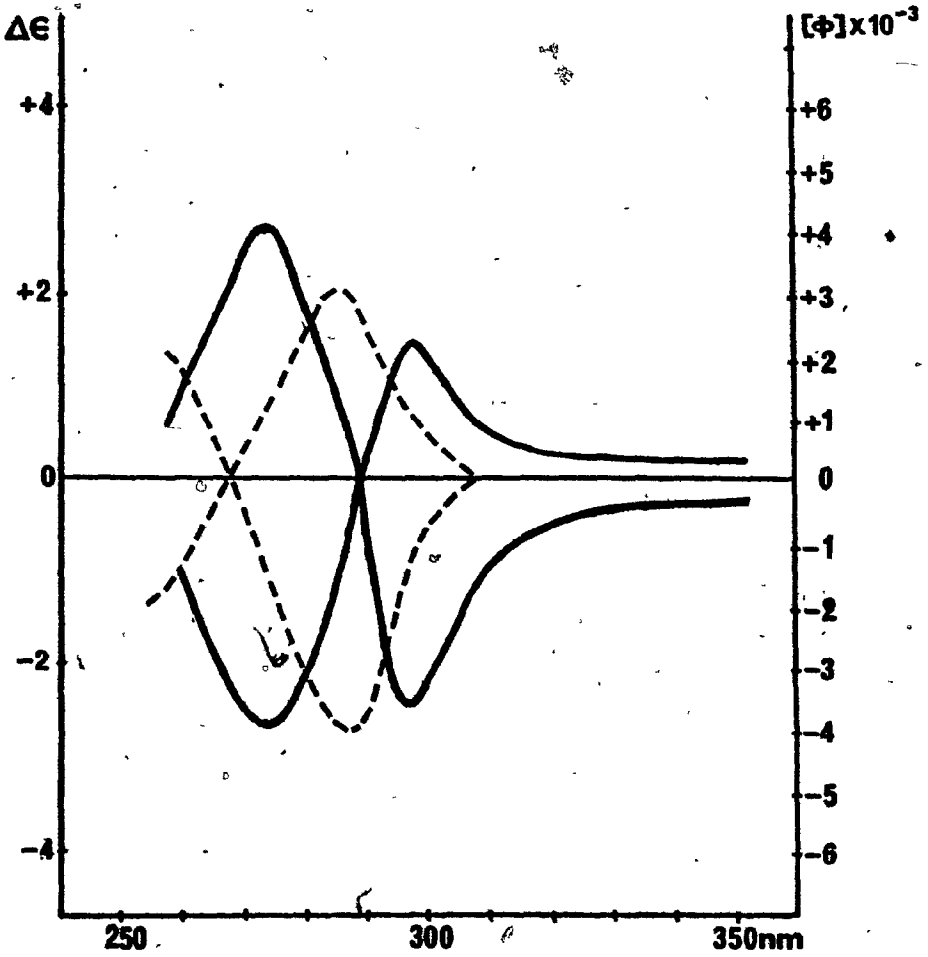


Figure 8. ORD and CD of 214 (MeOH)

——— ORD, ------ CD

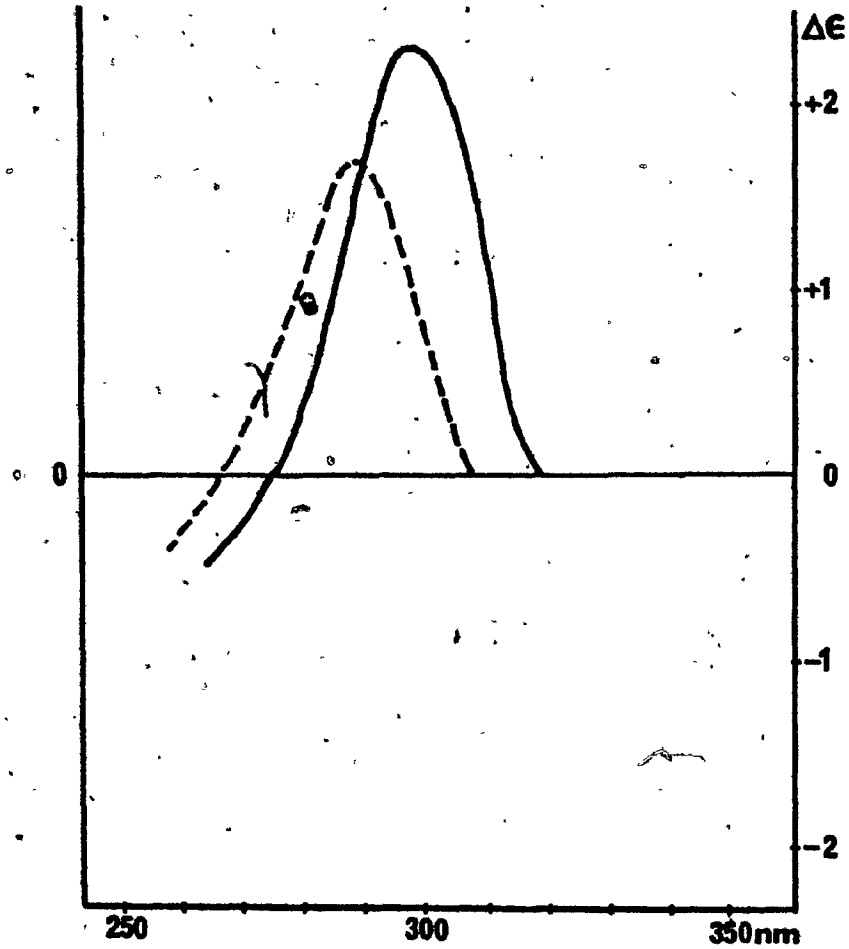


Figure 11. Comparison of the CD between 212 and 214

——— 212, ------ 214

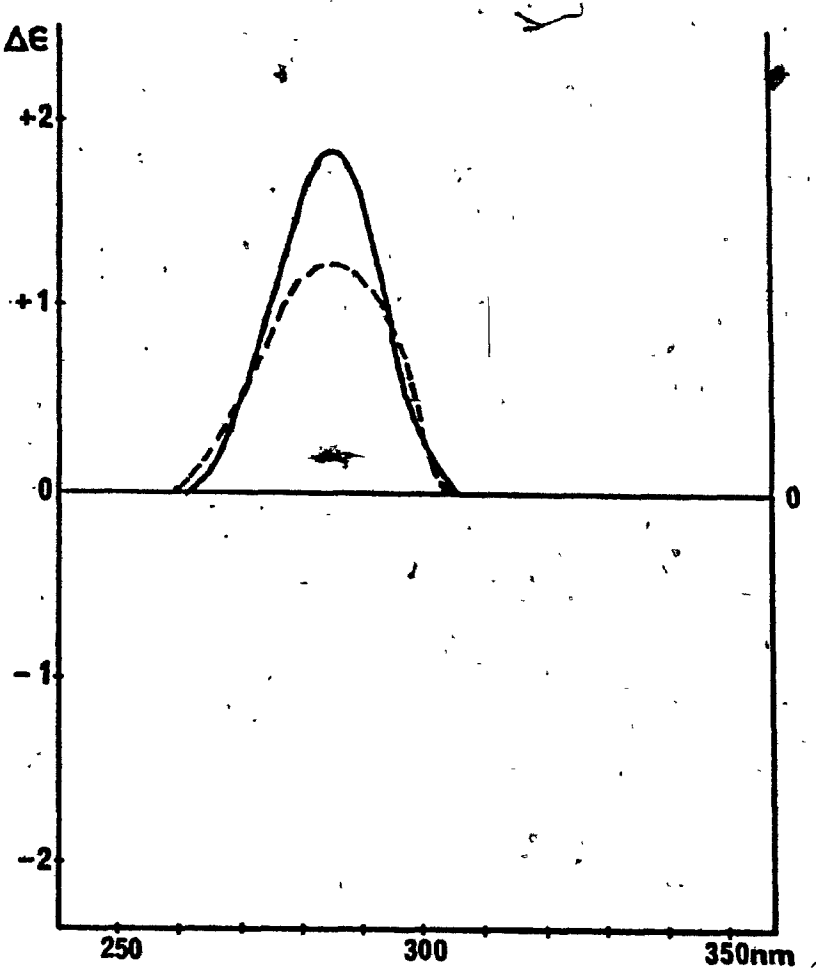


Figure 12. Comparison of the CD between 247 and 255

——— 247, ------ 255

CLAIMS TO ORIGINAL WORK

Methyl 4-trimethylsilyl-3-dialkylaminocrotonate was synthesized and introduced to organic synthesis for the first time. It reacts with carbonyl electrophiles at its γ-position. The unusual regiochemistry of this reaction is studied and rationalized. It reacts with enamines derived from acyclic ketones or cycloketones of large ring size (of 12 and 15 membered rings) to give aromatic compounds in a 3C+3C combination and with enamines derived from cycloketones of 5-8 membered rings to give aromatic compounds in a 4C+2C combination. The mechanism of this cycloaromatization reaction is investigated.

meta-Cyclophanes with a morpholino substituent are synthesized by the above cycloaromatization reaction. These meta-cyclophanes possess planar chirality and are successfully resolved.

A number of metacyclophanes with alkyl substituents at the intraannular position are synthesized. Depending on the ring size and the steric size of the alkyl group, some of them are also resolved. The rotation process of meta-cyclophane is studied through their temperature dependent ^1H NMR.

EXPERIMENTAL

Unless otherwise stated, common reagents were commercial products and were reagent grade. Melting and boiling points are uncorrected.

NMR Spectra were taken on a Varian T-60A NMR spectrometer and XL-200 NMR spectrometer. All ^{1}H and ^{13}C spectra are reported in chemical shift (δ) with tetramethylsilane as the standard.

Infrared spectra were taken on a Perkin-Elmer Model 257 infrared spectrophotometer and were calibrated with the 1602cm^{-1} band of polystyrene film.

Mass spectra were obtained on a 21-492B Mass spectrometer.

Specific rotation were measured at ambient temperature on a Perkin-Elmer 141 automatic polarimeter or a JASCO DIP-140 Digital polarimeter using the sodium D line.

CD and ORD curves were obtained using a JASCO ORD/UV-5 with CD attachment and a xenon lamp.

Chemical analyses were performed by Guelph Chemical Laboratories Ltd.

Chromatography

All of our diastereomers are separated by a similar procedure of TLC mesh chromatography [119]. The R_f values for the morpholine derivatives (234, 235) is about 0.02 and for the alkyl derivatives (246, 254) is 0 on analytical TLC. After separation, all the diastereomers are more than 90% (some are 95%) pure as judged by 200 MHz ^{1}H NMR spectra and the recoveries are between 60-80%.

A 20 mm column (internal diameter) was usually used for the

separation of 100 mg of mixtures. The height of silica gel is between 7.5-9 in. after forcing through contained air. This is an important consideration because if the column is below 7 in., the separation is not very efficient, whereas if it is above 9 in., the silica bed undergoes distortion during elution. Silica gel of size 40-63 μm which is recommended by Still for flash chromatography [120] has also been tried but the separation was found to be poor.

Actually no special techniques have been employed in our separations. The reason that we mention this here is simply to point out that this simple method might be more powerful than is generally recognised.

Preparation of methyl 3-pyrrolidinocrotonate 153a

To a solution of 8.7 g (0.075 mol) of acetoacetate in 30 ml of benzene was added 7.1 g pyrrolidine (0.1 mol) and 0.1 g p-toluenesulfonic acid monohydrate. The flask was attached with a water separator. The mixture was refluxed for 3 hrs and about 1.4 ml of water was collected. The reaction mixture was cooled to room temperature and solvent was removed by rotary evaporater. the residue was distilled under reduced presure to give 11.1 g 153a in 88% yield. bp: 116-118°C/2.5mm [82]

^{1}H NMR ($CDCl_3$): 1.77-2.00 (m,4H), 2.40 (s,3H), 3.13-3.37 (m,4H), 3.53 (s,3H), 4.40 (s,1H)

^{13}C NMR ($CDCl_3$): 16.2, 24.8, 47.5, 49.4, 82.5, 159.3, 169.2

Preparation of methyl 3-morpholinocrotonate 153b

Compound 153b was prepared in the same manner as 153a using morpholine in place of pyrrolidine. yield: 79%, bp: 131-132°C/4mm [82]

^{1}H NMR ($CDCl_3$): 2.42 (s,3H), 3.13-3.33 (m,4H), 3.62 (s,3H), 3.58-3.80 (m,4H), 4.80 (s,1H)

^{13}C NMR ($CDCl_3$): 15.0, 46.1, 49.1, 66.1, 87.6, 161.1, 169.1

Preparation of methyl 4-trimethylsilyl-3-pyrrolidinocrotonate 156a

Under N_2 at 0°C, to a solution of dry diisopropylamine (3.4ml, 24 mmol) in THF (50ml) was added n-BuLi (16ml of 1.5M in hexane, 24 mmol), followed by TMEDA (3.2ml). The solution was cooled to -78°C and methyl 3-pyrrolidinocrotonate 153a (3.38g, 20 mmol) was added. The reaction mixture was stirred for 0.5 hr, and then quenched with trimethylchlorosilane (4ml). The reaction mixture was allowed to warm to 0°C and concentrated on the rotary evaporater. the residue was triturated with dry hexane (100ml) and filtered. The fitrate was concentrated (finally under high vaccum) to give 4.43g 156a as a yellowish oil. yield: 92%, >95% pure by ^{1}H NMR

^{1}H NMR ($CDCl_3$): 0.1 (s,9H), 1.80-2.03 (m,4H), 2.73 (s,2H), 3.20-3.43 (m,4H), 3.60 (s,3H), 4.47 (s,1H)

^{13}C NMR ($CDCl_3$): -1.7, 21.65, 25.0, 48.0, 49.5, 81, 163, 169.3

IR (film, cm^{-1}): 1665, 1550, 1150

MS m/e (rel. intensity): 241 (M^+, 25.7), 226 (39.4), 210 (32.8), 168 (77.0), 138 (84.0), 110 (100)

Preparation of methyl 4-trimethylsilyl-3-morpholinocrotonate 156b

Compound 156b was made in the same way as 156a from 153b. yield: 90%, >90% pure by ^1H NMR

^1H NMR ($CDCl_3$): 0.1 (s,9H), 2.73 (s,3H), 3.10-3.33 (m,4H), 3.60 (s,3H), 3.55-3.80 (m,4H), 4.73 (s,1H)

^{13}C NMR ($CDCl_3$): -0.9, 19.5, 47.1, 50.2, 66.6, 86.2, 165.7, 169.5

IR (film, cm^{-1}): 1680, 1560, 1145

MS, m/e (rel. intensity): 257 (M^+, 26.1), 242 (58.4), 226 (62.2), 184 (72.9), 154 (29.9), 126 (33.8)

Reaction of 156a with benzaldehyde

To a mixture of benzaldehyde (1 mmol) and $TiCl_4$ (1 mmol) in 3 ml of CH_2Cl_2 at -78°C under N_2 was added 156a (1 mmol). The reaction mixture was stirred for 3 hrs at -78°C, and then overnight at room temperature. The reaction mixture was quenched with saturated sodium carbonate solution and then extracted with ether. The ether extract was dried with $MgSO_4$ and evaporated to give an oil which was column chromatographed (eluant, ether:hexane 2:1) to give methyl 5-phenyl-3-pyrrolidinopenta-2,4-dienoate 157a in 68% yield as a colorless liquid.

^1H NMR ($CDCl_3$): 1.95 (m,4H), 3.33 (m,4H), 3.60 (s,3H), 4.60 (s,1H), 6.66 (d,1H,J=17Hz), 7.20-7.60 (m,6H)

IR (film, cm^{-1}); 1680, 1550, 1140

MS m/e (rel. intensity): 257(M^+, 12.2), 226(17.9), 198(100)

Reaction of 156b with benzaldehyde

The reaction was performed in the same way as the reaction between 156a and benzaldehyde. Methyl 5-phenyl-3-morpholinopenta-2,4-dienoate 157b was obtained in 60% yield as a colorlees liquid.

^1H NMR ($CDCl_3$): 3.07(m,4H), 3.56(s,3H), 3.70(m,4H), 4.84(s,1H), 6.75(d,1H,J=16Hz), 7.10-7.50(m,6H)

IR (film, cm^{-1}): 1695, 1565, 1150

MS m/e (rel. intensity): 273(M^+,9.8), 242(13.2), 214(100)

Reaction of 156a with cinnamaldehyde

To a mixture of cinnamaldehyde (0.5 mmol) and $TiCl_4$ (0.5 mmol) in 3 ml of CH_2Cl_2 at -78°C under N_2 was added 156a (0.5 mmol). The mixture was stirred for 3 hrs at -78°C, then allowed to warm to room temperature. Saturated aqueous sodium carbonate solution was added and the mixture was extracted with ether. The ether extract was dried with $MgSO_4$ and fitered. The filtrate was concentrated to give a brown oil which was purified by alumina column chromatography (eluant, ether:hexane 2:1) to give 2E,4E,6E-methyl 7-phenyl-3-pyrrolidinohepta-2,4,6-trienoate 159a in 81% yield.

^1H NMR ($CDCl_3$, 200MHz): 1.93(m,4H), 3.33(m,4H), 3.60(s,3H), 4.57(s,1H), 6.54(d,1H,J=16Hz), 6.50(dd,1H,J=16 and 6Hz), 6.84(dd,1H,J=16 and 6Hz), 6.86(d,1H,J=16Hz), 7.12-7.34(m,5H)

IR (film, cm^{-1}): 1670, 1540, 1145

MS m/e (rel. intensity): 283(M^+,24.7), 252(8.2), 224(100)

Reaction of 156b with cinnamaldehyde

This reaction was carried out in the same manner as the reaction between 156a and cinnamaldehyde. 2E,4E,6E-methyl 7-

phenyl-3-morpholinohepta-2,4,6-trienoate 159b was obtained in 83% yield.

^{1}H NMR ($CDCl_3$, 200MHz): 3.10(m,4H), 3.63(s,3H), 3.73(m,4H), 4.90(s,1H), 6.62(d,1H,J=16Hz), 6.63(dd,1H,J=16 and 6Hz), 6.90(dd,1H,J=16 and 6Hz), 6.97(d,1H,J=16Hz), 7.16-7.38(m,5H)

IR (film, cm^{-1}): 1690, 1550, 1150

MS m/e (rel. intensity): 299(M^+,41.0), 268(9.1), 240(100)

Reaction of 156a with butanal

The reaction was done in the same manner as the reaction of 156a with benzaldehyde, except that a 2:1 mixture of ether and acetonitrile was used as eluant in the flash chromatography. 4-pyrrolidino-6-(n-propyl)-5,6-dihydro-1,2-pyrone 160a was obtained in 53% yield.

^{1}H NMR ($CDCl_3$): 0.73-1.77(m,7H), 1.93(m,4H), 2.40(d,2H,J=8Hz), 3.27(m,4H), 4.20(m,1H), 4.63(m,1H)

IR (film, cm^{-1}): 1660, 1570, 1240

MS m/e (rel. intensity): 209(M^+,33.6), 166(100), 150(29.2)

Reaction of 156b with butanal

The reaction was performed in the same way as the reaction of 156a with butanal. 4-morpholino-6-(n-propyl)-5,6-dihydro-1,2-pyrone 160b was obtained in 49% yield.

^{1}H NMR ($CDCl_3$): 0.80-1.90(m,7H), 2.40(d,2H,J=7Hz), 3.23(m,4H), 3.77(m,4H), 4.33(m,1H), 4.87(s,1H)

IR (film, cm^{-1}): 1660, 1565, 1230

MS m/e (rel. intensity): 225(M^+,13.1), 182(100), 166(19.5),

chemical analysis	cal.	C	64.04%	H	8.44%
	found	C	63.84%	H	8.54%

Reaction of 156b with acetone

To a mixture of acetone (2 mmol) which was freshly distilled over anhydrous K_2CO_3, and $TiCl_4$ (1 mmol) in 3 ml of CH_2Cl_2 at -78°C under N_2 was added 156b (1 mmol). The reaction mixture was stirred 3 hrs at -78°C then overnight at room temperature. Saturated sodium carbonate solution was added, and the mixture was extracted with ether. The ether extract was dried with $MgSO_4$ and filtered, the filtrate was concentrated to give an oil which was purified by flash chromatography (eluant hexane:ether 2:1). Methyl 5-hydroxy-5-methyl-3-oxohexanoate 162 was obtained in 44% yield. Spectroscopic data are identical to Lit. reported [118].

Reaction of 156b with cyclohexanone

The reaction was done by the same procedure as the reaction between 156b and acetone. Methyl 4-(1'-hydroxycyclohexanyl)-3-morpholinocrotonate 163 was obtained in 56% yield.

^1H NMR ($CDCl_3$): 1.57(m,10H), 3.07(s,2H), 3.23(m,4H), 3.50(b,1H), 3.68(s,3H), 3.77(m,4H),5.03(s,1H)

IR (film, cm^{-1}): 3400, 1650, 1570,1165

MS m/e (rel. intensity): 283(M^+,1.1), 265(4.3), 252(5.5)

Reaction of 156a with bezoyl chloride

To a mixture of 156a (1 mmol) and benzoyl chloride (1 mmol) in 5 ml CH_2Cl_2, was added $TiCl_4$ (1 mmol) at 0°C under N_2. The reaction mixture was stirred for 3 hrs at 0°C, then overnight at

room temperature. Saturated sodium carbonate solution was adeed and the mixture was extracted with ether. The ether extract was dried with $MgSO_4$ and filtered. The filtrate was evaporated to give a yellow oil which was purified by flash chromatography (eluant: ethyl acetae) to give 4-pyrrolidino-6-phenyl-1,2-pyrone 164 in 44% yield.

^1H NMR ($CDCl_3$): 1.93(m,4H), 3.30(m,4H), 4.87(d,1H,J=2Hz), 6.20(d,1H,J=2Hz), 7.17-7.80(m,5H)

IR (film, cm^{-1}): 1675, 1635, 1545

MS m/e (rel. intensity): 240(M^+,100), 213(51.5), 77(51.3)

chemical analysis	cal.	C	74.69%	H	6.22%
	found	C	74.52%	H	6.39%

Reaction of 156b with benzoyl chloride

The reaction was done in the same manner as the reaction of 156a with benzoyl chloride. Benzoyl morpholine 165 was obtained in 61% yield.

Diels-Alder reaction of 156a with dimethyl acetylenedicarboxylate

A mixture of 156a (1 mmol) and dimethyl acetylenedicarboxylate (2 mmol) in 15 ml of dry benzene was refluxed for 3 days. The reaction mixture was cooled to room temperature. A solution of 2 ml 1.5N HCl was adeed and the mixture was stirred for 0.5 hr. Saturated sodium bicarbonate solution was added until the mixture was basic. The mixture was extracted with ether and the ether extract was dried with $MgSO_4$ and then filtered. The filtrate was concentrated by rotary evaporator to give a brown oil which was

purified by flash chromatography to give 156 mg of dimethyl 2-hydroxy-4-pyrrolidino-o-phthaolate 167. The yield was 57%. mp: 128-130°C

^{1}H NMR ($CDCl_3$): 1.83-2.07(m,4H), 3.17-3.38(m,4H), 3.80(s,3H), 3.83(s,3H), 5.93(d,1H,J=3Hz), 6.03(d,1H,J=3Hz), 11.03(s,1H)

IR ($CHCl_3$, cm^{-1}): 3100, 1725, 1650

MS m/e (rel. intensity): 279(M^+,90.7), 248(56.6), 189(100)

Preparation of enamines

1-Morpholinobutene 112 was madde by the procedure of Mannic and Davidsen in 41% yield. bp:90-91 /14mm (lit.[45], bp 73.5-74.5°C/10mm)

The enamines of cyclopentanone, cyclohexanone and ethyl acetoacetae were made by the water separator method.

ethyl 3-morpholinocrotonate 189, yield: 77%, bp: 106-109°C/0.4mm

1-morpholinocyclopentene 193, yield: 82%, bp: 108-110°C/14mm (lit.[39], 104-106°C/12mm)

1-morpholinocycohexene 102, yield: 84%, bp: 112-114°C/14mm (lit. [39], bp 104-106°C/12mm)

The following enamines were made by the procedure of White and Weingarten [94].

1-morpholinocycloheptene 194, yield: 54%, bp: 130-133°c/15mm (lit. [93], 133-135°C/17mm)

1-morpholinocyclooctene 195, yield: 61%, bp: 81-83°C/1mm (lit. [93], 83-85°C/0.01mm)

1-morpholinocyclododecanene 211, yield: 90%, bp: 132-135°C/0.1mm (lit. [68], 128-130°C/0.05mm)

1-morpholinocyclopentadecanene 213, yield: 91%, bp: 158-161°C/0.1mm (lit. [68], 163-164°C/0.2mm)

3-morpholino-2-pentene 201, yield: 52%, bp: 50-51°C/0.5mm (lit. [93], 77-78°C/9mm)

4-morpholino-3-heptene 203, yield: 57%, bp: 67-69°C/0.2mm (lit. [93], 102-106°C/12mm)

3-pyrrolidino-2-pentene 202, yield: 57%, bp:36-38°C/0.5mm (lit. [93], 62-67°C/8mm)

4-pyrrolidino-3-heptene 204, yield: 60%, bp: 56-58°C/0.2mm

Self-condensation of methyl 4-trimethylsilyl-3-crotonate 156b

To a solution of 257 mg of 156b (1 mmol) in 5 ml CH_2Cl_2 was added 0.5 mmol of $TiCl_4$ under N_2 at -78°C. the reaction mixture was stirred for 3 hrs at -78°C then overnight at room temperature. It was added into a saturated sodium carbonate solution, stirred for 0.5 hr and extracted with ether. The extract was dried with $MgSO_4$, filtered and concentrated with rotary evaporator to give a yellow oil which was then purified by flash chromatography (eluted with a 1:1 mixture of ether and hexane). Methyl 2-methyl-4-morpholino-6-hydroxybenzoate 172 was obtained in 49% yield. mp:108-109°C

^1H NMR ($CDCl_3$): 2.13(s,3H,$-CH_3$), 3.07-3.23(m,4H, morpholino), 3.63-3.80(m,4H, morpholino), 3.83(s,3H, $-OCH_3$), 6.10(s,2H, aromatic), 11.63(s,1H, -OH)

IR (KBr, cm^{-1}): 1640, 1600, 1205

MS m/e (rel. intensity): 251(M^+, 76.5), 220(22), 219(50.3) 161(100), 133(28)

Self-condensation of methyl 3-morpholinocrotonate 153b in the presence of titanium tetrachloride

The reaction was performed in the same manner as the self-condensation of 156b. 1,4-pyrone 185 was obtained in 75% yield.

^{1}H NMR of 185 ($CDCl_3$): 2.27(s,3H,-CH_3), 2.37(s,3H, -CH_3), 3.88(s,3H,-OCH_3), 6.13(s,1H,vinyl)

IR (film, cm^{-1}): 1735, 1670, 1635

MS m/e (rel. intensity): 182(M^+, 9.9), 151(17.0), 124(29.5), 109(11.0), 67(63.7), 43(100)

Reaction of 156b with 153b

To a mixture of 257 mg of 156b (1 mmol) and 185 mg of 153b (1 mmol) in 5 ml CH_2Cl_2 was added 1 mmol titanium tetrachloride under N_2 at -78°C. The reaction mixture was stirred for 3 hrs at -78°C and then overnight at room temperature. Saturated sodium carbonate solution was added, and the mixture was extracted with ether. The ether extract was dried with $MgSO_4$, filtered and concentrated to give a yellow solid which was purified by flash chromatography (eluted with 1:1 mixture of ether and hexane). A quantity of 203 mg of 172 was obtained in 71% yield.

Reaction of 156a with 153a

The reaction was performed in the same manner as the reaction of 156b and 153b. Methyl 2-methyl-4-pyrrolidino-6-hydroxybenzoate 184 was obtained in 78% yield. mp: 101-102°C

^{1}H NMR ($CDCl_3$): 1.80-2.03(m,4H, pyrrolidino), 2.40(s,3H, -CH_3), 3.13-3.33(m,4H, pyrrolidino), 3.80(s,3H,-OCH_3), 5.83(s,2H,

aromatic), 11.80(s,1H,-OH)

IR (KBr, cm^{-1}): 1630, 1615, 1320

MS m/e (rel. intensity): 235(M^+, 100), 204(32.9), 203(88.8), 175(16.9), 147(22.4)

Self-condensation of 153b in the presence of TFA

The reaction was performed by Bohme's procedure: To 740 mg of 153b (4 mmol) was added 432 mg TFA (4 mmol) at 0°C, the reaction mixture was stirred for 1 hr at 0°C then overnight at 40-50°C. The reaction mixture was diluted with 50 ml of ether, washed with satrurated sodium bicarbonate. The ether phase was dried with $MgSO_4$ and filtered. The filtrate was then concentrated by rotary evaporator to give 416 mg of methyl 2-morpholino-4-methyl-6-hydroxybenzoate 154g. The yield was 83%. mp:115-116°C (lit. [82], mp: 116°C)

Decarboxylation of 172 to 3-morpholino-5-methylphenyl 174

To 50 mg of 172 was added 5 ml 20% KOH, the reaction mixture was refluxed overnight. It was cooled to room temperature and a solution of 1N HCl was added until the solution became acidic. The mixture was extracted with ether. The ether extract was dried with $MgSO_4$, filtered and then concentrated to give 27 mg of 174 [82]

^1H NMR ($CDCl_3$): 2.30(s,3H,$-CH_3$), 3.03-3.20(m,4H,morpholino), 3.78-3.95(m,4h, morpholino), 6.17-6.30(m,3H, aromatic)

IR ($CHCl_3$, cm^{-1}): 3600, 1610, 1590, 1120

Decarboxylation of 154g

The reaction was carried out under identical conditions as used for the decarboxylation of 172. A quantity of 30 mg of 174 was obtained. It is identical in all respects with the compound obtained from the decarboxylation of 172.

Reaction of 156a with ethyl 3-morpholinocrotonate 189

To a mixture of 241 mg of 156a (1 mmol) and 199 mg of 189 (1 mmol) in 5 ml of CH_2Cl_2 was added 1 mmol of titanium tetrachloride under N_2 at -78°C. The reaction mixture was stirred 6 hrs at -78°C then overnight at room temperature. Saturated sodium carbonate solution was added until the mixture became basic. The mixture was extracted with ether. The ether extract was dried with $MgSO_4$, filtered and the filtrate was concentrated to give a yellow solid which was purified by flash chromatography (eluted with ether and hexane, 1:1). A quantity of 162 mg of ethyl 2-methyl-4-pyrrolidino-6-hydroxybenzoate 190 was obtained. The yield was 65%. mp: 84-84°C

^1H NMR ($CDCl_3$): 1.37(t,3H,J=7HZ, $-OCH_2\underline{CH_3}$), 1.83-2.07(m,4H, pyrrolidino), 2.50(s,3H,$-CH_3$), 3.17-3.40(m,4H, pyrrolidino), 4.33(q,2H,J=7Hz,ethoxy), 5.90(s,2H, aromatic), 11.90(s,1H, -OH)

IR (KBr, cm^{-1}): 3400, 1635, 1310

MS m/e (rel. intensity): 249(M^+, 94.5), 204(79.9), 203(100), 175(75.8), 147(74.8)

The reaction of 156a with 1-morpholinocyclohexene 102

To a mixture of 241 mg of 156a (1 mmol) and 167 mg of 102 in 25 ml of CH_2Cl_2 was added 228 mg 0f trifluoroacetic acid at 0°C. The

reaction mixture was stirred for 1 hr at 0°C then refluxed for 24 hrs. The reaction mixture was diluted with 50 ml of ether and washed with saturated sodium bicarbonate. The organic phase was dried with $MgSO_4$, filtered and then concentrated with rotary evaporator to give a yellowish solid which was purified by flash chromatography (eluted with ethyl acetate and hexanem 1:1) to give 136 mg of 7-hydroxy-9-pyrrolidino-[4]-ortho-cyclophane 192. The yield of 192 was 63%. mp:157-159°C

^1H NMR ($CDCl_3$): 1.67-2.20(m,8H, two methylenes from pyrrolidine, two methylenes from cyclohexene), 2.40-2.83(m,4H, two methylenes adjacent to aromatic ring), 4.60(b,1H, -OH), 5.97(s,2H, aromatic)

IR (KBr, cm^{-1}): 3400, 1620, 1580

MS m/e (rel. intensity): 217(M^+, 100), 216(98.7), 189(54.5), 161(39.5)

Chemical analysis, calculated: C 77.42% H 8.76%

found: C 77.48% H 8.64%

Reaction of 156a with 1-morpholinocyclopentene 193

To a mixture of 241 mg of 156a (1 mmol) and 153 mg 193 (1 mmol) in 25 ml of 1,2-dichloroethane was added 228 mg of TFA (2 mmol) at 0°C. The reaction mixture was stirred for 1 hr at 0°C and then refluxed for 24 hrs. The mixture was diluted with 50 ml of ether, washed with saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated to give a yellow solid which was purified by flash chromatography (eluted with petroleum ether and ethyl acetate,

5:1) to give [3]-ortho-cyclophane 196 in 64% yield. mp: 166-168°C

^{1}H NMR ($CDCl_3$): 1.90-2.20(m,6H,-CH_2-CH_2- from pyrrolidine, -CH_2- from cyclopentene), 2.80(t,2H, -CH_2- adjacent to aromatic ring), 2.93(t,2H, another -CH_2- adjacent to aromatic ring), 3.17-3.37(m,4H, pyrrolidine), 5.92(d,1H, J=2Hz, aromatic), 6.13(d,1H,J=2Hz, aromatic)

IR (KBr, cm^{-1}): 3310, 1630, 1600, 1580

MS m/e (rel. intensity): 203(M^+, 87.6), 202(100), 174(21.0), 147(31.8), 133(22.3)

Reaction of 156a with 1-mortholinocycloheptene 194

The reaction was performed in the same manner as the reaction between 156a and 193. [5]-ortho-Cyclophane 197 was obtained in 59% yield. mp: 149-150°C

^{1}H NMR ($CDCl_3$): 1.53-2.12(m,10H,-$(CH_2)_2$- from pyrrolidine, -$(CH_2)_3$- from side hydrocarbon ring), 2.67-2.87(m,4H, pyrrolidine), 4.80(b,1H,-OH), 5.88(d,(1H,J=2Hz,aromatic), 6.05(d,1H,J=2Hz,aromatic)

IR (KBr, cm^{-1}): 3400, 1610, 1570, 1500

MS m/e (rel. intensity): 231(M^+, 100), 230(82.1), 203(23.1), 202(44.2)

Reaction of 156a with 1-morpholinocyclooctene 195

The reaction was performed in the same manner as the reaction between 156a and 193. [6]-ortho-Cyclophane 198 was obtained in 67% yield. mp: 157-159°C

^{1}H NMR ($CDCl_3$): 1.47(b,8H, -$(CH_2)_4$- from side hydrocarbon

ring), 1.87-2.08(m,4H, pyrrolidine), 2.63-2.83(m,4H, 2-CH_2-adjacent to aromatic ring), 4.73(s,1H,-OH), 6.00(AB quartet,2H,J=2Hz, aromatic)

IR (KBr, cm^{-1}): 3400, 1610, 1570

MS m/e (rel. intensity): 245(M^+, 100), 244((54.9), 217(41.4), 202(67.3)

Chemical analysis: cal. C 78.37% H 9.37%

found C 78.30% H 9.51%

The reaction of 156b with 1-morpholinocyclohexene 102

The reaction was performed in the same manner as the reaction between 156a and 102. Methyl 3-morpholino-4-cyclohexylidenecrotonate 199 was isolated in 52% yield.

^1H NMR ($CDCl_3$): 1.57(b,6H, -$(CH_2)_3$-), 2.00-2.40(m,4H, 2-CH_2-connected to the double bond), 3.25-3.45(m,4H, morpholine), 2.63-3.83(m,4H,morpholine), 3.65(s,3H,-OCH_3), 4.83(s,1H,vinyl), 5.83(s,1H,vinyl)

IR ($CHCl_3$, cm^{-1}): 1685, 1560, 1145

MS m/e (rel. intensity): 265(M^+, 60.2), 234(25.1), 222(68.7), 206(66.5), 122(100)

Reaction of 156a with 3-morpholino-pentene-2 201

To a mixture of 241 mg of 156a (1 mmol) and 310 mg of 201 (2 mmol) in 25 ml of 1,2-dichloroethane was added 342 mg of TFA (3 mmol) at 0°C. The reaction mixture was stirred for 1 hr at 0°C then refluxed for 48 hrs. It was allowed to cool to room temperature and was diluted with 50 ml of ether. The solution was

washed with saturated sodium bicarbonate solution. The organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated to give a brown oil which was purified by flash chromatography (eluted with hexane and ethyl acetate, 2:1) to give 92 mg of 2,4,5,-trimethyl-3-morpholinophenol 200 plus 54 mg of 184. The yield for 200 was 41%. mp: 163-164°C .

^1H NMR of 200, ($CDCl_3$): 2.20(s,6H, 2-CH_3), 2.23(s,3H, -CH_3), 3.03-3.18(m,4H, morpholine), 3.73-3.88(m,4H, morpholine), 4.83(s,1H, -OH), 6.50(s,1H, aromatic)

IR (KBr, cm^{-1}): 3300, 1600, 1585, 1100

MS m/e (rel. intensity): 221(M^+, 90.5), 220(55.1), 206(32.2), 176(63.2), 163(100)

Chemical analysis: cal. C 70.59% H 8.60%

found C 70.68% H 8.77%

Reaction of 153a with 201

The reaction was performed under identical conditions used for the reaction between 156a and 201. Only compound 184 was isolated.

Reaction of 156a with 201 in the presence of titanium tetrachloride

To a mixture of 241 mg of 156a (1 mmol) and 310 mg of 201 (2 mmol) in 10 ml of CH_2Cl_2 was added 0.17 ml of $TiCl_4$ (1.5 mmol), at -23°C under N_2. The reaction mixture was stirred for 3 hrs at -23°C and then overnight at room temperature. Concentrated sodium carbonate solution was added to the mixture. It was then extracted with ether. The organic layer was dried with $MgSO_4$ and filtered.

The filtrate was concentrated by rotary evaporator to give a brown oil which was purified by flash chromatography to give 200 in 38% yield. A quantity of 62 mg of self-condensation product of 156a was also isolated.

Reaction of 156a with 3-pyrrolidinopentene-2 202

The reaction was performed under the same conditions as the reaction of 156a with 201 in the presence of TFA. 2,4,5-trimethyl-3-pyrrolidinophenol 205 was obtained in 42% yield.

^{1}H NMR ($CDCl_3$): 1.93-2.13(m,4H, pyrrolidine), 2.13(s,3H,-CH_3), 2.16(s,3H,-CH_3),2.22(s,3H,-CH_3), 3.10-3.30(m,4H,pyrrolidine), 4.48(s,1H,-OH), 6.50(s,1H,aromatic)

IR ($CHCl_3$, cm^{-1}): 3600, 1580, 1460, 1070

MS m/e (rel. intensity): 205(M^+, 99.6), 204(100), 190(57.5), 176(65.9), 162(70.1)

Reaction of 156a with 4-morpholinoheptene-3 203

The reaction was performed under the same condition as the reaction of 156a with 201 in the presence of TFA. 5-methyl-2,4-diethyl-3-morpholinophenol 206 was obtained in 37% yield. mp: 185-187°C

^{1}H NMR ($CDCl_3$): 1.15(t,3H,J=7Hz,ethyl), 1.23(t,3H,J=7Hz,ethyl), 2.28(s,3H,-CH_3), 2.73(q,2H,J=7Hz,ethyl), 2.77(t,2H,J=7Hz,ethyl), 3.13-3.30(m,4H,morpholine), 3.77-3.93(m,4H,morpholine), 4.83(s,1H,-OH), 6.53(s,1H,aromatic)

IR (KBr, cm^{-1}): 3260, 1590, 1410, 1100

MS m/e (rel. intensity): 249(M^+, 95.3), 234(19.7), 220(65.8),

170(100).

Chemical analysis: cal. C 72.29% H 9.24%

found C 72.20% H 9.17%

Reaction of 156a with 4-pyrrolidinoheptene-4 204

The reaction was performed in the same manner as the reaction between 156a and 201 in the presence of TFA. 5-Methyl-2,4-diethyl-3-pyrrolidinophenol 207 was obtained in 36% yield.

^{1}H NMR ($CDCl_3$): 1.13(t,3H,J=7Hz,ethyl), 1.23(t,3H,J=7Hz,ethyl), 1.93-3.12(m,4H,pyrrolidine), 2.28(s,3H,$-CH_3$), 2.63(q,4H,J=7Hz, two ethyls), 3.13-3.33(m,4H,pyrrolidine), 6.50(s,1H,aromatic).

IR ($CHCl_3$, cm^{-1}): 3600, 1580, 1255, 1085

MS m/e (rel. intensity): 233(M^+, 100), 232(73.1), 218(95.4), 204(86.9), 160(30.8)

Reaction of 156a with 1-morpholinocyclododecanene 211

To a mixture of 2.57 g of 211 (10 mmol) and 1.20 g of 156a (5 mmol), 1.14 g of TFA (10 mmol) was added dropwise at 0°C with stirring. The mixture was warmed to room temperature and stirred for 10 minutes and then heated to 80°C. It was stirred for 3 days at 80°C. To the cooled reaction mixture, 300 ml of ether was added. The ether solution was washed with aqueous acid (1.5N HCl), dried with $MgSO_4$ and filtered. The filtrate was concentrated to give 2.45 g of brown oil, which was purified by flash chromatography (eluted with petroleum ether and ethyl acetate, 9:1) to give 12-hydroxy-14-methyl-15-morpholino-[9]-metacyclophane 212 in 51% yield. mp: 174-177°C

^{1}H NMR ($CDCl_3$): 0.24-0.44(m,2H,-CH_2- from the side chain), 0.70-1.20(m,8H,4-CH_2- of the side chain) 1.48-1.74(m,4H,2-CH_2- of the side chain), 2.20(s,3H,-CH_3), 2.56-3.16(m,4H, 2-CH_2- of the side chain, adjacent to aromatic ring), 3.18-3.30(m,4H, morpholine), 3.72-3.87(m,4H, morpholine), 4.68(s,1H,-OH), 6.44(s,1H,aromatic)

IR (KBr, cm^{-1}): 3290, 1590, 1440, 1100 850

MS m/e (rel. intensity): 317(M^+, 91.2), 260(36.9), 249(100), 204(62.5), 176(90.6), 149(77.3)

Chemical analysis: cal. C 75.71% H 9.78%

found C 75.76% H 9.78%

Reaction of 153a with 211

The reaction was performed under the same conditions as the reaction between 156a and 211. Only compound 154c and cyclododecanone were isolated from the reaction mixture.

Reaction of 156a with 1-morpholinocyclopentadecene 213

The reaction was performed in the same manner as the reaction between 156a and 211. [12]-meta-Cyclophane 214 was obtained in 25% yield. mp: 210-214°C

^{1}H NMR ($CDCl_3$): 0.76-1.34(m,16H,side chain), 1.50-1.84(m,4H,side chain), 2.20(s,3H,-CH_3), 2.42-3.54(m,8H, 4H from morpholine, 4H from side chain), 3.70-3.84(m,4H,morpholine), 4.48(s,1H,-OH), 6.46(s,1H,aromatic)

IR (KBr, cm^{-1}): 3300, 1595, 1150

MS m/e (rel. intensity): 359(M^+, 100), 316(22.1), 302(46.2),

149(44.0)

Reaction of 156a with 1-morpholinobutene 112

The reaction was performed by the same fashion as the reaction between 156a and 201 in the presence of TFA. After the usual wokup a black sticky oil was obtained. No aromatic peak was observed in the ^1H NMR. No identifiable compound was isolated by flash chromatography. This reaction was repeated by using $TiCl_4$ as the catalyst instead of TFA. This time, only compound 184 was isolated.

The preparation and separation of diastereomers 234 (method A)

R-(-)-Methoxyphenylacetic acid (116 mg, 1 mmol) was dissolved in a ten-fold excess of thionyl chloride. The solution was refluxed for about 10 minutes in an oil bath, then cooled to room temperature. Thionyl chloride was removed from the mixture by water aspirator and then under high vaccum for 30 minutes. The crude acid chloride was diluted with 10 ml of dry THF. To the mixture was added a solution of 158 mg 212 in 10 ml of THF, followed by 122 mg of dimethylaminopyridine under vigrous stirring and N_2. The reaction mixture was stirred for 30 minutes at room temperature and overnight at 50°C. To the cooled reaction mixture 100 ml of ether was added. This solution was washed with 5% HCl, saturated sodium carbonate solution and then water. The ether solution was dried with $MgSO_4$, filtered and the filtrate was concentrated by rotary evaporator to give 204 mg of yellow oil. Purification by flash chromatography, eluted with petroleum ether

and ethyl acetate, gave 188 mg of colorless oil. ^{1}H NMR spectrum of this oil showed a 1:1 mixture of α-234 and β-234. This mixture was separated by TLC Mesh chromatography. The same operation procedure as described in the literature [119] was followed except that more silica gel was used in our case. To a 24 mm diameter column with 8.5 in. high silica gel was loaded 150 mg of the above mixture. It was eluted with a combination solvent (pentane:acetonitrile:ethyl acetate=20:1:1) at a rate of 2ml/minte. There was obtained 44 mg of α-234 and 79 mg of β-234, each with >95% purity.

^{1}H NMR of α-234 ($CDCl_3$): 0.1-1.9(m,14H, side chain), 2.15(s,3H,-CH_3), 2.40-3.00(m,4H,2-CH_2- of the side chain, adjacent to the aromatic ring), 3.00-3.10(m,4H,morpholine), 3.51(s,3H,-OMe), 3.64-3.74(m,4H,morpholine), 4.96(s,1H,-$\overset{|}{C}$H-), 6.54(s,1H,aromatic), 7.32-7.54(m,5H,-Ph)

^{1} NMR of β-234 ($CDCl_3$): 0.1-1.9(m,14H, side chain), 2.15(s,3H, -Me), 2.50-3.10(m,4H, 2-CH_2- of the side chain adjacent to the aromatic ring), 3.10-3.20(m,4H,morpholine), 3.48(s,3H,-OMe), 3.64-3.74(m,4H,morpholine), 4.96(s,1H, -$\overset{|}{C}$H-), 6.62(s,1H, aromatic), 7.32-7.54(m,5H,-Ph)

MS of 234 (rel. intensity): 465(M^+, 38.4), 317(37.2), 149(22.3) 121(100)

Reduction of α-234 to give (-)-212

To 5 ml of dry THF was added 20 mg of lithium aluminum hydride, followed by the addition of 40 mg of α-234 in 5 ml of THF dropwise with stirring. The reaction mixture was stirred for 1 hr

at 50°C, then refluxed overnight. The cooled reaction mixture was diluted with 50 ml of ether and acidified with 1.5N HCl, washed with water and dried with $MgSO_4$. After the filtration the filtrate was concentrated by rotary evaporator to give 72 mg of crude product. Purification of this crude product by flash chromatography (eluted with petroleum ether and ethyl acetate, 7:1) gave 19 mg of (-)-212 (67% yield). Its NMR and IR spectra are identical to those of racemic 212. It has $[\alpha]_D^{20}=-30.0°$ (c=0.010g/ml, acetone).

Reduction of β-234 to give (+)-212

A quantity of 70 mg β-234 was reduced by the same method as in the reduction of α-234. A quantity of 33 mg of (+)-212 was obtained (69% yield). Its NMR and IR spectra are identical to those of the racemic 212. It has $[\alpha]_D^{20}=+26.4°$ (0.005g/ml, acetone).

Preparation and separation of diastereomers 235

A quantity of 190 mg of racemic 214 was converted to 235 by method A described above. The reaction gave 225 mg of 235 which was a 1:2 mixture of α-235 and β-235 by ^1H NMR. The above mixture (150 mg) was separated by TLC mesh chromatography (eluted with pentane, acetonitrile and ethyl acetate 20:1:1) to give 47 mg of α-235 (95% pure) and 72 mg of β-235 (90% pure).

^1H NMR ($CDCl_3$): α-235: 0.80-1.60(m,20H, side chian), 2.23(s,3H,$-CH_3$), 2.16-3.46(m,8H, 2-CH_2- for the side chain and 2-CH_2- for the morpholine),3.46(s,3H,$-OCH_3$), 4.94(s.1H,-CH-),

6.66(s,1H,aromatic), 7.34-7.60(m,5H,-Ph); β-isomer: 0.8-2.0(m,20H, side chain), 2.23(s,3H,-OCH_3), 2.44-3.40(m,8H), 3.46(s,3H,-OCH_3), 4.94(s,1H), 6.66(s,1H, aromatic), 7.34-7.60(m,5H, Ph).

MS of 235 (rel. intensity): 507(M^+, 46.2), 359(19.9),149(17.9), 121(100)

Reduction of α-235 to (-)-214

A quantity of 40 mg of α-235 was reduced by excess LAH to give 23 mg of (-)-214 (82% yield). Its ^1H NMR and IR are identical to those of racemic 214. It has $[\alpha]_D^{20}$=-17.3° (c=0.015g/2ml, THF).

Reduction of β-235 to (+)-214

A quantity of 36 mg of β-235 was reduced by LAH to give 19 mg of (+)-214 (75% yield). Its ^1H NMR and IR spectra are identical to those of racemic 214. It has $[\alpha]_D^{20}$=10.8° (c=0.007g/ml, THF).

Preparation of 1,3-Bis(trimethylsiloxy)-1-methoxybuta-1,3-diene 17

Compound 17 was prepared by literature [12] method in 92% yield. Its ^1H NMR was identical to that reported.

preparation of cyclotetradecanedione-1,3 241

To a mixture of 16 g 1-morpholinocyclododecanene 211 (0.063 mol) and 7.07 g triethylamine (0.07 mol) was added a solution of 4.9 g acetyl chloride(0.063 mol) in 10 ml chloroform (free of ethanol) dropwise at 0°C under N_2 with vigrous stirring. The reaction mixture was stirred for 5 hrs at room temperature, then

diluted with 50 ml chloroform and acidified with 60 ml of 2.5N HCl. The mixture was stirred for 5 hrs at room temperature, extracted with chloroform and dried with $MgSO_4$. It was filtered and the filtrate was concentrated to give a yellow oil which gave 5.1 g crude product after vaccum distillation. The crude product was purified by flash chromatography on silica gel to give 4.2 g pure 241 (28% yield). mp: 30-32°C (lit.[67], mp: 31-32°)

Preparation of 2-bezyl-cyclotetradecanedione-1,3 242 (method B)

To 1.12 g 241 in 5 ml of 5% potassium hydroxid was added 0.86 g of bezyl bromide dropwise with stirring. The reaction mixture was stirred for 2 hrs at room temperature and then acidified with 2.5N HCl and extracted with ether. The ether extract was dried with $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporator and the residue was purified by flash chromatography on silica gel, eluted with petroleum ether and ethyl acetate (20:1), to give 1.47 g 242 (94% yield) mp: 81-83°C

^1H NMR ($CDCl_3$): 1.0-1.8(m,18H, side chain), 2.2-2.6(m,4H, side chain), 3.66(d,2H,J=7Hz, -CH_2-Ph), 3.93(t,1H,J=7Hz,-CH-), 7.07(s,5H,-Ph).

IR (KBr, cm^{-1}): 1690, 740, 695

MS m/e (rel. intensity): 314(M^+, 41.8), 286(91.9), 159(71.5), 146(67.5), 55(100)

Preparation of 2-benzyl-3-trimethylsiloxy-cyclotetradecan-2-en-one 243 (method C)

Compound 243 was prepared by Danishefsky's method [104] in

quantitative yield. ^1H NMR spectrum shows a 2:1 mixture of two geometry isomers.

^1H NMR ($CDCl_3$): 0.13(s,9H, trimethylsilyl), 0.4-2.7(m,24H, side chain), 3.43(s,2H, -$\underline{CH_2}$-Ph, major isomer), 3.60(s,2H, -$\underline{CH_2}$-Ph, minor isomer), 7.04(s,5H,-Ph).

IR (film, cm^{-1}): 1670, 1600, 1450, 840

MS m/e (rel. intensity): 386(M^+, 9.2), 371(35.5), 296(47.8), 169(49.5),73(100)

Preparation of 14-(methyl carboxylate)-15-hydroxy-17-benzyl-[11]-metacyclophane 244 (method D)

To a mixture of 0.77 g 243 (2 mmol) and 0.78 g 17 (3 mmol) in 30 ml of dry CH_2Cl_2 was added 0.22 ml of $TiCl_4$ (2 mmol) under N_2 at -23°C. The reaction mixture was stirred for 8 hrs at -23°C then overnight at room temperature. Concentrated sodium bicarbonate solution was added until the mixture was basic. The mixture was extracted with ether and dried with $MgSO_4$. It was filtered and the filtrate was concentrated to give 0.71 g yellowish solid which was purified by flash chromatography on silica gel to give 0.54 g of 244 (69% yield). mp: 112-114°C

^1H NMR ($CDCl_3$): 0.4-2.0(m,18H, side chain), 2.06-3.70(m,4H, side chain), 3.84(s,3H, -OMe), 4.20(s,2H,-$\underline{CH_2}$-Ph), 6.63(s,1H,aromatic), 6.70-7.27(m,5H,-Ph), 10.90(s,1H,-OH).

IR (KBr, cm^{-1}): 3470, 1650,1240

MS m/e (rel. intensity): 394(M^+, 11.3), 362(38.9), 314(34.8), 286(99.9), 159(93.8), 91(100)

Chemical analysis: cal. C 79.19% H 8.63%

found C 79.23% H 8.67%

Preparation of S-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride 245

To 10 ml of thionyl chloride was added 4.0 g of R-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and 0.1 g of sodium chloride crystal. The reaction mixture was refluxed for 50 hrs. thionyl chloride was removed by rotary evaporator and the residue oil was distilled under vaccum to give 3.52 g 245 (81.2% yield). bp: 67-68° /2mm (lit. [105], bp: 54-55° /1mm)

Preparation and separation of the diastereomers 246

To a solution of 253 mg 245 (1 mmol) in 10 ml dry THF was added a solution of 197 mg (0.5 mmol) 244 and 122 mg of dimethylaminopyridine (1 mmol) in 10 ml dry THF slowly under vigrous stirring. The reaction mixture was stirred overnight at room temperature. To the mixture, 100 ml ether was added. It was washed with 1.5N HCl, then concentrated sodium carbonate solution and finally with water. The organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporator and a 1:1 mixture of α-246 and β-246 was obtained in quantitative yield. The two diastereomers were separated by TLC mesh chromatography (eluted with petroleum ether and ethyl acetate, 35:1). 66 mg of α-246 and 75 mg of β-246 were obtained from 180 mg of the mixture.

^1H NMR ($CDCl_3$,200MHz), α-246: 0.66-1.76(m,18H, side chain), 2.20-3.00(m,4H, side chain), 3.66(s,6H, -OMe and $-CO_2Me$),

4.25(AB q,2H,J=3Hz,-$\underline{CH_2}$-Ph), 6.82(s,1H,aromatic), 6.92-7.64(m,10H,2-Ph). β-246: 0.66-1.76(m,18H, side chain), 2.20-3.00(m,4H, side chain), 3.58(s,3H,-CO_2Me), 4.25(ABq,2H,J=3Hz,-$\underline{CH_2}$-Ph), 6.85(s,1H,aromatic), 6.92-7.64(m,10H,2-Ph).

MS of 246, m/e, (rel. intensity): 610(M^+, 9.1), 409(33.6), 190(49.8), 189(100), 91(48.8)

Reduction of α-246

α-246 (40 mg) was reduced with excess LAH in 15 ml dry THF. The reaction mixture was stirred for two days. A solution of 5% HCl was added until the mixture was slightly acidic (never add too much HCl, side reaction may occur). It was extracted with ether, dried with $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporator to give 38 mg crude product. The crude product was purified by flash chromatography on silica gel to give 18 mg (+)-247 (77% yield). mp: 138-139°C, $[\alpha]_D^{20}$=+12.6° (c=0.012g/2ml, acetone)

^1H NMR ($CDCl_3$): 0.37-1.90(m,18H, side chain), 2.0-3.1(m,4H, side chain), 4.16(s,2H,-$\underline{CH_2}$-Ph), 4.93(s,2H,-$\underline{CH_2}$-OH), 6.50(s,1H,aromatic), 6.80-7.5-(m,5H,-Ph).

IR (KBr, cm^{-1}): 3415, 1600, 1080

MS m/e (rel. intensity): 366(M^+, 11.6), 350(100), 348(87.9), 91(99.4).

Reduction of β-246

β-246 (34 mg) was reduced by LAH in THF to give (-)-247 (12 mg), mp: 138-140° , $[\alpha]_D^{20}$=-14.4° (c=0.006g/2ml, acetone). Its ^1H

NMR and IR spectra were identical to those of (+)-247

Preparation of 2-methyl-cyclotetradecanedione-1,3 251

Compound 251 was prepared in a similar manner as the literature [115] method. To 5 ml of 1M solution of tetrabutylamoniun fluoride in THF was added 1.12 g 241 (5 mmol) in 10 ml of THF. The solvent was removed by rotary evaporator. The residue was dissolved in 20 ml of chloroform, and to this solution was added 1.42 g of methyl iodide (10 mmol). The reaction mixture was stirred for 2 hrs at room temperature. Chloroform was removed by rotary evaporator and the residue was poured into ether and filtered. The filtrate was concentrated to give a white solid which was then purified by flash chromatography on silica gel and 1.04 g pure 251 was obtained (81% yield). mp: 35-37° (lit. [115], mp: 35-37°)

Preparation of 252

Compound 251 (714 mg, 3 mmol) was converted quantitatively to 252 by method C (see the preparation of 243). Two geometrical isomers are shown in its ^1H NMR spectrum.

^1H NMR ($CDCl_3$): 0.27(s,9H, trimethylsilyl of one isomer), 0.30(s,9H,trimethylsilyl of the other isomer), 1.35(m,18H, side chain), 1.80(s,3H,-Me, major isomer), 1.87(s,3H,-Me, minor isomer), 2.2-2.7(m,4H, side chain)

Preparation of 14-(methyl carboxylate)-15-hydroxy-17-methyl-[11]-metacyclophane 253

Compound 253 was synthesized by method D (see the preparation of 244) in 63% yield. It was a colorless needle after recrystalization from hexane. mp: 89-91°C

^{1}H NMR ($CDCl_3$): 0.4-1.8(m,18H, side chain), 2.27(s,3H,-Me), 2.1-3.5(m,4H, side chain), 3.93(s,3H,-OMe), 6.63(s,1H,aromatic), 10.07(s,1H,-OH).

IR (KBr, cm^{-1}): 3420, 1660, 1220

MS m/e (rel. intensity): 318(M^+, 49.0), 287(49.5), 286(100), 189(33.0)

Preparation and separation of diastereomers 254

Compound 253 (159 mg, 0.5 mmol) was converted into the diastereomeric esters 254 in 90% yield by the same procedure used for the preparation of 246. The two diastereoisomers were separated by TLC mesh chromatography on silica gel (eluted with petroleum ether and ethyl acetate, 35:1). There was obtained 53 mg of α-254 and 41 mg of β-254 from 140 mg of 254 mixture.

^{1}H NMR ($CDCl_3$): α-isomer, 0.46-1.80(m,18H, side chain), 2.32(s,3H,-Me), 2.36-3.18(m,4H, side chain), 3.66(s,3H,-OMe), 3.68(s,3H,-CO_2Me), 6.76(s,1H,aromatic), 7.44-7.65(m,5H,-Ph); β-isomer, 0.46-1.80(m,18H, side chain), 2.32(s,3H,-Me), 2.31-3.18(m,4H, side chain), 3.58(s,3H,-CO_2Me), 6.80(s,1H,aromatic), 7.44-7.65(m,5H,-Ph).

MS m/e (rel. intensity): 534(M^+, 2.6), 332(61.7), 189(100), 91(26.8)

Reduction of α-254 to (+)- 255

To 10 ml of dry ether was added 40 mg of LAH and 80 mg of α-254. The reaction mixture was stirred overnight at room temperature, then diluted with 50 ml ether and acidified with 1N HCl, the organic layer was washed with water and dried with $MgSO_4$. After filtration, the filtrate was concentrated to give 54 mg of white solid. It was purified twice by flash chromatography to give 36 mg of (+)-255 (83% yield). mp:123-125°C $[\alpha]_D^{20}$=+6.3° (c=0.036g/2ml, acetone)

^1H NMR ($CDCl_3$): 0.3-1.9(m,18H, side chain), 2.30(s,3H,-Me), 2.40-3.30(m,4H,side chain),4.90(s,2H,-$\underline{CH_2}$-OH), 6.53(s,1H,aromatic)

IR (KBr, cm^{-1}): 3610, 3400, 3200, 1600, 960

MS m/e (rel. intensity): 290(M^+, 9.0), 274(99.6), 272(82.4), 257(33.5), 136(100)

Chemical analysis: cal. C 78.62% H 10.34%

found C 78.71% H 10.32%

Reduction of β-254 to (-)-255

Compound β-254 was similarly reduced to (-)-255 in 74% yield. Its ^1H NMR and IR spectra were identical to those of (+)-255. mp: 123-125°C , $[\alpha]_D^{20}$=-8° (c=0.024g/2ml, acetone)

Preparation of 256

Compound 256 was synthesized from 241 in quantitative yield by method C (see the preparation of 243). Its ^1H NMR spectrum showed two geometrical isomers.

^1H NMR ($CDCl_3$): 0.07(s,9H,trimethylsilyl, minor isomer),

0.20(s,9H,trimethylsilyl, major isomer), 0.90-1.90(m,18H, side chain), 2.06-2.93(m,4H, side chain), 5.42(s,1H,vinyl, minor isomer), 5.50(s,1H, vinyl, major isomer).

IR (film, cm^{-1}): 1675, 1580, 1250, 840

Preparation of 14-(methyl carboxylate)-15-hydroxy-[11]-metacyclophane 257

Compound 257 was obtained by method D from the condensation of 256 and 17 in 59% yield. mp: 69-71°C

^1H NMR ($CDCl_3$): 0.62-1.90(m,18H, side chain), 2.40-2.67(m,2H, side chain), 2.80-3.03(m,2H, side chain), 3.83(s,3H,-OMe), 6.43(s,2H,aromatic), 10.70(s,1H,-OH).

IR (KBr, cm^{-1}): 3410, 1660, 1560, 1250

MS m/e (rel. intensity): 304(M^+, 54.1), 273(46.8), 272(100), 91(19.2).

Preparation of 258

Compound 258 was prepared from 257 by the same procedure as the preparation of 246. The yield was 92%.

^1H NMR ($CDCl_3$): 0.67-2.00(m,18H, side chain), 2.50-2.87(m,4H, side chain), 3.63(s,6H,-OMe and $-CO_2Me$), 6.80(s,1H,aromatic), 7.07(s,1H,aromatic), 7.33-7.73(m,5H,-Ph).

IR (CCl_4, cm^{-1}): 1770, 1730, 1260

MS m/e (rel. intensity): 520(M^+, 0.5), 488(4.4), 304(40.1), 205(42.3), 189(100).

Preparation of 260

The reaction was performed in the same manner as the

preparation of 241, except that propanoyl chloride was used instead of acetyl chloride. The yield of 260 was 62%.

Preparation of 261

Compound 261 was synthesized from 260 in quantitative yield by method C. Its ^1H NMR spectrum showed two geometrical isomers.

^1H NMR ($CDCl_3$): 0.2(s,9H,trimethylsilyl, major isomer), 0.24(s,9H,trimethylsilyl, minor isomer), 0.77-1.90(m,24H, side chain), 1.77(s,3H,-Me, major isomer), 1.83(s,3H,-Me, minor isomer), 2.33-2.73(m,4H, side chain)

IR (film, cm^{-1}): 1670, 1610, 1250, 840

Preparation of 17-(methyl carboxylate)-18-hydroxy-20-methyl-[14]-metacyclophane 262

The condensation reaction of 261 with 17 was performed by method D. Compound 262 was obtained in 54% yield. mp: 102-105°C

^1H NMR ($CDCl_3$): 0.70-1.90(m,24H, side chain), 2.17(s,3H,-Me), 2.43-3.20(m,4H, side chain), 3.85(s,3H,-OMe), 6.54(s,1H,aromatic), 10.30(s,1H,-OH).

IR (KBr, cm^{-1}): 3410, 1650, 1430

MS m/e (rel. intensity): 360(M^+, 70.9), 329(59.7), 328(100), 302(21.7).

Preparation of 263

Compound 262 was converted to 263 in 90% yield by the same procedure used for the preparation of 246.

^1H NMR ($CDCl_3$): 0.70-1.80(m,24H, side chain), 2.27(s.3H,-Me), 2.53-2.90(m,4H, side chain), 3.60(s,6H,-OMe, and $-CO_2Me$),

6.77(s,1H,aromatic), 7.23-7.70(m,5H,-Ph).

IR (film, cm^{-1}): 3420, 1665, 1220

MS m/e (rel. intensity): 576(M^+, 3.6), 545(3.2), 374(30.2), 189(100).

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