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Studies In Organic Synthesis: I Demethylation Of Methyl Enol Ethers And Methyl Aryl Ethers Ii Toward Sexiphenylene Iii Toward A New Method For Vinylcyclopropanation

Jeffrey Robert Walker

STUDIES IN ORGANIC SYNTHESIS: (1) DEMETHYLATION OF METHYL ENOL ETHERS AND METHYL ARYL ETHERS (2) TOWARD SEXIPHENYLENE (3) TOWARD A NEW METHOD FOR VINYLCYCLOPROPANATION

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ABSTRACT

Cycloseychellene, a tetracyclic sesquiterpene, has been a synthetic target of our group for some time and earlier work had ended with the preparation of a methyl enol ether intermediate. A possible pathway for the completion of this total synthesis had, as its key step, an intramolecular Prins (ene) reaction. Studies were conducted in order to examine possible methods for the formation of the enolate which this approach required. The possible use of a silyl enol ether, as the enolate precursor, was examined in a model study, but the preparation of the enol ether was not successful. In addition, model studies examined the demethylating ability of lithium dimethylamide for methyl aryl ethers and a methyl enol ether. It was thought that lithium dimethylamide might serve to demethylate the methyl enol ether intermediate prepared earlier, provide the necessary enolate, and so set the stage for the intramolecular Prins (ene) reaction. Although lithium dimethylamide was found to be a reasonably useful demethylating agent for aryl methyl ethers, no demethylation of the enol ether was observed.

Buckminsterfullerene possesses an equatorial belt of five benzene rings joined at the *para* positions. Although the cyclic oligoparaphenylenes (COPs) have yet to be synthesized, the knowledge gained from their preparation and the physical and electronic properties they possess, should provide further insight into the understanding of aromaticity. Central to our synthetic approach to

[0_6]paracyclophane, or *sexiphenylene* as we refer to it, is the reductive dimerization of a dicarbonyl compound via McMurry reactions. The preparation of this diketone was successful, but attempts to achieve its reductive dimerization were not successful.

Organic chemists have found vinylcyclopropanes to be effective synthetic intermediates. Although these compounds can be prepared by a variety of methods, many of these approaches are of the multi-step variety. In order to add to the current collection of one-pot procedures, we have investigated an approach centred on the vinylcyclopropanation of α,β-unsaturated ketones. At the heart of this strategy was a two step (one pot) operation consisting of a conjugate addition followed by an intramolecular S_N' displacement of a silyloxy group from an allylic position. The conjugative delivery of an appropriately silyloxyated vinyl anion was effected by higher-order organocuprate reagents. Efforts to induce the expulsion of two different silyloxy groups were not successful.

To my Father's parents

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TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

GLOSSARY OF ABBREVIATIONS

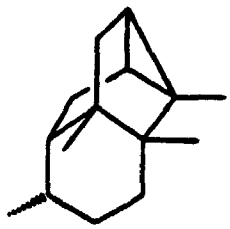
AIBN:	Azobisisobutyronitrile
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP:	4-Dimethylaminopyridine
DME:	1,2-Dimethoxyethane
HMDS:	1,1,1,3,3,3-Hexamethyldisilazane
HMPA:	Hexamethylphosphoramide
HPLC:	High-performance liquid chromatography
LDA:	Lithium diisopropylamide
NMR:	Nuclear magnetic resonance
TBAF:	Tetra-*n*-butylammonium fluoride
TBS:	*t*-Butyldimethylsilyl
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
THP:	Tetrahydropyran
TLC:	Thin layer chromatography
TMEDA:	*N,N,N',N'*-Tetramethylethylenediamine
TMSCl:	Chlorotrimethylsilane
TMSI:	Iodotrimethylsilane
TMU:	Tetramethylurea
TPS:	*t*-Butyldiphenylsilyl
TPSCl:	*t*-Butylchlorodiphenylsilane

Chapter 1

DEMETHYLATION OF METHYL ENOL ETHERS AND METHYL ARYL ETHERS

1.1 Introduction

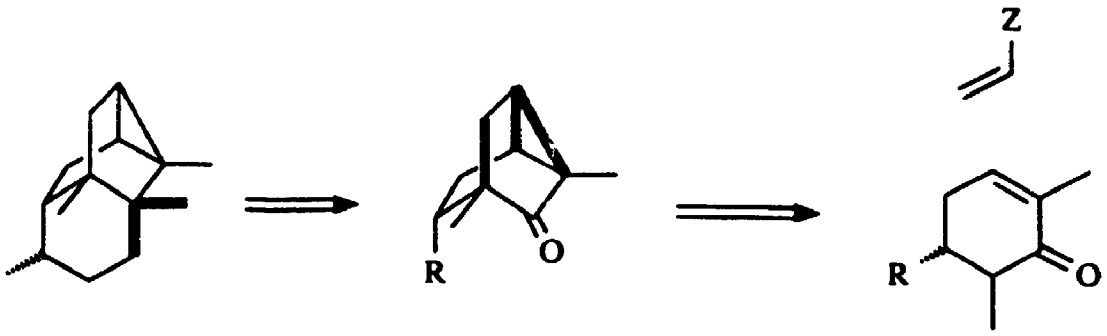
Over the past decade, our research group has been working on a total synthesis of cycloseychellene (**1.1**), a tetracyclic sesquiterpene, which is a minor constituent of the essential oil of *Pogostemon cablin* Benth.[1.1]



1.1

The first total synthesis of (+/-)-cycloseychellene was reported in 1983 by Yamada.[1.2] It required a total of twenty-two steps and had an overall yield of just 0.6%. One year later, Welch reported a twenty-one step synthesis of (+/-)-cycloseychellene having an overall yield of only 0.1%. [1.3] The challenge, then, was to develop a shorter and more efficient synthesis of cycloseychellene. Our retrosynthetic analysis of cycloseychellene is shown in Scheme 1-1. The bond disconnections shown for cycloseychellene (**1.1**) give tricyclic ketone **1.2**. Further

bond disconnections show that this intermediate could be synthesized by a bicycloannulation reaction using a vinyl bicycloannulation reagent and a properly substituted cyclohexenone.[1.5]

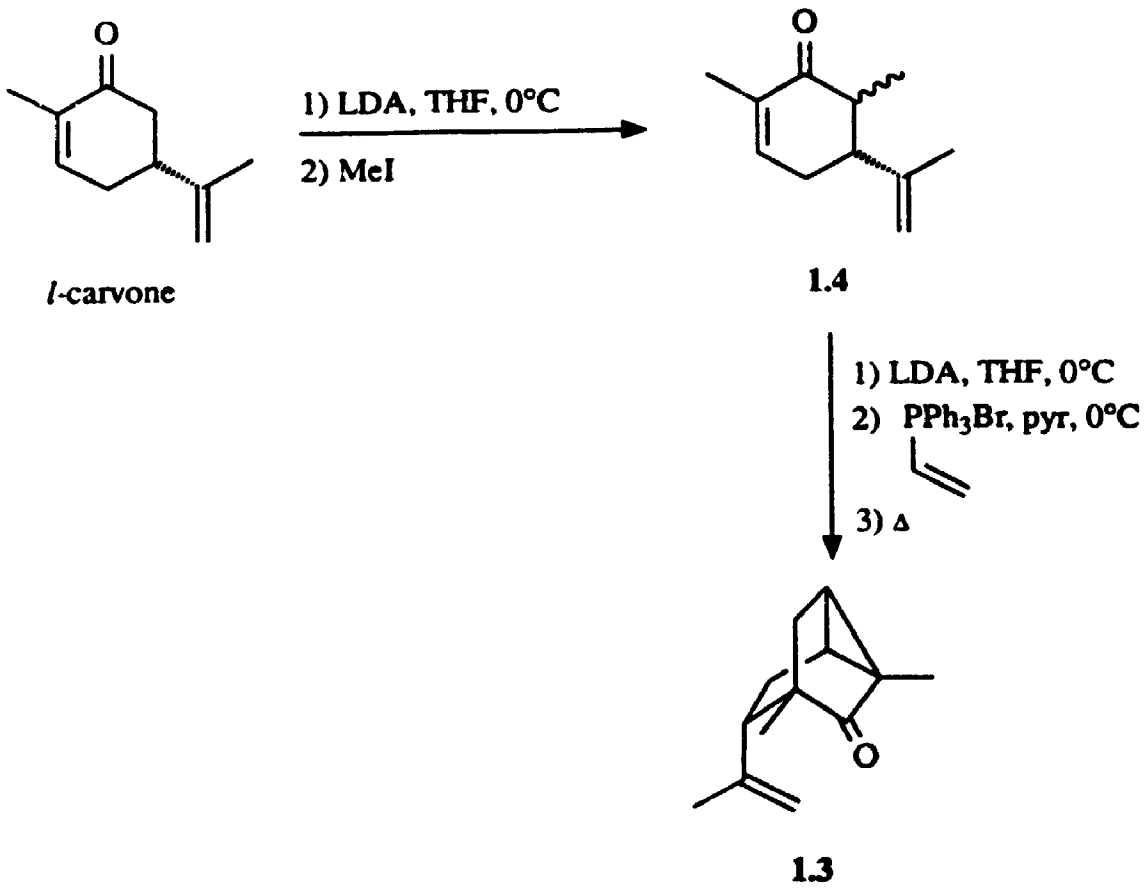


1.1 **1.2**

Scheme 1-1: Retrosynthetic analysis for cycloseychellene

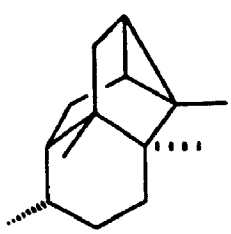
(-)-Carvone was chosen as the starting material since it conveniently contains two of the substituents required for the substituted enone in Scheme 1-1. In addition, its use would ultimately give optically active cycloseychellene, which until this time has only been prepared as a racemic modification.

Methylation of *l*-carvone at the α' position gave methyl carvone **1.4**, and the reaction of the kinetic enolate of cyclohexenone **1.4** with vinyl phosphonium bromide proceeded stereoselectively to yield the bicycloannulation product, ketone **1.3**, as the sole product (Scheme 1-2).[1.4] Compound **1.3** is thus prepared in only two steps from *l*-carvone in an overall yield of 59%, and it possesses most of the major structural features of the target (**1.1**).[1.4]

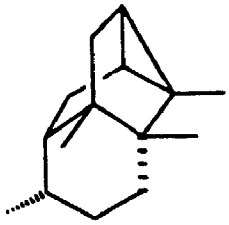


Scheme 1-2: Methylation of carvone and bicycloannulation of methyl carvone

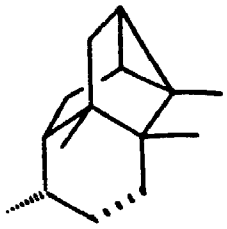
Three construction tasks remain to be completed: a one-carbon extension, ring closure to provide the final six-membered ring, and the addition of a methyl group. If one considers the transformation of **1.3** to **1.1** retro-synthetically, then there are six possible orders in which the three carbon-carbon bonds involved in these steps may be formed. The three possible retro-synthetic bondsets for the last bond formed are **1.5**, **1.6** and **1.7**.



1.5

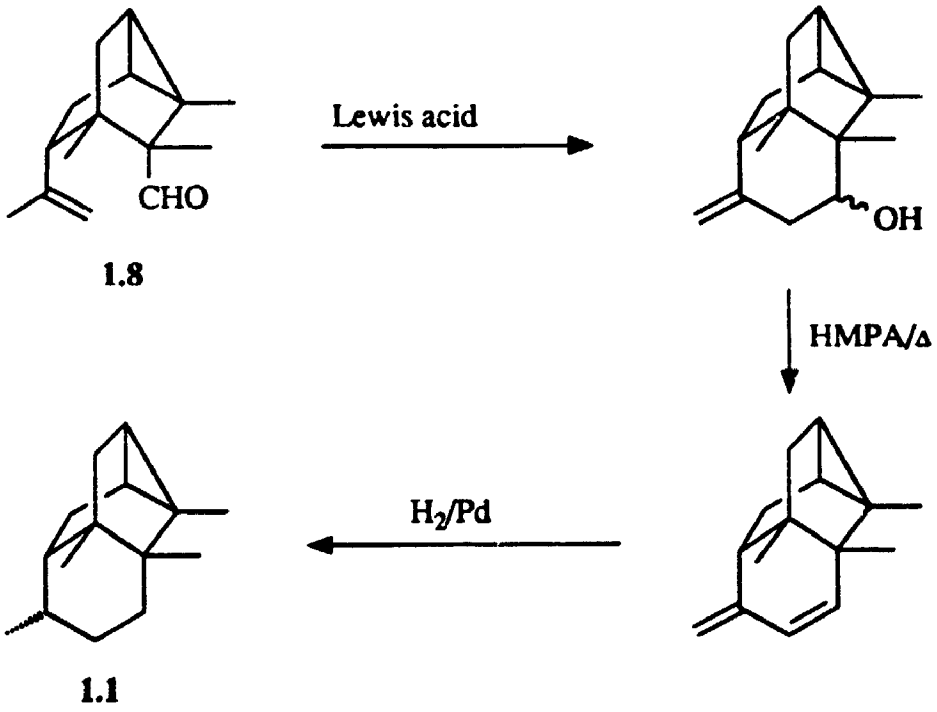


1.6



1.7

Past work by Murray Bailey[1.4,1.5] was centred on attempts to develop and implement tactics based on bondsets **1.5** and **1.6**. Unfortunately these did not meet with success. More recently, Daniel Tse[1.4,1.6] investigated various approaches based on bondset **1.7**. One of the pathways which was pursued had as its key step an intramolecular (Prins) ene reaction of olefinic aldehyde **1.8** (Scheme 1-3).

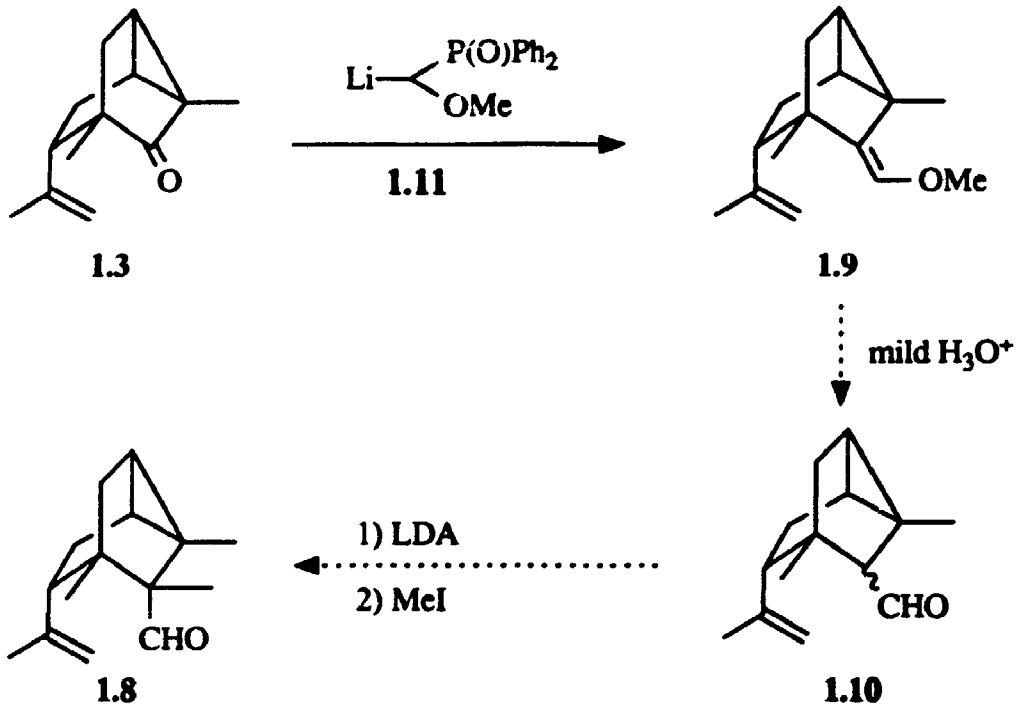


1.8

1.1

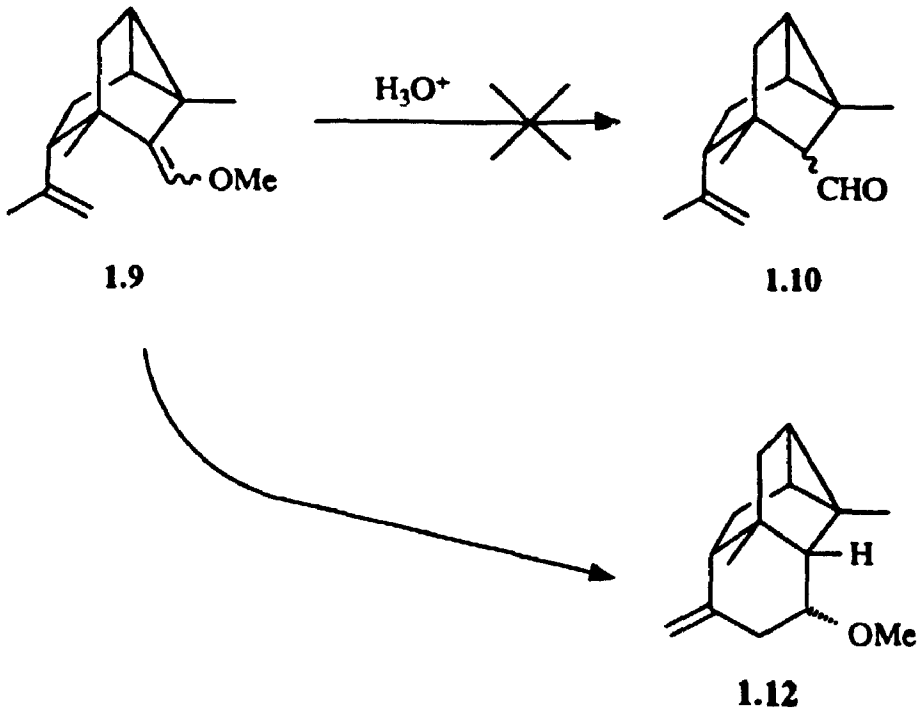
Scheme 1-3: Proposed synthesis of cycloseychellene via an intramolecular Prins ene reaction

It was proposed that the required aldehyde could be prepared in three steps from ketone **1.3** (Scheme 1-4). The first step involved a Wittig-type reaction yielding methyl enol ether **1.9**, and mild hydrolysis in the second step would give aldehyde **1.10**. In the last step, α-methylation would give the desired compound (**1.8**).



Scheme 1-4: Proposed synthesis of aldehyde **1.8**

Unfortunately, attempts to hydrolyze enol ether **1.9** to aldehyde **1.10**, under a variety of conditions, were not successful. Surprisingly, olefinic ether **1.12** was isolated instead, presumably arising from intramolecular trapping of the intermediate carbocation resulting from protonation of the enol ether moiety.[1.4,1.6]



1.9 **1.10**

1.12

Scheme 1-5: Hydrolysis of enol ether **1.9**

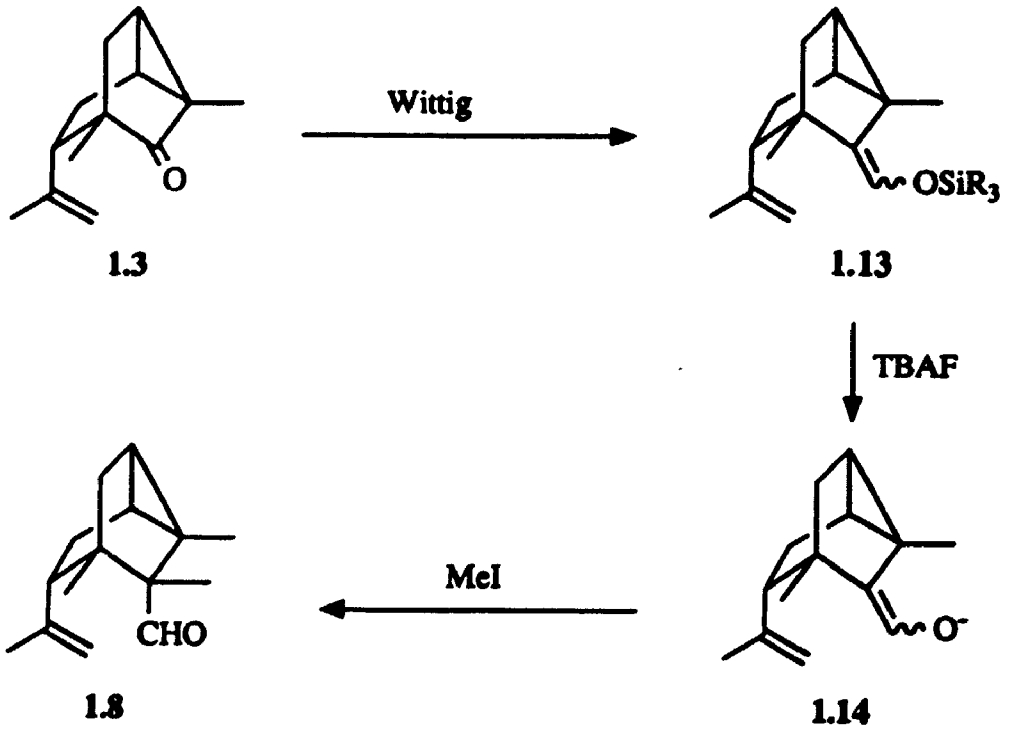
Although it possesses the ring system of cycloseychellene, this compound (**1.12**) lacks a methyl group at the C-1 position. Repeated attempts to convert ether **1.12** to cycloseychellene were not successful.

One purpose of the present work was therefore to study alternative pathways from methyl enol ether **1.9** to cycloseychellene. In addition, new chemical equivalents of bondset **1.7** have also been investigated.

1.2 Silyl Horner-Wittig Approach

As mentioned previously, Daniel Tse encountered difficulty while attempting the mild acid hydrolysis of methyl enol ether **1.9** to olefinic aldehyde **1.10**. Although many different reagents and reaction conditions were tried, the desired product was not obtained.

One pathway which we have proposed would still have at its heart a Prins (ene) reaction (of the type depicted in Scheme 1-3) but would make use of a silyl enol ether as an alternative to the methyl enol ether employed by Tse. This approach would first require the conversion of keto-olefin **1.3** to a silyl enol ether (**1.13**) using a Wittig-type reaction (Scheme 1-6).



1.3 **1.13** **1.8** **1.14**

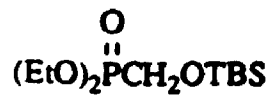
Scheme 1-6: Proposed synthesis of cycloseychellene via silyl enol ether **1.13**

Secondly, fluoride induced generation of enolate **1.14** and subsequent treatment *in situ* with methyl iodide, would give rise to the desired aldehyde (**1.8**) (Scheme 1-6). The synthesis of cycloseychellene would be completed by the intramolecular Prins (ene) reaction, dehydration and hydrogenation, as shown earlier in Scheme 1-3. Since the desilylation of the silyl enol ether using tetra-butylammonium fluoride (TBAF) would take place under neutral or basic conditions, cationic cyclization is precluded.

In order to test the feasibility of this approach, a model study was conducted. The first task was to prepare a suitable Wittig-type reagent possessing appropriate silicon functionality. In the traditional Wittig reaction, an aldehyde or ketone is treated with a phosphorous ylide giving an olefin and a phosphine oxide. Such ylides are usually prepared by the treatment of a phosphonium salt with a base. Work done by Tse en route to methyl enol ether **1.9**, which attempted to make use of this conventional procedure, failed to give satisfactory results. Similar difficulties were encountered by Warren[1.7] when he attempted to use the same ylide with hindered ketones. These problems were overcome, and the desired enol ethers were obtained, when Warren switched from a phosphorane to the Horner-Wittig reagent, α-lithio phosphine oxide **1.11**. This reagent was used by Tse in his successful preparation of enol ether **1.9** (Scheme 1-4).

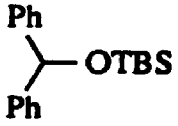
Kluge and Cloudsdale, as part of their investigations into the development of new methods for the synthesis of enol ethers, explored the use of various phosphonates within the context of a Horner-Wittig reaction.[1.8] Of particular

relevance to our proposal was their work with silyloxyphosphonate **1.15**.

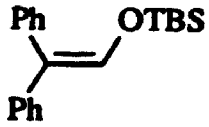


1.15

Although good yields of 1,2-adducts were obtained from both benzophenone and cyclohexanone, this reagent was deemed "not effective" since the reaction of these adducts with potassium *tert*-butoxide gave complicated mixtures instead of the desired silyl enol ethers.[1.8] The authors speculate that trans-silylation may have been responsible, either in part or in whole, for the depressed yield in the benzophenone case. The isolation of benzhydrol derivative **1.16**, in 18% yield, was offered as support for this claim. When the addition/elimination was carried out as a one-pot procedure, the desired silyl enol ether (**1.17**) was isolated, although in only 29% yield.



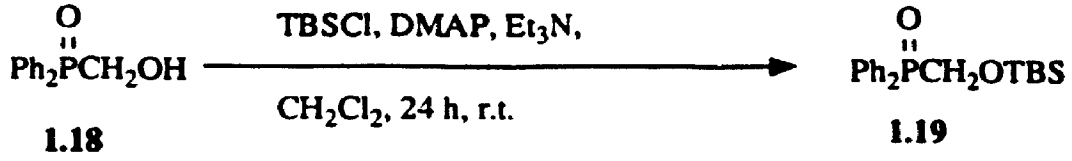
1.16



1.17

In light of these observations, we decided to investigate the diphenylphosphine oxide analogue of phosphonate **1.15** in a model study. Silyloxyphosphine oxide **1.19** was prepared from the readily available hydroxymethyldiphenylphosphine oxide (**1.18**)[1.9] (Scheme 1-7). Treatment of **1.18** in methylene chloride at 0°C with *tert*-butyldimethylchlorosilane, in the presence

of DMAP and triethylamine, gave the desired product (**1.19**) as a white crystalline solid in 85% yield.



Scheme 1-7: Preparation of silyloxyphosphine oxide **1.19**

The 200 MHz ^{1}H NMR spectrum of **1.19** showed a singlet due to the protons of the *tert*-butyl group at 0.77 ppm and a singlet due to the silyl methyl protons at -0.11 ppm. The protons of the -CH_2O- group give rise to a doublet at 4.34 ppm with a coupling constant of J_{HP} = 7.2 Hz. The four ortho protons of the phenyl groups give rise to a multiplet at 7.85 ppm, while the remaining phenyl protons give rise to a multiplet at 7.5 ppm. The ^{13}C NMR data for **1.19** were assigned as shown in Figure 1-1.

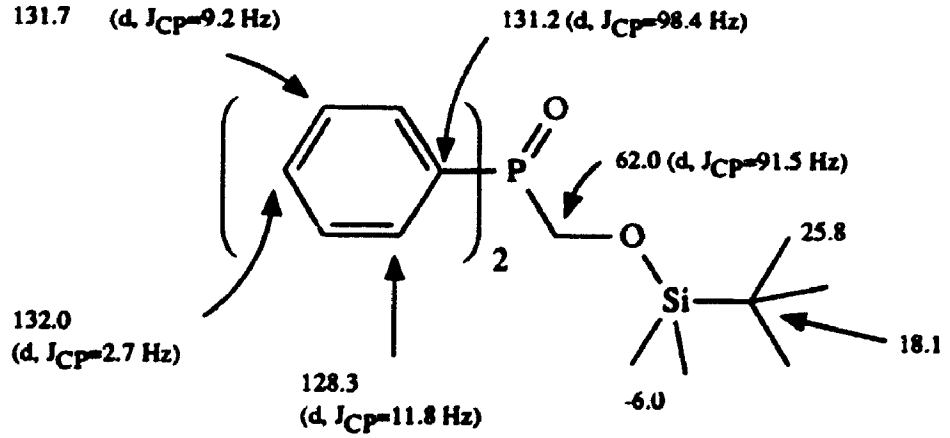
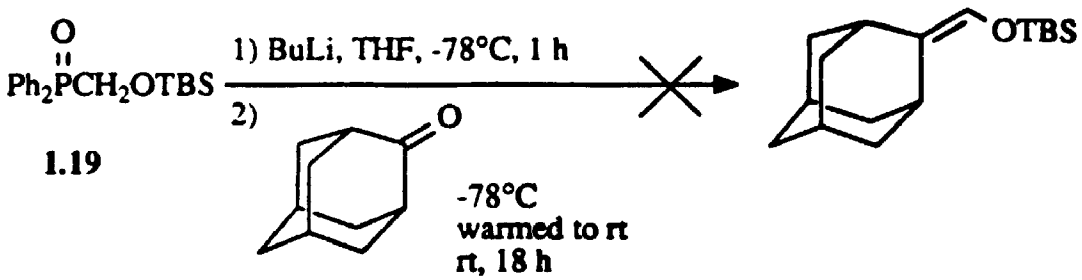


Figure 1-1: ^{13}C NMR analysis of silylphosphine oxide **1.19**

With silyloxyphosphine oxide **1.19** now in hand, a model study was conducted in order to determine the suitability of its lithio-derivative as a Horner-Wittig reagent (Scheme 1-8). Initial attempts used butyllithium, under a variety of conditions, to deprotonate phosphine oxide **1.19**. The ketone, 2-adamantanone, was then added to complete the reaction sequence. Unfortunately, complex mixtures were obtained, typically containing eight to ten components.



Scheme 1-8: Attempted Horner-Wittig reactions with silyloxyphosphine oxide **1.19**

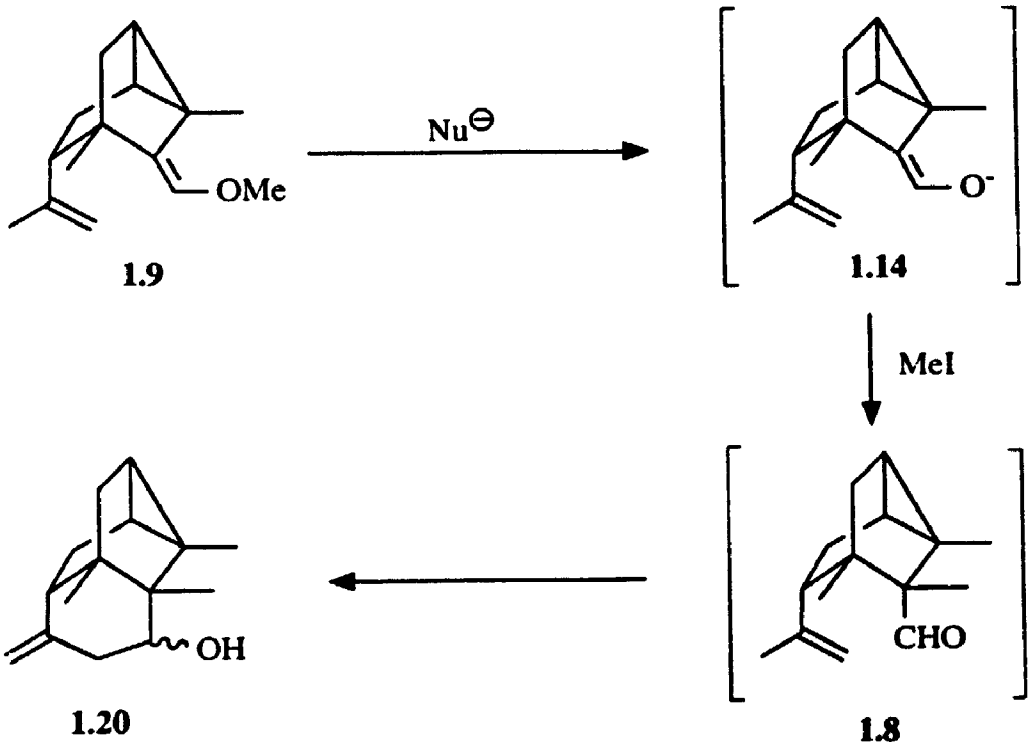
Warren has reported similar difficulty with butyllithium.[1.7] Therefore, lithium diisopropylamide (LDA), prepared in the usual way from diisopropylamine and butyllithium, was tried. In these cases, only unreacted starting materials were recovered. Apparently, this particular phosphine oxide (**1.19**) is simply too hindered for LDA.

1.3 The Direct Demethylation Approach to Cycloseychellene

1.3.1 Lithium Dimethylamide as a Demethylating Agent

Another pathway which we have proposed would still have at its heart the

intramolecular (Prins) ene reaction of aldehyde **1.8** to alcohol **1.20**. However, the main feature of this approach would be the development of a new demethylation reaction in which a nucleophilic reagent (Nu^-) would convert methyl enol ether **1.9** directly to enolate **1.14** (Scheme 1-9).



1.9 **1.14** **1.20** **1.8**

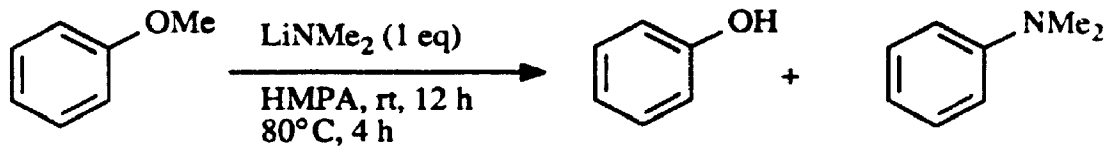
Scheme 1-9: Proposed one-pot conversion of methyl enol ether **1.9** to alcohol **1.20** via O-demethylation-methylation-intramolecular ene reaction

This approach would therefore avoid the problematic formation of aldehyde **1.10** altogether, as in the ill-fated silyl enol ether approach described above. Enols and phenols are known to have comparable pKa values,[1.10] and leaving group

ability often parallels acidity. Consequently, it is reasonable to expect that enol ethers and aryl ethers should react in a similar fashion with nucleophiles. Accordingly, we postulated that it should be possible to adapt a known methodology for the nucleophilic demethylation of aryl methyl ethers to that of methyl enol ethers.

There are many examples in the literature of non-acidic reagents which are reported to effectively demethylate methyl aryl ethers. These include a variety of anionic nitrogen compounds (PhMeNNa[1.11] and R_2NLi[1.12]), anionic sulfur compounds (EtSNa,[1.13] ArSNa,[1.14] Na_2S[1.15]), anionic phosphorous compounds (Ph_2PLi[1.16]) and anionic selenium compounds ($PhCH_2SeNa$[1.17]). Unfortunately, there are drawbacks with most of these. Selenium reagents[1.18] can be highly toxic, while phosphorous and sulfur based compounds, like the selenium reagents, are quite unpleasantly odorous. In light of these considerations, we decided to opt for an anionic nitrogen reagent. Specifically, we wanted a reagent which had demonstrated demethylating ability, is readily available, and is easy to handle. With such a material in hand, we could then try to effect the demethylation of enol ether **1.9** (to give enolate **1.14** *in situ*). Quenching with methyl iodide would give the desired olefinic aldehyde **1.8** which should spontaneously cyclize by an ene reaction under the reaction conditions. The net result would be the formation of alcohol **1.20** in only one synthetic step from enol ether **1.9** (Scheme 1-9). The synthesis of cycloseychellene would then be completed by dehydration and hydrogenation, as shown in Scheme 1-3.

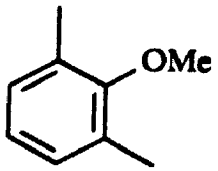
In 1973, Normant and co-workers reported that lithium dimethylamide, when prepared and used in HMPA, cleaved methyl aryl ethers (Scheme 1-10).[1,12] Unfortunately, significant amounts of the corresponding *N,N*-dimethylanilines, arising from nucleophilic aromatic substitution, were also formed. For example, the treatment of anisole (**1.21**) with lithium dimethylamide (one equivalent) in HMPA at room temperature for 12 hours and 80°C for 4 hours yielded N,N-dimethylaniline (**1.23**) (41%), phenol (**1.22**) (28%) and unreacted starting material (27%). The use of two equivalents of the amide provided aniline **1.23** and phenol in 74% and 20% yield respectively (All of the starting material had been consumed).



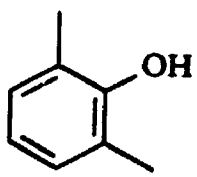
1.21 **1.22** **1.23**

Scheme 1-10: Normant's demethylation of anisole using lithium dimethylamide

Interestingly, the reaction of 2,6-dimethylanisole (**1.24**) with lithium dimethylamide yielded a single product, 2,6-dimethylphenol (**1.25**), presumably due to steric congestion.

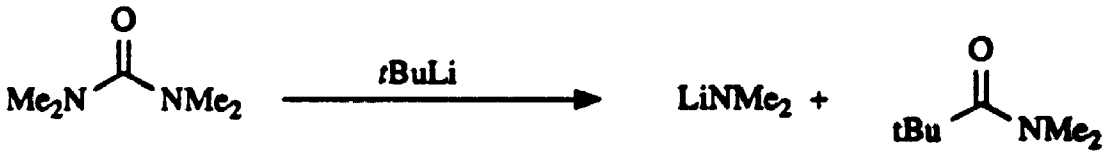


1.24



1.25

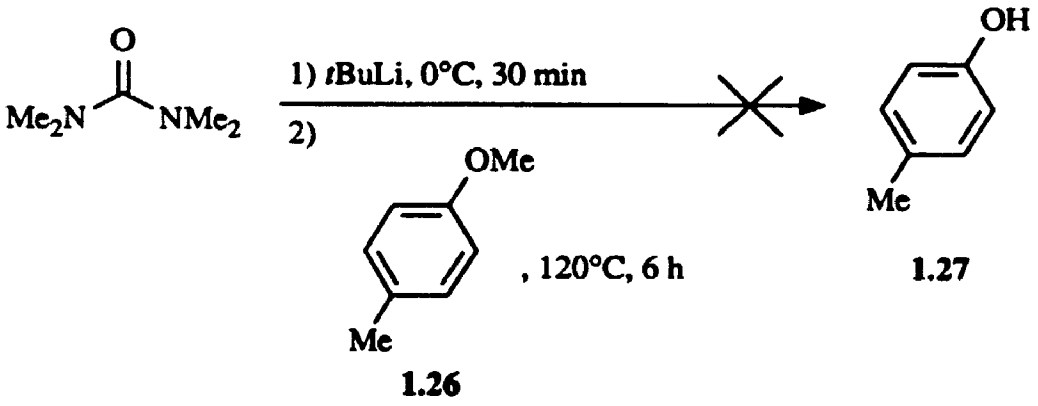
In spite of the relatively high levels of nucleophilic aromatic substitution associated with the use of lithium dimethylamide under these reaction conditions, we decided to investigate the demethylation chemistry of this material more closely. The prospect of using lithium dimethylamide was particularly attractive since the byproduct of the reaction, trimethylamine, is a gas at room temperature. This would simplify the isolation and purification of the product. However, the most compelling reason for deciding to look at lithium dimethylamide more closely was the possibility of using tetramethylurea (TMU) as the solvent. The preparation of lithium dimethylamide can then be envisioned to be carried out by the treatment of TMU with *tert*-butyllithium (Scheme 1-11). Demethylation could be effected by the resulting amide ion *in situ*. Since Normant's demethylation occurred under fairly mild conditions, the selection of TMU seemed a reasonable alternative to HMPA. In addition, it was convenient to try this proposal out on methyl aryl ethers before attempting to demethylate methyl enol ethers, which are more reactive and not as readily available.



Scheme 1-11: Proposed preparation of lithium dimethylamide

Our initial investigation involved attempts to carry out the demethylation of

p-methylanisole (**1.26**). (Scheme 1-12). Ether **1.26** was added at room temperature to the red solution resulting from addition of *tert*-butyllithium to TMU at 0°C, which was assumed to contain lithium dimethylamide. The reaction mixture was then stirred at 125-130°C for 7 hours. Unfortunately, examination of the ^{1}H NMR spectra of the crude product revealed only the presence of the starting aryl ether, *p*-methylanisole (**1.26**), and TMU.



Scheme 1-12: Attempted demethylation of *p*-methylanisole(**1.26**) using "lithium dimethylamide" prepared *in situ* from *tert*-butyllithium and TMU

In light of these results, it was clear that our proposal to use lithium dimethylamide prepared *in situ*, by the reaction of *t*-butyllithium with TMU, needed revision. We therefore decided to try commercially available lithium dimethylamide in TMU. This involved treating *p*-methylanisole (**1.26**) with lithium dimethylamide in TMU at temperatures ranging from 130-200°C for varying lengths of time. Unfortunately, these reactions only gave very meagre

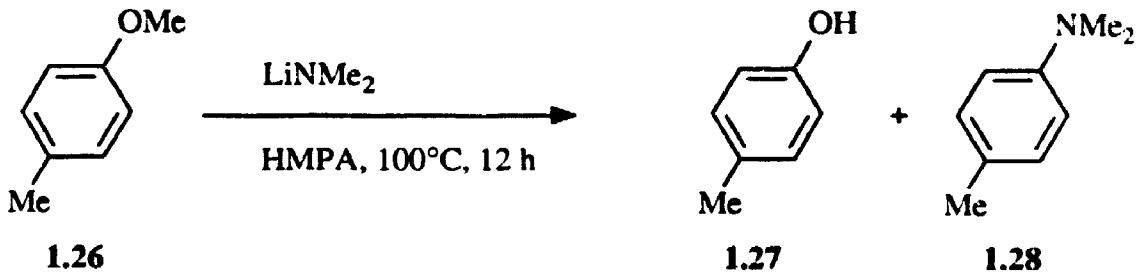
yields (ca. 18%) of the corresponding phenol, in spite of the harshness of the reaction conditions. It was evident at this point that TMU was not a suitable solvent for this application, at least under these specific reaction conditions. We therefore decided to abandon our work with TMU in favour of HMPA.

Initially, we examined the effect of commerically available lithium dimethylamide and higher temperature on the Normant procedure. Attempts to demethylate *p*-methylanisole (**1.26**) employed 1.2 equivalents of lithium dimethylamide, HMPA as solvent and a reaction time of 7 hours at a temperature of 130°C. Although a slight excess of the reagent was used, the extent of demethylation was found (by monitoring the reaction over time) to level off at approximately 55-60%.

Loubinoux has reported that good yields are obtained when two equivalents of the amide base, sodium N-methylanilide, were used for the demethylation of methyl aryl ethers.[1.11] In addition, other groups have reported the need to use at least two equivalents of the nucleophilic reagent.[1.13] In some instances, up to four equivalents are required.[1.14] We therefore increased the proportion of the reagent, and it was found that when three equivalents of lithium dimethylamide were used, the demethylation of *p*-methylanisole (**1.26**) had gone to completion within 4 hours at 200°C. Both *p*-cresol (**1.27**) and *N,N*-dimethyltoluidine (**1.28**) were formed, specifically in a 4:1 ratio.

Based upon these findings, the use of 2-3 equivalents of lithium dimethylamide became the standard. The demethylation of *p*-methylanisole (**1.26**)

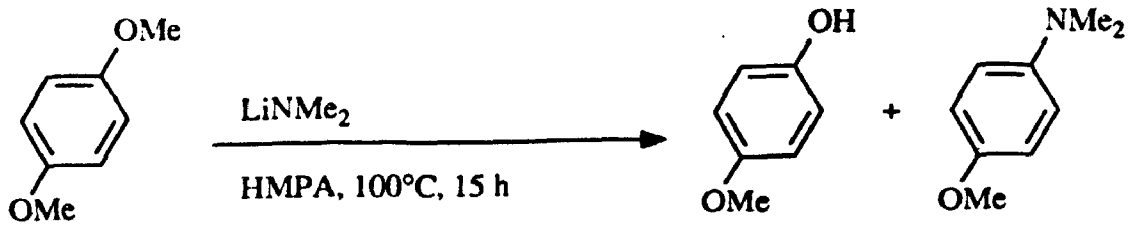
was also studied at 100°C in order to see if such severe conditions (T=200°C) were really necessary. Reaction of *p*-methylanisole (**1.26**) with lithium dimethylamide in HMPA at 100°C for 12 hours did, indeed, proceed to completion and again yielded both *p*-cresol (**1.27**) (68%) and *N,N*-dimethyltoluidine (**1.28**) (12%) (Scheme 1-13).



1.26 **1.27** **1.28**

Scheme 1-13: Demethylation of **1.26** with lithium dimethylamide in HMPA at 100°C

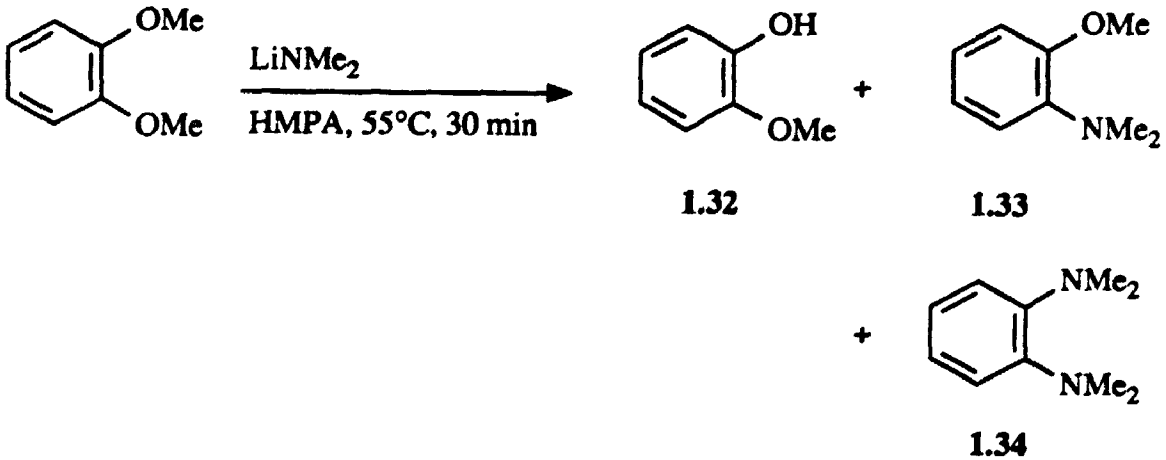
This method was also applied to the demethylation of 1,4-dimethoxybenzene and 1,2-dimethoxybenzene for comparison with Normant's results. In the case of 1,4-dimethoxybenzene (**1.29**), reaction with lithium dimethylamide in HMPA at 100°C for 15 hours gave the desired product, *p*-methoxyphenol (**1.30**) in 70% yield, as well as a small quantity of the nucleophilic aromatic substitution product, *p*-(*N,N*-dimethylamino)anisole (**1.31**) (Scheme 1-14). Normant, on the other hand, reported a much lower yield of demethylation and a substantial amount of nucleophilic aromatic substitution.[1,12]



1.29 **1.30** **1.31**

Scheme 1-14: Demethylation of 1,4-dimethoxybenzene with lithium dimethylamide in HMPA at 100°C

The conditions employed for the demethylation of 1,2-dimethoxybenzene are outlined in Scheme 1-15. Reaction with lithium dimethylamide in HMPA at 55°C for 30 minutes gave the desired product, 2-methoxyphenol (**1.32**) (54%), as well as 2-methoxy-*N*,*N*-dimethylaniline (**1.33**) (21%) and 1,2-bis-(*N*,*N*-dimethylamino)benzene (**1.34**) (5%).

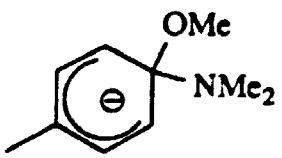


1.32 **1.33** **1.34**

Scheme 1-15: Demethylation of 1,2-dimethoxybenzene with lithium dimethylamide in HMPA

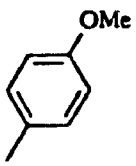
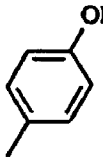
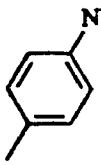
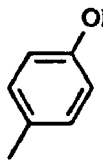
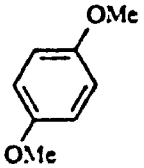
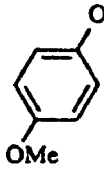
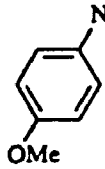
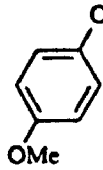
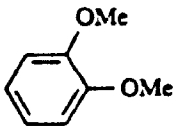
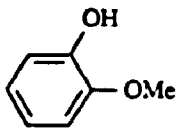
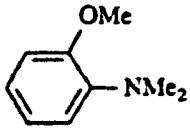
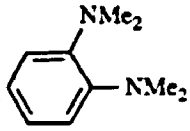
Normant and coworkers reported that diamine **1.34** was the major product, only small amounts of the other two products having been observed.[1.12] Our results are tabulated on the following page. Normant's results for the same substrates are included for comparison purposes.

The demethylation of these methyl aryl ethers presumably occurs via nucleophilic attack of dimethylamide ion at the carbon atom of the methoxy group by way of an S_N2 mechanism. As mentioned earlier, no appreciable levels of demethylation were observed when TMU was used. Conversely, HMPA proved to be well suited for this reaction, as was reported earlier by Normant. The success which HMPA brings to this reaction most likely arises from its ability to solvate cations, through its sterically accessible $O^{\delta-}$ atom.[1.21] Sequestering of the lithium ion in this way therefore leads to an increase in the ionic character of the lithium-nitrogen bond. This frees up the nucleophile which is not strongly solvated, thus enhancing its nucleophilicity, and the rate of the S_N2 reaction increases. As for the formation of the aromatic substitution products, Normant speculates that they arise from direct nucleophilic substitution by dimethylamide ion, the intermediate adduct (eg. **1.35**) being stabilized by the inductively electron-withdrawing methoxy substituent.[1.12]



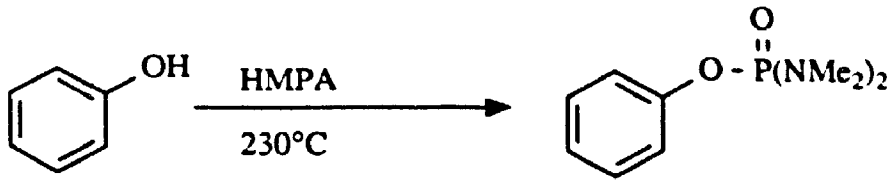
1.35

DEMETHYLATION OF SOME METHYL ARYL ETHERS

aryl ether	amide/ether	T/°C	t/h	products		
 **1.26**				 **1.27**	 **1.28**	 **1.26**
	3.1/1	100	12	68	12	
	*2/1**			*39*	*40*	*19*
 **1.29**				 **1.30**	 **1.31**	 **1.29**
	2.5/1	200	2	70	4	
	*2/1**			*45*	*26*	*27*
				 **1.32**	 **1.33**	 **1.34**
	3.0/1	55	0.5	54	21	5
	*2/1**			*5*	*13*	*78*

** Normant and coworkers; rt/t=12 h; 60-80°C/t=5-6 h*

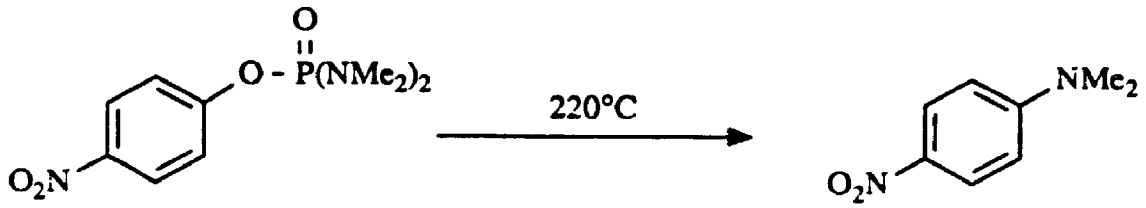
However, concurrent work by Pedersen and coworkers points to the possible implication of an intermediate phosphoramidate ester. For example, they have shown that phenol reacts with excess HMPA at elevated temperatures to give phosphoramidate ester **1.36** (Scheme 1-16).[1.19] This product reacts with phenol in a similar fashion, and all three amino groups on phosphorus may be displaced by phenoxy groups in this manner.



1.36

Scheme 1-16: Reaction of phenol with HMPA

Pedersen and coworkers have also shown that phosphoramidate ester **1.37** undergoes thermal decomposition to the corresponding amine (**1.38**) (Scheme 1-17).[1.20]

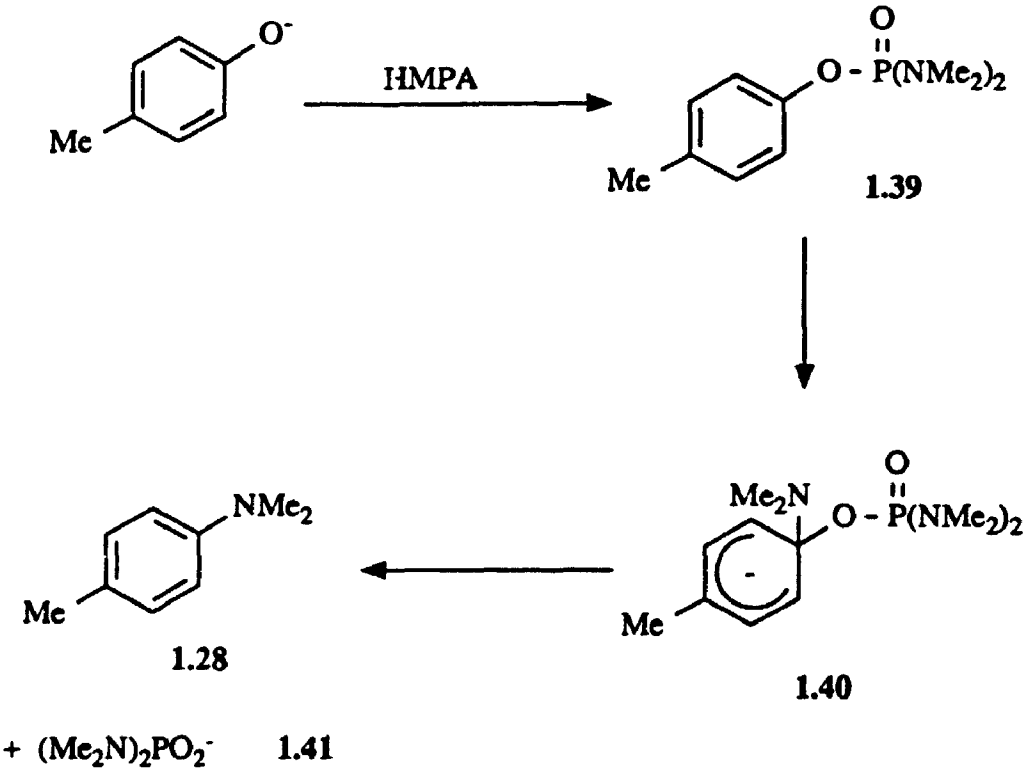


1.37 **1.38**

Scheme 1-17: Thermal decomposition of phosphoramidate ester **1.37** to *N,N*-dimethylamino-*p*-nitro-aniline (**1.38**)

Since our conditions are basic the phenoxide ion produced by demethylation could, in principle, react to a small extent with HMPA to give a small concentration of phosphoramidate ester **1.39**. This species would then be responsible for the formation of the amine (**1.28**) through nucleophilic aromatic substitution by dimethylamide ion. Attack on **1.39** by dimethylamide ion gives intermediate adduct **1.40** which then gives **1.28** by expulsion of the better leaving group,

phosphoramidate **1.41** (Scheme 1-18).

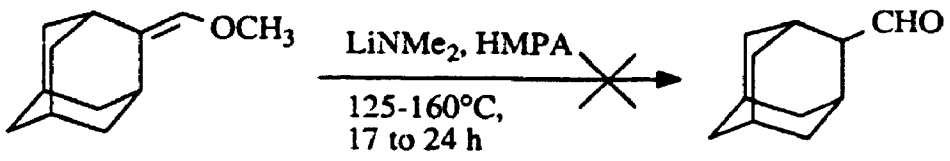


Scheme 1-18: Possible pathway for the formation of amine **1.28**

If this mechanism is correct, prolonged heating of the demethylation reaction mixtures should lead to decreasing amounts of phenolic products and increasing amounts of amine products. If, on the other hand, Normant's hypothesis is correct, the proportion of amines and phenols should not change once the methyl aryl ether has been completely consumed. Our observations that the demethylation of *p*-methylanisole had gone to completion within 4 hours at 200°C and that the amine to phenol ratio was unaffected by further stirring at this temperature would

suggest that the amine products are forming via the Normant mechanism.

As depicted earlier in Scheme 1-11, the ultimate aim of this work was the development of a new method for the conversion of methyl enol ether **1.9** to α-methylaldehyde **1.8**. Since this proposal involves tandem O-demethylation and C-methylation, it was imperative that the first stage, the demethylation, be demonstrated before the combination could be attempted. Having demonstrated the demethylating ability of lithium dimethylamide in hot HMPA, for a number of methyl aryl ethers, we attempted to demethylate a methyl enol ether under the same conditions. The methyl enol ether of 2-adamantanecarboxaldehyde, **1.42**, was selected as the substrate for the initial tests of this proposed demethylation procedure and was prepared from 2-admantanone as reported by Alberts and co-workers.[1.22] Attempts to demethylate **1.42** involved reaction with lithium dimethylamide (3.6 equivalents) in HMPA at temperatures ranging from 125-160°C for varying lengths of time ranging from 17 to 24 hours (Scheme 1-19).



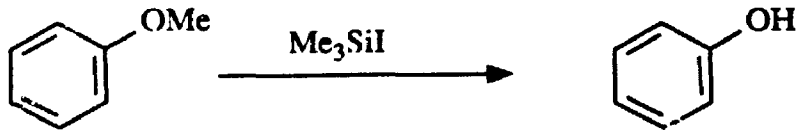
1.42 **1.43**

Scheme 1-19: Attempted demethylation of methyl enol ether **1.42**

In each case none of the desired aldehyde, **1.43**, was formed and only starting methyl enol ether (**1.42**) was recovered.

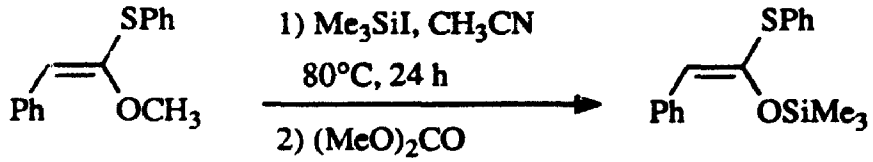
1.3.2 Iodide Ion as a Potential Demethylating Agent

Olah[1.23] has reported that iodotrimethylsilane (TMSI) effectively cleaves methyl aryl ethers as well as methyl alkyl ethers (Scheme 1-20).



Scheme 1-20: TMSI cleavage of ethers

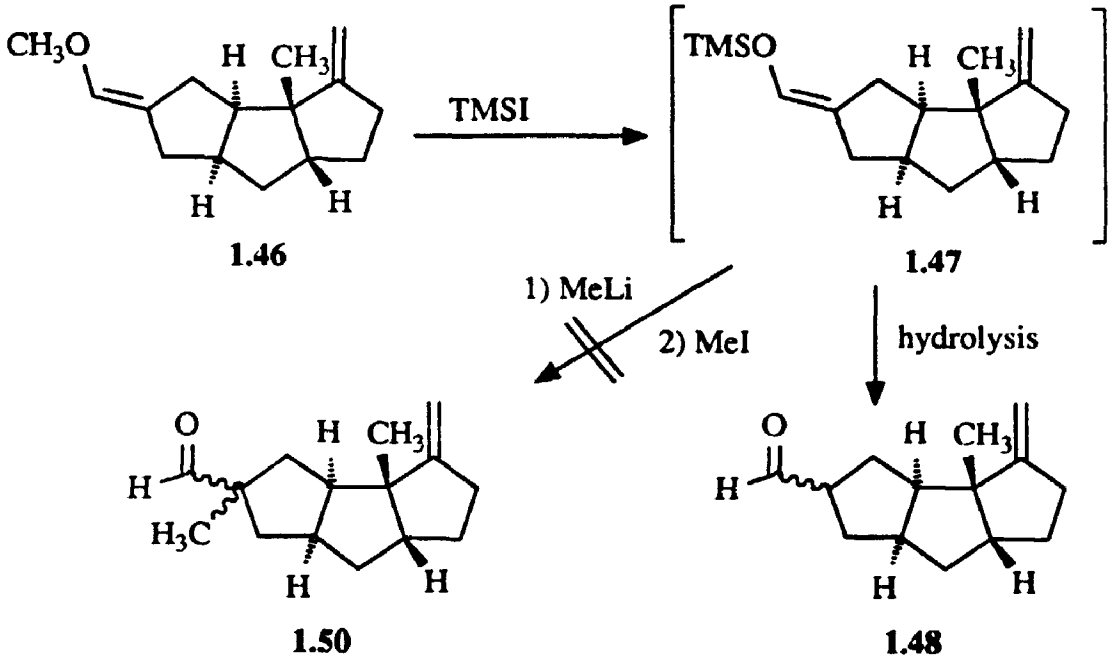
Work by Hacket and Livinghouse[1.24] has demonstrated that this reagent is quite effective in the demethylation-silylation of ketene O-methyl-S-phenyl-O,S-acetals. This was the first reported synthesis of a silyl enol ether (**1.44**) directly from its corresponding methyl enol ether (**1.45**) (Scheme 1-21). Desilylation followed by C-methylation of the resulting enolate would give the corresponding α-methylthioester.



1.45 **1.44**

Scheme 1-21: Demethylation of a ketene-O,S-acetal (**1.45**)

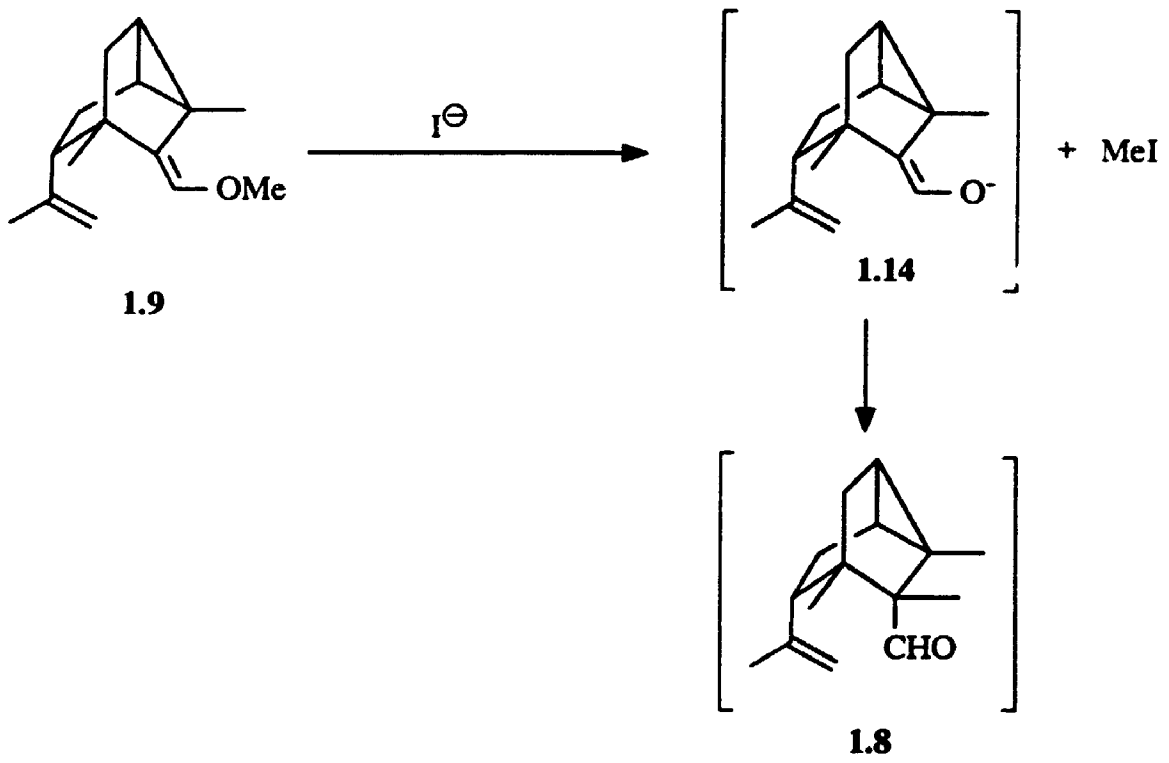
In later work en route to a total synthesis of hirsutene, Majetich and Defauw used TMSI for demethylation of an aldehyde methyl enol ether (**1.46**).[1.25] They had envisioned a one-pot procedure whereby the corresponding silyl enol ether (**1.47**), generated *in situ*, could be C-alkylated directly via the enolate. Although aldehyde **1.48** was obtained, they were not able to isolate the silyl enol ether (**1.47**) nor were they able to alkylate it *in situ* (Scheme 1-22).



Scheme 1-22: Demethylation of enol ether **1.46** using TMSI

Although attempts by Daniel Tse to use this reagent for the demethylation of enol ether **1.9** proved unfruitful,[1.6] we thought that perhaps iodide ion alone, as sodium iodide, would serve the same purpose provided that hot HMPA was used as the solvent. If this reaction was to be performed in a sealed tube, so as to

prevent the loss of methyl iodide, the resulting enolate (**1.14**) should be re-alkylated at carbon to give the desired olefinic aldehyde (**1.8**) (Scheme 1-24).

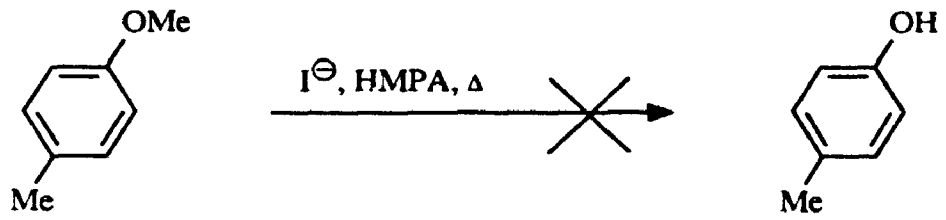


1.9 **1.14** **1.8**

Scheme 1-23: Proposed Iodide catalyzed O-demethylation/C-methylation of enol ether **1.9**

The demethylating ability of sodium iodide in HMPA was investigated with *p*-methylanisole (**1.26**), under a variety conditions. Initially, a mixture of sodium iodide and *p*-methylanisole in HMPA was stirred at 165°C for 17 hours. Unfortunately, none of the expected *p*-cresol (**1.27**) was formed. Only the starting ether was isolated (Scheme 1-24). Even the heating of similar mixtures at 200°C

for 16 hours failed to effect demethylation.



1.26 **1.27**

Scheme 1-24: Attempted demethylation of *p*-methylanisole (**1.26**) by NaI in HMPA

1.5 Summary

Silyloxymethyldiphenylphosphine oxide **1.19** was prepared from hydroxymethyldiphenylphosphine oxide in 85% yield. A model study, designed to determine the suitability of its lithio-derivative as a Horner-Wittig reagent with 2-adamantanone, was conducted. Butyllithium was initially used as the deprotonating agent under a variety of conditions. The desired product was not obtained. Complex mixtures, which typically contained eight to ten components, were recovered instead. Unfortunately, the use of lithium diisopropylamide also failed to effect the Horner-Wittig reaction. Only unreacted starting materials were recovered.

Our initial attempts to effect the demethylation of a methyl aryl ether involved the addition of *p*-methylanisole (**1.26**) to solutions resulting from the addition of *tert*-butyllithium to TMU at 0°C, which was assumed to contain lithium dimethylamide. This was followed by stirring at 125-130°C for 7 hours. Examination of the ^{1}H NMR spectra of the crude product revealed only the presence of the starting aryl ether (**1.26**) and TMU. The use of commerically available lithium dimethylamide in TMU, at 130-200°C, for the demethylation of *p*-methylanisole (**1.26**), only gave very meagre yields (ca. 18%) of the corresponding phenol.

Monitoring of the reaction of *p*-methylanisole with 1.2 equivalents of lithium dimethylamide revealed that the demethylation had leveled off at

approximately 55-60% after seven hours at 130°C in HMPA. The reaction of *p*-methylanisole with three equivalents of lithium dimethylamide, in HMPA at 200°C, resulted in the formation of a 4:1 mixture of *p*-cresol (**1.27**) and *N,N*-dimethyltoluidine (**1.28**). The starting aryl ether had been consumed. Reaction of *p*-methylanisole with 2.5 equivalents of lithium dimethylamide, in HMPA at 100°C for 12 hours resulted in the formation of both *p*-cresol (**1.27**) (68%) and *N,N*-dimethyltoluidine (**1.28**) (12%). In the case of 1,4-dimethoxybenzene (**1.29**), reaction with lithium dimethylamide in HMPA at 100°C for 15 hours gave the desired product, *p*-methoxyphenol (**1.30**) in 70% yield, as well as a small quantity of *p*-(*N,N*-dimethylamino)anisole (**1.31**). The reaction of lithium dimethylamide (3 equivalents) with 1,2-dimethoxybenzene in HMPA at 55°C for 30 minutes gave the desired product, 2-methoxyphenol (**1.32**) (54%), as well as 2-methoxy-*N,N*-dimethylaniline (**1.33**) (21%) and 1,2-bis-(*N,N*-dimethylamino)benzene (**1.34**) (5%).

Attempts to demethylate methyl enol ether **1.42** involved reaction with lithium dimethylamide (3.6 equivalents) in HMPA, at temperatures ranging from 125-160°C, for 17 to 24 hours. In each case though, none of the desired aldehyde, **1.43**, was formed and only starting methyl enol ether (**1.42**) was recovered.

Finally, we attempted to demethylate *p*-methylanisole with sodium iodide in HMPA, under a variety conditions. The use of sodium iodide in HMPA at 165°C for 17 hours as well as at 200°C for 16 hours, failed to effect

demethylation.

1.6 Conclusions

Our aim of synthesizing silyl enol ether **1.13**, via a Horner-Wittig reaction, for use as a possible precusor in our proposed intramolecular Prins (ene) route to cycloseychellene was not realized. Silyloxymethyldiphenylphosphine **1.19**, upon reaction with butyllithium, appears to decompose to non-useful materials. The desired product was not formed under these conditions. These observations are consistent with similar reports by Warren.[1.7] The use of lithium diisopropylamide (LDA) resulted in the recovery of starting materials. It would appear that this particular phosphine oxide (**1.19**) is simply too hindered to permit proton abstraction by LDA.

Our aim of developing a new demethylating procedure for methyl enol ethers utilizing lithium dimethylamide, in hot HMPA, was not realized. Although this reagent system eventually proved effective for the demethylation of a variety of methyl aryl ethers, it did not effect demethylation of **1.42**, the methyl enol ether of 2-adamantanone. With respect to the demethylation of methyl aryl ethers, our results inexplicably differ from those cited by Normant. He reports that the major products in his work were those which arose from nucleophilic aromatic substitution. In our hands, this reagent system instead afforded the desired demethylated compounds accompanied by small quantities of the corresponding substitution products.

Our work with sodium iodide in hot HMPA examined its demethylating ability on *p*-methylanisole. Based upon our results, this reagent system does not appear to be an effective demethylating agent for *p*-methylanisole.

1.7 Experimental

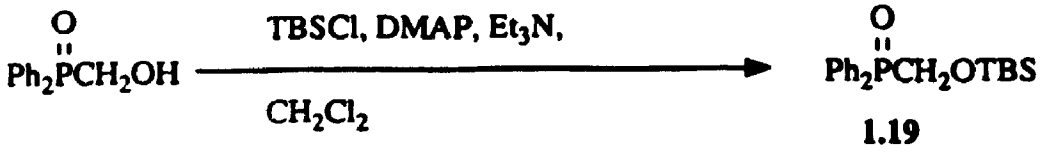
General

All reactions were run in flame dried or oven-dried glassware under a positive pressure of argon. THF (tetrahydrofuran), DME (1,2-dimethoxyethane), *p*-dioxane and diethyl ether, when used as solvents, were dried by distillation from sodium benzophenone ketyl. HMPA, triethylamine, diisopropylamine and methylene chloride were dried by distillation from calcium hydride and stored over 4 Å molecular sieves under a blanket of argon. Reagents were purchased from Aldrich Chemical Company, and were utilized without further purification, unless noted. Dry column flash chromatography[1.26] was performed using Merck 60 grade, 230-400 mesh (60 Å) silica gel. TLC was performed using 250 μm layer, pre-coated silica gel on PET polyester plates, with a fluorescent indicator.

The ^{1}H NMR spectra were recorded on either a Varian XL200 spectrometer at 200 MHz, or a Varian Gemini 200 spectrometer at 200 MHz. The ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 50 MHz, or on a Varian XL300 spectrometer at 75 MHz. All ^{1}H NMR spectra were run in deuterated chloroform with chemical shifts reported in parts-per-million (ppm) with $CHCl_3$ as the reference (7.24 ppm). All ^{13}C NMR spectra were run in deuterated chloroform with chemical shifts reported in ppm relative to the centre line of the $CHCl_3$ triplet (77.0 ppm). Carbon multiplicities were determined by APT and DEPT experiments. Mass spectra were determined by electron impact on a Finnegan-MAT 8230 spectrometer employing an ionizing voltage of 70 eV.

Coupled GC-MS was performed on a Varian 3400 GC fitted with a 30 m DB-5 methyl silicone capillary column which was attached to a Finnegan-MAT 8230 mass spectrometer. FT-IR spectra were recorded on a Bruker IFS32 infrared spectrometer.

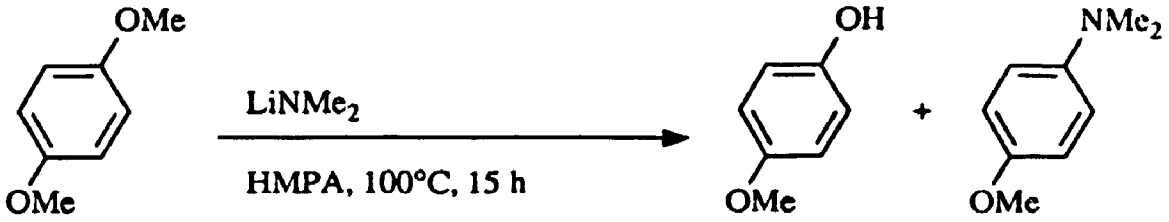
Tert-butyldimethylsilyloxymethyldiphenylphosphine oxide (**1.19**)



To a solution of 2.65 g (17.6 mmol) of *tert*-butyldimethylchlorosilane, 1.82 g (18.0 mmol) of triethylamine and 30 mg (0.41 mmol) of DMAP in 10 mL of CH_2Cl_2 at 0°C was added 4.0 g (17.6 mmol) of hydroxymethyldiphenylphosphine oxide in 20 mL of CH_2Cl_2. The mixture was stirred at room temperature for 20 h and then quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with water (25 mL) and saturated aq. NaCl (25 mL). After drying over anhydrous sodium sulfate the solvent was evaporated under reduced pressure. Dry column flash chromatography (ethyl acetate/cyclohexane) yielded 5.2 g of the silyloxyphosphine oxide **1.19** as colourless crystals (85% yield). mp 110-112°C; TLC (same solvent) R_f=0.15; ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 4H, aromatic), 7.47 (m, 6H, aromatic), 4.34 (d, 2H, J = 7.2 Hz, OCH_2), 0.77 (s, 9H, *tert*-butyl), -0.11 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$): δ 132.0 (aromatic CH, d, J = 2.7 Hz), 131.7 (aromatic CH, d, J = 9.2 Hz), 131.2 (aromatic C, d, J = 98.4 Hz), 128.3 (aromatic CH, d, J = 11.8 Hz), 62.0 (OCH_2, d, J = 91.5 Hz), 25.8 (tBu CH_3), 18.1 (CSi), -6.0 ($SiCH_3$); MS (CI), *m/e* (relative intensity): 347 (M^+ + H, 40), 331 (4), 289 (100), 259 (2), 233 (3), 201 (7), 183 (5), 135 (14); high resolution (CI) *m/e* calcd. for $C_{19}H_{28}O_2PSi$: 347.1596, found: 347.1604; high resolution

m/e calcd for $C_{15}H_{18}O_2PSi$ (M^+-C_4H_9) 289.0814, found 289.0819.

Demethylation of *p*-methylanisole (**1.26**) with lithium dimethylamide in HMPA at 100°C

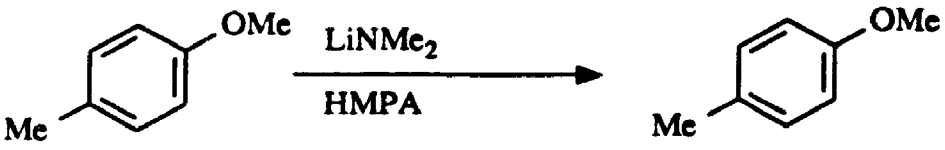


1.29 **1.30** **1.31**

To a solution of lithium dimethylamide (1.31 g, 25.7 mmol) in 8 mL of HMPA was added 1.0 g (8.2 mmol) of *p*-methylanisole (**1.26**). The reaction mixture was heated and stirred at 100°C for 12 h. The reaction was quenched with water (5 mL), acidified with 6 *M* aq. HCl and extracted with ether (4x30 mL). The combined organic layers were extracted with 10% aq. NaOH (4x20 mL). The combined basic aqueous layers were acidified with 6 *M* aq. HCl and extracted with ether (2x100 mL). The combined organic layers were washed with water (3x50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 0.60 g of **1.27** (68%). The original aqueous layer was basified with 10% aq. NaOH, extracted with ether (2x100 mL), washed with water (3x50 mL) and concentrated *in vacuo* to give 0.14 g of **1.28** (12%). **1.27**: ^{1}H NMR ($CDCl_3$): δ 6.85 (m, 4H), 5.8 (b, OH), 2.24 (s, 3H). **1.28**: ^{1}H NMR ($CDCl_3$): δ 6.86 (m,

4H), 2.87 (s, 6H), 2.25 (s, 3H); MS, m/z (relative intensity): 135 (80), 134 (100); high resolution m/z calcd. for $C_9H_{13}N$: 135.1048, found: 135.1052.

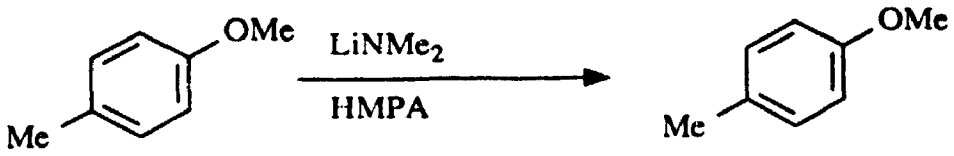
Demethylation of *p*-methylanisole (**1.26**) with lithium dimethylamide in HMPA at 200°C



1.26 **1.27**

To a solution of lithium dimethylamide (0.51 g, 10.0 mmol) in 5 mL of HMPA was added 0.50 g (4.1 mmol) of *p*-methylanisole (**1.26**). The reaction mixture was heated and stirred at 200°C for 24 hours. The reaction was quenched with water (10 mL), acidified with 5 *M* aq. HCl and extracted with ether (4x20 mL). The combined organic layers were washed with 5% aq. HCl (20 mL) and then extracted with 10% aq. NaOH (3x20 mL). The basic extracts were acidified with 5 *M* aq. HCl and extracted with ether (3x30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 360 mg (81%) of *p*-cresol (**1.27**).

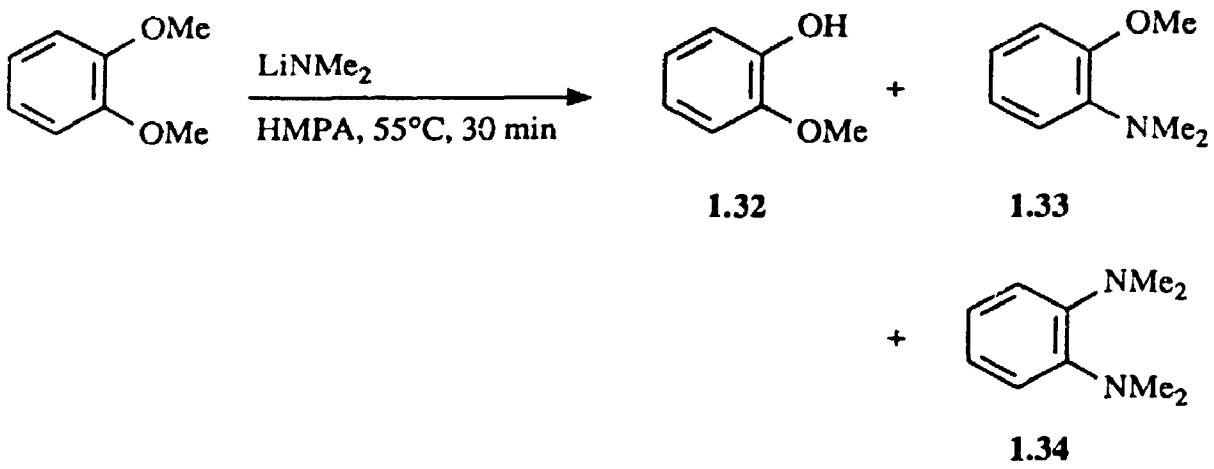
Demethylation of *p*-methylanisole (**1.26**) with lithium dimethylamide in HMPA at 130°C



1.26 **1.27**

To a solution of lithium dimethylamide (0.51 g, 10.0 mmol) in 5 mL of HMPA was added 0.50 g (4.1 mmol) of *p*-methylanisole. The reaction mixture was heated and stirred at 130°C for 72 hours. The reaction was quenched with water (20 mL), and the mixture was acidified with 5 *M* aq. HCl and extracted with ether (4x20 mL). The combined ether layers were washed with 5% aq. HCl and then extracted with 10% aq. NaOH (3x20 mL). The basic extracts were acidified with 5 *M* aq. HCl and extracted with ether (1x20 mL, 1x60 mL). The combined ether layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 0.33 g (75%) of *p*-cresol (**1.27**).

Demethylation of 1,2-dimethoxybenzene with lithium dimethylamide in HMPA at 55°C

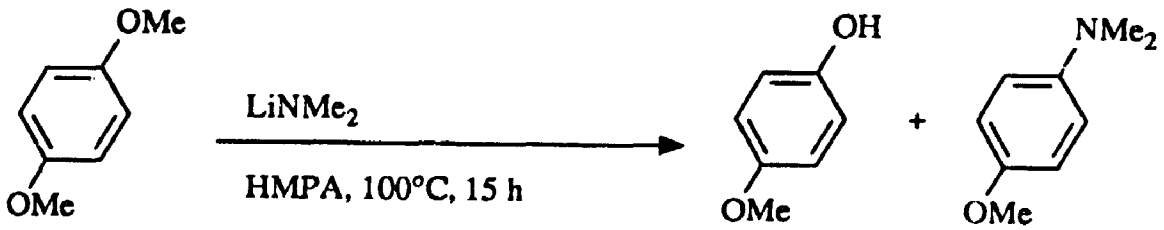


To a solution of lithium dimethylamide (0.75 g, 14.7 mmol) in 5 mL of HMPA was added 0.66 g (4.8 mmol) of 1,2-dimethoxybenzene. The reaction mixture was stirred at 55°C for 30 minutes. The reaction was quenched with water (5 mL), acidified with 6 *M* HCl and extracted with ether (3x25 mL). The combined organic layers were extracted with 10% aq. NaOH (3x20 mL). The combined basic aqueous layers were acidified with 6 *M* HCl and extracted with ether (3x25 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Dry column flash chromatography (ethyl acetate/cyclohexane) afforded 0.32 g of **1.32** (54%). The original aqueous phase was basified with 10% aq. NaOH and extracted with ether (3x25 mL). The combined organic layers were dried over anhydrous sodium magnesium sulfate and concentrated *in vacuo*. Dry column flash chromatography (ethyl acetate/cyclohexane) gave 0.04 g of **1.34** (5%) and 0.15 g of **1.33** (21%).

1.32: (R_f* 0.46); ^{1}H NMR ($CDCl_3$): δ 6.82-7.00 (m, 4H), 5.70 (bs, OH), 3.90

(s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.4 (aromatic C), 145.7 (aromatic C), 121.4 (aromatic CH), 120.1 (aromatic CH), 114.5 (aromatic CH), 110.7 (aromatic CH), 55.8 (OCH_3). **1.33**: (R_f* 0.33); ^1H NMR ($CDCl_3$): δ 6.8-7.1 (m, 4H), 3.91 (s, 3H), 2.82 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 152.2 (aromatic C), 142.2 (aromatic C), 122.3 (aromatic CH), 120.6 (aromatic CH), 117.9 (aromatic CH), 110.8 (aromatic CH), 55.1 (OCH_3), 43.2 (NCH_3); GC/MS, *m/e* (relative intensity): 151 (100), 136 (74), 120 (22), 108 (15); high resolution *m/e* calcd for $C_9H_{13}NO$: 151.0997, found: 151.0998. **1.34**: (R_f* 0.60); ^1H NMR ($CDCl_3$): δ 6.99 (s, 4H), 2.88 (s, 12H); ^{13}C NMR ($CDCl_3$): δ 145.2 (aromatic C), 121.6 (aromatic CH), 117.8 (aromatic CH), 41.3 (NCH_3); GC/MS, *m/e* (relative intensity): 164 (100), 147 (23), 133 (80), 120 (23), 106 (14); high resolution *m/e* calcd for $C_{10}H_{16}N_2$: 164.1313, found: 164.1314. [* 50% ethyl acetate/cyclohexane]

Demethylation of 1,4-dimethoxybenzene (**1.29**) with lithium dimethylamide in HMPA at 100°C



1.29 **1.30** **1.31**

To a solution of lithium dimethylamide (1.2 g, 23.5 mmol) in 8 mL of HMPA was added 1.3 g (9.4 mmol) of 1,4-dimethoxybenzene (**1.29**). The reaction mixture

was stirred at 100°C for 15 h. The reaction was quenched with water (25 mL), acidified with 6 *M* HCl and extracted with ether (3x25 mL). The combined organic layers were extracted with 10% aq. NaOH (4x25 mL). The combined basic aqueous layers were acidified with 6 *M* HCl, extracted with ether (4x50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 0.82 g of **1.30** (70%). The original aqueous phase was basified with 10% aq. NaOH, extracted with ether (4x50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 0.15* g of **1.31**. (* judged by NMR to be a 1:1.9 mixture of **1.31** and HMPA)

1.30: ^{1}H NMR ($CDCl_3$): δ 6.81 (s, 4H), 4.2 (bs, OH), 3.81 (s, 3H). **1.31**: ^{1}H NMR ($CDCl_3$): δ 6.7-6.85 (m, 4H), 3.75 (s, 3H), 2.85 (s, 6H).

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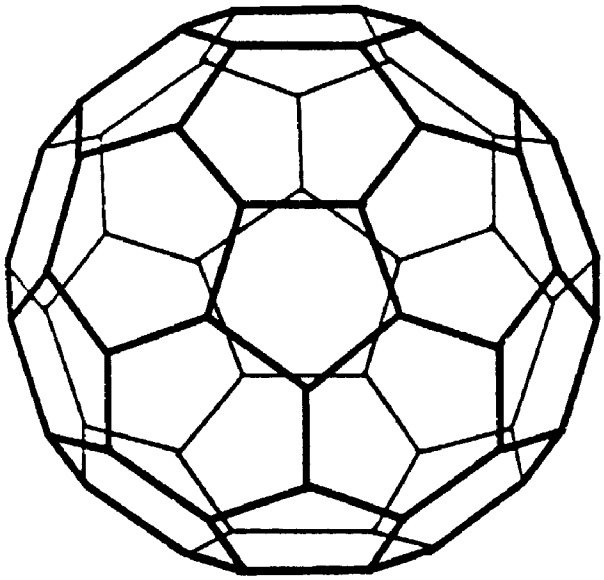
Chapter 2

TOWARD *SEXIPHENYLENE*

2.1 Introduction

Spheroid **2.1**, a semiregular solid possessing Platonic symmetry, is one of the thirteen *Archimedean solids*.[2.1] Nearly twenty-two centuries after Archimedes described it, physicists Huffman and Lamb of Rice University and Krätschmer and Fostiropoulos of the Max Planck Institute reported the synthesis of its all carbon analogue in macroscopic quantities.[2.2,2.3]

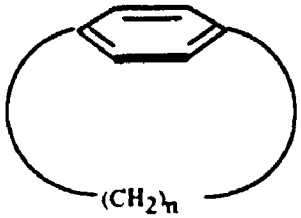


2.1

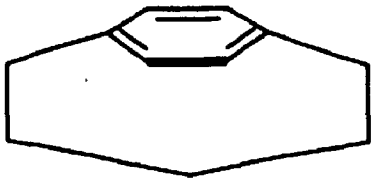
This new form of pure, solid carbon is a 60-atom molecule possessing the geometry of a truncated icosahedron. It was named buckminsterfullerene in honour of Buckminster Fuller, the designer of the geodesic dome. The existence of this type of carbon framework was first proposed by Kroto, Smalley, Curl and

co-workers as an explanation for the mass spectrometric predominance of the C_{60} peak observed in their work on the laser induced vaporization of graphite.[2.4]

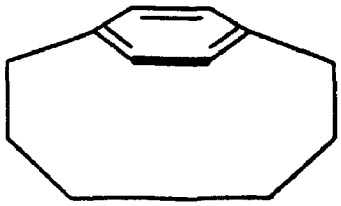
The total synthesis of buckyball by rational means (assuming anyone has the desire to do it, now that a trivial synthesis is available) is most certainly many years off, and synthetic chemists are currently attempting to prepare much simpler partial structures. Close examination of buckyball reveals that it possesses an equatorial belt of five benzene rings joined at the *para* positions. Although this type of macrocyclic cyclophane, which may be referred to as a cyclic oligoparaphenylene (COP), has yet to be synthesized, a large number of cyclic compounds comprising one or more *para*-bridged phenyl rings (paracyclophanes) are known. In 1985, Bickelhaupt and co-workers conducted a study designed to examine the relationship between bridge length and aromaticity in the [*n*]paracyclophanes (**2.2**).[2.5] Until this time n=6, ie. the known [6]paracyclophane (**2.3**), had generally been considered the lower limit, in terms of stability, in this family of cyclophanes.[2.6] However, Bickelhaupt and co-workers were able to synthesize [5]paracyclophane (**2.4**). As would be expected, **2.4** is less stable than **2.3** due to the higher strain energy in the former. While [6]paracyclophane (**2.3**) is stable at room temperature, [5]paracyclophane (**2.4**) undergoes thermal decomposition. Based on the high-field multiplets of the two homobenzylic *in*-protons and the *in*-proton of the central methylene group, it was concluded that the benzene ring of [5]paracyclophane (**2.4**) retains some aromatic character.



2.2

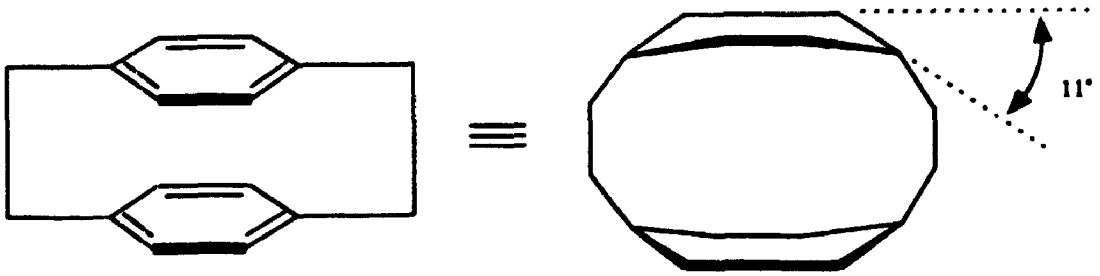


2.4



2.3

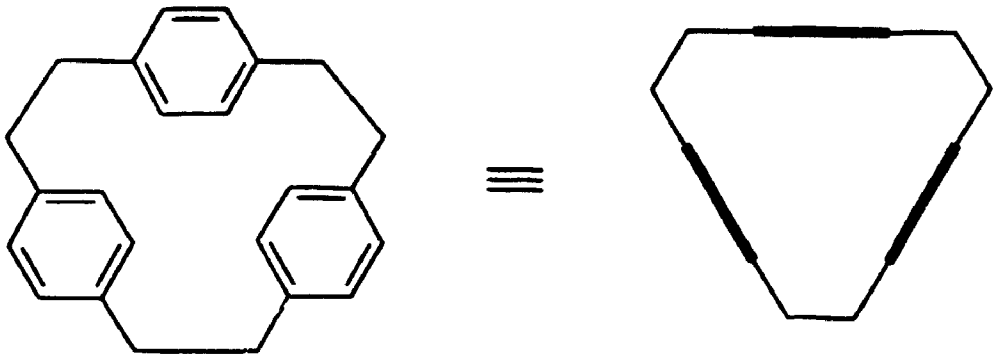
In 1949, Brown and Farthing reported that the polymerization of *p*-xylylene yielded small quantities of [2.2]paracyclophane (**2.5**).[2.7] Two years later, Cram and co-workers reported the formation of this same compound, although they prepared it by a different synthetic route.[2.8] X-ray crystallographic analysis has shown that the aromatic rings of **2.5** are puckered (boat shaped), not planar, with two 11° bends in each benzene ring.



2.5

Another example of a paracyclophane containing more than one benzene

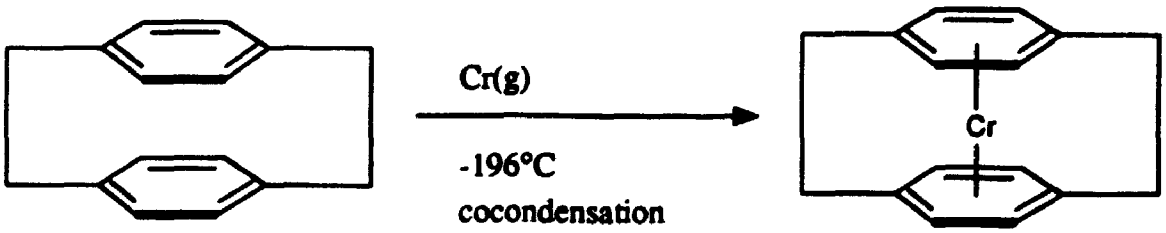
ring is [2.2.2]paracyclophane (**2.6**). This compound was first prepared by Baker.[2.9]



2.6

Notwithstanding the knowledge gained from the preparation of these types of compounds and the physical and electronic properties they possess, their chemistry has also proven to be very informative. The ability of paracyclophanes to form addition compounds is now well established.

For example, paracyclophanes **2.5** and **2.6** are each capable of forming electron donor-accepter (EDA) complexes. Elschenbroich and co-workers have reported that cyclophane **2.5**, when cocondensed with chromium atoms, gives addition product **2.7** (Scheme 2-1).[2.10]

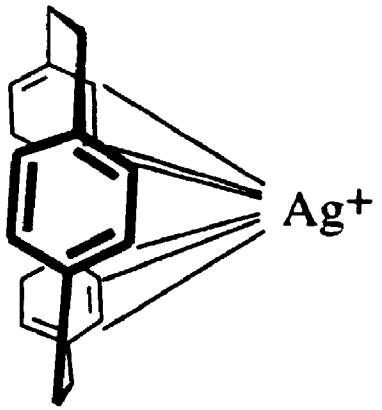


2.5 **2.7**

Scheme 2-1: Synthesis of addition product **2.7**

This is remarkable, if not impossible, considering that there is no space available between the two benzene rings of the cyclophane!

The reaction of paracyclophane **2.6** with silver triflate gave a 1:1 complex of **2.6** and silver ion.[2.11] Although it was postulated that the silver ion was held within the cavity of the cyclophane, more recent work by Boekelheide, Hanson and co-workers has shown that the silver ion is actually external to the cyclophane moiety (**2.8**).[2.12]



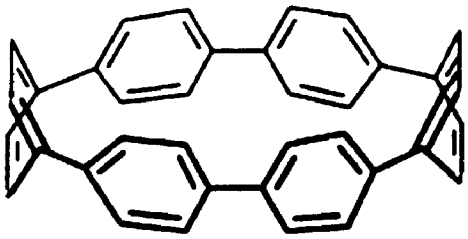
2.8

Their X-ray crystallographic analysis of **2.8** indicated that the silver ion is positioned at an average distance of 2.59Å from the nearest six aromatic carbon atoms. This corresponds to a average distance of 2.49Å from the centres of the nearest aromatic bonds. Another feature of this complex is the orderly twisting of the three ethylene bridges. In each case, one methylene carbon atom lies to one side of the bridging bond while the second methylene carbon atom lies to the other side. In view of this structure, the structure assigned to chromium complex **2.7** is also suspect, but no x-ray study has been reported.

These examples, and similar cases in the literature, demonstrate the ability

of benzene rings in paracyclophanes to form addition compounds with metals. In theory the benzene rings of the as yet unknown cyclic oligoparaphenylenes (COPs) should form similar, and perhaps much stronger, metal complexes.

We therefore decided to pursue, as one of the aims of our research, the synthesis of [O_6]paracyclophane (**2.9**), a cyclic oligoparaphenylene, [6]COP, for which we suggest the trivial name, *sexiphenylene*.



2.9

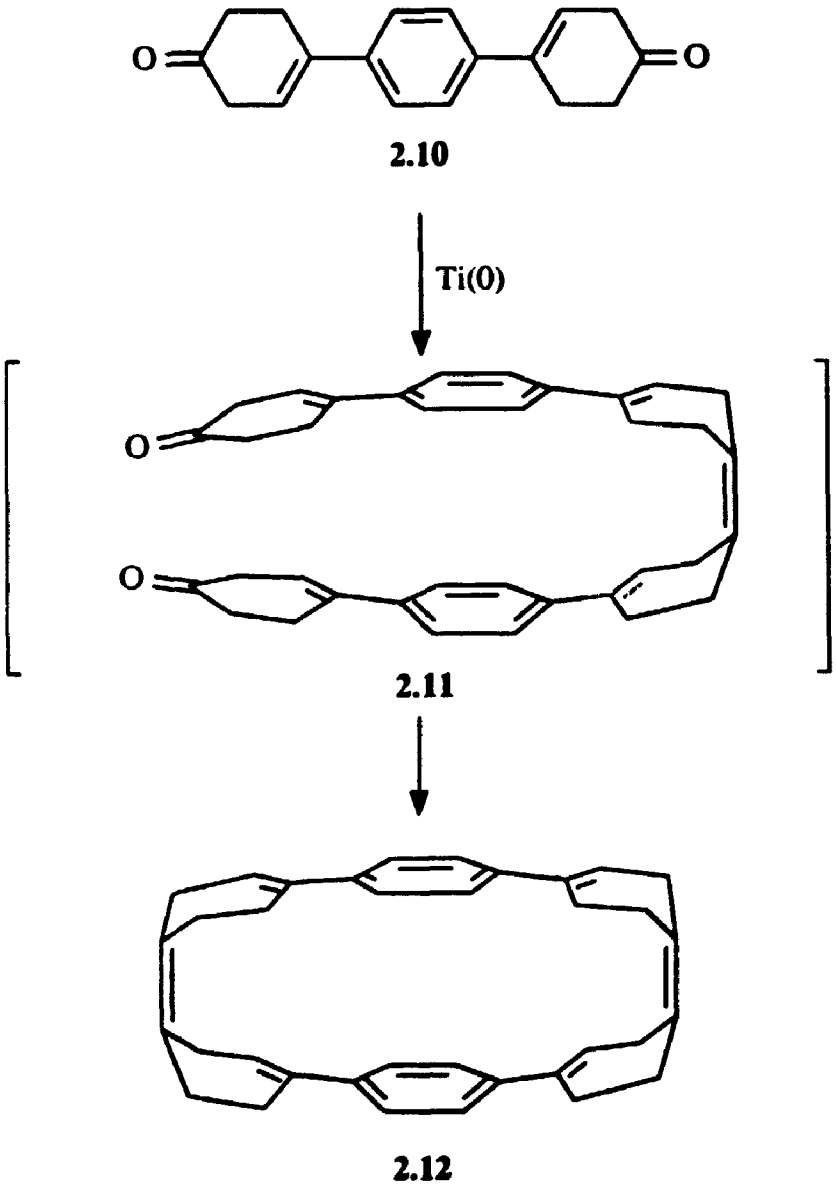
This is the next higher homologue in the series after [O_5]paracyclophane, the partial structure of buckyball mentioned earlier.

Although a synthetic chemist is primarily concerned with the challenges associated with the preparation of this new type of compound, the physical and electronic characteristics of a cyclic oligoparaphenylene, particularly as they relate to aromaticity, would be of considerable interest to theoreticians. Once it has been synthesized, studies designed to explore the chemistry of this new class of organic compounds could begin.

2.1.1 The Proposal

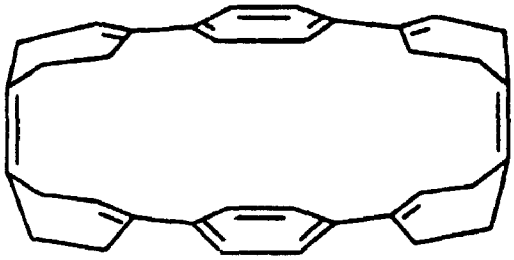
The key step in our proposed synthesis of *sexiphenylene* involves initially the reductive dimerization of diketone **2.10** to diketone **2.11** (isomeric mixture) via

a McMurry reaction. The folding of diketone **2.11**, into the conformation indicated, would maximize the Van der Waals attractive forces between the two "halves" of the molecule. In this conformation, the two remaining carbonyl groups are brought into close proximity, thus facilitating cyclization to macrocyclic cyclophane **2.12** (isomeric mixture) via a second (intramolecular) McMurry reaction (Scheme 2-2).



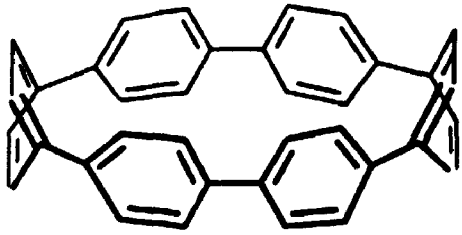
Scheme 2-2: Proposed dimerization of diketone **2.10**

This would then be followed by a dehydrogenative aromatization of **2.12** to the target, **2.9**, using Pd/C, or some similar reagent (Scheme 2-3).



2.12

Pd/C



2.9

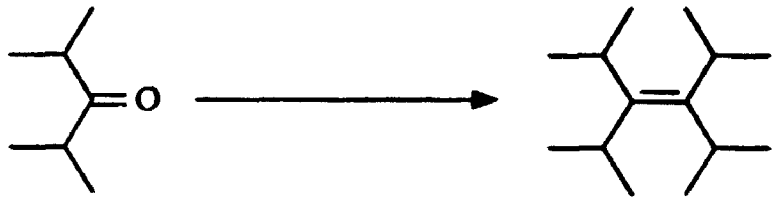
Scheme 2-3: Aromatization of **2.12** to *sexiphenylene*

2.1.2 The McMurry Reaction

In the mid 1970's, three different research groups reported the formation of alkenes from the deoxygenative coupling of ketones and aldehydes in the presence of low-valent titanium. Mukaiyama's reagent was prepared by the reaction of $TiCl_4$ with zinc,[2.14] Tyrlik's by the reaction of $TiCl_3$ with magnesium[2.15] and McMurry's by the reaction of $TiCl_3$ with $LiAlH_4$.[2.13] Since

these discoveries, a wide variety of new methods have been developed for the generation of the low-valent titanium reagent, among which are those using $TiCl_3/K$,[2.16] $TiCl_3/Li$,[2.17] $TiCl_3/Zn$-Cu,[2.18] $TiCl_4/Zn$/pyridine,[2.19] and $TiCl_3/K$/graphite.[2.20,2.21,2.22] More recently, McMurry reported an optimized procedure for titanium-induced carbonyl coupling employing a $TiCl_3(DME)_{1.5}/Zn$-Cu couple reagent system.[2.23] The striking feature of this approach is the ease with which old samples of $TiCl_3$ can be converted into this highly pure source of titanium (III).

Morton's use of $TiCl_3/LiAlH_4$ (the original McMurry reagent) in the carbonyl coupling of diisopropylketone (**2.13**) resulted in only a 12% yield of the olefin, tetraisopropylethylene (**2.14**).[2.24] However, McMurry and co-workers report an 87% yield for the same reaction when $TiCl_3(DME)_{1.5}/Zn$-Cu couple is used instead (Scheme 2-4).[2.23]

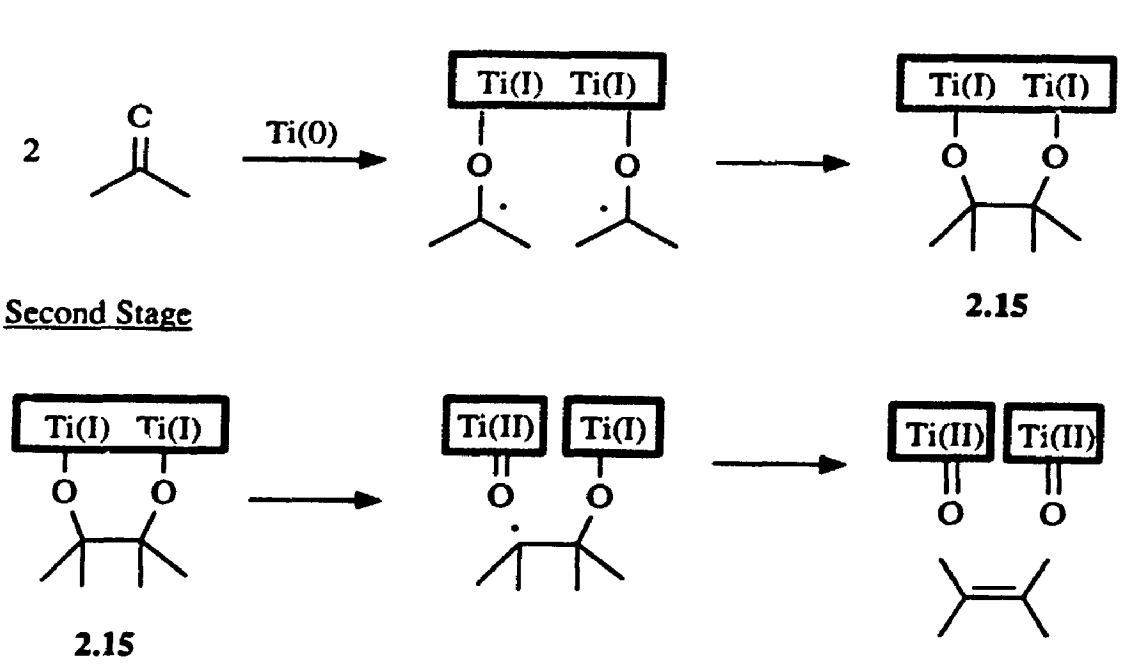


2.13 **2.14**

Reagent	Yield
1) $TiCl_3(DME)_{1.5}/Zn$-Cu	87%
2) $TiCl_3/LiAlH_4$	12%

Scheme 2-4: Carbonyl coupling of diisopropylketone (**2.13**)

The mechanism of these carbonyl-coupling reactions is bel eved to consist of a reductive dimerization of the carbonyl compound, to form a carbon-carbon bond, followed by a deoxygenation to the olefin, both stages occurring on the surface of Ti(0) particles (in some cases accompanied by Ti(II), as well) (Scheme 2-5).[2.25]

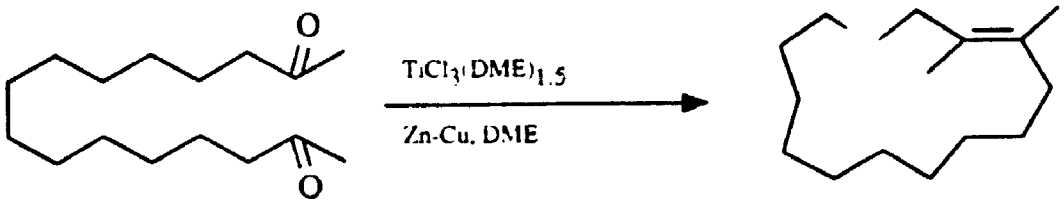


Scheme 2-5: Mechanism of the McMurry reaction

The first stage involves the formation of a radical anion through transfer of an electron from titanium to the carbonyl group. The resulting ketyl radical then dimerizes to the pinacolate intermediate (**2.15**).[2.26] The second stage involves the step-wise reductive cleavage of the C-O bonds giving an oxide-coated titanium surface and the alkene.[2.25] This type of deoxygenation was mechanistically

unprecedented at the time of its discovery and is uniquely carried out by low-valent titanium.[2.25]

While this methodology, based on the $TiCl_3(DME)_{1.5}$/Zn-Cu reagent system, is very effective for the intermolecular coupling of monocarbonyl compounds, it has also proven to be a powerful tool for the intramolecular coupling of dicarbonyl compounds. For example, this reagent system, under conditions of high dilution, efficiently promoted the intramolecular deoxygenative coupling of diketone **2.16** to olefin **2.17** (Scheme 2-6).[2.23]

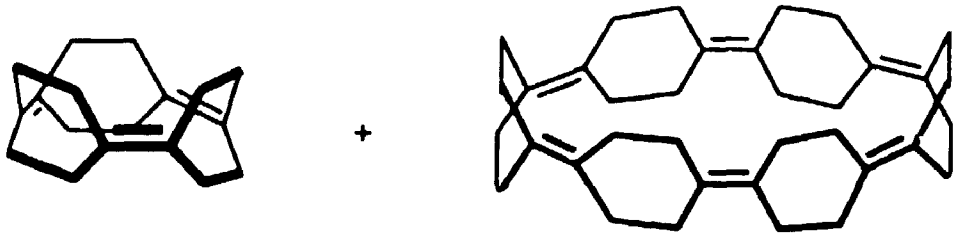


2.16 **2.17**

Scheme 2-6: Intramolecular coupling of diketone **2.16** to olefin **2.17**

One of the earlier reagent systems, $TiCl_3$/Zn-Cu, was used under conditions of high dilution to induce the cyclization of diketone **2.18**.[2.27] The desired product, triene **2.19**, was also accompanied by a small quantity of hexaene **2.20**, arising from reductive dimerization (Scheme 2-7).

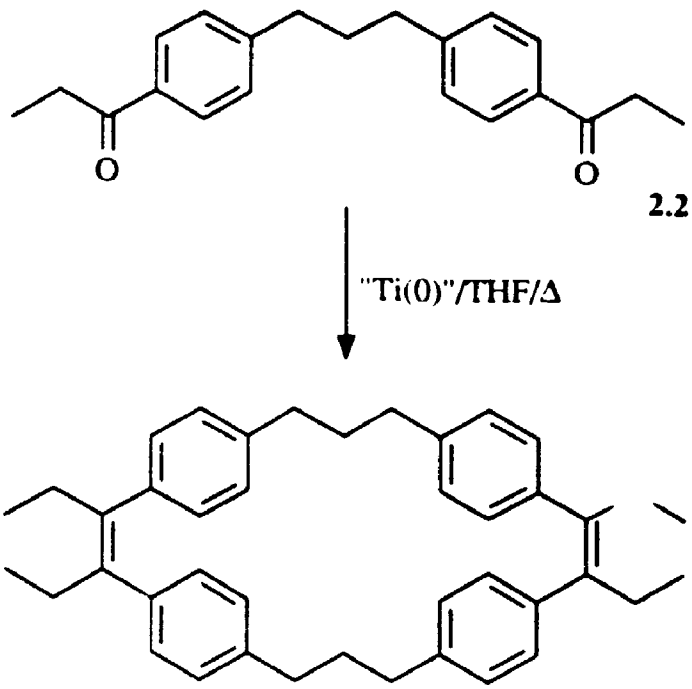
2.18



2.19 + **2.20**

Scheme 2-7: Titanium-induced cyclization of diketone **2.18** to triene **2.19**

The McMurry reaction has also been employed by Grützmacher and co-workers in the synthesis of the macrocyclic cyclophane, [3.2.3.2]paracyclophane-10,27-diene **2.22**, via the reductive dimerization of diketone **2.21** (Scheme 2-8).[2.28] The low-valent titanium species for this reaction was prepared *in situ* by the reduction of $TiCl_4$ with zinc dust. The reaction was completed by the addition of diketone **2.21** over 12 hours using high-dilution techniques. The desired compound (**2.22**) was obtained in 58% yield.

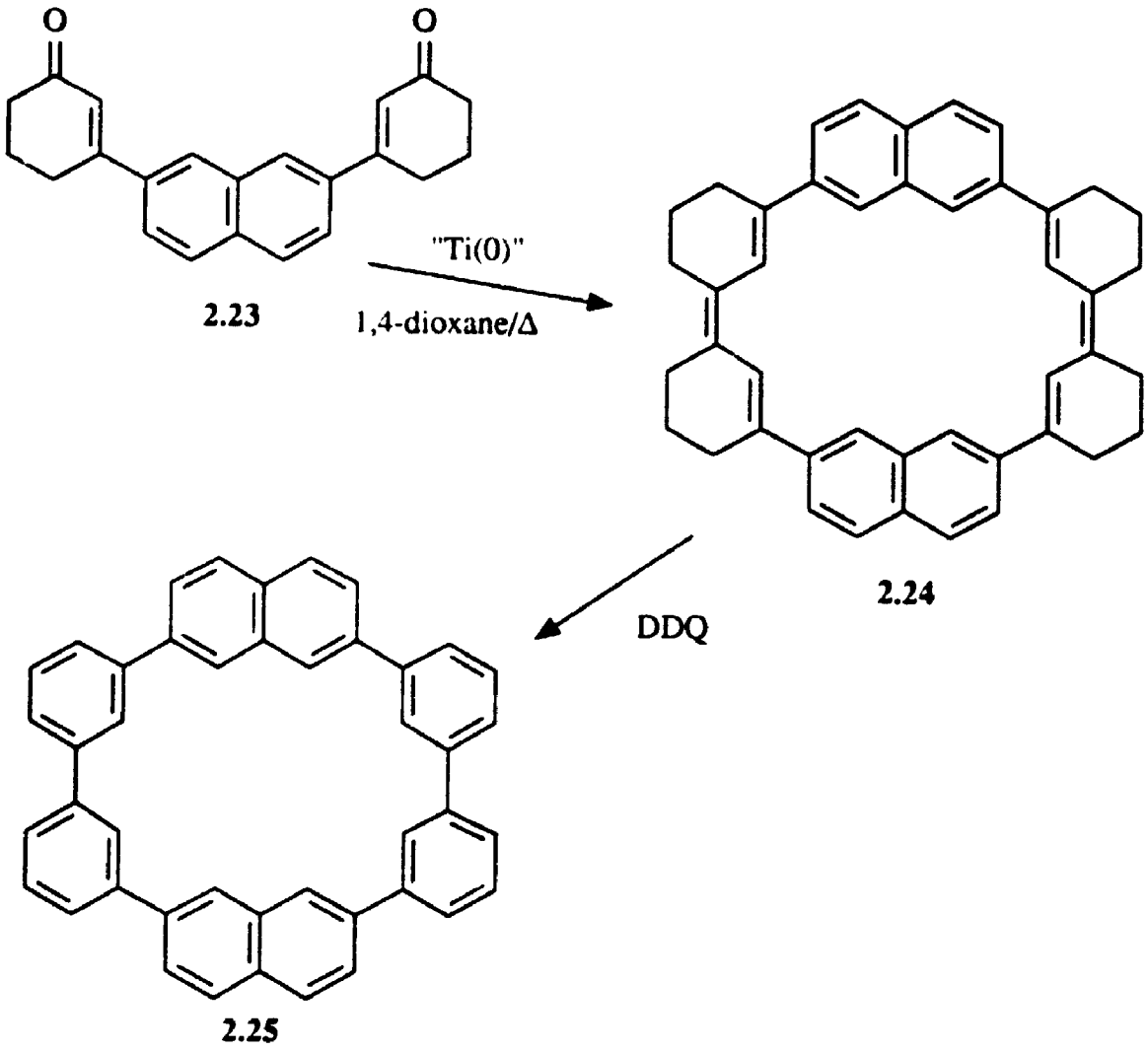


2.21

2.22 (58%)

Scheme 2-8: Reductive dimerization of diketone **2.21** to paracyclophane **2.22**

Vögtle and Thilgen have used the McMurry reaction to effect the cyclodimerization of diketone **2.23** (Scheme 2-9).[2.29] The addition of **2.23** to the low-valent titanium reagent, prepared in a manner analogous to that of Grützmacher and co-workers, was carried out under conditions of moderate dilution which resulted in a 20% yield of cyclic alkene **2.24**. Treatment of **2.24** with the oxidizing agent 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) yielded the fully aromatized product, **2.25**.[2.29]



2.23 **2.24** **2.25**

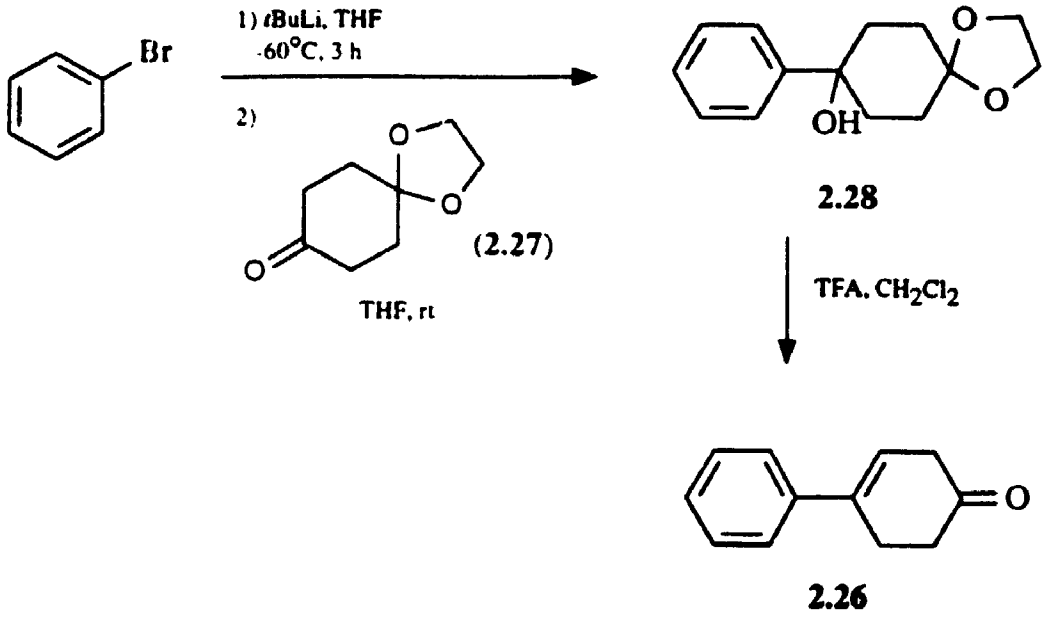
Scheme 2-9: Cyclodimerization of diketone **2.23** to **2.24** followed by oxidation to **2.25**

2.2 Reductive Dimerization of 4-phenyl-3-cyclohexenone (2.26)

Initially, we conducted a model study which examined the reductive dimerization of the known enone, 4-phenyl-3-cyclohexenone (**2.26**). This particular substrate was chosen since it possesses the same β,γ-unsaturated carbonyl moiety as diketone **2.10**, the proposed starting material in our planned synthesis of *sexiphenylene* (**2.9**). It was hoped that such an investigation would provide insight into the reactivity of this specific substructure and thus give some indication as to the suitability of diketone **2.10** as the starting material. It was also hoped that the NMR spectral data of this model dimer would sufficiently mirror that of macrocyclic cyclophane **2.12** so as to assist in the assessment of our attempts to reductively dimerize diketone **2.10**.

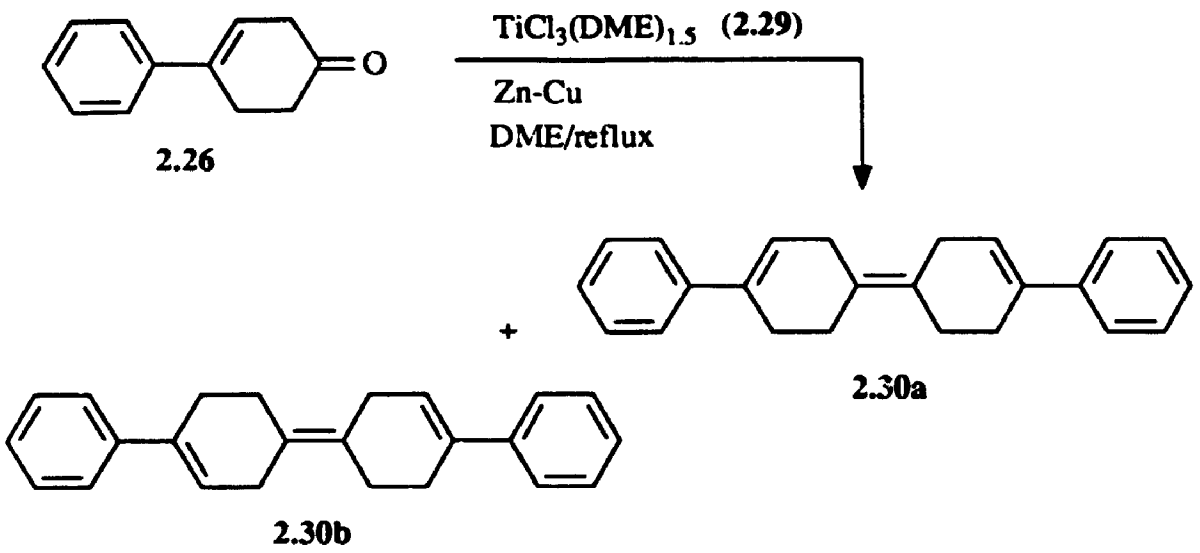
Although a variety of methods for the preparation of cyclohexenone **2.26** can be found in the literature, we found the following new procedure, starting from bromobenzene, to be straightforward and efficient (Scheme 2-10). Lithiobenzene was prepared by treatment of a solution of bromobenzene in THF at -60°C with *tert*-butyllithium (2 equivalents). The reaction mixture was stirred for three hours. A solution of 1,4-cyclohexanedione *mono*-ethylene ketal (**2.27**) in THF was then added. The mixture was gradually warmed to room temperature and stirred overnight to give, after work up, the intermediate hydroxy ketal, **2.28**, as a white crystalline solid in 77% yield. Further reaction with trifluoroacetic acid in methylene chloride effected concomitant dehydration and removal of the acetal protecting group. Trituration of the crude product with hexanes afforded the

desired cyclohexenone (**2.26**) as a white crystalline solid in 66% yield. The spectral data obtained for this compound were consistent with literature values.[2.30]



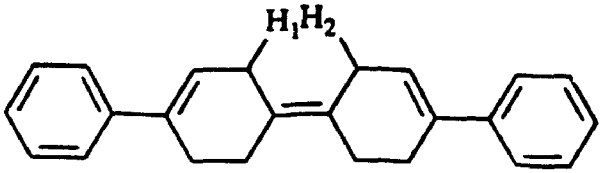
Scheme 2-10: Preparation of 4-phenyl-3-cyclohexenone (**2.26**)

The reductive dimerization of cyclohexenone **2.26** was carried out employing McMurry's $TiCl_3$/DME solvate/Zn-Cu couple reagent system (Scheme 2-11).[2.23] The low-valent titanium reagent was generated *in situ* by the reaction of zinc-copper couple with the $TiCl_3(DME)_{1.5}$ complex, **2.29**, in refluxing dimethoxyethane (DME).[2.23] A solution of cyclohexenone **2.26** in DME was added and the reaction mixture was stirred at reflux for 12 hours. Purification of the crude product by dry column flash chromatography (ethyl acetate/cyclohexane) yielded the desired product, triene **2.30**, a yellow solid (mp 110-112°C), in 31% yield, presumably as a mixture of geometric isomers (**2.30a** and **2.30b**).

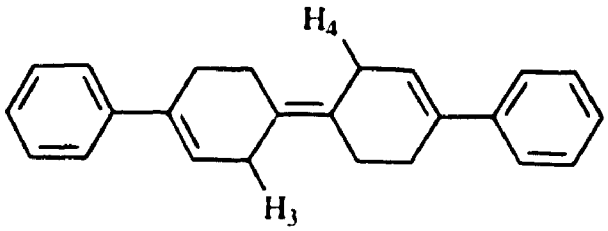


Scheme 2-11: Reductive dimerization of cyclohexenone **2.26**

Separation of the two isomers, so as to determine the relative amounts of **2.30a** and **2.30b**, was not attempted. However, examination of the 200 MHz ^{1}H NMR spectrum of the product mixture revealed that the two isomers were present in a 43:57 ratio. Protons H_1 and H_2 are isochronous due to the plane of symmetry which bisects the central double bond of **2.30a**, at right angles and perpendicular to plane of the molecule. Protons H_3 and protons H_4 are isochronous due to the C_2 axis of symmetry in isomer **2.30b**, which passes through the midpoint of the central double bond perpendicular to the plane of the molecule. The doubly allylic methylene protons of one isomer appear as a doublet at 3.12 ppm, with a coupling constant of 3.3 Hz, while the corresponding methylene protons of the other isomer appear as a doublet at 3.06 ppm, with a coupling constant of 2.3 Hz.



2.30a

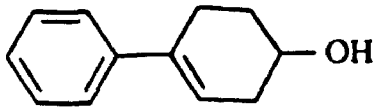


2.30b

The 43:57 ratio, indicated earlier, is based on the integration of these two doublets (δ3.12 ppm/δ3.06 ppm:43/57). The aromatic, olefinic and remaining aliphatic protons of **2.30a** and **2.30b** appear as unresolved multiplets at 7.2-7.45 ppm, 6.1-6.2 ppm and 2.5-2.65 ppm, respectively. The ^{13}C NMR data observed for **2.30** are also consistent with a mixture of geometric isomers in unequal amounts. The isomeric methylene carbons give rise to pairs of major and minor signals in the carbon NMR spectrum at δ 30.0/29.5*, 29.1/28.8*, and 26.7*/26.3 where * denotes the minor isomer. The isomeric olefinic carbons similarly give rise to pairs of major and minor signals at δ 137.1*/137.0, 125.8/125.7*, and 124.1/123.9*. The isomeric phenyl carbons are isochronous. The mass spectrum of **2.30** exhibited a molecular ion (M^+) peak at m/e=312 [312.1878(calcd); 312.1875(found)], as expected. A M^{2+} peak was also observed at m/e = 156.

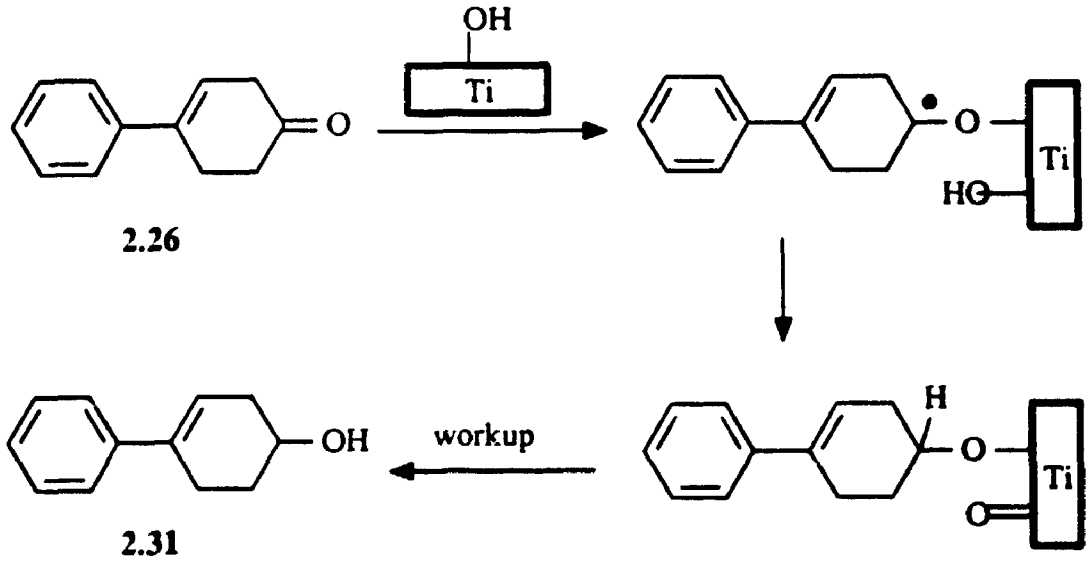
Interestingly, on a number of attempts to carry out this reaction, 4-phenyl-3-cyclohexenol (**2.31**) was isolated as the sole product. The identity of this material was confirmed by comparison with published spectral data for this known

compound.[2.31]



2.31

One possible explanation for the formation of this compound is that adventitious moisture, as "TiOH" on the surface of the Ti(0) particles, transfers hydrogen to the intermediate radical as shown in Scheme 2-12. Extreme care was therefore taken to exclude moisture at all stages of the reaction, and this alcohol was then not obtained.



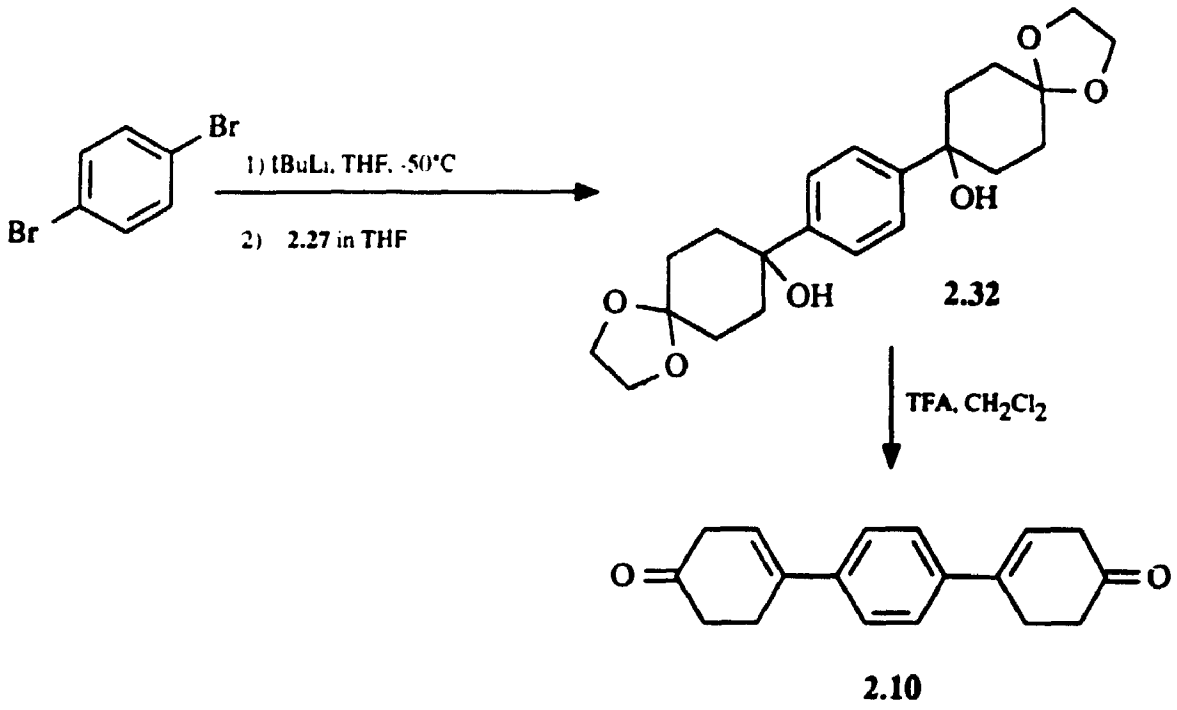
Scheme 2-12: Possible mechanism for the formation of cyclohexenol **2.31**

Having shown that this type of β,γ-enone could successfully undergo McMurry coupling, we were able to turn our attention to studies on the reductive dimerization of diketone **2.10** to macrocyclic cyclophane **2.12**.

2.3 Synthetic Approaches to *Sexiphenylene* (2.9)

2.3.1 Introduction

The required diketone, **2.10**, was originally prepared by Pierre Zabel, a former member of our research group, in two steps from *p*-dibromobenzene (Scheme 2-13).[2.32]

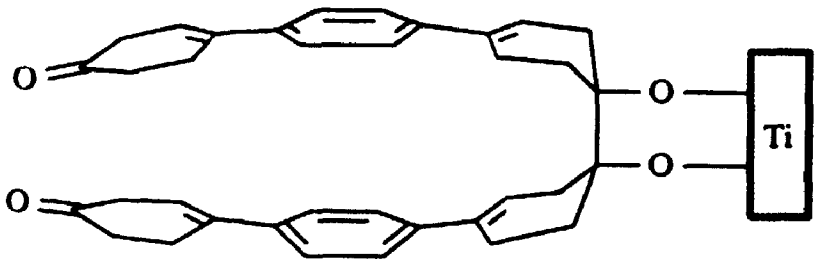


Scheme 2-13: Preparation of diketone **2.10**

This synthesis involved the preparation of 1,4-dilithiobenzene by the treatment of a solution of *p*-dibromobenzene in THF at -50°C with *tert*-butyllithium. Further reaction with 1,4-cyclohexanedione *mono*-ethylene ketal (**2.27**), followed by workup, yielded the dihydroxy diketal intermediate, **2.32**, in 70% yield.[2.32] Zabel completed the synthesis of crude **2.10** (in unspecified yield) by using trifluoroacetic

acid to effect dehydration and to catalyze the removal of the acetal protecting groups. In our hands, this method afforded the desired diketone (**2.10**) in 42% overall yield (based on 1,4-dibromobenzene) after purification by recrystallization from cyclohexane/methylene chloride.

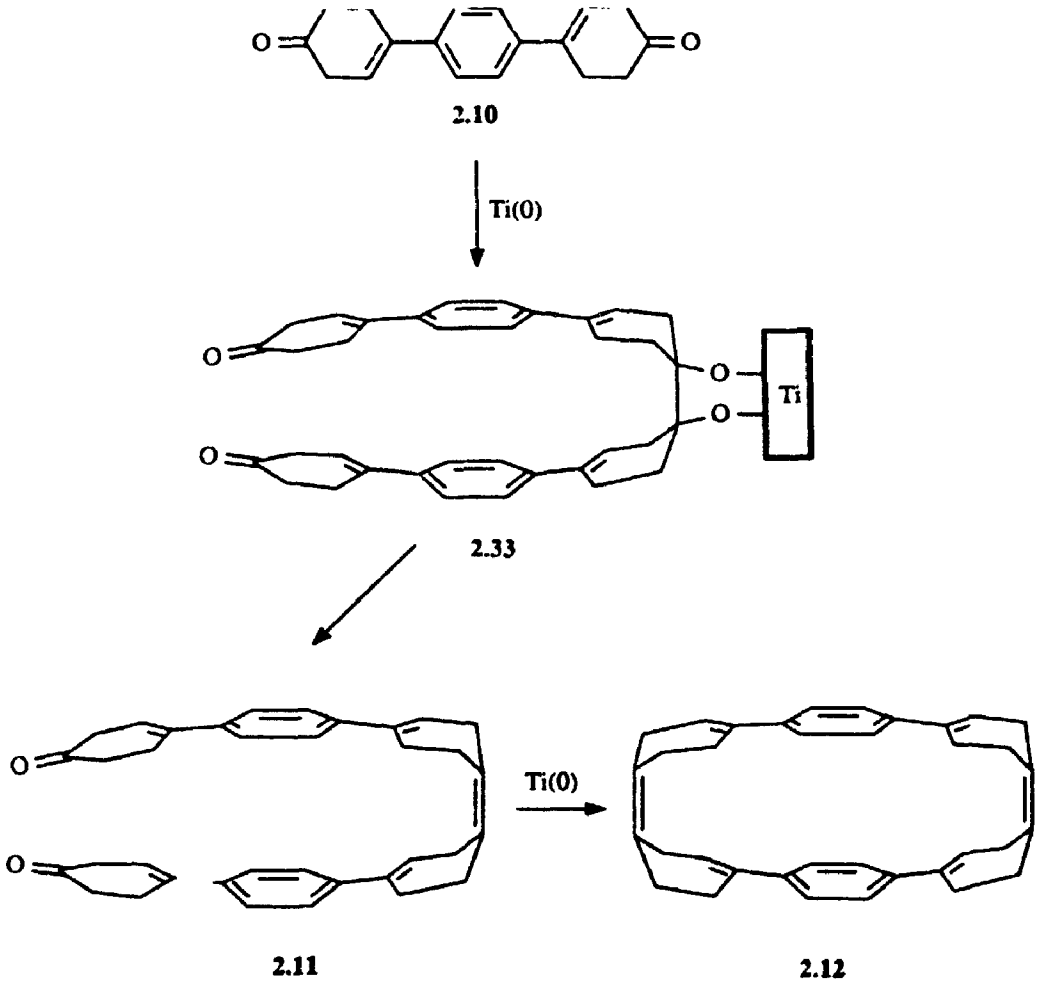
With diketone **2.10** now in hand, attention turned to the study of its reductive dimerization to provide macrocyclic cyclophane **2.12**. As mentioned earlier, in general terms, our proposal for the synthesis of *sexiphenylene* (**2.9**) consists of two synthetic operations: reductive dimerization of diketone **2.10** to macrocyclic cyclophane **2.12** (Scheme 2-2) and aromatization of this intermediate (Scheme 2-3). The reductive dimerization is envisaged to proceed via two separate, though similar, McMurry reactions. The first would involve the coupling of two molecules of **2.10** to give diketone **2.11**. The second would be an intramolecular McMurry reaction designed to close up the macro-ring by coupling the two remaining carbonyl groups of diketone **2.11**. This second, intramolecular, McMurry reaction is the *crucial* step in our proposal and its success is expected to be governed partly by the extent to which diketone **2.11** can fold back on itself (under the influence of Van der Waals attractive forces), thereby facilitating closure by bringing the carbonyl groups into sufficiently close proximity. This, however, implicitly assumes diketone **2.11** to be the reactive intermediate. This need not be the case. Assuming that these McMurry reactions are following the mechanistic pathway outlined in Scheme 2-5, pinacolate **2.33** will be formed in the first stage of the first McMurry reaction.



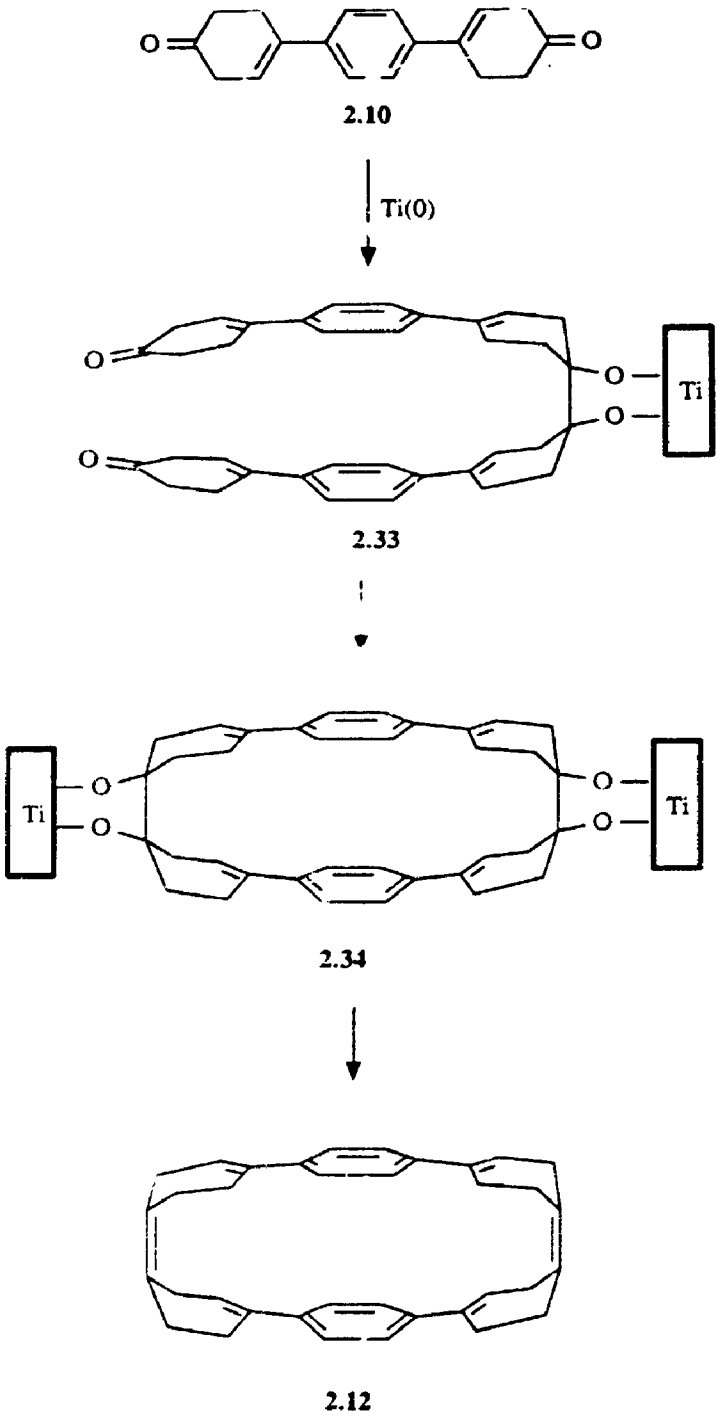
2.33

Therefore, in principle the macrocyclic product (**2.12**) can be formed via two different synthetic paths. Pinacolate **2.33** may be so short-lived that it never encounters a second particle of Ti(0) before collapsing to diketone **2.11** (Scheme 2-14). The formation of macrocyclic cyclophane **2.12** would be completed by a second McMurry reaction, subject to the ability of diketone **2.11** to assume the necessary folded conformation.

With a longer lifetime, however, the likelihood that pinacolate **2.33** will encounter another Ti(0) particle increases (Scheme 2-15). The result would be ring closure of pinacolate **2.33**, via intramolecular coupling, to dipinacolate **2.34**. This cyclization would also depend upon the ability of the substrate (**2.33**) to assume the necessary folded conformation, which may be easier for **2.33** than for **2.11**. Double deoxygenation would then complete the formation of macrocyclic cyclophane **2.12**.



Scheme 2-14: Synthetic pathway to macrocyclic cyclophane **2.12** via the diketone intermediate (**2.11**)



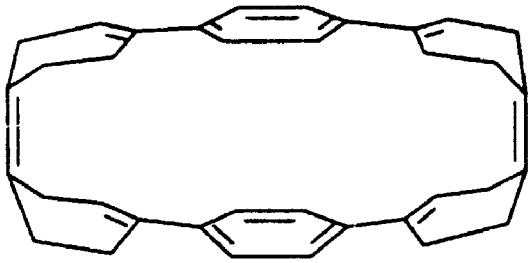
Scheme 2-15: Synthetic pathway to macrocyclic cyclophane **2.12** via the pinacolate intermediate (**2.33**)

2.3.2 Attempted Reductive Dimerization of Diketone 2.10

The titanium reagent was freshly prepared, as before, by reaction of zinc-copper couple with $TiCl_3(DME)_{1.5}$ complex in refluxing DME. A 0.1 *M* solution of diketone **2.10** in DME was then added to this "Ti(0)" reagent over a period of 12 hours via syringe pump, conditions designed to sufficiently dilute the substrate so as to encourage the second, intramolecular, McMurry reaction. The titanium/substrate ratio was 7.33:1. After the addition was complete, the reaction mixture was stirred at reflux for 6 hours (Scheme 2-16).

2.10

$TiCl_3(DME)_{1.5}$, Zn-Cu couple
DME, reflux

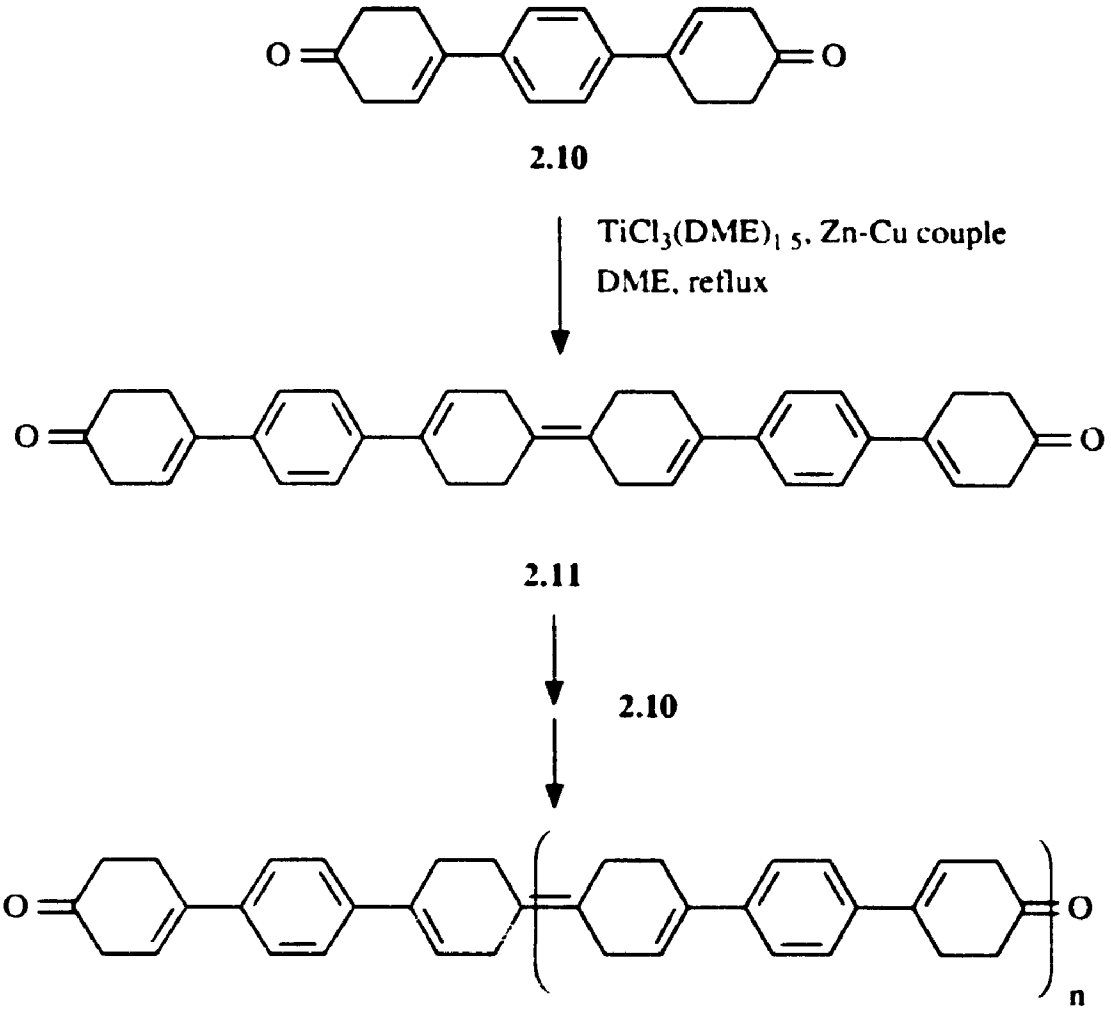


2.12

Scheme 2-16: Attempted reductive dimerization of diketone **2.10** to cyclophane **2.12**

The insoluble material was removed by filtration through a column of Florisil.

Subsequent washing of the Florisil with pentane and ether, followed by evaporation of the solvent under reduced pressure, yielded only 10 mg of material, ca. 4% of the mass of the starting diketone. In case the remainder of the product was still on the column of Florisil, it was washed successively with 50% ethyl acetate/methylene chloride, methylene chloride and methanol. Evaporation after each washing failed to yield any material. Examination of the ^{1}H NMR spectrum of the 10 mg sample which was isolated revealed that the starting diketone (**2.10**) was not present. However, the aromatic, vinylic and aliphatic peaks which we expected the product to exhibit, by analogy with the dimer of 4-phenyl-3-cyclohexenone (**2.30**), were absent. When considered together, the total consumption of diketone **2.10**, the very low mass recovery and the absence of any useful products suggested that the starting diketone may have polymerized to insoluble material. This raised some interesting questions. Was the polymerization due to an overly high concentration of diketone **2.10**? Alternatively, did polymerization occur because the intermediate, be it diketone **2.11** or pinacolate **2.33**, is simply unable to assume the required folded conformation? Substrate concentration is an important issue in macro-cyclizations, examples of which were seen earlier (Schemes 2-6, 2-8 and 2-9). If the concentration of diketone **2.10** is too high, the *mono*-coupled intermediate (either **2.11** or **2.33**) will instead react with another molecule of **2.10**. This intermolecular coupling would ultimately result in polymerization to give **2.35** (Scheme 2-17).



Scheme 2-17: Possible polymerization of diketone **2.10** to **2.35**

In order to try to minimize polymerization of this type in our subsequent attempts at the dimerization of diketone **2.10**, we altered the reaction conditions in two ways. First, a more dilute solution of the diketone (in DME) was used. Secondly, this solution was added over a much longer period of time. Both of

these changes would lead to a decrease in the concentration of diketone **2.10** thus encouraging intramolecular coupling of the reactive intermediate (either **2.11** or **2.33**) to the macrocyclic cyclophane (**2.12**). The use of 0.10 *M* solution of diketone **2.10** in DME (entry 2) added over 12 hours lead to a 0% mass recovery, despite attempts to recover any soluble material.

An examination of the literature revealed that intramolecular McMurry couplings occasionally require an excess of the titanium reagent.[2.23,2.28] Unfortunately, the combination of a 0.054 *M* solution of diketone **2.10** in DME (entry 3), a period of addition of 122 hours and a titanium/substrate ratio of 16.6:1 failed to give any soluble material, as before. We therefore concluded that polymerization, of the type depicted in Scheme 2-17, was most likely occurring despite our attempts to curtail it.

At this point, it was beginning to look as if the intermediate diketone (**2.11** or **2.33**) might be unable to fold back on itself, despite modelling studies to the contrary and any Van der Waals attractive forces which might be at work. It was also possible that the concentration of diketone **2.10** was still too high! We therefore decided to make two additional modifications to our procedure. In order to further dilute the solution of diketone **2.10** before addition to the reaction mixture, a dilution trident was employed. This simple apparatus consisted of a three-socket adaptor equipped with a collar, thus providing a reservoir for 12 mL of condensate.[2.33] Entries 4 to 6 represent experimental runs employing the dilution trident. In addition the solvent was changed from DME to the higher

boiling solvent, *p*-dioxane, in the hope that the higher temperature would provide sufficient energy for the intermediate diketone to assume the conformation needed for cyclization. Other researchers have reported the use of *p*-dioxane as solvent as opposed to THF and DME, the traditional solvents of the McMurry reaction.[2.29]

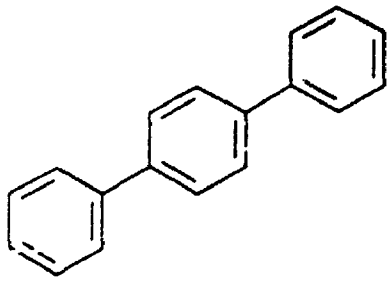
TABLE 2-1: Attempted reductive dimerization/cyclization of diketone **2.10**

Entry	[**2.10**][a]	solvent	time[b]/h	DT[c]	Ti/**2.10** ratio	% mass recovery
1	0.75	DME	2	N	7.9	0
2	0.10	DME	12	N	7.33	0
3	0.054	DME	122	N	16.6	0
4	0.094	dioxane	130	Y	18.3	10
5	0.042	dioxane	132	Y	33.1	25
6	0.042	dioxane	135	Y	21.4	15

[a]molesL^{-1}; [b]period of addition via syringe pump; [c]dilution trident

Better mass recoveries were achieved with this combination of concentration, solvent, period of addition and dilution trident (entries 4 to 6). The ^{1}H NMR data of these crude products were very similar. Attempts to purify these mixtures (entries 4 to 6) by dry column flash chromatography were not successful. As discussed below, these reactions appear to give very complex reaction mixtures which were only resolvable by reverse phase HPLC.

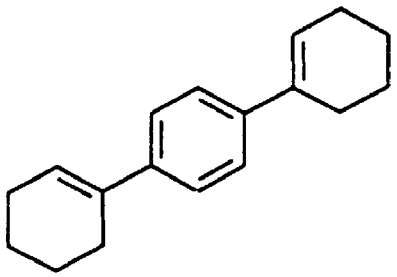
After preparation of the activated titanium reagent a 0.094 *M* solution of diketone **2.10** (1.0 g) in *p*-dioxane was added over a 130 hour period by syringe pump via the dilution trident (entry 4). After the addition was complete, the reaction mixture was stirred at reflux for a further 4 hours. Purification by dry column flash chromatography yielded 100 mg of a yellow solid (ca. 10% of the mass of the starting diketone), which showed a single spot on TLC. Analysis of this material by reverse phase HPLC revealed it to be a mixture consisting of two major components and a number of other components present in smaller amounts. Samples of the two major components, each comprising ≈15% of the mixture, were collected. The ^{1}H NMR spectrum of the first one to elute showed only aromatic absorptions, as a multiplet at 7.3-7.75 ppm. The mass spectrum of this component, which exhibited a M^+ peak at *m/e*=230, was identical to that reported in the literature for *p*-terphenyl (**2.36**).[2.34] High resolution MS confirmed this assignment [*m/e* = 230.1096(calcd); 230.1090(found)].



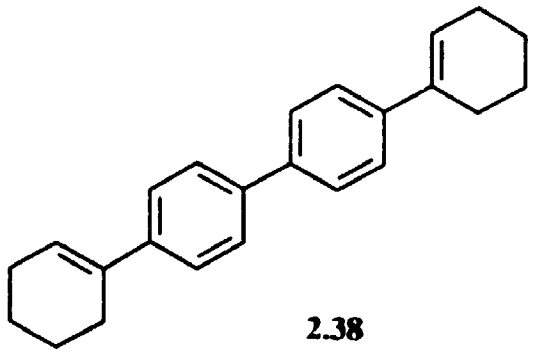
2.36

The ^{1}H NMR spectrum of the second major component to elute consisted of multiplets at 7.3-7.7, 6.2, 2.4-2.5, 2.2-2.3 and 1.6-1.9 ppm in a ratio of

≈8:1:2:2:4. Interestingly, the spectrum is remarkably similar to that reported for diene **2.37**[2.35] as well as that of diene **2.38,** which we had prepared earlier (see experimental section).

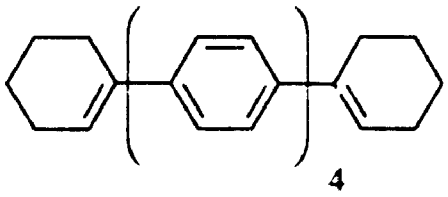


2.37



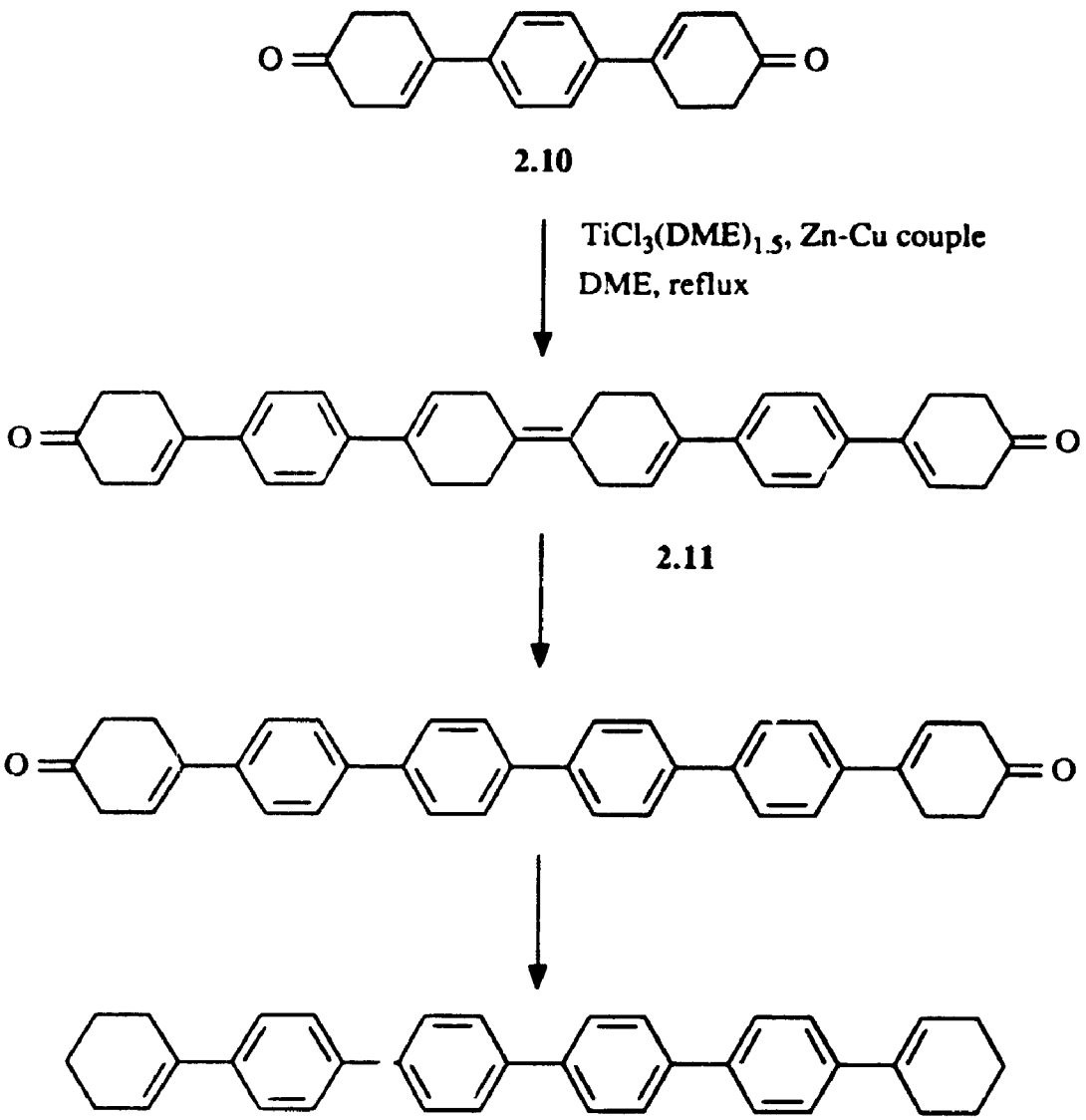
2.38

The dimer-derived quaterphenyl, **2.39**, is consistent with the integration, but the mass spectrum was messy, and an expected strong molecular ion peak at $m/e = 466$ was not observed. Only a small 466 peak was vi · ·le among a forest of other small peaks.



2.39

Th" formation of a product like **2.39** would require the deoxygenation of the ketone functions as well as the aromatization of the intervening cyclohexenylidene unit (see Scheme 2-18).

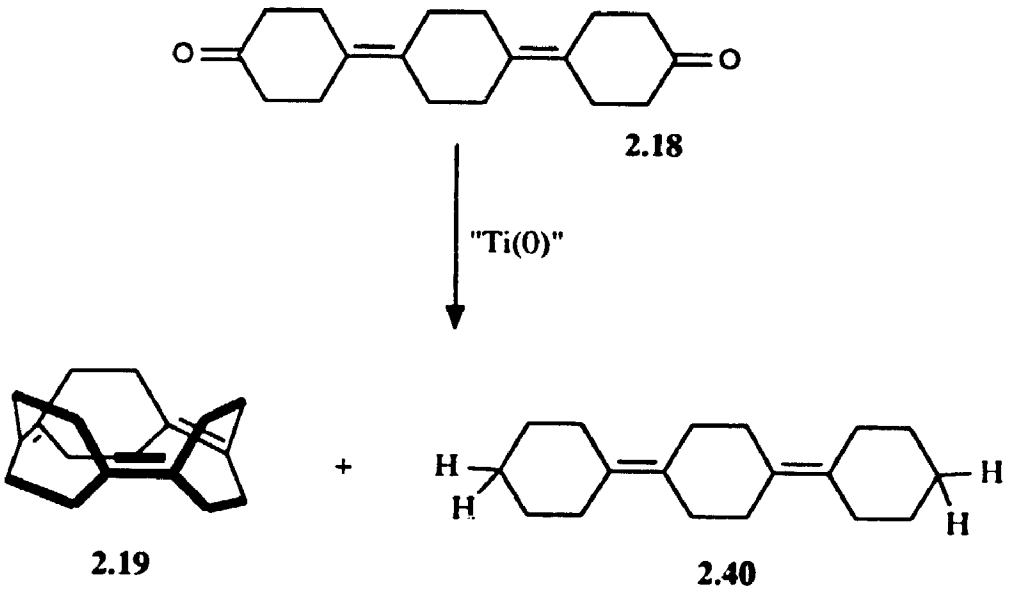


2.39

Scheme 2-18: Possible pathway for the formation of diene **2.39**

This type of carbonyl reduction to a methylene unit has been previously observed within the context of a low-valent titanium induced reductive coupling of a ketone. Specifically, McMurry reported that diene **2.40**, and its double bond isomers, were

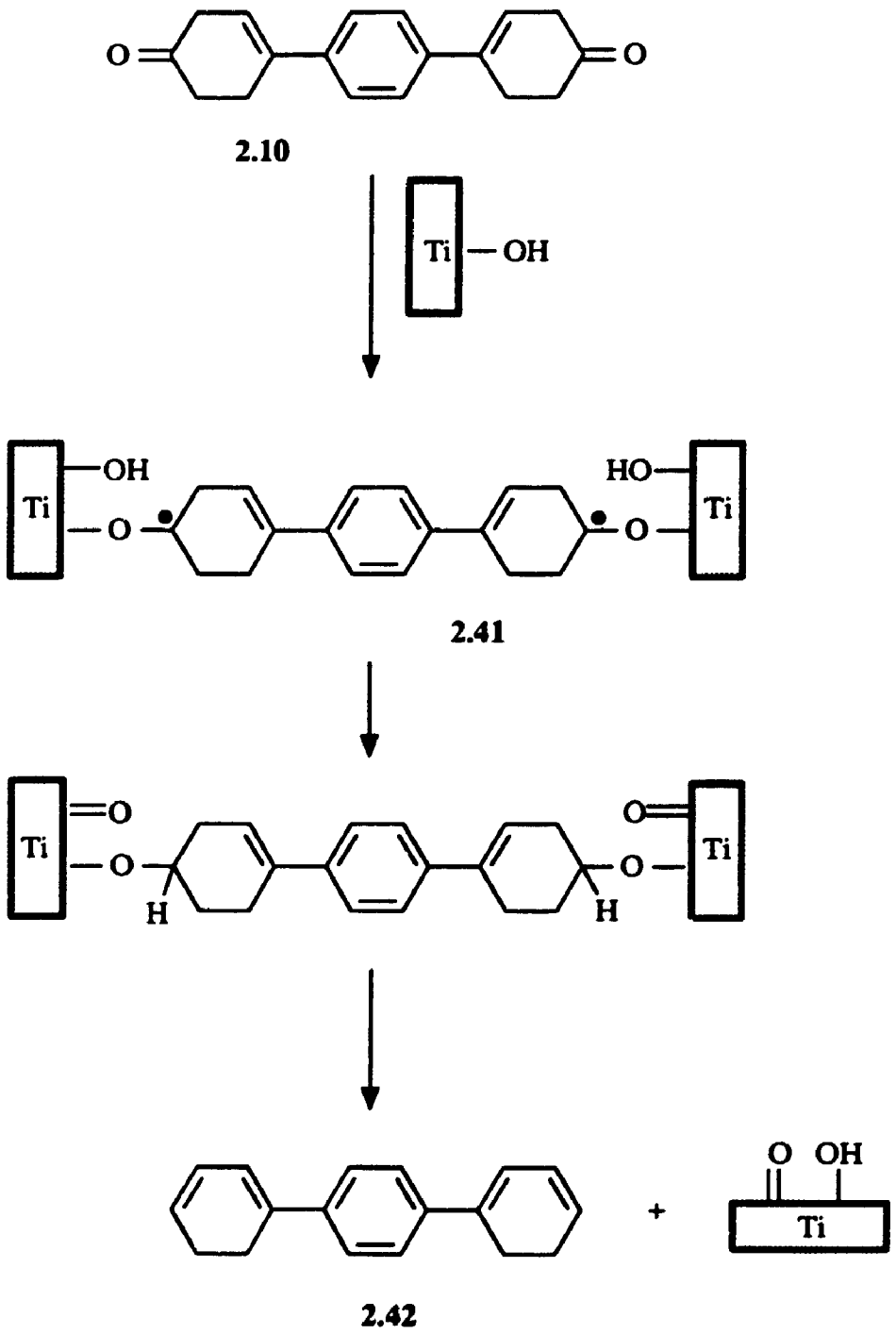
the major byproducts in the reaction of diketone **2.18** with Ti(0) (Scheme 2-19).[2.27] As seen earlier in Scheme 2-7, triene **2.19**, the desired product of this reaction, was isolated in only 24% yield.



Scheme 2-19: Synthesis of triene **2.19** accompanied by the formation of diene **2.40**

A possible mechanism for the formation of *p*-terphenyl (**2.36**) is shown in Schemes 2-18 and 2-19. In the first step (Scheme 2-20), adventitious moisture, as "TiOH" on the surface of the Ti(0) particles, transfers hydrogen to the intermediate diradical (**2.41**). This is analogous to the mechanism proposed for the formation of alcohol **2.31**, seen in Scheme 2-12. In the second step, loss of 2 equivalents of "TiOH" would give tetraene **2.42**. GC/MS analysis of the product from a previous McMurry reaction, not discussed earlier, showed two

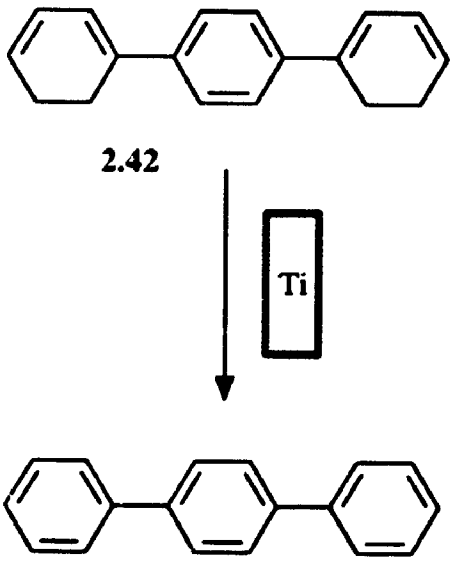
main peaks, of comparable intensity, at *m/e* = 230 and 234. The presence of the 234 peak offers some support for the implication of tetraene **2.42** in the formation of terphenyl **2.36** (*m/e* = 230 peak).



2.10 **2.41** **2.42**

Scheme 2-20: Proposed mechanism for the formation of tetraene **2.42**

The aromatization of six-membered rings, especially those already containing one or two double bonds, is well documented. Often, this can be accomplished through the use of an hydrogenation catalyst, such as platinum or palladium.[2.36] With titanium acting in a similar manner, tetraene **2.42** would be expected to readily lose two equivalents of hydrogen in the final step to give terphenyl **2.36** (Scheme 2-21).



2.42

2.36

Scheme 2-21: Proposed pathway for the conversion of tetraene **2.42** to terphenyl **2.36**

Although we were able to assign a structure to one of the two major HPLC fractions, we were unable to find any evidence for either the starting diketone or the desired product, cyclophane **2.12**. In the event the concentration of diketone **2.10** had been too high in previous attempts, this reaction used a syringe pump in

conjunction with a dilution trident. The solvent was even switched to higher boiling *p*-dioxane, for the reasons discussed earlier. Interestingly, these types of measures have been successfully employed by the Grützmacher (Scheme 2-8) and Vögtle (Scheme 2-9) groups, among others. It would therefore appear that the problems which we have encountered are most likely due to the inability of the intermediate diketone, either diketone **2.11** or pinacolate **2.33**, to fold back on itself so as to assume the conformation required for the second intramolecular McMurry reaction.

2.4 Summary

Enone **2.26** was prepared in two steps from bromobenzene via a new, straightforward and efficient procedure. Reaction with *n*-butyllithium gave lithiobenzene which, when reacted with 1,4-cyclohexanedione *mono*-ethylene ketal (**2.27**), gave hydroxy ketal **2.28** in 77% yield. Reaction with trifluoroacetic acid in methylene chloride then effected concomitant dehydration and removal of the acetal protecting group to give enone **2.26** in 66% yield. Reductive dimerization of cyclohexenone **2.26** was carried out employing McMurry's $TiCl_3$/DME solvate/Zn-Cu couple reagent system.[2.23] The desired product, triene **2.30**, was obtained in 31% yield as a 43:57 mixture of geometric isomers.

Having shown that this type of β,γ-enone could undergo McMurry coupling, attention turned to studies on the reductive dimerization of diketone **2.10** to macrocyclic cyclophane **2.12**. Zabel originally reported the synthesis of diketone **2.10**, although in unspecified yield.[2.32] In our hands, his method afforded **2.10** in 42% overall yield. As before, the $TiCl_3$/DME solvate/Zn-Cu couple reagent system was used for the coupling attempts. The slow addition of a dilute solution of diketone **2.10** in *p*-dioxane over a period of 130 hours to a refluxing suspension of the McMurry reagent yielded a small amount of crude material, which was subjected to purification by flash chromatography and reverse phase HPLC. Although only two components were isolated, both in minute amounts, one of them was positively identified as *p*-terphenyl. The other remains unidentified but was not the desired cyclophane.

2.5 Conclusions

Our aim of synthesizing *sexiphenylene*, which would be the first example of a cyclic oligoparaphenylene [COP], via reductive dimerization of diketone **2.10** followed by aromatization, was not achieved. Although a model study involving 4-phenyl-3-cyclohexenone demonstrated that this type of β,γ-unsaturated carbonyl moiety is capable of undergoing successful reductive dimerization, we were unable to find evidence for the formation of the *sexiphenylene* precursor, macrocyclic cyclophane **2.12**, from **2.10** under a variety of conditions, including high dilution.

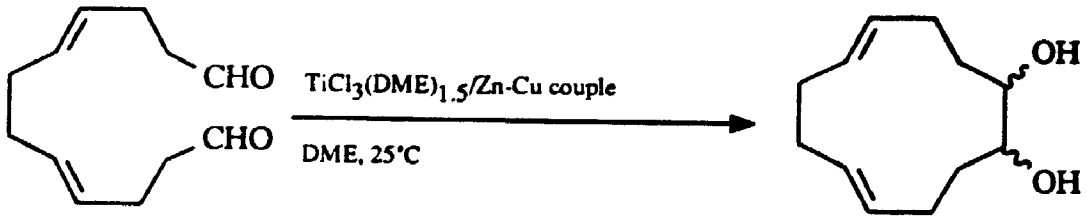
We were able to identify one of the two major HPLC fractions as *p*-terphenyl (**2.36**), however the vast majority of the starting diketone was apparently converted to insoluble material. It is likely that diketone **2.10** underwent polymerization of the type depicted in Scheme 2-15.

The failure of diketone **2.10** to undergo reductive dimerization to cyclophane **2.12** is believed to be due to the rigidity of the intermediate diketone (**2.11**). This being the case, then one of two possible scenarios may hold the solution to the problem.

1. If diketone **2.11** is the intermediate which must undergo cyclization, then any changes which increase the flexibility of the substrate warrant investigation. For example, if one reduced the double bonds of **2.10**, to give **2.43**, macrocyclization might be favored.

2.43

2. If the pinacolate formed by dimerization (**2.33**) is the intermediate which must undergo cyclization, but is so short-lived that it never encounters a second particle of Ti(0), it might be possible for **2.33** to undergo reductive cyclization if one could increase its lifetime. The literature precedent for this approach is provided McMurry and Rico. They have reported that low valent titanium induces intramolecular pinacol couplings at room temperature, which must necessarily proceed through a pinacolate intermediate (Scheme 2-22).[2.38]



2.44

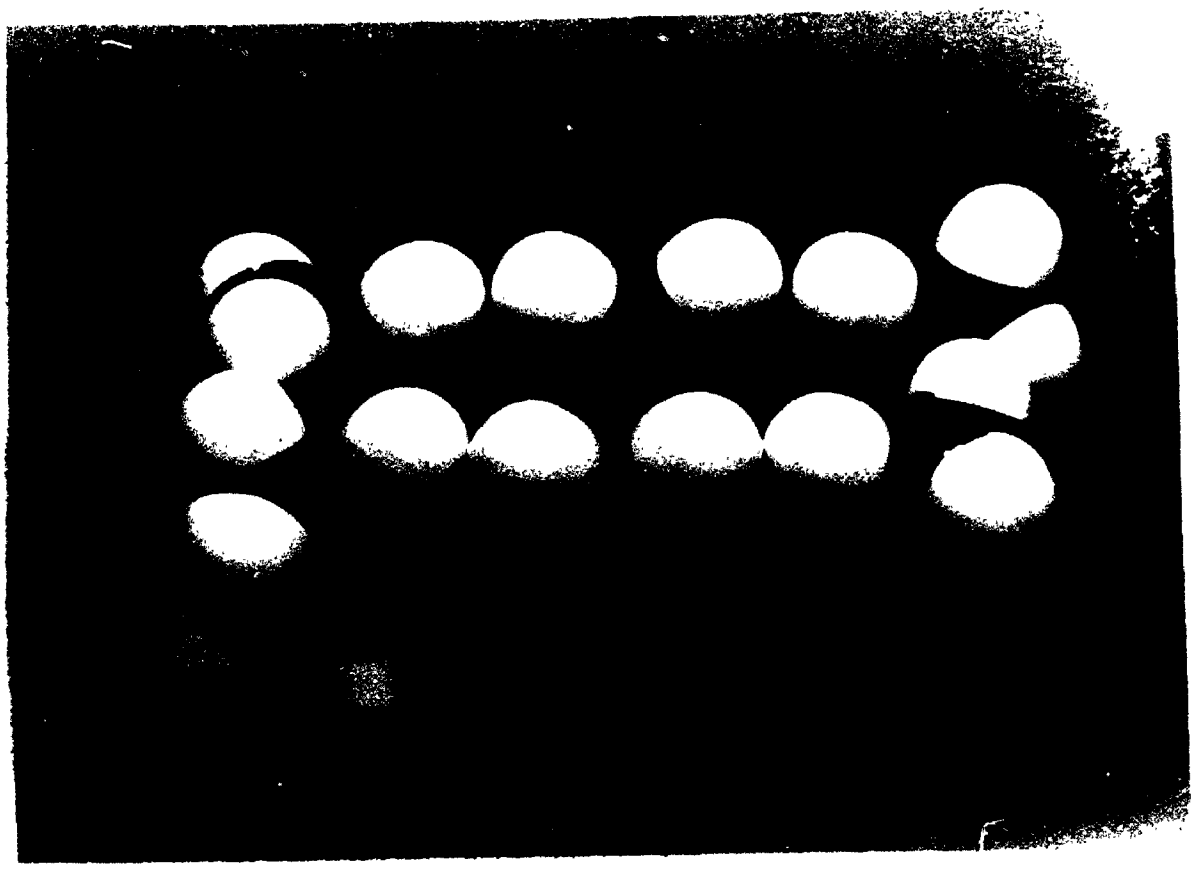
(30 h, syringe pump)

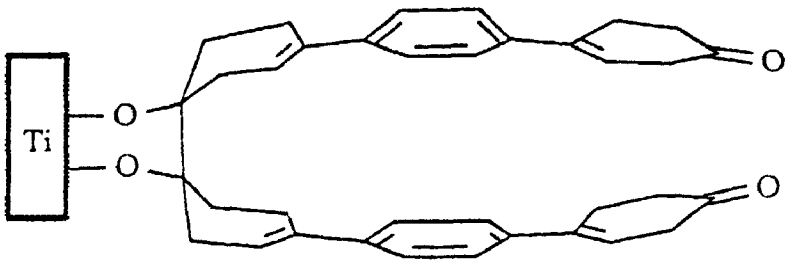
Scheme 2-22: The intramolecular pinacol coupling of aldehyde **2.44**

They have also reported that these diols can be converted by low valent titanium to the corresponding alkenes at higher temperatures.[2.39] Therefore, it might be

possible to allow the formation and cyclization of **2.33** to occur at room temperature to give dipinacolate **2.34**, before raising the temperature to induce olefin formation.

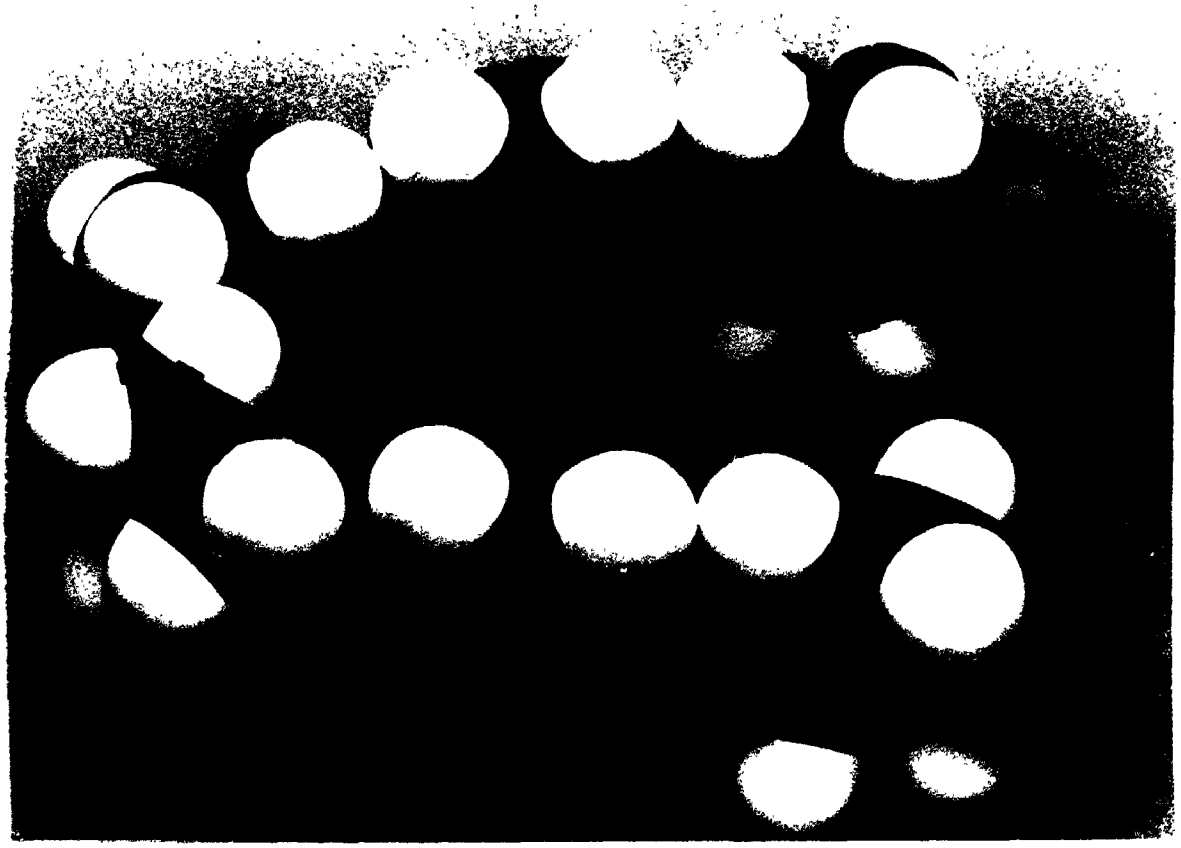
Finally, examination of Stuart/Briegleb models of diketone **2.11** and pinacolate **2.33** provides evidence that this alternative pinacolate-based approach might prove successful. The model of pinacolate **2.33** (Figure 2-1) can easily assume a conformation in which the two "halves" of the molecule are intimately stacked and the two remaining carbonyl groups are in extreme close proximity. The reaction to the dipinacolate (**2.34**) would therefore seem quite likely. The model of diketone **2.11** (Figure 2-2), although possessing a degree of flexibility, is unable to assume the same folded conformation.

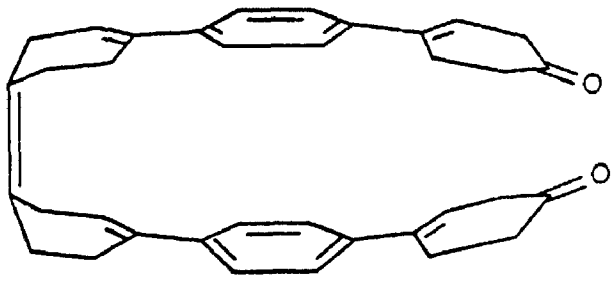




2.33

Figure 2-1: Stuart/Briegleb model of pinacolate **2.33** (oriented with carbonyl groups at right of photo)



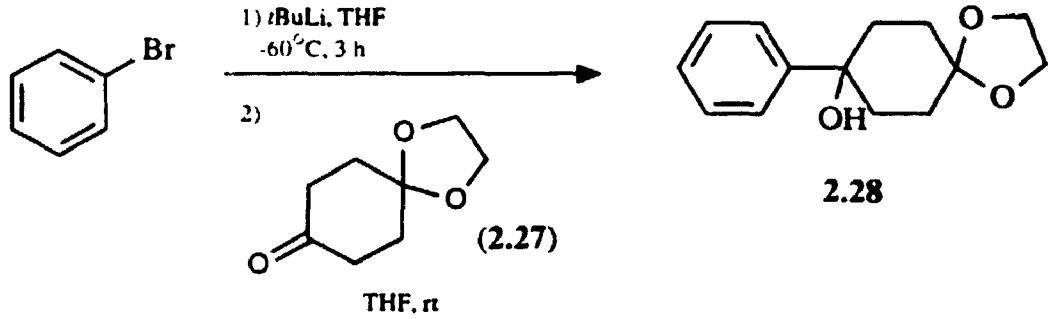


2.11

Figure 2-2: Stuart/Briegleb model of diketone **2.11** (oriented with carbonyl groups at right of photo)

2.6 Experimental

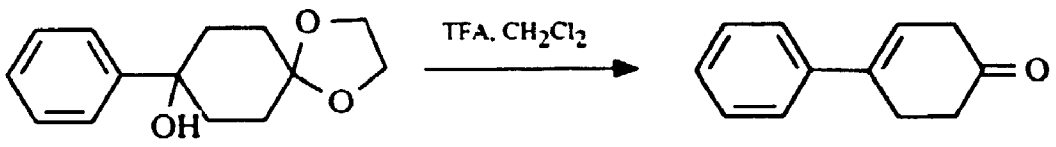
4-Hydroxy-4-phenylcyclohexanone ethylene ketal (2.28)



To 1.49 g (9.5 mmol) of bromobenzene in 20 mL of THF at -60°C was added 11.2 mL (1.7 *M*; 19.0 mmol) of *tert*-butyllithium dropwise, with stirring, via syringe. The reaction mixture was stirred at -60°C for 3 h. 1,4-Cyclohexanedione *mono*-ethylene ketal (**2.27**) (1.5 g, 9.5 mmol) in 10 mL of THF was added via syringe. The reaction mixture was warmed to room temperature by evaporation of the dry ice from the cooling bath and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were washed with saturated aq. NaCl (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 1.7 g of **2.28** as a white crystalline solid (77%): mp 94-96°C; ^{1}H NMR ($CDCl_3$): δ 7.2-7.6 (m, 5H), 4.01 (s, 4 H), 2.40 (bs, 1H), 2.0-2.3 (m, 4H), 1.6-1.9 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 148.7 (quaternary), 128.4 (CH), 127.0 (CH), 124.6 (CH), 108.5 (O_2C), 72.3 (COH), 64.3 (CH_2), 36.4 (CH_2), 30.6 (CH_2).

MS, *m/e* (relative intensity): 234 (M^+, 0.1), 217 (0.2), 99 (100), 87 (72); high resolution *m/e* calcd. for $C_{14}H_{18}O_3$: 234.1256, found: 234.1258.

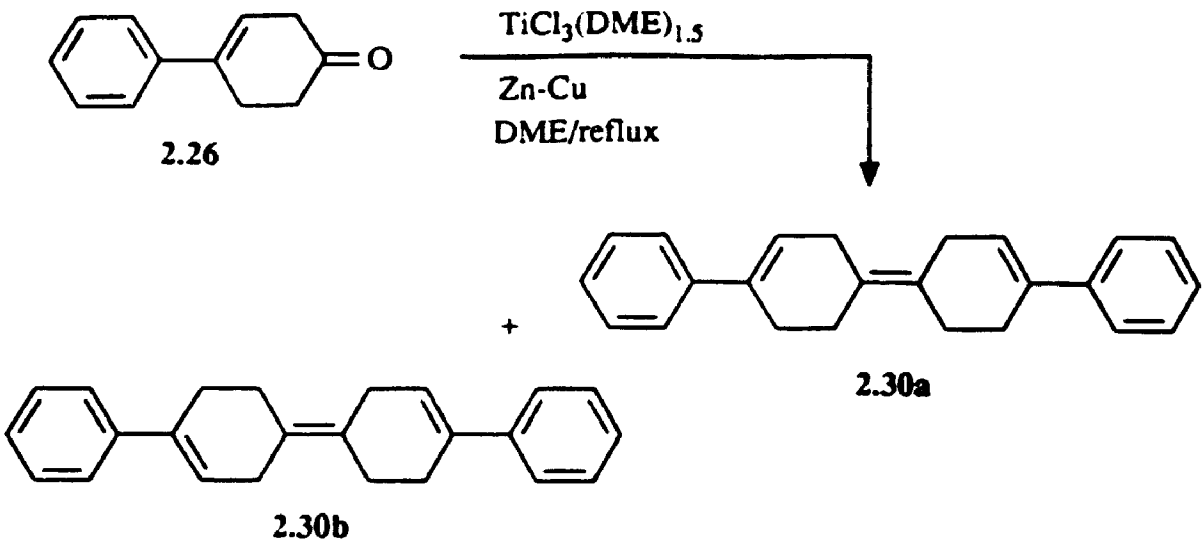
4-Phenyl-3-cyclohexenone[2.30] (2.26)



2.28 **2.26**

To 1.70 g (7.3 mmol) of **2.28** in 15 mL of CH_2Cl_2 was added 5 mL (0.065 mol) of CF_3COOH. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aq. sodium bicarbonate (added until the acid was neutralized) and the aqueous layer was extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were washed with saturated aq. sodium chloride (75 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a white solid. Trituration with hexanes yielded 0.83 g of **2.26** as a white crystalline solid (66%): mp 72-73°C; ^1H NMR ($CDCl_3$): δ 7.2-7.45 (m, 5H), 6.10 (m, 1H), 3.07 (m, 2H), 2.92 (m, 2H), 2.65 (t, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 209.8 (C=O), 140.5 (quaternary), 137.3 (quaternary), 128.2 (CH), 127.1 (CH), 124.9 (CH), 120.7 (CH), 39.3 (CH_2), 38.1 (CH_2), 27.2 (CH_2); MS, *m/e* (relative intensity): 172 (M^+, 78), 160 (12), 130 (100), 115 (71), 105 (30), 91 (17), 77 (29). high resolution *m/e* calcd. for $C_{12}H_{12}O$: 172.0888, found: 172.0883.

Bis(4-phenyl-3-cyclohexenylidene) (**2.30**)



2.26

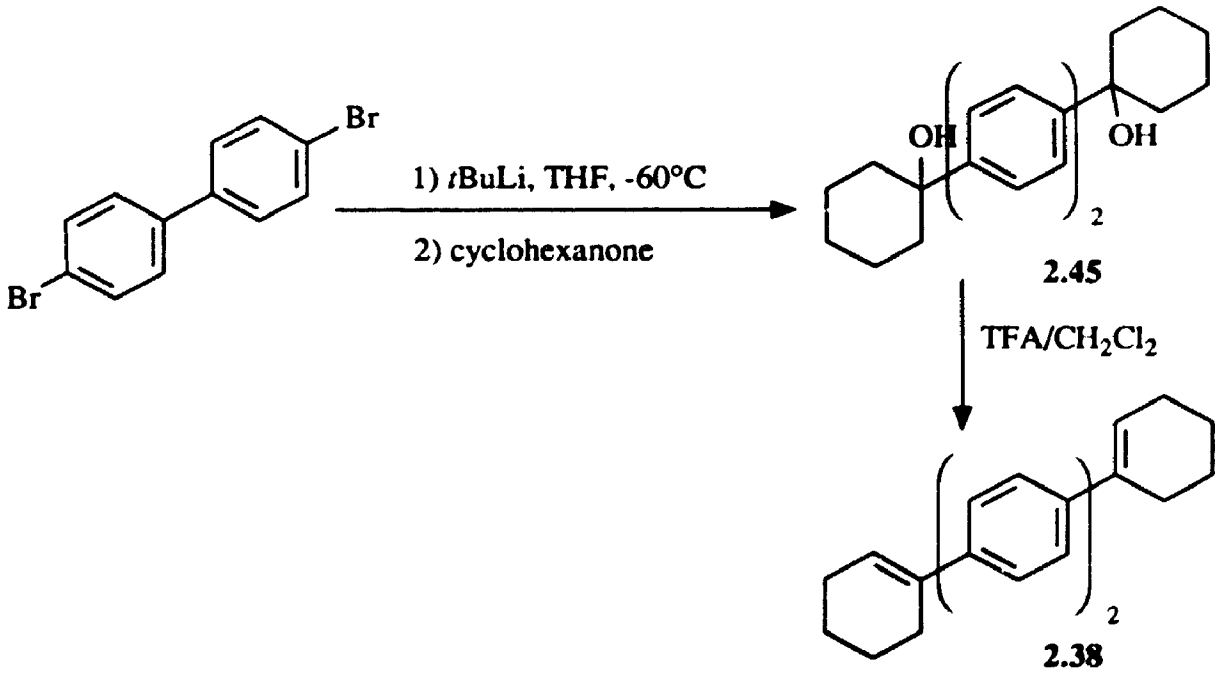
2.30a

2.30b

A slurry of 5.06 g (17.4 mmol) of $TiCl_3(DME)_{1.5}$[2.23] and 4.81 g (68 mmol) of Zn/Cu couple[2.23] in 50 mL of DME was stirred at reflux for 2.5 h. A solution of enone **2.26** (0.65 g, 3.8 mmol) in 15 mL of DME was added via syringe. The reaction mixture was stirred at reflux for 12 h, cooled to room temperature and filtered through Florisil. The Florisil was washed with pentane (3x50 mL; 1x100 mL). The organic layer was concentrated *in vacuo* to give a yellow solid. Purification by dry column flash chromatography (ethyl acetate/cyclohexane) yielded 0.18 g of a mixture of **2.30a** and **2.30b** as a light-yellow solid (31% yield): mp 110-112°C; TLC (10% ethyl acetate /cyclohexane) R_f=0.61. *Minor isomer* (43 mole%): ^{1}H NMR ($CDCl_3$): δ 7.2-7.45 (m, 10H, aromatic H), 6.15 (m, 2H, vinylic H), 3.13 (bd, J = 3.3 Hz, 4H, C=CH-C$\underline{H}_2$), 2.62 (m, 8H, CH_2); ^{13}C NMR ($CDCl_3$): δ 142.1 (quaternary), 137.0 (quaternary), 128.3 (aromatic CH), 126.6 (aromatic CH), 125.7 (quaternary), 125.0 (aromatic CH),

124.1 (olefinic CH), 29.6 (CH_2), 28.8 (CH_2), 26.8 (CH_2); *Major isomer* (57 mole%): ^{1}H NMR ($CDCl_3$): δ 7.2-7.45 (m, 10H, aromatic H), 6.15 (m, 2H, vinylic H), 3.06 (d, J = 2.3 Hz, 4H, C=CH-C<u>H</u>$_2$), 2.57 (m, 8H, CH_2); ^{13}C NMR ($CDCl_3$): δ 142.1 (quaternary), 137.1 (quaternary), 128.3 (aromatic CH), 126.6 (aromatic CH), 125.8 (quaternary), 125.0 (aromatic CH), 124.0 (olefinic CH), 30.1 (CH_2), 29.2 (CH_2), 26.4 (CH_2). MS, *m/e* (relative intensity): 312 (M^+, 32), 196 (15), 182 (43), 167 (14), 156 (100), 141 (20), 129 (16), 115 (21), 105 (15), 91 (35); high resolution *m/e* calcd for $C_{24}H_{24}$: 312.1878, found: 312.1875.

<u>4,4'-Bis[cyclohexen-1-yl]biphenyl (2.38)</u>

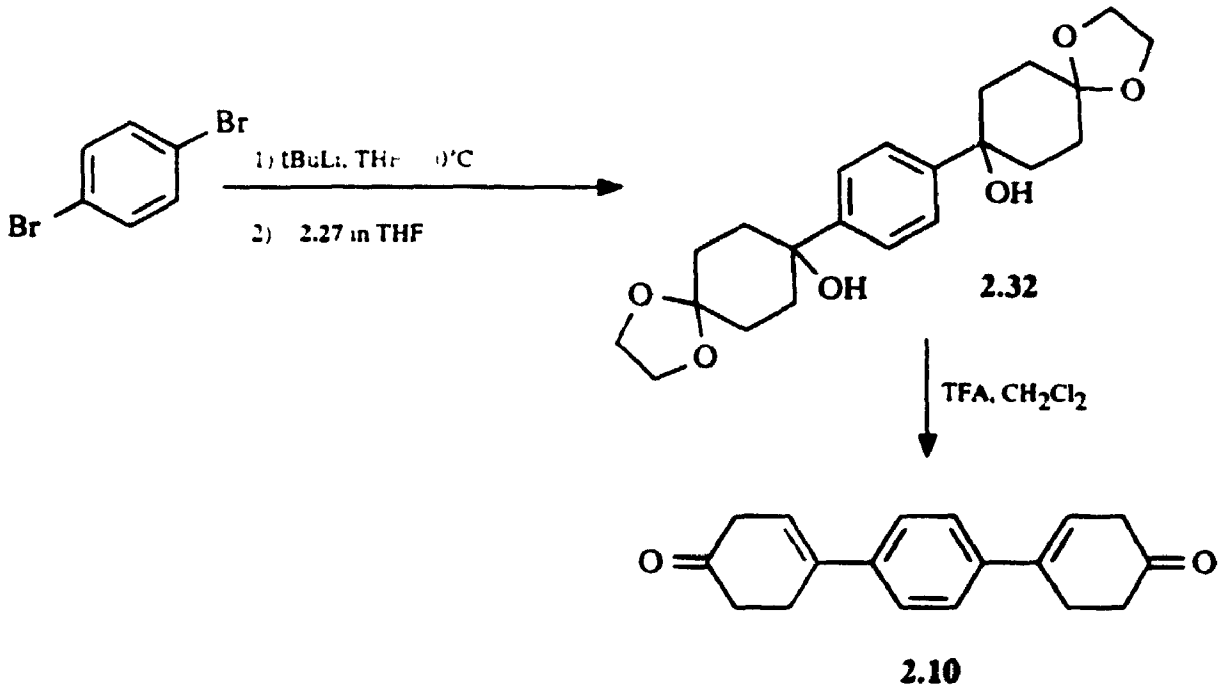


To 0.56 g (1.8 mmol) of *p*-dibromobiphenyl in 4 mL of THF at -60°C was added 4.3 mL (1.7 *M*; 7.3 mmol; 4.06 eq) of *tert*-butyllithium dropwise, with stirring,

via syringe over 1 hour. The reaction mixture was stirred at -60°C for 2 h. This was followed by the addition of cyclohexanone (0.4 g, 4.08 mmol). The reaction mixture was warmed to room temperature by evaporation of the dry ice of the cooling bath and stirred for 20 h. The reaction was quenched with saturated aq. NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were washed with saturated aq. sodium chloride (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give diol **2.45**. [**2.45**: ^1H NMR ($CDCl_3$): δ 7.56 (s, 8H), 1.6-1.9 (m, 10H), 1.2-1.4 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 148.6 (quaternary), 139.4 (quaternary), 127.0 (aromatic CH), 125.2 (olefinic CH), 73.1 (COH), 38.7 (CH_2), 25.4 (CH_2), 22.0 (CH_2); MS, *m/e* (relative intensity): 350 (M^+, 100), 332 (134, 314 (24), 307 (77), 289 (19), 279 (21), 221 (12), 209 (13), 191 (12), 167 (15), 152 (17); high resolution *m/e* calcd. for $C_{24}H_{30}O_2$: 350.2246, found: 350.2246]. The diol, **2.45**, was taken up in 20 mL of CH_2Cl_2 and 2 mL (26.0 mmol) of CF_3COOH was added. The reaction mixture was stirred at room temperature for 20 min. The reaction was quenched with saturated aq. sodium bicarbonate (added until the acid was neutralized) and the aqueous layer was extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were washed with saturated aq. sodium chloride (75 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give 0.38 g of **2.38** (67%). mp 180-182°C (lit[2.37]: 182°C); ^1H NMR ($CDCl_3$): δ 7.25-7.5 (m, 4H, aromatic H), 6.05-6.1 (m, 1H, vinylic H), 2.3-2.4 (m, 2H, allylic CH_2), 1.05-2.2 (m, 2H, allylic CH_2), 1.5-1.8 (m, 4H, aliphatic H); MS, *m/e* (relative intensity):

314 (M^+, 100), 286 (11), 261 (6), 234 (25), 205 (18), 191 (12), 178 (10), 165 (6); high resolution *m/e* calcd. for $C_{24}H_{26}$: 314.2034, found: 314.2035.

1,4-Bis(4-oxocyclohex-1-enyl)benzene (**2.10**)



2.10

To 4.0 g (16.9 mmol) of *p*-dibromobenzene in 200 mL of THF at -78°C was added 40.0 mL (1.7 *M*; 68.0 mmol) of *tert*-butyllithium dropwise, with stirring, via syringe over 1 h. The reaction mixture was stirred at -50°C for 6 h. This was followed by the addition of a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (5.3 g, 33.9 mmol) in 18 mL of THF via syringe. The reaction mixture was warmed to room temperature by evaporation of the dry ice of the cooling bath and stirred overnight (16 h). The reaction mixture was quenched with saturated aq. NH_4Cl (200 mL) and extracted with CH_2Cl_2 (3x200 mL). The combined organic

layers were washed with saturated aq. sodium chloride (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give hydroxy ketal **2.32** as a white solid. The crude hydroxy ketal, **2.32**, was taken up in 50 mL of CH_2Cl_2 and 8 mL (0.10 mol) of CF_3COOH was added. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched and neutralized with saturated sodium bicarbonate and extracted with CH_2Cl_2 (2x100 mL). The CH_2Cl_2 layer was washed with saturated aq. sodium chloride (100 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a yellow solid. Recrystallization (cyclohexane/CH_2Cl_2) yielded 1.9 g of diketone **2.10** as a light yellow coloured solid (42% yield): mp 126-128°C; IR (CCl_4): 1700 cm^{-1};[2.32] TLC (1% ethyl acetate/CH_2Cl_2) R_f 0.35; ^1H NMR ($CDCl_3$): δ 7.38 (s, 4H), 6.11 (m, 2H), 3.06 (m, 4 H), 2.89 (tm, J = 6.8 Hz, 4H), 2.63 (tm, J = 6.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 210.7 (<u>C</u>=O), 140.2 (quaternary), 137.7 (quaternary), 125.7 (CH), 121.5 (CH), 40.2 (CH_2), 38.9 (CH_2), 28.0 (CH_2); MS, *m/e* (relative intensity): 266 (M^+, 100), 224 (61), 182 (48), 129 (44); high resolution *m/e* calcd. for $C_{18}H_{18}O_2$: 266.1307, found: 266.1306.

<u>Attempted reductive dimerization of diketone **2.10**</u>

A slurry of 20.0 g (68.8 mmol) of $TiCl_3(DME)_{1.5}$[2.23] and 13.4 g (189 mmol) of Zn/Cu couple[2.23] in 200 mL of *p*-dioxane was stirred at reflux for 5 h. A solution of diketone **2.10** (1.0 g, 3.76 mmol) in 40 mL of *p*-dioxane was added via syringe

pump over 130 h. The reaction mixture was quenched with 10% aq. K_2CO_3 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by dry column flash chromatography (methylene chloride) yielded a single 0.10 g sample. TLC (methylene chloride) R_f=0.67.

HPLC (Varian Vista Model 5500; LiChrospher 60RB-select B, 5 um, 250x4 mm; 95% acetonitrile/water) T_r 7.87 min.

^{1}H NMR ($CDCl_3$): 7.3-7.75 (m).

MS, *m/e* (relative intensity): 230 (M^+, 100), 202 (8), 152 (4), 115 (12); high resolution *m/e* calcd. for $C_{18}H_{14}$: 230.1096; found 230.1090.

2.7 References

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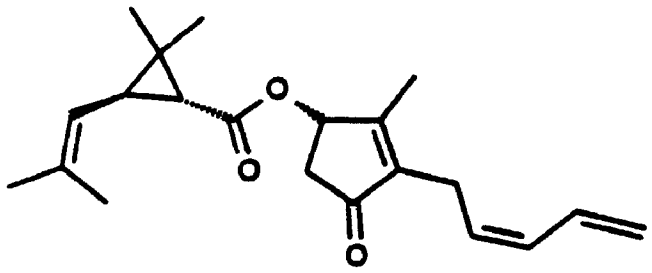
Chapter 3

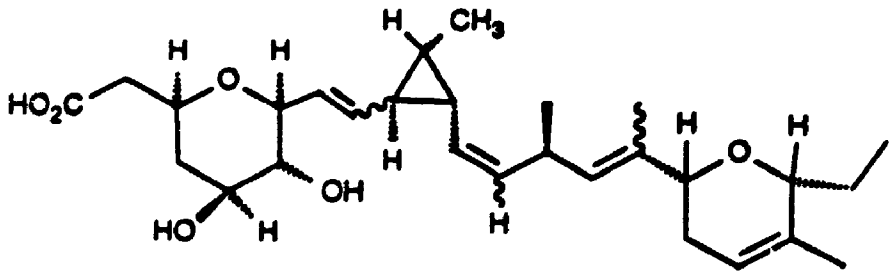
TOWARD A NEW METHOD FOR VINYLCYCLOPROPANATION

3.1 Introduction

Compounds containing functionalized vinylcyclopropane moieties very often exhibit interesting physiological properties.[3.1] Specifically, some have been observed to demonstrate antibiotic[3.2] activity while others insecticidal[3.3] activity. For example, studies of the pyrethroid insecticides have shown that these agents are superior to main-line insecticides such as carbamates, organophosphates, and organochlorines.[3.4]



Pyrethrin I



Ambruticin

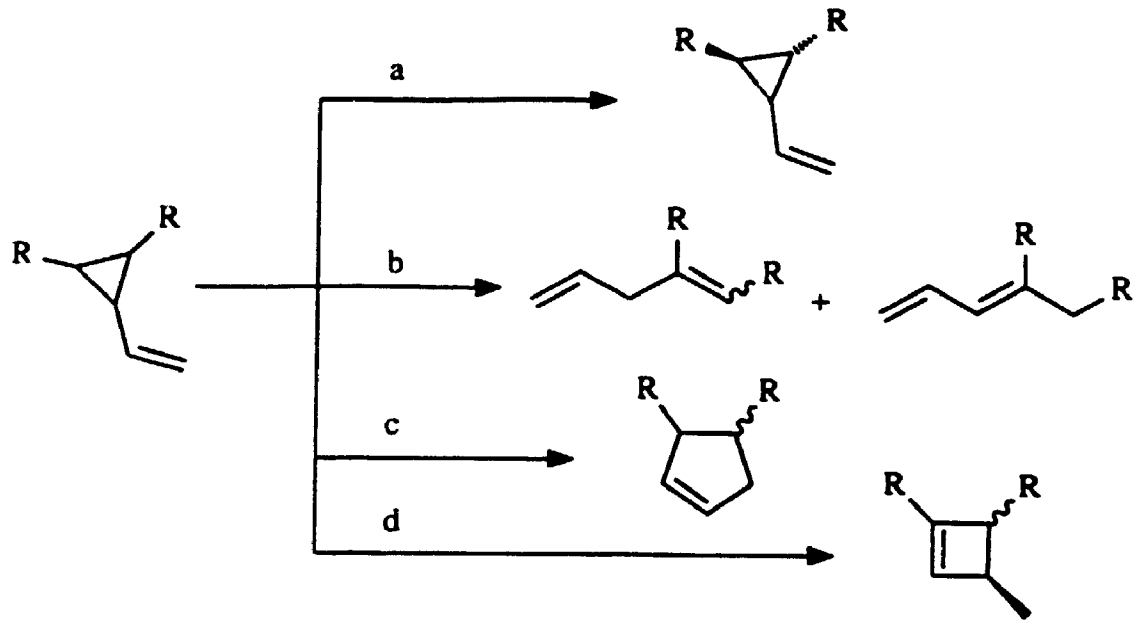
The pyrethroid pyrethrin I, which is isolated from the chrysanthemum

plant, is an especially effective insecticide.[3.5] It contains two methyl groups on C-2 of the cyclopropane ring and an isobutenyl group on C-3. This substituted vinylcyclopropane, with a carboxyl group at C-1, is the common structural feature of the pyrethroids. The antibiotic ambruticin possesses a divinylcyclopropane moiety.

While these are just two examples of the many physiologically active functionalized vinylcyclopropanes, they demonstrate the commercial and therapeutic value of this particular class of organic compounds.

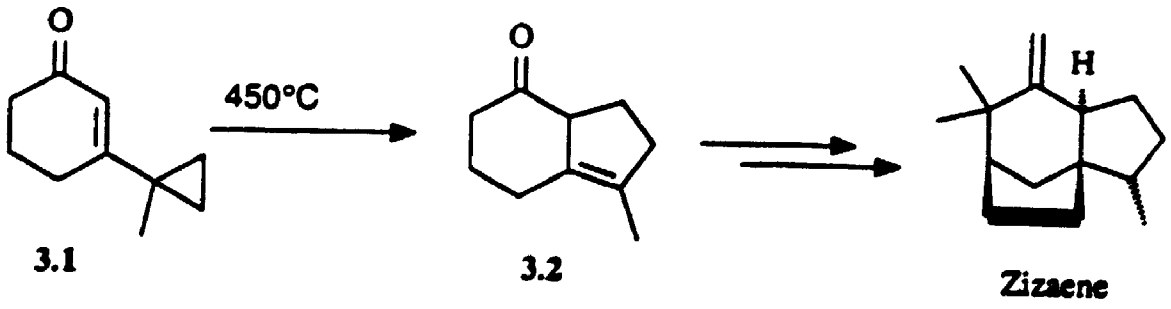
3.1.1 Synthetic Uses of Vinylcyclopropanes

It is, however, the potential use of vinylcyclopropanes as key intermediates in the synthesis of natural products which has recently caught the imagination of many organic chemists. This is a consequence of the numerous ways in which the carbon skeleton of a vinylcyclopropane can be altered in a synthetically useful manner. In the simplest case, one can effect *cis-trans* isomerization with respect to the substituents on the cyclopropane ring (Scheme 3-1, route a). In addition, pentadienes can be obtained as a result of ring opening (Scheme 3-1, route b) while ring enlargement to either cyclopentenes (Scheme 3-1, route c) or methyl cyclobutenes is also possible. In each case, the desired transformation can proceed via a thermal, catalytic or photochemical pathway.[3.6]



Scheme 3-1: Carbo-skeletal transformations of vinylcyclopropanes

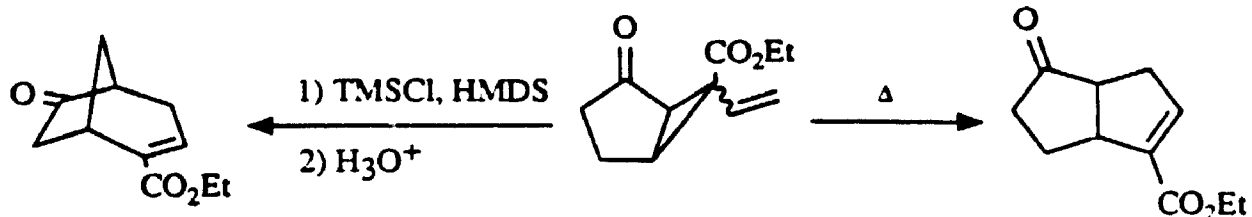
An example of a vinylcyclopropane undergoing a ring enlargement via route c, is shown in Scheme 3-2. Enroute to the sesquiterpene zizaene, Piers utilized the thermal rearrangement of vinylcyclopropane **3.1** to cyclopentene **3.2**.[3.7]



Scheme 3-2: Piers' synthesis of zizaene

Recently, Hudlicky reported that it is possible to control the course of

these rearrangements through subtle changes in the reaction conditions. He has demonstrated that vinylcyclopropanes, of the type shown in Scheme 3-3, can be converted to either cyclopentenes (**3.3**) or to bicyclo[3.2.1] octenes (**3.4**).[3.8]

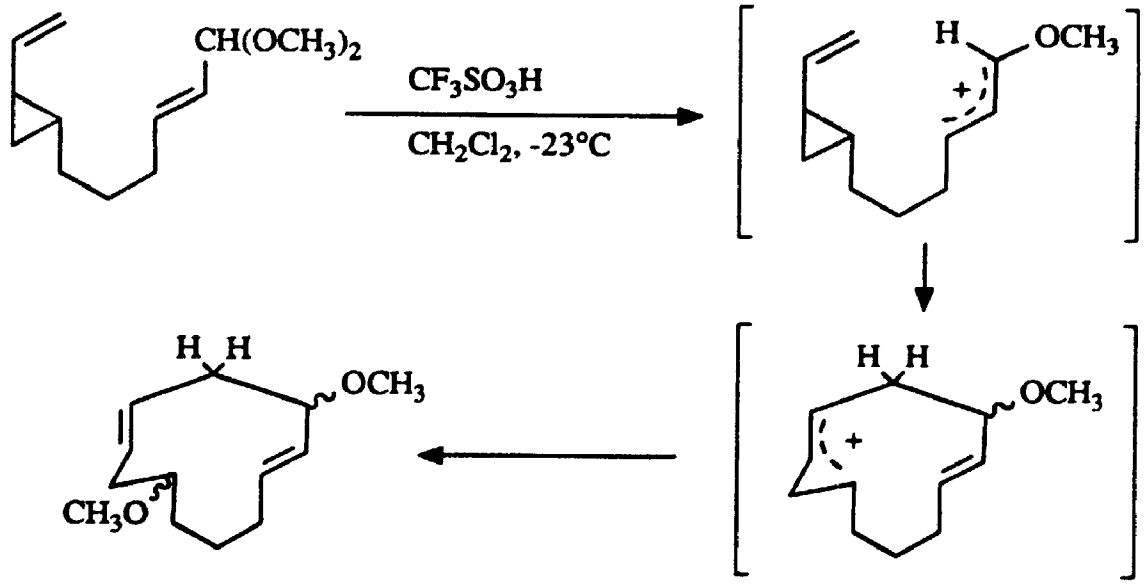


(endo vinyl) (exo vinyl)

3.4 **3.3**

Scheme 3-3: Selective rearrangements of a vinylcylcopropane

Gassman has also shown the vinylcyclopropane moiety to be useful in the preparation of eleven-membered carbocyclic structures.[3.9] In this particular instance, it serves as an efficient intramolecular trap for allyl cations (Scheme 3-4).

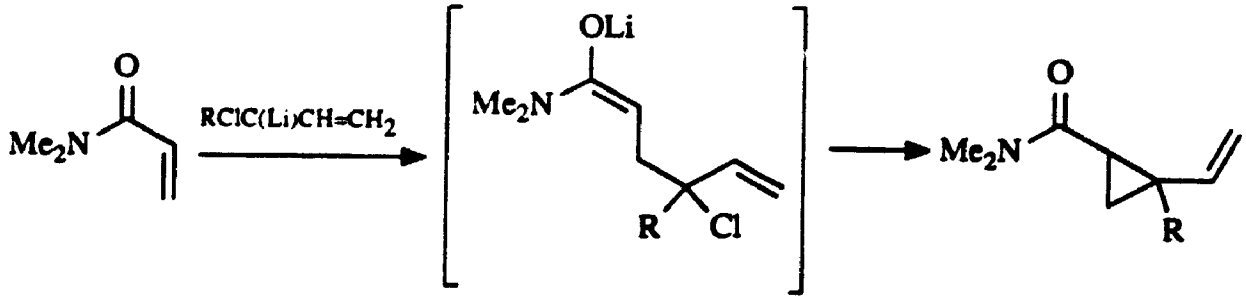


Scheme 3-4: A vinylcyclopropane as an intramolecular cation trap

3.1.2 Current One-Pot Methods for the Synthesis of Vinylcyclopropanes

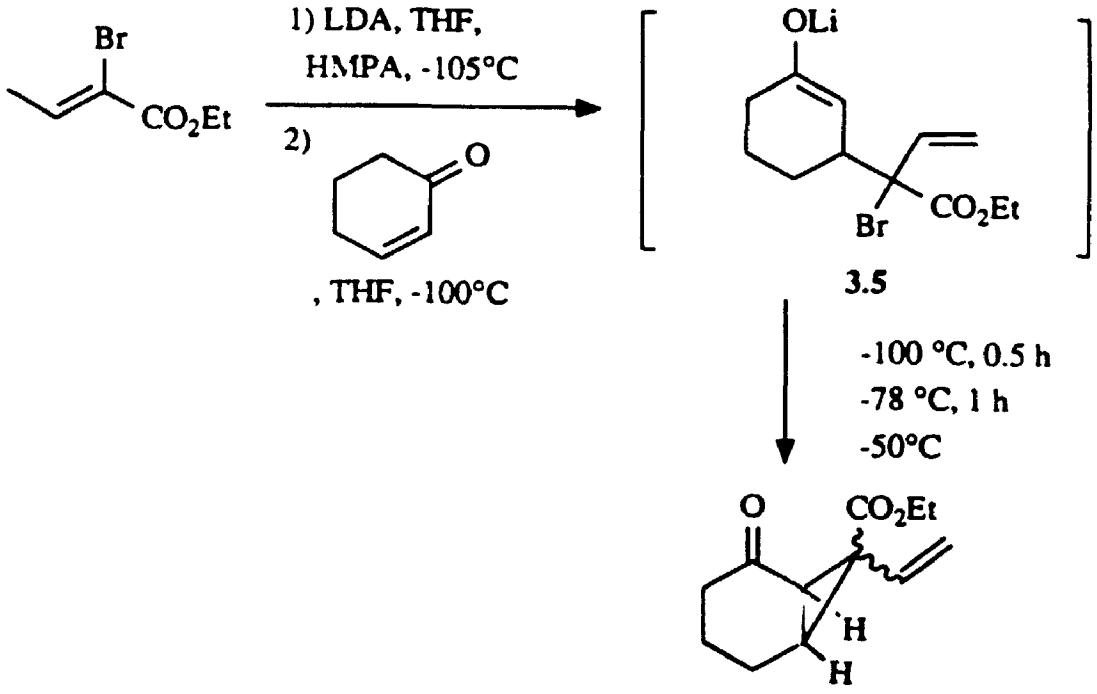
Many methods are currently available for the preparation of vinylcyclopropanes. Since most of these are of the multi-step variety, their use often results in a large number of steps in a given total synthesis. Consequently, attention has recently turned to the development of novel one-step methods. Some of the most interesting approaches have been in the vinylcyclopropanation of substrates possessing an α,β-unsaturated carbonyl moiety. These typically begin with a conjugate addition followed by an intramolecular displacement of a leaving group from an allylic position. The following examples represent the currently available one-pot methods for the vinylcyclopropanation of enones.

A one-pot route to the 1-carboxamidoyl-2-vinylcyclopropanes, developed by Miginiac,[3.11] involves the conjugate addition of a monohalogenated allyl lithium to an α-ethylenic tertiary amide which then loses chloride via an intramolecular displacement to give the desired vinylcyclopropane derivative (Scheme 3-5).



Scheme 3-5: Preparation of the 1-carboxamidoyl-2-vinylcyclopropanes

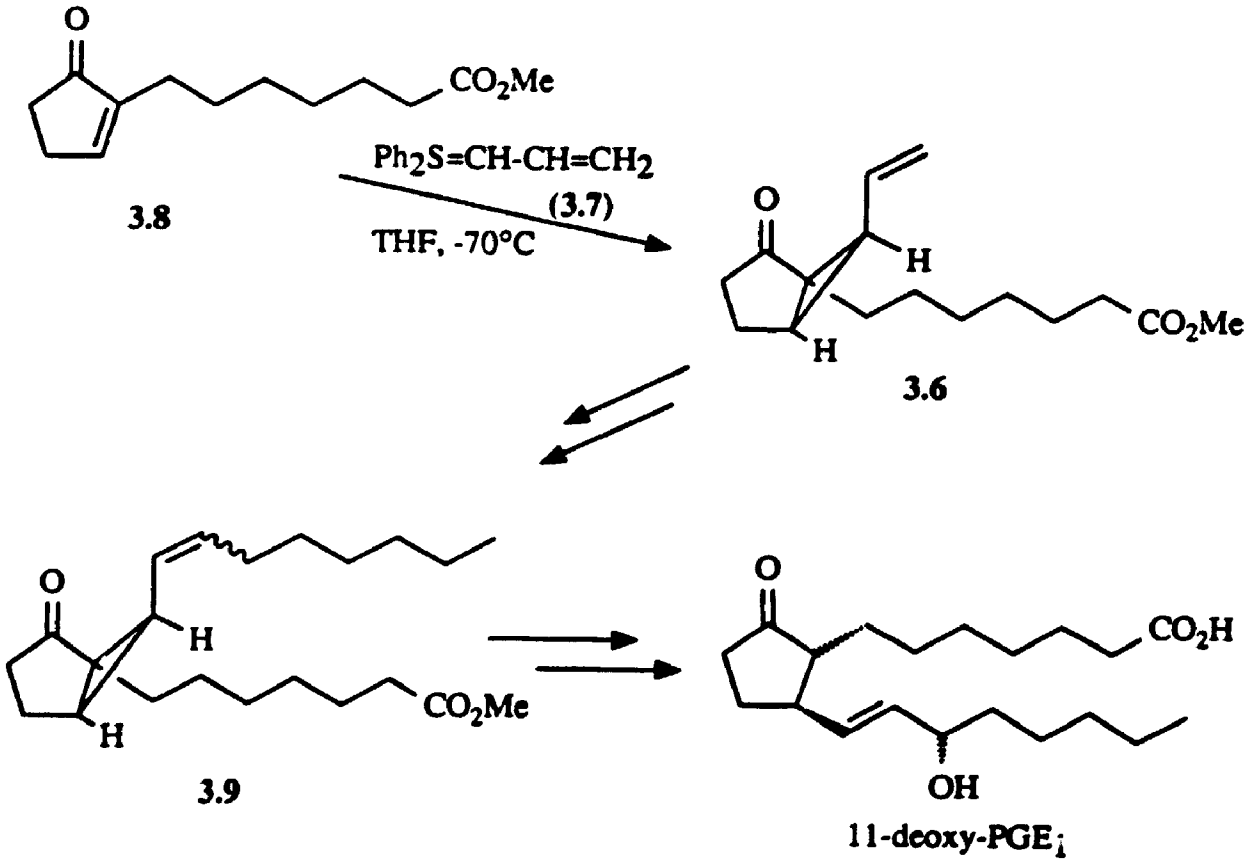
Hudlicky has shown that lithium dienolates of various α-bromocrotonates undergo smooth conjugate addition to enones, the resulting adducts (**3.5**) of which readily undergo intramolecular displacement of bromine to give the corresponding vinylcyclopropanes in excellent yields (Scheme 3-6).[3,10]



Scheme 3-6: Hudlicky's vinylcyclopropanation of α,β-unsaturated ketones

One of the major stereochemical challenges encountered during the synthesis of prostaglandins has been the stereoselective creation of an *S* configuration at C-15. Dyadchenko and co-workers reasoned that the limited conformational mobility of vinylcyclopropane **3.9** would give rise to an asymmetric epoxidation, thus introducing the necessary stereochemistry at C-15

(Scheme 3-7).[3.12] Their interesting one-pot method for the preparation of vinylcyclopropane **3.6** involves the reaction of diphenylallylidenesulfurane (**3.7**) with an α-substituted cyclopentenone (**3.8**).[3.12] As in the above-mentioned examples, this also involves conjugate addition followed by intramolecular displacement, this time of a diphenylsulfonium group. Vinylcyclopropane **3.6** was then converted to 11-deoxyprostaglandin E_1 via the homologous vinylcyclopropane, **3.9**.[3.13]

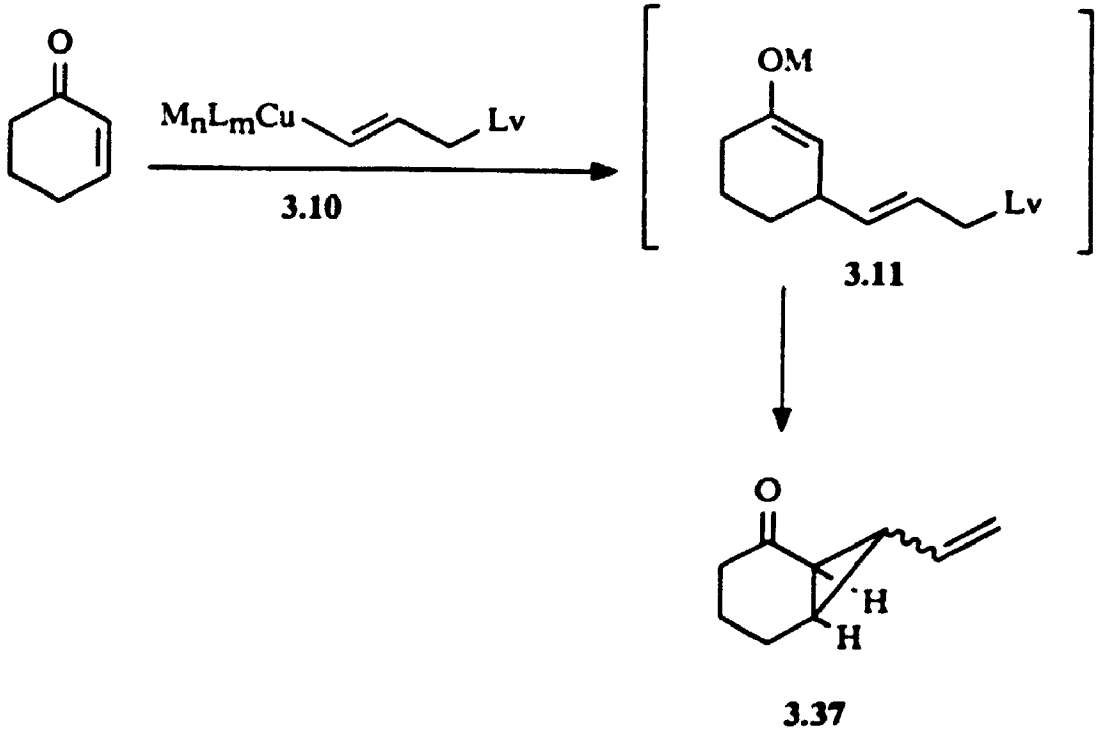


Scheme 3-7: Dyadchenko's route to 11-deoxyprostanglandins

3.1.3 The Proposal

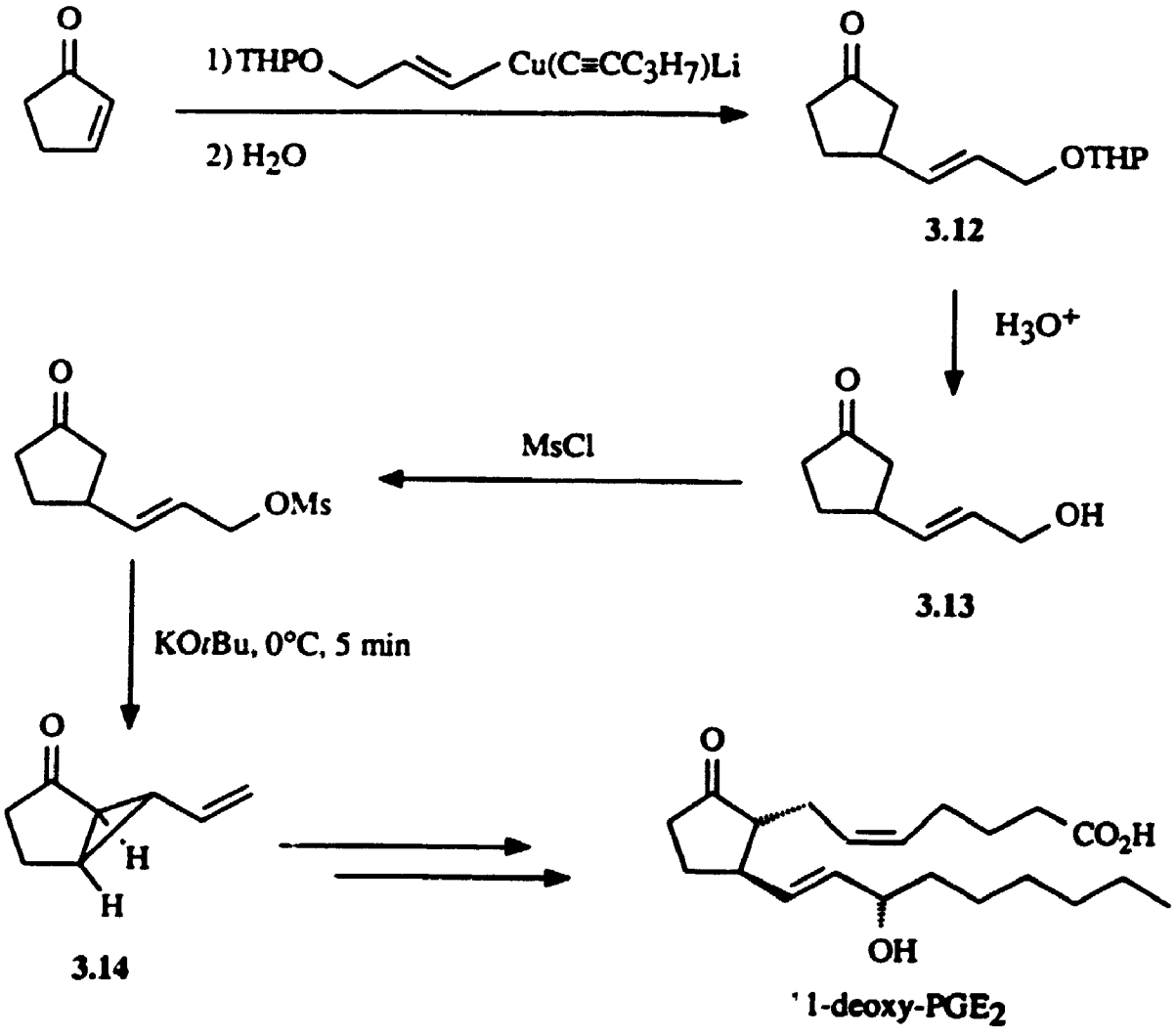
Keeping in mind the utility of vinylcyclopropane derivatives in organic synthesis, we have chosen as one of the aims of our research to develop a new one-pot method for the vinylcyclopropanation of α,β-unsaturated ketones. This would serve as an efficient route to this one type of vinylcyclopropane and increase the availability of these useful organic compounds.

.n our proposal, the initial step would be the copper mediated conjugate addition of an appropriately substituted "vinyl anion equivalent" (**3.10**) to an enone (Scheme 3-8). In the second step the potential leaving group would be activated in some way thus setting the stage for an intramolecular vinylogous nucleophilic displacement (S_N') by enolate **3.11**.



Scheme 3-8: Proposed vinylcylcopropanation of an enone

This particular approach to these types of vinylcyclopropanes is modelled closely after the method developed by Corey and Wollenberg,[3.14] which they used in a synthesis of 11-deoxyprostaglandin E_2 (Scheme 3-9).



Scheme 3-9: Corey's four-step vinylcyclopropanation

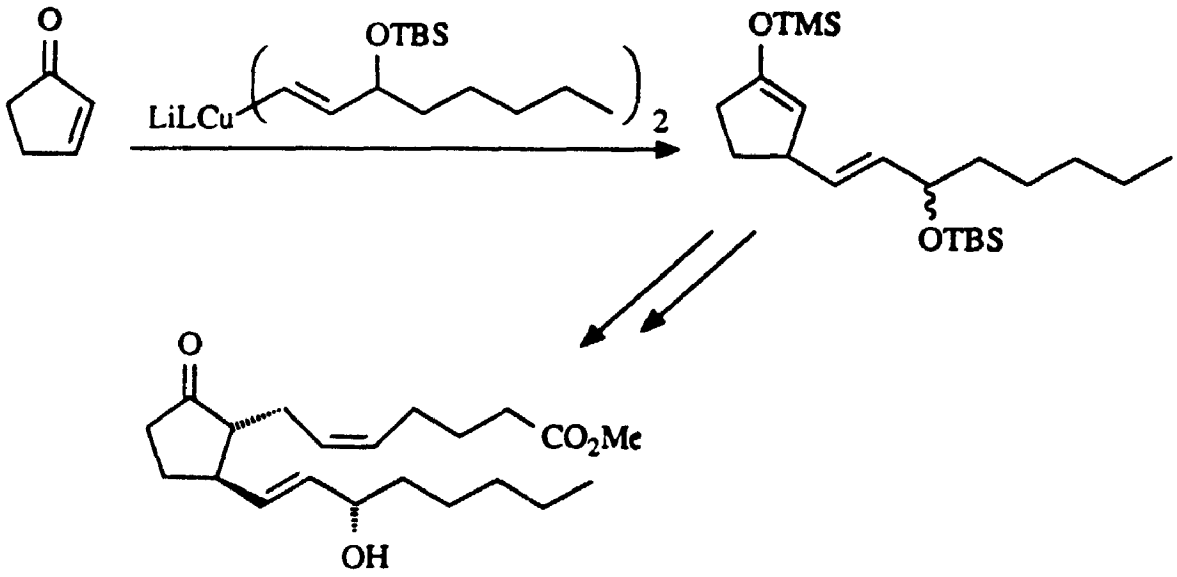
Although Corey's approach is related to our proposal, there are a number of very important differences, primarily having to do with the fact that the -OTHP group in conjugate addition product **3.12** is a very poor leaving group and

would not undergo an S_N' displacement. Consequently, the desired product was not prepared directly, it being necessary to first hydrolyze the tetrahydropyranyl ether (**3.12**) to the allylic alcohol (**3.13**). Conversion then to the mesylate put a suitable leaving group in position, and the internal S_N' reaction proceeded smoothly to furnish the vinylcyclopropane (**3.14**).

The challenge for us then, was to find a potential leaving group which would not interfere with the conjugate addition and yet would undergo S_N' displacement once it had been activated in some way. This could be accomplished by an increase in the temperature of the reaction mixture and/or the addition of a facilitating solvent such as HMPA.

3.1.4 Choice of the Leaving Group

In the course of prostaglandin synthetic studies, the *tert*-butyldimethylsilyl (TBS) group was developed as an hydroxyl protecting group, and Negishi's synthesis of prostaglandin E_2 (PGE_2) methyl ester, employs it as such (Scheme 3-10).[3.15]

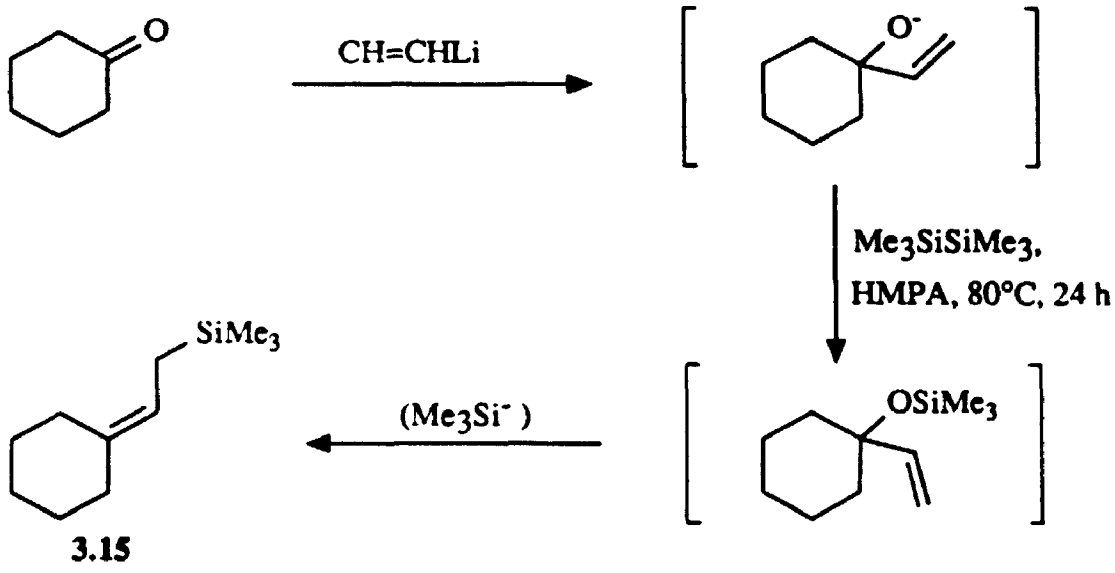


PGE_2 methyl ester

Although this application demonstrates the utility of the TBS group as an hydroxyl protecting group, more importantly, it shows that the silyloxy group does not interfere with nor prevent formation of the vinyl cuprate and the conjugate addition. Under these conditions it is not displaced in an intramolecular S_N' reaction.

Recent work by other groups has however demonstrated that a silyloxy group *can* act as a leaving group. Hwu and Lin, in studies involving the "counterattack reagent" hexamethyldisilane, proposed an S_N' displacement of an

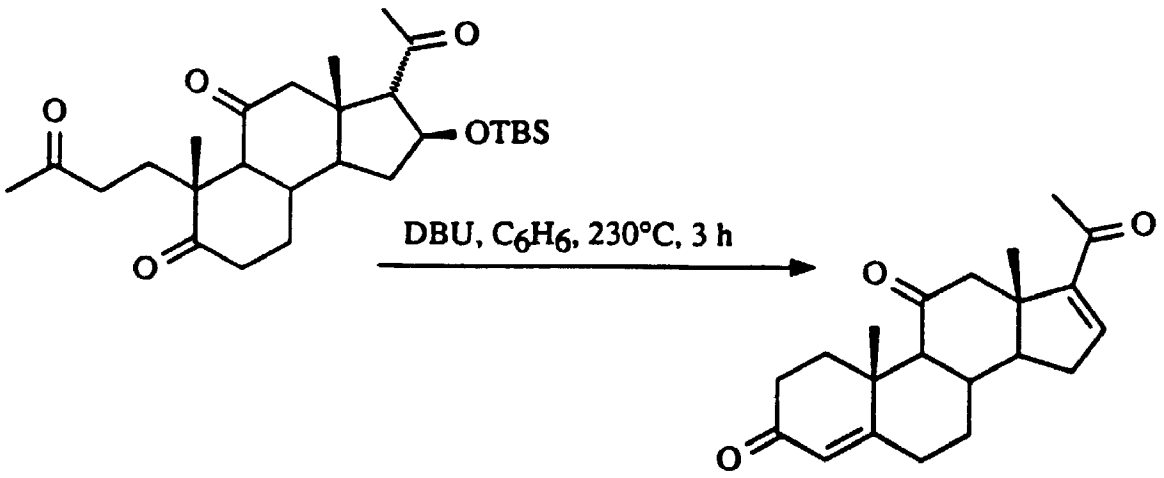
allylic trimethylsilyloxy group as the last step in the conversion of cyclohexanone to allyltrimethylsilane **3.15** (Scheme 3-11).[3.16] Noteworthy was the fact that the reaction does not take place in the absence of HMPA.



3.15

Scheme 3-11: Conversion of a ketone to an allyl-trimethylsilane

The leaving group ability of OTBS has also been shown in eliminations from β-silyloxy ketones, although quite forceful conditions are required (Scheme 3-12).[3.17]



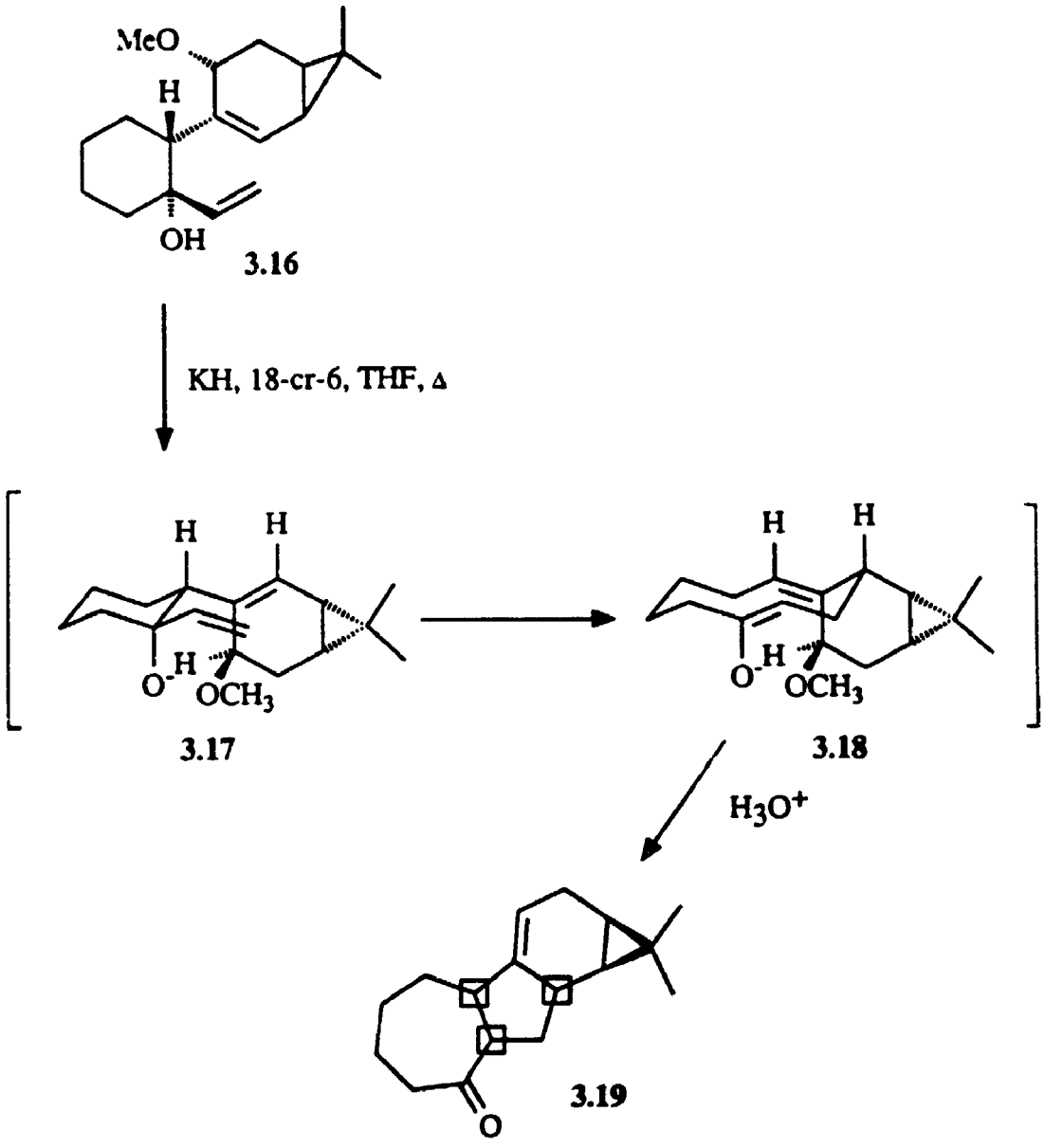
Scheme 3-12: Elimination of OTBS from a β-silyloxy ketone

Although the use of HMPA was not reported in this case, taken together, these two reports provide some encouragement for the idea that the OTBS group could be used as a leaving group in a vinylcyclopropanation of the type proposed in Scheme 3-8.

Further support for our choice of the OTBS group was given by Paquette's report of a surprisingly facile intramolecular S_N' allylic methoxide displacement[3.19] (Scheme 3-13). Electrocyclic ring formation via the chair transition state (**3.17**) gives the *trans-trans*-cyclodecadiene, **3.18**. The proximity of the two double bonds in **3.18** facilitates the transannular S_N' displacement of methoxide.[3.19]

Since leaving group ability often parallels acidity, and silanols are known to be more acidic than alcohols,[3.18] the OTBS group should in principle be a better leaving group than methoxide, the conjugate base of the weaker acid,

methanol.



Scheme 3-13: S_N' allylic methoxide displacement

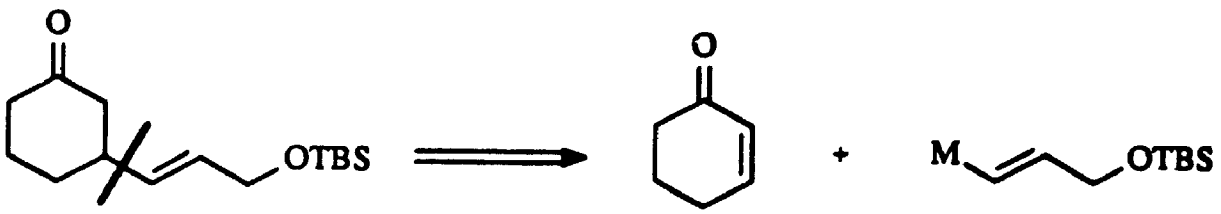
3.2 The Conjugate Addition

In order to simplify the investigations of our proposed one-pot method for the vinylcyclopropanation of enones, as outlined in Scheme 3-8, the

preparation of the conjugate addition product (**3.20**) was initially studied alone. Once the necessary reaction conditions for the conjugate addition had been determined, the S_N' displacement and the combination of the two steps in one pot were studied.

Organocopper chemistry has progressed remarkably over the past two decades.[3.20] One of the more important contributions has been the development of Gilman reagents (R_2CuLi) capable of transferring ligands to α,β-unsaturated ketones by conjugate addition. In many instances, however, problems with the solubility and/or stability of these materials are encountered.[3.21] As a consequence, additives such as dimethyl sulfide,[3.22] HMPA,[3.23] triethyl phosphite[3.24] and tributylphosphine[3.25] must often be used. In 1982, Lipshutz reported a new class of organocuprate reagents ($R_2Cu(CN)Li_2$), which he refers to as "higher order" cuprates. These new reagents, derived from a wide assortment of alkyl, vinyl, and aryl ligands, react quickly and efficiently with mono-, di-, and trisubstituted α,β-unsaturated ketones.[3.21]

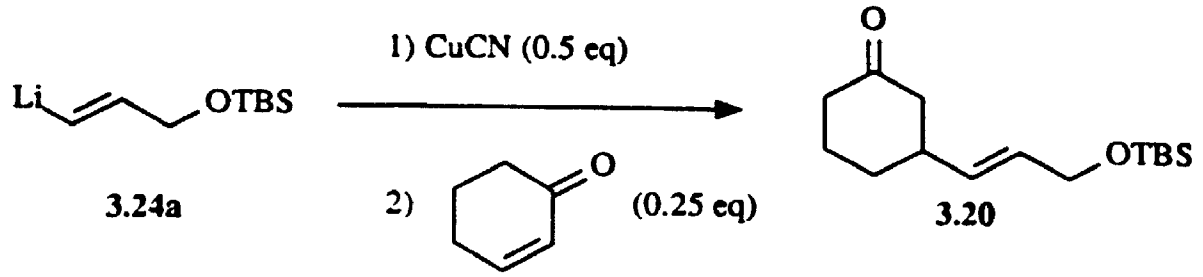
Our retrosynthetic analysis for ketone **3.20** is shown in Scheme 3-14.



3.20 **3.21**

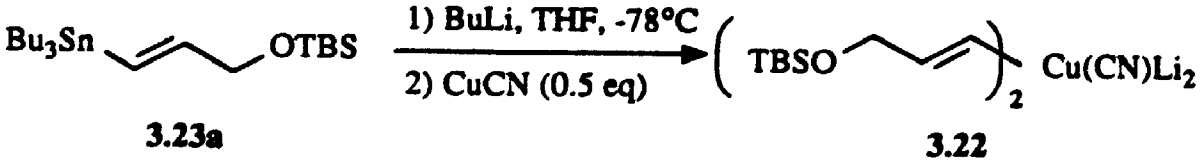
Scheme 3-14: Retrosynthetic analysis of ketone **3.20**

In light of the above work by Lipshutz, the conjugate delivery of the vinyl anion synthon (**3.21**) arising from the bond disconnection to cyclohexenone could best be accomplished through the use of a higher order organocuprate such as $R_2Cu(CN)Li_2$ (Scheme 3-15), where R is the vinyl moiety.



Scheme 3-15: Proposed conjugate addition route to ketone **3.20**

An examination of the literature revealed that this divinyl cuprate (**3.22**) had been used by Ohfune for the regiospecific opening of epoxide rings.[3.26] Unfortunately, the conditions reported for its preparation were sketchy (Scheme 3-16). Cuprate **3.22** was prepared *in situ* from vinylstannane **3.23a** by reaction first with one equivalent of butyllithium (-78°C in THF) followed by cuprous cyanide (0.5 equivalents).

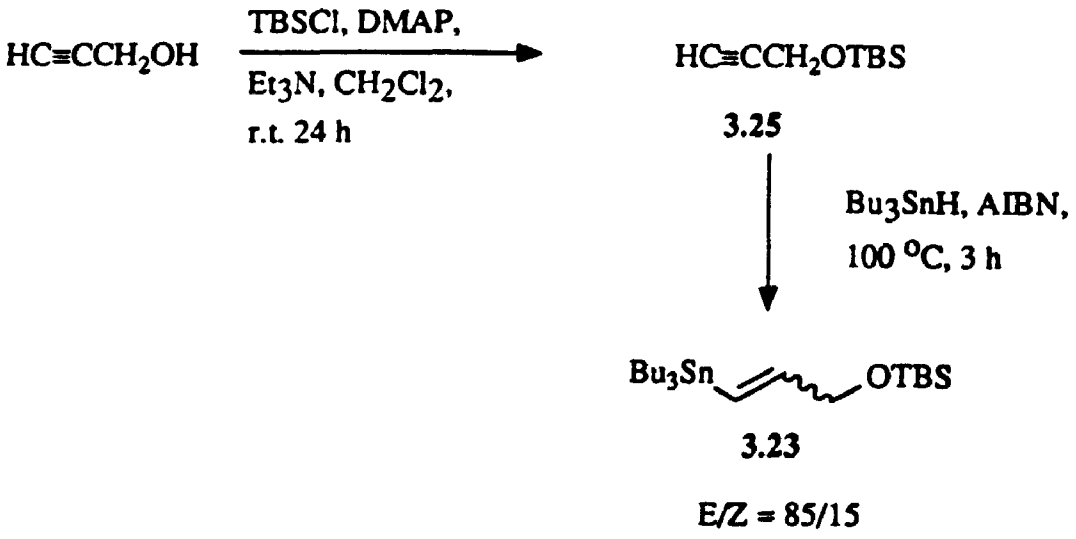


Scheme 3-16: Preparation of divinyl cuprate **3.22**

With this literature procedure in hand for the preparation of cuprate **3.22**, we

turned to the synthesis of the known vinylstannane, **3.23**.[3.27,3.28,3.29]

Vinylstannane **3.23** was prepared in two steps from propargyl alcohol in good yield (Scheme 3-17).

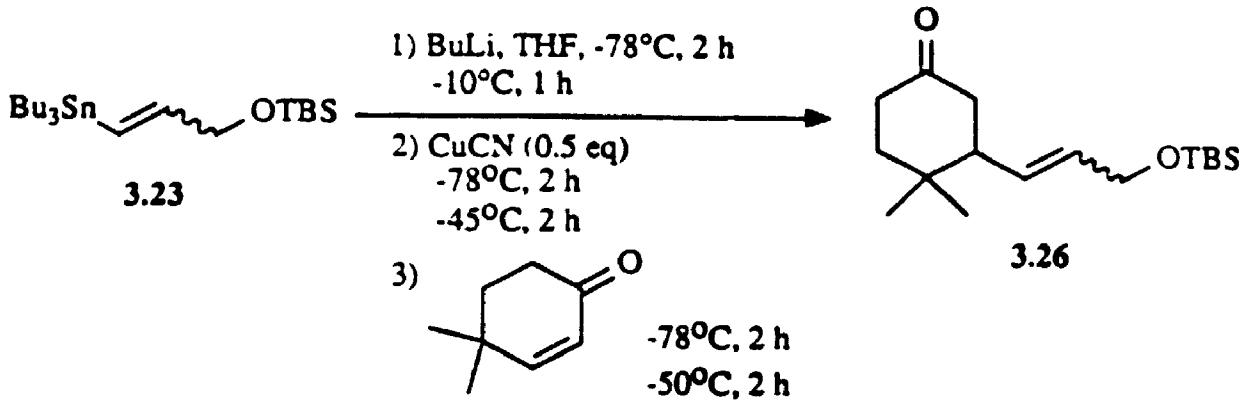


Scheme 3-17: Preparation of vinylstannane **3.23**

Silylation of propargyl alcohol with *tert*-butyldimethylchloro silane gave silyl ether **3.25**.[3.27] Hydrostannylation of this acetylenic ether with tributyltin hydride/AIBN yielded vinylstannane **3.23** as a mixture of the desired *E* isomer (**3.23a**) and a small amount of the unwanted *Z* isomer (**3.23b**).[3.28] ^{1}H NMR analysis of the various batches of **3.23** showed them to consist of ca. 83-85% of the *E* isomer, as judged by the relative integrations of the allylic methylene protons for each of the two isomers.

Our initial attempts to carry out the conjugate addition reaction employed the Ohfune cuprate and were based on the Lipshutz method discussed earlier.[3.21] This procedure had also been used earlier by the author during his

Honors B.Sc. research project[3.31] and is depicted in Scheme 3-18. The vinyllithium was prepared by treatment of a solution of vinylstannane **3.23** in THF at -78°C with butyllithium. The reaction mixture was stirred at -78°C for two hours and at -10°C for one hour before being recooled to -78°C. Cuprous cyanide was added and the reaction mixture was stirred at -78°C for two hours and at -45°C for one hour before being recooled to-78°C. A solution of the enone in ether was added, and the reaction mixture was stirred at -78°C for 2 hours and at -50°C for 2 hours.



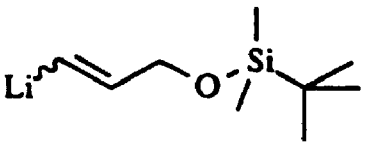
Scheme 3-18: Conjugate addition approach to ketone **3.26** using CuCN (Lipshutz's method)

Although both 2-cyclohexenone and 4,4-dimethyl-2-cyclohexenone had been tried in our earlier work, only the latter gave a conjugate addition product (**3.26**), though only in trace amounts.[3.31] ^{1}H NMR analysis of **3.26** had showed it to be a 8.6:1 ratio of *E* and *Z* isomers.[3.31] Since the *E*/*Z* ratio of the vinylstannane used in this experiment was 4.55:1, either the conjugate addition

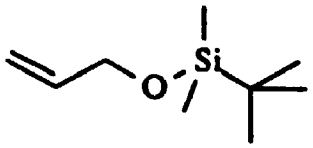
of the *E* vinyl cuprate is more favorable than that of the *Z* vinyl cuprate, or the *E* vinylstannane undergoes preferential tin-lithium exchange. Greene's observation that the *Z* isomer in similar mixtures tends to undergo transmetallation with butyllithium more slowly than the *E* isomer supports the latter possibility.[3.30] The ^{1}H NMR spectrum also provided a means of assessing the success of all subsequent conjugate addition reactions. The vinyl protons give rise to a distinctive set of peaks at a chemical shift of $\approx$5.6 ppm. This greatly simplified the analysis of spectra for all subsequent reactions since neither the starting materials, nor the other products of the reaction, give rise to peaks in this particular region.

As a continuation of this earlier work, attempts were made to prepare ketone **3.26** once again using the method outlined in Scheme 3-18. Unfortunately, the ^{1}H NMR spectrum of the crude product indicated the presence of the starting enone, 4,4-dimethyl-2-cyclohexenone. Although all of the *E*-vinylstannane (**3.23a**) had undergone transmetallation, a very small amount of *Z*-vinylstannane (**3.23b**) was recovered. This result provides further evidence that these two particular vinylstannanes do undergo transmetallation at significantly different rates under these conditions. Ketone **3.26** was not present, as judged by the absence of the characteristic peaks at $\approx$5.6 ppm. Allyl silyl ether **3.27** was also recovered and presumably arose from protonation of unreacted vinyllithium **3.24** in the workup and/or from protonation of the vinyl cuprate which had failed to undergo addition to the

enone.



3.24



3.27

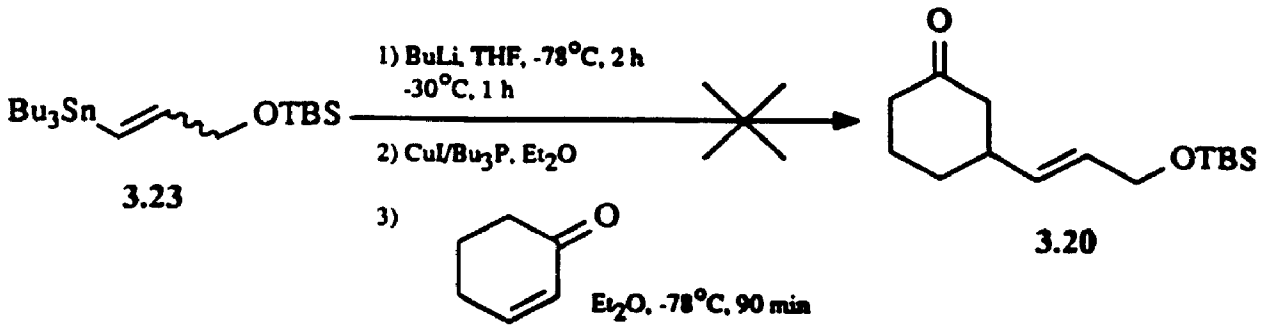
The identity of this material was confirmed by comparison with published spectral data for this known compound.[3.32]

We speculated at this point that the aged cuprous cyanide which was being used was responsible for the failed conjugate addition reactions. An examination of the literature revealed that other groups have experienced similar difficulties with copper (I) mediated reactions. According to Fuchs and Hutchinson, the source and purity of the copper (I) salt greatly affect the conjugate addition of (α-alkoxymethyl)cuprates to enones.[3.33] These reactions proceeded smoothly only when fairly fresh batches of copper (I) bromide-dimethyl sulfide complex were used. When cuprous cyanide or old (> 3 months) batches of the complex were used, chromatographically inseparable dimers arising from the cuprates were obtained.[3.33] The authors attribute these problems to suspected high levels of copper (II) impurities. Smith and Wikman report that the preparation of lithium bis(isopropenyl) cuprate is dependent on the purity of the copper (I) iodide used.[3.34] Acceptable yields for conjugate additions were achieved only when they used sufficently pure cuprous iodide.

Danishefsky has reported that the reagent derived from the reaction of vinylmagnesium bromide with tributylphosphine-cuprous iodide complex reacts

well with 4,4-dimethylcyclopentenone.[3.35] Noyori has shown that organocopper reagents of the type $RCu[PBu_3]_n$[3.36,3.37,3.38] effect smooth reaction with a wide variety of α,β-unsaturated ketones.[3.37] These reagents are prepared by the reaction of equimolar amounts of copper (I) iodide and an organolithium species, and 2-3 equivalents of tributylphosphine. The efficiency of this synthetic approach is a function of the type of phosphine used and the phosphine to copper ratio.[3.37] The highest yields were observed when 2-3 equivalents of tributylphosphine were employed. The phosphine additive is thought to stabilize and solubilize the organocopper reagent.

One of the striking features of this approach is the economical use of the group which is to undergo transfer. As mentioned previously, the earlier methods of Lipshutz used organocopper reagents derived from cuprous cyanide and 2 equivalents of an organolithium. The methods of Noyori, Danishefsky, and others, eliminate this waste of the potentially costly ligand which is undergoing the transfer. Another compelling reason for turning to the Noyori method was Noyori's report that this procedure is an effective mode for the delivery of vinylic moieties.[3.36] Consequently, it appeared to be ideally suited for our synthetic needs. Our attempts to prepare ketone **3.20** using the Noyori method followed the synthetic path outlined in Scheme 3-19.



Scheme 3-19: Conjugate addition approach to ketone **3.20** using CuI/Bu_3P (Noyori's method)

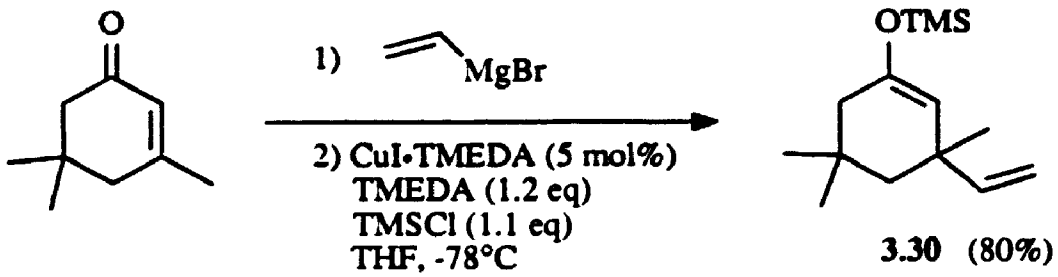
The vinyllithium was prepared by treatment of a solution of vinylstannane **3.23** in THF at -78°C with butyllithium. The reaction mixture was stirred at -78°C for 2 hours and at -30°C for 1 hour, before being recooled to -78°C. The copper (I) iodide·tributylphosphine complex was prepared separately by treatment of a suspension of cuprous iodide at room temperature with tributylphosphine. The copper complex reaction mixture was stirred for 10 minutes before being cooled to -78°C. The vinyllithium solution was added, and the reaction mixture was stirred at -78°C for 30 minutes. A solution of cyclohexenone in ether was added, and the reaction mixture was stirred at -78°C for 90 minutes. Unfortunately, only allyl silyl ether **3.27**, and starting cyclohexenone were isolated. No conjugate addition product was formed. We then purified this rather old cuprous iodide by Soxhlet extraction with acetone over a period of 2 days. However, failure was also met when this purified

cuprous iodide was used. There was no spectral evidence for the formation of the desired product, ketone **3.20**.

Corey and Boaz have reported that chlorotrimethylsilane (TMSCl) serves to accelerate and improve 1,4-additions to enones.[3.39] They propose that this rate enhancement is due to the trapping of an initial d,π^*-complex by TMSCl which then forces the conversion of the complex to a β-carbon adduct.[3.39] This acceleration is more pronounced in THF than in ether.[3.39] In 1986, Nakamura and Kuwajima reported that the combination of TMSCl and a polar additive, such as hexamethylphosphoric triamide (HMPA) or 4-(dimethylamino)-pyridine (DMAP), allows otherwise unreactive RCu-type reagents to undergo efficient conjugate addition.[3.40] They also reported that cuprates derived from cuprous bromide-dimethyl sulfide complex are more effective than those prepared from cuprous iodide.[3.40]

In 1987, work by Johnson and Marren[3.41] explored the use of tetramethylethylenediamine (TMEDA) as a possible alternative to HMPA, which is toxic and expensive. Their choice of TMEDA was based upon the idea that this ligand might serve to stabilize and solubilize the copper reagents as well as increase the reactivity of the TMSCl.[3.41] Despite Nakamura and Kuwajima's claim regarding the ineffectiveness of cuprous iodide, Johnson and Marren do report good results when commercially available, unpurified cuprous iodide is used. In general, the method involves the preparation of an organocopper reagent (RCu) by the reaction of equimolar amounts of an

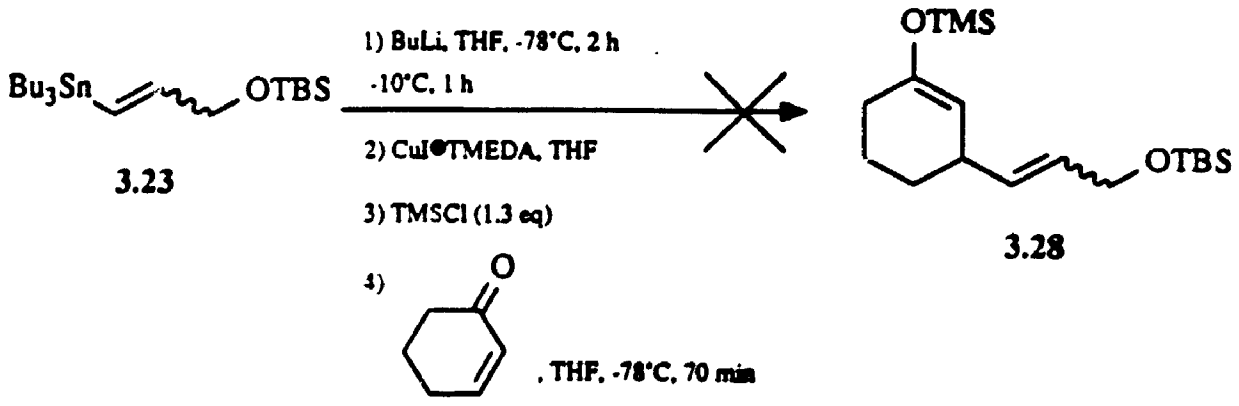
alkyllithium reagent and CuI at room temperature in the presence of TMEDA (1.1-2.5 equivalents). Once this reaction mixture has been cooled to -78°C, TMSCl (1.1-2.5equivalents) is added followed by the enone. A variety of enone substrates and alkyllithiums (R=Me, Bu, *s*-Bu, *t*-Bu) were studied. The yields were typically greater than 80%, depending upon the quantities of TMSCl and TMEDA present. Johnson and Marren postulate that the promoter in these reactions is either the salt of, or the complex formed from, TMSCl and TMEDA.[3.41] However when they tried these same reactions with vinyllithium, the yield of the desired silyl enol ether dropped markedly to less than 20%. When vinylmagnesium bromide served as the vinyl anion source the addition to isophorone proceeded smoothly and in good yield (80%) (Scheme 3-20). Interestingly, this reaction requires only a catalytic amount of the cuprous iodide-TMEDA complex.



Scheme 3-20: Johnson's catalytic procedure for conjugate addition using vinylmagnesium bromide

Both of these methods were investigated for our conjugate addition.

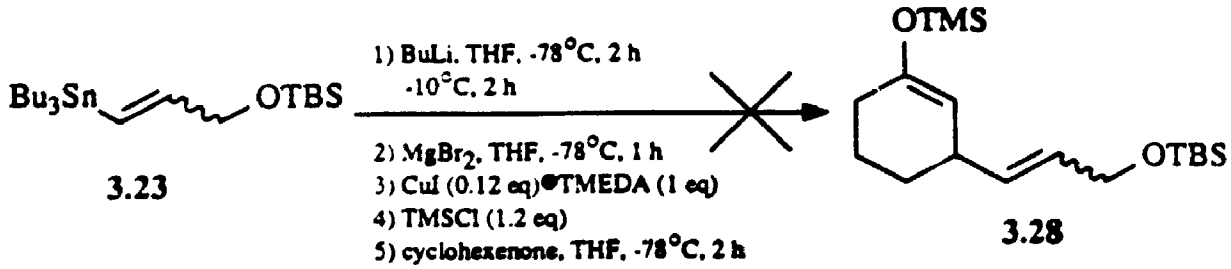
Scheme 3-21 depicts the vinyllithium route. The vinyllithium was prepared from vinylstannane **3.23** and butyllithium in exactly the same way as described for Scheme 3-18. The copper (I) iodide·TMEDA complex was prepared separately by treatment of a suspension of cuprous iodide in THF with TMEDA (1.8 equivalents). The copper complex reaction mixture was stirred for 5 minutes before being cooled to -78°C. The previously prepared vinyllithium solution was added, and the reaction mixture was stirred at -78°C for 30 minutes. TMSCl (3 equivalents) was added, followed by a solution of cyclohexenone in THF. The reaction mixture was stirred at -78°C for 2 hours, and then warmed to room temperature over 2.5 hours. Unfortunately, only the allyl silyl ether (**3.27**) and starting enone were isolated.



Scheme 3-21: Conjugate addition approach to silyl enol ether **3.28** using the vinyllithium route with CuI/TMEDA/TMSCl

Therefore a modification of the organomagnesium method, as depicted in

Scheme 3-22, was tried. The copper (I) iodide·TMEDA complex was prepared by treatment of a suspension of cuprous iodide (0.12 equivalents) in THF at room temperature with TMEDA (1 equivalent). The reaction mixture was stirred at -78°C for 20 minutes. The vinyl Grignard reagent was generated separately by treatment of anhydrous magnesium dibromide, prepared *in situ* according to the method of Rieke[3.42], in THF at -78°C with vinyllithium prepared separately, as before. This reaction mixture was stirred at -78°C for 1 hour before being transferred to the solution of the copper complex. The cuprate reaction mixture was stirred at -78°C for 20 minutes, after which TMSCl (1.2 equivalents) was added, followed by a solution of cyclohexenone (1 equivalent) in THF. The reaction mixture was stirred at -78°C for 2 hours. Once again, this route failed to give the desired product, and only the allyl silyl ether and starting enone were isolated.



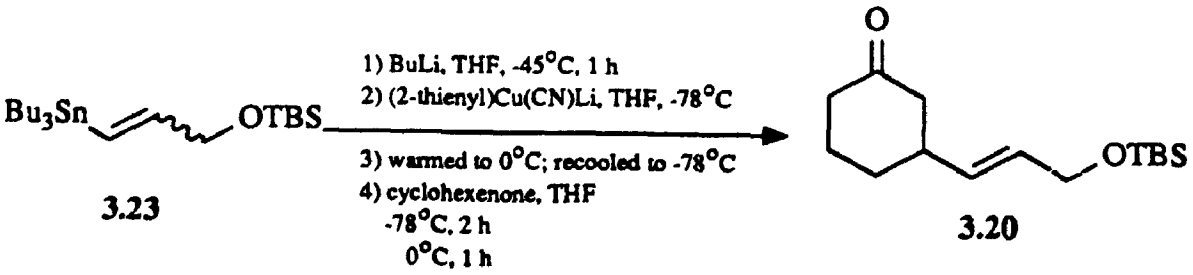
Scheme 3-22: Conjugate addition approach to silyl enol ether **3.28** using $MgBr_2$ with CuI/TMEDA/TMSCl

Interestingly, at about the time that we were having these difficulties with our cuprous iodide-based cuprate reactions, Bertz and co-workers reported

that their cuprate formation (R_2CuLi) from CuI (99.999%, Aldrich) was "very non-reproducible".[3.43] After considering our failures in light of the apparently conficting observations from the laboratories of Smith, Danishefsky, Noyori, Nakamkura, Johnson and Bertz, we decided to abandon our work with cuprous iodide.

The preparation of the desired conjugate addition product was finally realized through the use of the higher order cyanocuprate, "R_T(2-thienyl)$Cu(CN)Li_2$" [R_T=alkyl group to undergo transfer]. This type of reagent was developed by Lipshutz and co-workers[3.44] and is modelled after Ullenius' study on the conjugate addition of the lower order cuprate, R_T(2-thienyl)CuLi.[3.45] In each of these cases, the "2-thienyl" (2-thiophenyl) group serves as a non-transferable "dummy" ligand and thus permits the selective transfer of the R_T ligand.

The experimental conditions which were employed for the preparation of **3.20** are depicted in Scheme 3-23.



Scheme 3-23: Conjugate addition approach to ketone **3.20** using lithium 2-thienylcyanocuprate Route (Lipshutz's method)

The vinyllithium was prepared by treatment of a solution of vinylstannane **3.23** in THF at -50°C with butyllithium.[3.46] This new transmetallation procedure was adopted since it cut the length of time needed to effect tin-lithium exchange by one-third. After being cooled to -78°C, this solution was transferred to a solution of lithium 2-thienylcyanocuprate in THF at -78°C. The reaction mixture was then warmed to 0°C before being recooled to -78°C. A solution of cyclohexenone in THF was added, and the reaction mixture was then stirred at -78°C for two hours, -50°C for thirty minutes and finally at 0°C for one hour. Purification of the crude product by flash chromatography (ethyl acetate/hexanes) yielded the desired product, ketone **3.20**. The 200 MHz ^{1}H NMR spectrum showed the protons of the *tert*-butyl group as a singlet at 0.88 ppm and the protons of the methyls directly bonded to silicon as a singlet at 0.04 ppm. The olefinic protons (H_1 and H_2) give rise to a multiplet at 5.6 ppm. The protons of the -CH_2O- group appeared as a doublet at 4.12 ppm with a coupling constant of 3.3 Hz. By comparison with the carbon spectra of similar compounds, the ^{13}C NMR data for **3.20** was assigned as shown in Figure 3-1.

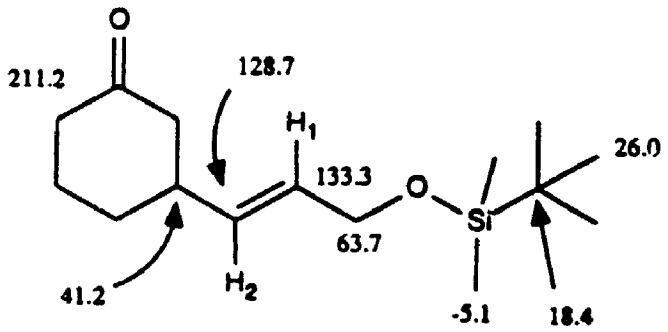
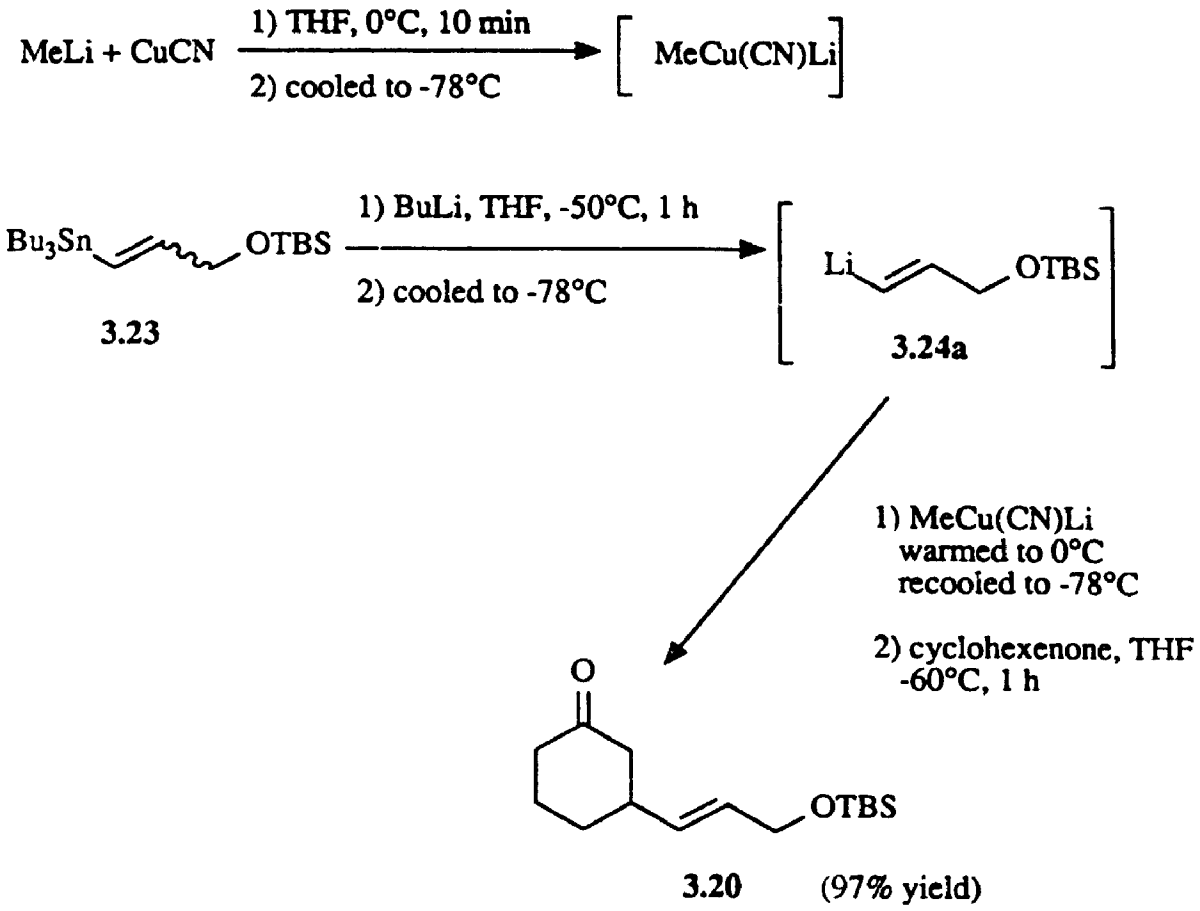


Figure 3-1: ^{13}C NMR analysis of ketone **3.20**

For the most part, this method proved to be a fairly convenient route to conjugate addition product **3.20** and provided sufficient quantities of this ketone for our studies on the S_N' displacement of -OTBS, which was the second step of our proposed one-pot method for the vinylcyclopropanation of enones. The isolated yields typically ranged from 53-73%. However, there were occasions when the reaction simply failed altogether. Although the lithium 2-thienylcyanocuprate which was employed in these reactions was purchased from Aldrich Chemical Co. it became increasingly clear over time that the quality of this cuprate was varying considerably from bottle to bottle. In those instances where an insoluble precipitate was present, difficulties were encountered. Conversely, when the cuprate was a clear, light-brown coloured solution the reactions fared much better.

A much simpler and more reliable method was eventually found for the preparation of ketone **3.20** (Scheme 3-24):



Scheme 3-24: Conjugate addition approach to ketone **3.20** using $R_TMeCu(CN)Li_2$ (Lipshutz's method)

It utilized a cuprate of the type, $R_TMeCu(CN)Li_2$ [R_T=alkyl group to undergo transfer]. These reagents, also developed by Lipshutz, are derived from the reaction of MeCu(CN)Li with the alkyllithium (R_TLi) destined to undergo conjugative transfer.[3.47] Of particular relevance to our work is Lipshutz's report that these cuprates preferentially release vinyl groups over methyl. The ratios ranged from 37-142:1, depending upon the nature of the substrate and the cuprate.

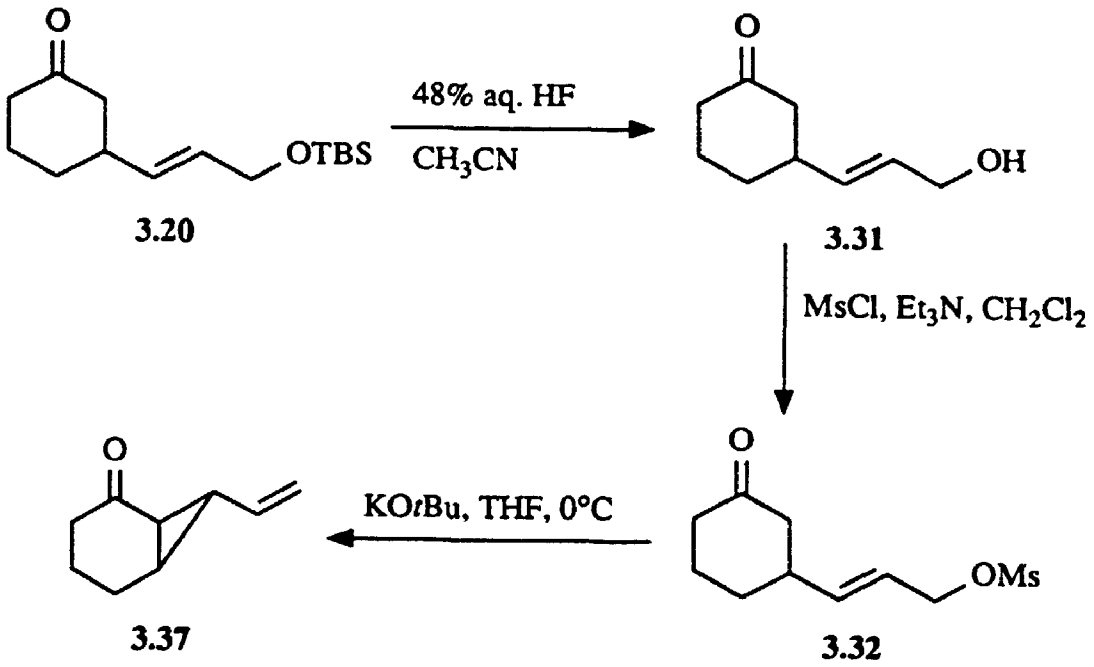
The methyl cyano cuprate was prepared by treating a suspension of cuprous cyanide in THF at 0°C with methyllithium. The cuprate solution was stirred at 0°C for ten minutes before being transferred to a preformed solution of vinyllithium (**3.24**). The reaction mixture was warmed to 0°C before being recooled to -78°C. A solution of cyclohexenone in THF was added and the mixture was stirred at -60°C for one hour. Purification by dry column flash chromatography afforded ketone **3.20** in 97% yield.

3.3 Attempted Preparation of Vinylcyclopropanes by Intramolecular S_N' Displacement of a Silyloxy Group

Our proposed one-pot method for the vinylcyclopropanation of α,β-unsaturated ketones involves two synthetic operations. The first step involves the copper mediated conjugate addition of a "vinyl anion equivalent", possessing an allylic *tert*-butyldimethylsilyloxy group, to an enone. The vinylcyclopropane would then be formed in the second step through an intramolecular S_N' displacement of the silyloxy group. Our target vinylcyclopropane, **3.37**, had been synthesized previously by Hudlicky, although via a different synthetic route.[3.49] Unfortunately, the ^{1}H NMR data which he cites for this compound are vague. In particular, the chemical shifts and coupling constants of the individual vinyl protons are not reported. These protons are simply referred to as a multiplet at 4.83-5.8 ppm.

In order to be able to gauge the success of our attempts to prepare

vinylcyclopropane **3.37** by our proposed new one-pot method, we required accurate spectral data for these vinyl protons. Vinylcyclopropane **3.37** was prepared in three steps starting with ketone **3.20** (Scheme 3-25). This sequence was modelled after the preparation of vinylcyclopropane **3.14** (Scheme 3-9) by Corey and Wollenberg.[3.14]

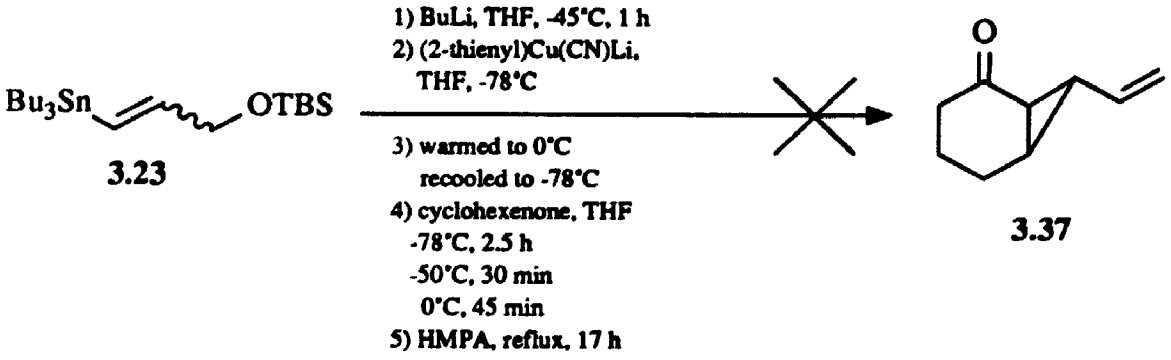


Scheme 3-25: Preparation of vinylcyclopropane **3.37**

TBS ether **3.20**, when treated with 48% aqueous hydrofluoric acid in acetonitrile[3.50], afforded alcohol **3.31** in 49% yield. Reaction with mesyl chloride and triethylamine gave mesylate **3.32**, which was used in the next step without further purification. The addition of a solution of mesylate **3.32** to a solution of potassium *tert*-butoxide in THF (Aldrich) at 0°C gave the desired

vinylcyclopropane in 42% yield (**3.37**). The spectral data for this compound were consistent with Hudlicky's results.[3.49] They were also consistent with those of Vedejs', reported later in 1988 for **3.37**.[3.51]

Attention then turned to attempts to effect the S_N' displacement of the *tert*-butyldimethylsilyloxy group. As mentioned earlier, we wanted to prepare vinylcyclopropane **3.37** directly from the enolate which is generated *in situ* during the conjugate addition reaction. We had initially hoped to do this by simply increasing the temperature of the reaction mixture resulting from the conjugate addition reaction. However, in those cases where commercial lithium 2-thienylcyanocuprate had been employed by us in the preparation of ketone **3.20**, stirring at 0°C for one to two hours had failed to produce any of the desired vinylcyclopropane (**3.37**) (Scheme 3-26).

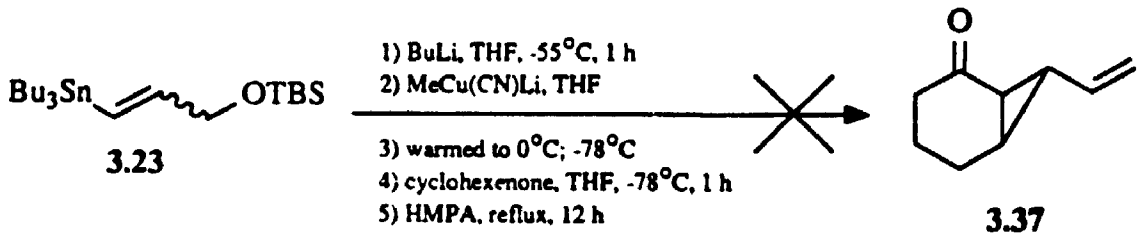


Scheme 3-26: Attempted preparation of vinylcyclopropane **3.37** directly from vinylstannane **3.23** via the cuprate derived from lithium 2-thienylcyanocuprate

It was therefore concluded that a temperature greater than this might be necessary in order to effect the desired displacement, all other conditions being the same. The use of HMPA as co-solvent was also investigated, in the hope that it would help to facilitate the loss of the -OTBS group (Scheme 3-26).The vinyllithium was prepared by treatment of a solution of stannane **3.23** in THF at -45°C with butyllithium. After being cooled to -78°C, this solution was transferred to a solution of lithium 2-thienylcyanocuprate in THF at -78°C. The reaction mixture was warmed to 0°C over a period of ten minutes before being recooled to -78°C. A solution of cyclohexenone in THF was added, and the reaction mixture was stirred at -78°C for 2.5 hours, -50°C for 30 minutes and at 0°C for 45 minutes. Finally, HMPA was added, and the reaction mixture was refluxed for 17 hours. During the course of the reaction, considerable charring took place. The ^{1}H NMR spectrum of the isolated crude product indicated that the product of simple conjugate addition, ketone **3.20**, and a trace of allyl silyl ether **3.27** were present. Thiophene and tetrabutyltin, the two expected organic by-products of the reaction, were present as well. There was no evidence for the desired vinycyclopropane (**3.37**).

We therefore turned our attention to the other method which had been used successfully in the conjugate addition reaction. This was based on the cuprate, $R_TMeCu(CN)Li_2$ (Scheme 3-27). The vinyllithium was prepared by treatment of a solution of vinylstannane **3.23** in THF at -50°C with butyllithium. The reaction mixture was stirred at -55°C for one hour before

being cooled to -78°C. The methyl cyano cuprate was prepared by treatment of a suspension of cuprous cyanide in THF at 0°C with methyllithium.



Scheme 3-27: Attempted preparation of vinylcyclopropane **3.37** directly from vinylstannane **3.23** via the cuprate, $R_TMeCu(CN)Li_2$

The cuprate reaction mixture was stirred at 0°C for 10 minutes before being transferred to the vinyllithium solution. The reaction mixture was warmed to 0°C before being cooled to -60°C. A solution of cyclohexenone in THF was added, and the reaction mixture was stirred at -78°C for 1 hour. HMPA was added and the reaction mixture was refluxed for 12 hours. The ^1H NMR spectrum of the isolated crude product indicated that only the conjugate addition product, ketone **3.20**, and the usual organic by-product, tetrabutyltin, were present. Vinylcyclopropane **3.37** was not formed.

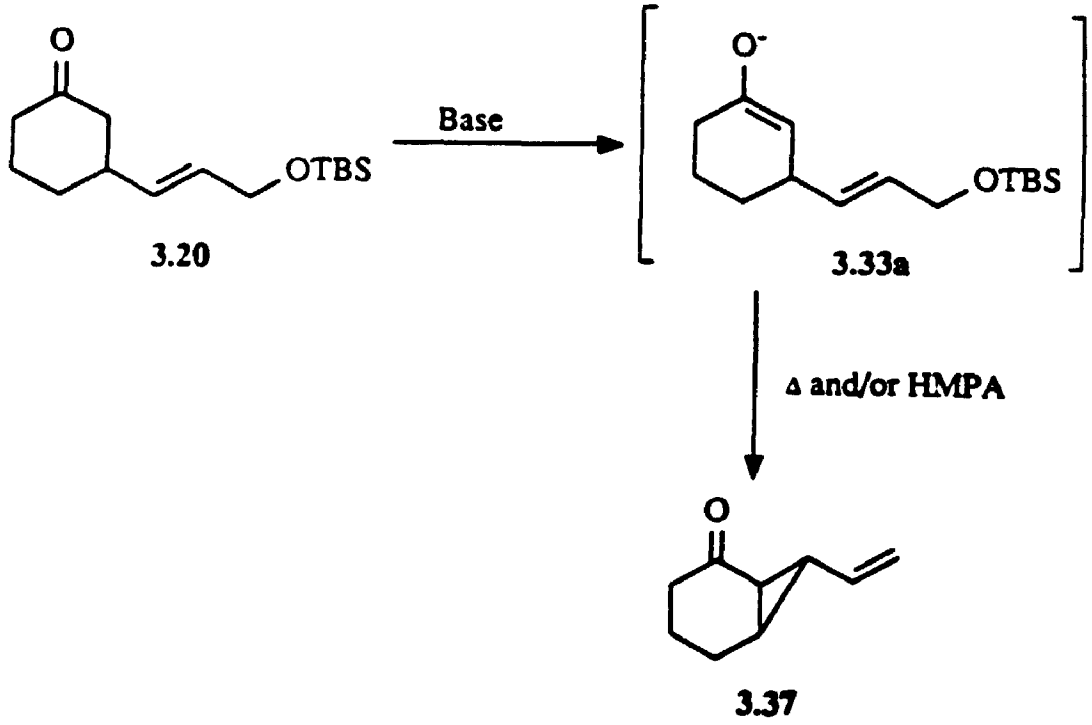
Since the conjugate addition took place, but not the intramolecular S_N', it was possible that the latter process could be induced by modifying the conditions. Therefore, the above reaction was repeated, but after the enone had been added, the reaction mixture was stirred at -50°C for 1 hour. The bulk of the THF was then removed by distillation. HMPA was added, and the reaction mixture was stirred at 150°C for 12 hours. Examination of the ^1H NMR

spectrum of the crude product revealed that neither vinylcyclopropane **3.37** nor the conjugate addition product, ketone **3.20**, was present. To summarize these attempts to carry out a one-pot vinylcyclopropanation, the combination of refluxing THF with HMPA as co-solvent failed to induce the S_N' displacement of the -OTBS group. Only the conjugate addition product, ketone **3.20**, was obtained. The use of a higher temperature with only HMPA as solvent led to decomposition.

As stated at the outset, the *crucial* step in our proposed one-pot method for the vinylcyclopropanation of enones is the S_N' displacement of the *tert*-butyldimethylsilyloxy group, which we had hoped to effect by simply increasing the temperature of the reaction mixture from the conjugate addition reaction. Unfortunately, this approach failed, as did the use of HMPA, even at elevated temperatures.

At this point we were faced with a number of important questions. Was it possible that the failures seen thus far were due to interference from the constituents of the cuprate reaction mixture? Is the -OTBS group actually capable of undergoing this type of S_N' displacement? In order to try to answer these questions, the conjugate addition product, ketone **3.20**, was treated with a variety of bases in a manner analogous to that employed by Corey and Wollenberg in their preparation of ketone **3.14** (Scheme 3-9).[3.14] The use of elevated temperatures, and the combination of elevated temperatures with HMPA, were then investigated in order to probe the "leaving group ability" of

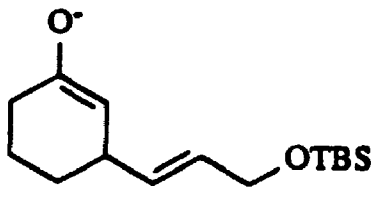
the -OTBS group under these much "cleaner" conditions. Scheme 3-28 depicts the general approach we proposed.



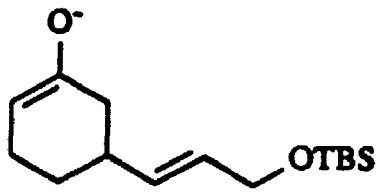
3.20 3.33a 3.37

Scheme 3-28: Proposed approach to vinylcyclopropane **3.37** via base induced cyclization of ketone **3.20**

Formation of enolate **3.33a** by deprotonation of ketone **3.20** in the first step would be followed by internal displacement of the -OTBS group. The reaction of ketone **3.20** with a suitable base would be expected to give a mixture of the two possible enolates, **3.33a** and **3.33b**.



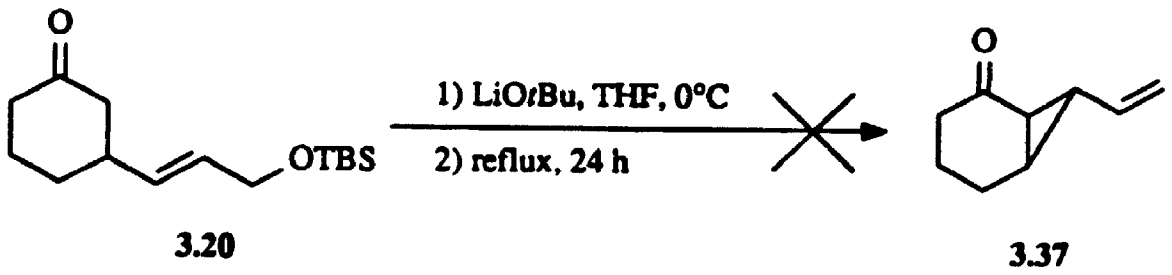
3.33a



3.33b

When *tert*-butoxide is used as the base, as in the method of Corey and

Wollenberg,[3.14] a small equilibrium concentration of the two enolates would be produced. Since cyclization of **3.33b** would probably not be favourable, only **3.33a** would cyclize, and eventually **3.33b** would be converted to **3.37** through **3.33a**. Since lithium *tert*-butoxide had been used successfully in our synthesis of vinylcyclopropane **3.37** via the mesylate (Scheme 3-25), this base was a logical first choice for the direct conversion of ketone **3.20** to **3.37** (Scheme 3-29). Accordingly, it was generated by treatment of 2-methyl-2-propanol in THF at 0°C with butyllithium. The reaction mixture was stirred at 0°C for 10 minutes. Ketone **3.20** in THF was added, and the reaction mixture was refluxed for 24 hours. The ^{1}H NMR spectrum of the crude product showed no evidence for the desired vinycyclopropane (**3.37**). Only starting ketone was recovered. This approach was therefore modified by adding HMPA as co-solvent and using a much higher bath temperature (150°C). Once again, there was no evidence for vinylcyclopropane **3.37** in the ^{1}H NMR spectrum of the crude product. Only starting ketone was isolated.

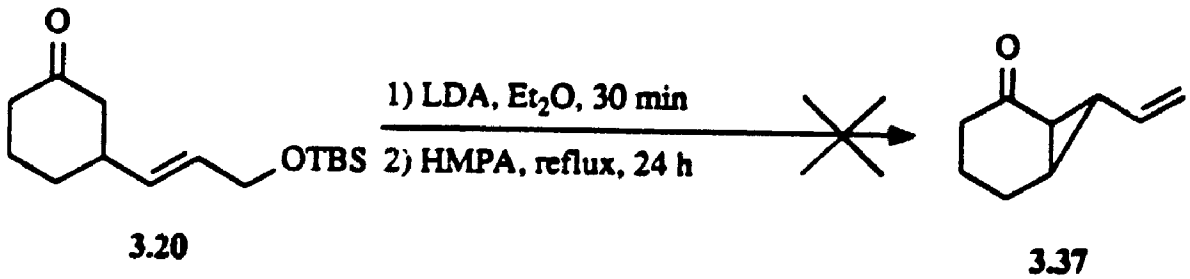


3.20 **3.37**

Scheme 3-29: Attempted S_N' displacement of OTBS using lithium *tert*-butoxide

In order to increase the concentration of the enolate, **3.33a**, and hence to encourage cyclization to the desired vinylcyclopropane, **3.37**, *tert*-butoxide was replaced by diisopropylamide as the base (Scheme 3-30). It was our intent to set up an equilibrium between the two enolates by using a slight excess of the ketone (**3.20**). Furthermore, as enolate **3.33a** reacts to give vinylcyclopropane **3.37** via S_N displacement of the silyloxy group, not only the excess ketone (**3.20**), but also the product, **3.37**, would be expected to catalyze the conversion of enolate **3.33b** to enolate **3.33a**. This is important since, again, *only* enolate **3.33a** gives rise to the desired product, and cyclization of **3.33b** would not be favourable.

The reaction with LDA proceeded as follows. A solution of ketone **3.20** in diethyl ether at 0°C was treated with 0.88 equivalents of lithium diisopropylamide. HMPA was added, and the reaction mixture was refluxed for 24 hours. The ^1H NMR spectrum of the crude product indicated that vinylcyclopropane **3.37** was not formed, nor was the starting ketone recovered.

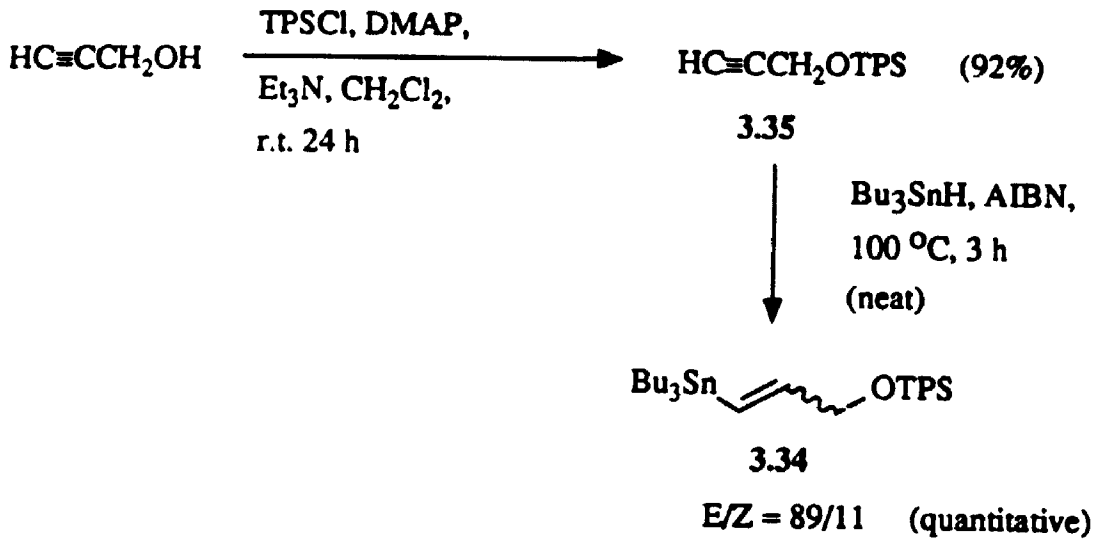


3.20 **3.37**

Scheme 3-30: Attempted cyclization of ketone **3.20** using LDA

At this point we concluded that further attempts to synthesize vinylcyclopropane **3.37** via S_N' displacement of the *tert*-butyldimethylsilyloxy group were not justified in that no indication of even the slightest success had been observed. Not wanting to abandon the project at this stage, however, we sought a replacement for the *tert*-butyldimethylsilyloxy group which would have to meet the same criteria that were set out when the -OTBS group was originally selected. We were also still hopeful that some sort of silyloxy group could be coaxed into undergoing the proposed S_N' displacement. Since leaving group ability often parallels acidity, the parent silanol of any new silyloxy leaving group to be considered should be more acidic than *tert*-butyldimethylsilanol. The *tert*-butyldiphenylsilyloxy group (-OTPS) would be expected to be a better leaving group, since phenyl is known to have an acidifying effect, at least in the gas phase. Recent determinations of $G°_{acid}$ gave +352 kcal/mol for H_3SiOH and +348 kcal/mol for $PhSiH_2OH$ [3.51] Alkyl groups, on the other hand, have the opposite effect ($G°_{acid}$ = +353 kcal/mol for $MeSiH_2OH$).[3.51] Therefore the -OTPS group was chosen as the replacement for -OTBS. The preparation of this -OTPS analogue followed the same synthetic pathway employed for the synthesis of ketone **3.20**. The required vinyl stannane (3.34) was prepared in two steps from propargyl alcohol (Scheme 3-31). Propargyl ether **3.35** and vinyl stannane **3.34** have apparently not been previously reported, but their spectral characteristics were completely consistent with their structures and analogous to those of the corresponding -

OTBS derivatives.

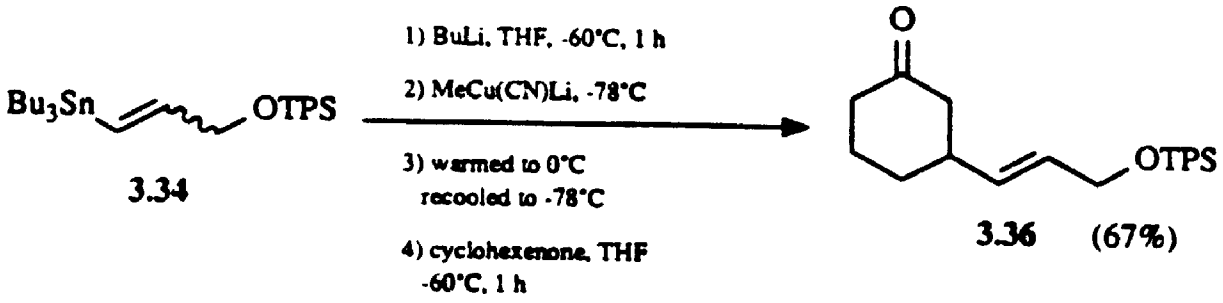


Scheme 3-31: Preparation of vinylstannane **3.34**

Silylation of propargyl alcohol with *tert*-butyldiphenylchlorosilane gave silyl ether **3.35** in 92% yield. Hydrostannylation of this acetylenic ether with tributyltin hydride/AIBN yielded the desired product (**3.34**). ^{1}H NMR analysis of **3.34** showed it to be a 89:11 mixture of E and Z stereoisomers, as judged by the relative integrations of the allylic methylene protons for each of the two isomers. This ratio is consistent with literature results for this type of compound,[3.28] including vinylstannane **3.23**. With the vinylstannane now in hand, attention turned to the preparation of ketone **3.36** (Scheme 3-32).

The required vinyllithium was prepared by treatment of vinylstannane **3.34** in THF at -60°C with butyllithium, and the solution of the vinyllithium was then cooled to -78°C. The methyl cyano cuprate was prepared separately

as before from cuprous cyanide and methyllithium in THF and was then transferred to the vinyllithium solution. The reaction mixture was warmed to 0°C before being cooled to -78°C. A solution of cyclohexenone in THF was added, and the reaction mixture was stirred at -60°C for 1 hour.

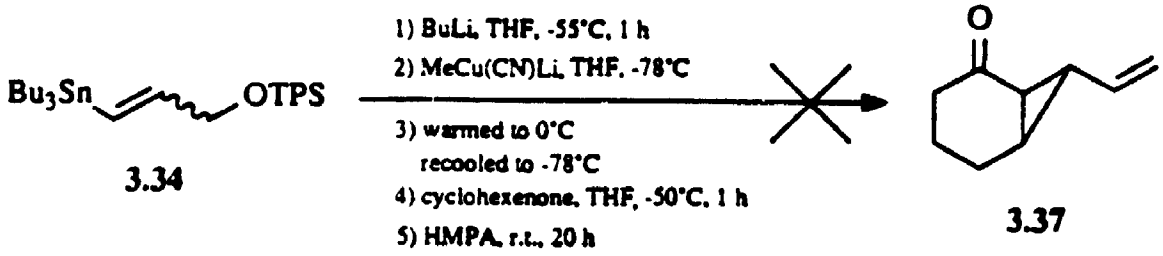


Scheme 3-32: Preparation of ketone **3.36** by conjugate addition

Ketone **3.36** was obtained in 67% yield after purification by flash chromatography. The 200 MHz ^{1}H NMR spectrum showed the protons of the *tert*-butyl group as a singlet at 0.83 ppm. The olefinic protons give rise to a multiplet at 5.6 ppm. The Lanthanide shift reagent, $Eu(fod)_3$, resolved this multiplet into a doublet of doublets at 6.32 ppm (J=15.5, 6 Hz) and a doublet of triplets at 6.1 ppm (J 15.5, 4 Hz). The protons of the CH_2O group appeared as a doublet at 4.3 ppm (J 3.2 Hz).

Attention then turned to attempts to effect the S_N' displacement of the *tert*-butyldiphenylsilyloxy group. As before, we wanted to prepare vinylcyclopropane **3.37** directly from the enolate generated *in situ* during the

course of the conjugate addition reaction. Scheme 3-33 depicts the method we used in our attempt to synthesize vinylcyclopropane **3.37** directly from the enolate arising from the conjugate addition using the cuprate, $R_TMeCu(CN)Li_2$.

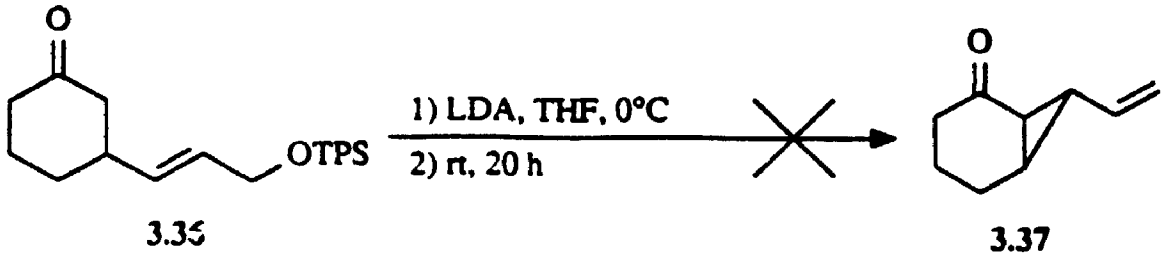


Scheme 3-33: Attempted preparation of vinylcyclopropane **3.37** from vinylstannane **3.34** via the cuprate, $R_TMeCu(CN)Li_2$

The procedure followed exactly that for the conjugate addition, except that at the end HMPA was added and the reaction mixture was stirred at room temperature for 20 hours. The ^1H NMR spectrum of the crude product indicated that vinylcyclopropane **3.37** was not formed. Some of the conjugate addition product, ketone **3.36**, was recovered. At this point we faced the same questions we had faced when OTBS had failed to undergo the desired S_N' displacement directly from the cuprate mixture. As before, we decided to attempt the preparation of vinvylcyclopropane **3.37** by treating the conjugate addition product, ketone **3.36**, with different bases followed by stirring at a variety of different temperatures. The effects of the use of HMPA as co-solvent were also investigated.

Initial attempts utilized lithium diisopropylamide as base and are outlined

in Scheme 3-34.



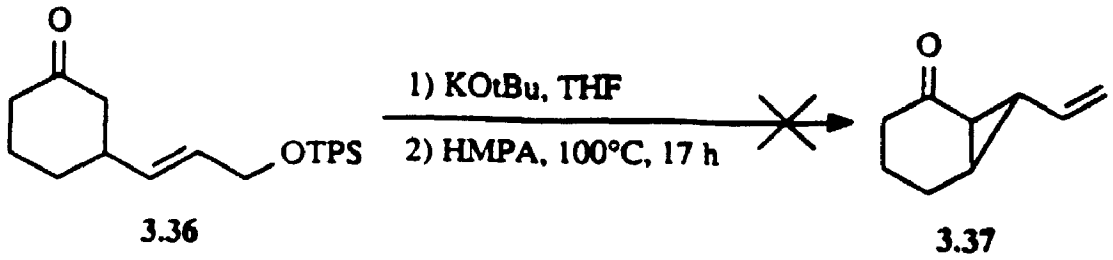
3.35 3.37

Scheme 3-34: Attempted intramolecular S_N' displacement of OTPS using lithium diisopropylamide

Ketone **3.36** was treated with 0.9 equivalents of LDA in THF. The reaction mixture was stirred at room temperature for 20 hours. The ^{1}H NMR spectrum of the isolated crude product showed no evidence of the desired vinylcyclopropane. Only starting ketone was recovered. This reaction was repeated with HMPA as co-solvent, but again only starting ketone was isolated. Since no vinylcyclopropane was formed at room temperature, the reaction was repeated with HMPA and heating and refluxing for 24 hours (the temperature of the oil bath was 200°C). The ^{1}H NMR spectrum of the isolated crude product showed no evidence for the desired vinylcyclopropane (**3.37**) nor for the starting ketone (**3.36**). However, in this case desilylation occurred to give alcohol **3.31**.

Since Corey and Wollenberg had carried out the cyclization of their mesylate to a vinylcyclopropane using potassium *tert*-butoxide, we also attempted to effect displacement of the OTPS group using the enolate generated

from the free ketone (**3.36**) employing this base, as outlined in Scheme 3-35.



3.36 **3.37**

Scheme 3-35: Attempted S_N' displacement of OTPS using HMPA and potassium *tert*-butoxide

Ketone **3.36** was treated with potassium *tert*-butoxide in THF at 0 C, HMPA was added, and the reaction mixture was refluxed for 17 hours. The ^1H NMR spectrum of the crude product showed no evidence for the desired vinylcyclopropane (**3.37**).

3.4 Summary

Ketone **3.20** was prepared by conjugate addition of a vinyl cuprate, generated from the corresponding vinyllithium, to cyclohexenone. Although our early attempts to carry out the conjugate addition reaction were plagued with problems, the desired ketone (**3.20**) was eventually prepared through the use of commercially available lithium 2-thienylcyanocuprate in yields ranging from 55 to 73%. In spite of this success there were instances in which the reaction simply failed altogether, and we attribute this to poor quality lithium 2-thienylcyanocuprate solutions. Subsequently, the cuprate, $R_TMeCu(CN)Li_2$, proved to be a much simpler and considerably more reliable vehicle for the conjugate addition, as evidenced by the consistently much higher yield (97%).

In order to be able to gauge the success of our attempts to prepare vinylcyclopropane **3.37** by our proposed one-pot method, we needed accurate spectral data. Vinylcyclopropane **3.37** was therefore prepared in two steps from alcohol **3.31** in a reaction sequence modelled after Corey and Wollenberg's synthesis of vinylcyclopropane **3.14**.[3.14] Reaction with mesyl chloride and triethylamine gave mesylate **3.32**, which when treated with potassium *tert*-butoxide afforded the desired product, vinylcyclopropane **3.37**, in 42% yield.

Efforts to prepare vinylcyclopropane **3.37** directly from the enolate generated *in situ* during the conjugate addition reaction, by simply increasing the temperature of the reaction mixture were not successful. Even the

combination of refluxing THF with HMPA as co-solvent failed to induce the intramolecular S_N' displacement of the *tert*-butyldimethylsilyloxy (OTBS) group. In each case, only the conjugate addition product, ketone **3.20**, was obtained. The use of a still higher temperature (150°C), with only HMPA as solvent, led to decomposition.

In order to determine whether or not the OTBS group could actually undergo this type of S_N' displacement, the conjugate addition product, ketone **3.20**, was treated with bases. The use of lithium *tert*-butoxide with elevated temperatures and with HMPA, failed to give the desired vinylcyclopropane (**3.37**). Even the stronger base, lithium diisopropylamide, proved to be unsuccessful.

In the hope that the *tert*-butyldiphenylsilyloxy group might be a better leaving group than OTBS, our proposal was tested with OTPS in place of OTBS.

The preparation of the OTPS analogue, ketone **3.36**, followed the same general synthetic pathway employed for the synthesis of ketone **3.20**. The required vinylstannane (**3.34**) was prepared from propargyl alcohol in two steps and in good yield (92%). Once again, the cuprate, $R_TMeCu(CN)Li_2$, was used for the conjugate addition, and ketone **3.36** was obtained in satisfactory yield (67%). As before, we initially attempted to prepare vinylcyclopropane **3.37** directly from the enolate generated *in situ* during the conjugate addition reaction, by simply increasing the temperature of the reaction mixture to room

temperature in the presence of HMPA. Unfortunately, only the conjugate addition product, ketone **3.36**, was recovered, even on reaction at a much higher temperature (200°C).

Finally, we attempted to induce the S_N' displacement of the OTPS group by heating the enolate(s) prepared by the reaction of ketone **3.36** with potassium *tert*-butoxide and LDA in the presence of HMPA. In the former case only starting ketone (**3.36**) was recovered. In the latter, alcohol **3.31**, arising from desilylation, was the exclusive product.

3.5 Conclusions

Our goal of developing a new one-pot method for the vinylcyclopropanation of α,β-unsaturated ketones, via conjugate addition and intramolecular S_N' displacement of a silyloxy group, was not achieved. In spite of the examples cited earlier which demonstrate the leaving group ability of the -OTBS group, we were unable to effect its S_N' displacement to give the desired vinylcyclopropane. Hwu and Lin's work with the "counterattack reagent", hexamethyldisilane, is most closely related to our proposal. It is puzzling that their S_N' displacement of the trimethylsilyloxy group occurred under relatively mild conditions, whereas our attempts to expel the -OTBS group under a wide range of reaction conditions were not successful. The use of the -OTPS group, which we had considered to be, at least qualitatively, a better leaving group, also proved unsatisfactory.

Among possible alternative strategies for inducing this type of displacement of a silyloxy group, the use of electron withdrawing substituents on the phenyl rings of the -OTPS group could be examined. For example, the use of nitro or nitrile groups might increase the leaving group ability of the silyloxy group sufficently through stabilization of the negative charge on oxygen via the inductive effect. However, the presence of these aryl substitutes precludes the use of butyllithium in the preparation of the cuprate reagent, since nucleophilic aromatic substitution of butyl ion would be preferred over tin-lithium exchange. A possible solution is Lipshutz's "hydrozirconation-transmetallation" procedure in which terminal acetylenes are converted directly and rapidly to vinyl cuprates via zirconium intermediates.[3.52]

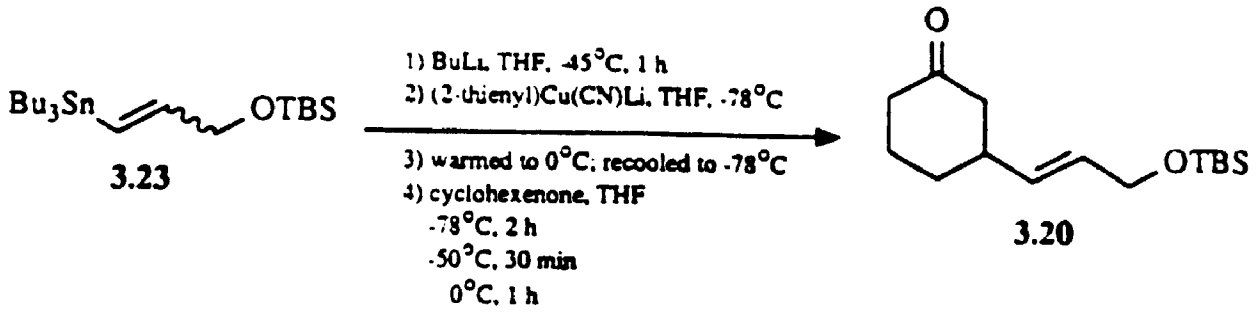
Alternatively, a simpler course would be to examine the effect that crown ethers might have on the reactivity of the enolates generated either during the conjugate addition reaction or via the separate treatment of the conjugate addition product with a base. This proposal is based upon the apparent requirement of crown ether 18-crown-6 in Paquette's intramolecular S_N' displacement of methoxide.

Technically, the basic idea is sound, even if silyloxy groups have proven to be unsuitable. Eventually, it should be possible to find a leaving group which survives the conjugate addition but allows displacement on raising the temperature and/or adding a cosolvent such as HMPA. We leave this to our successors.

3.6 Experimental

E-3-[3-(*tert*-butyldimethylsilyloxy)-1-propenyl]cyclohexanone (3.20)

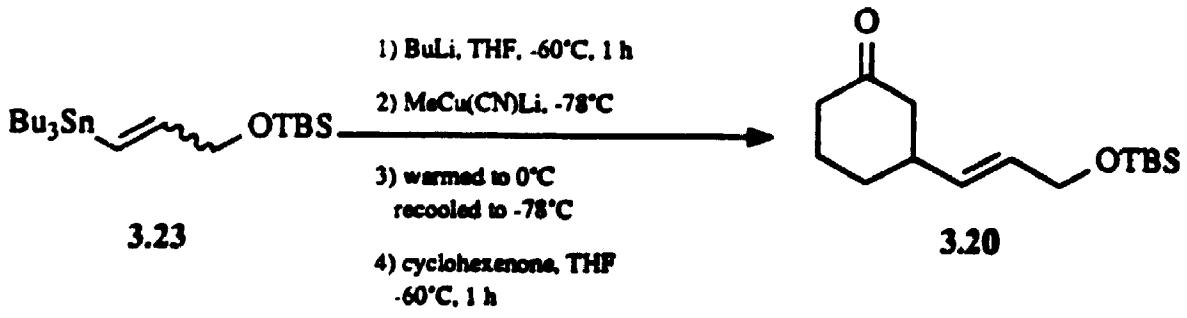
(Method A)



To a solution of vinyl stannane **3.23**[3.28] (14.0 g, 30.4 mmol) in 35 mL of THF at -45°C was added 12.3 mL of butyllithium (2.5 M; 30.8 mmol) dropwise via syringe at such rate so as to maintain a temperature of -45°C. The reaction mixture was stirred at -45°C for 50 min before being cooled to -78°C. This solution was then transferred via cannula to a solution of lithium 2-thienylcyanocuprate (0.25 M in THF; 123 mL; 30.8 mmol) at -78°C. The reaction mixture was stirred at -78°C for 10 min before being warmed to 0°C over 15 min. It was then recooled to -78°C. Cyclohexenone (2.5 g, 26 mmol) was then added neat via syringe. The reaction mixture was stirred at -78°C for 2 h and at 0°C for 1 h. The reaction was quenched with 200 mL of 90% saturated aq. NH_4Cl/10% conc.NH_4OH, and the aqueous layer was extracted with ether (5x200 mL). The combined organic layers were washed with water (3x200 mL), followed by saturated aq. NaCl (2x200 mL). The organic layer

was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford an oil. Purification by dry column flash chromatography (silica gel, 25% ethyl acetate/petroleum ether) gave 5.1 g of ketone **3.20** as a clear colourless oil (73% yield); TLC (same solvent) R_f=0.35; GC (210°C, OV-101) t_r=6.75 min; IR(film): 1717, 1680 cm^{-1}; ^1H NMR ($CDCl_3$):δ 5.6 (m, 2H, vinylic H), 4.12 (d, 2 H, J = 4 Hz, OCH_2), 1.1-2.5 (m, 9H, ring H), 0.88 (s, 9H, *tert*-butyl), 0.04 (s, 6H, SiMe); ^{13}C NMR ($CDCl_3$):δ 211.2 (C=O), 133.3 (olefinic CH), 128.7 (olefinic CH), 63.7 (OCH_2), 47.4 (ring CH_2), 41.3 (ring CH_2), 41.2 (ring CH), 31.3 (ring CH_2), 26.0 (*t*Bu, CH_3), 25.0 (ring CH_2), 18.4 (CSi), -5.1 ($SiCH_3$); MS, *m/e* (relative intensity): 253 (3), 211 (100), 181 (10), 169 (21), 131 (16), 119 (29), 91 (34); high resolution *m/e* calcd. for $C_{11}H_{19}O_2Si$ (M^+-C_4H_9): 211.1154, found: 211.1155; MS (CI) *m/e* (relative intensity): 269 (M^++H, 12), 253 (12), 211 (51), 155 (23), 137 (100); high resolution *m/e* calcd. for $C_{15}H_{29}O_2Si$ (M^++H) 269.1937, found 269.1942.

(Method B)

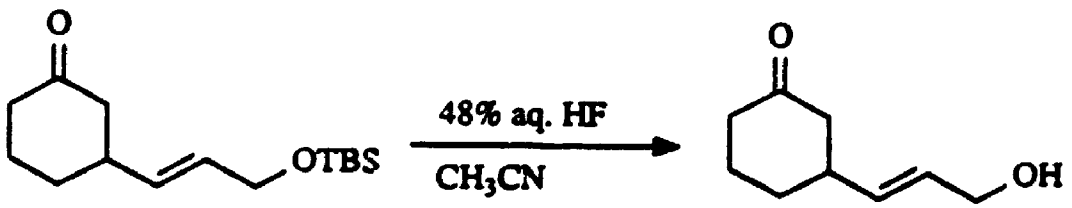


3.23 **3.20**

To a solution of vinyl stannane **3.23** (1.23 g, 2.67 mmol) in 5 mL of THF at -60°C was added 1.25 mL of butyllithium (2.2 M; 2.75 mmol) dropwise via

syringe. The reaction mixture was stirred at -60°C for 1 h before being cooled to -78°C. MeCu(CN)Li was prepared in a separate flask through treatment of a suspension of cuprous cyanide (239 mg, 2.67 mmol) in 5 mL of THF at 0°C with methyllithium (1.95 mL; 1.4 M in cyclohexane, 2.73 mmol). The resulting clear colourless solution was stirred at 0°C for 10 min. It was then cooled to -78°C before being transferred via syringe to the vinyllithium solution. The reaction mixture was allowed to warm to 0°C after which it was recooled to -78°C. A solution of cyclohexenone (265 mg; 2.76 mmol) in 6 mL of THF was added via syringe. The reaction mixture was stirred at -60°C for 1 h. The reaction was quenched with 20 mL of 90% saturated NH_4Cl/10% conc.NH_4OH, and the aqueous layer was extracted with ether (3x25 mL). The combined organic layers were washed with saturated aq. NaCl (25 mL) before being dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Purification by dry column flash chromatography (silica gel, 20% ethyl acetate/petroleum ether) yielded 0.70 g of **3.20** (97% yield).

E-3-(3-hydroxy-1-propenyl)cyclohexanone (3.21)

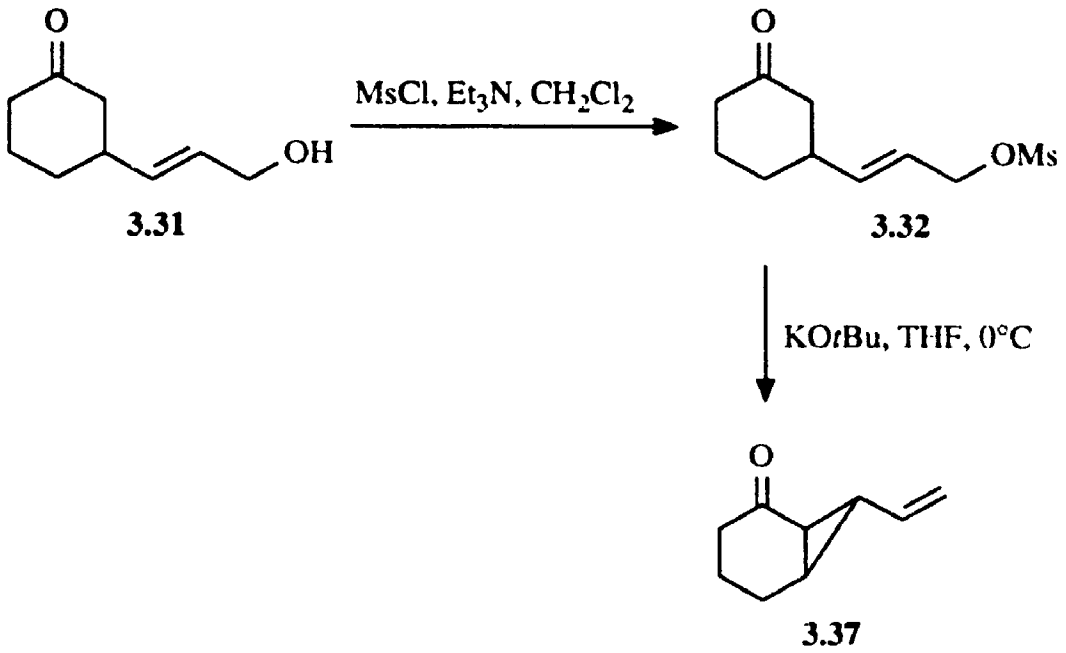


3.20 **3.31**

To a solution of ketone **3.20** (2.3 g, 8.6 mmol) in 20 mL of acetonitrile at

room temperature was added 12 mL of 48% aqueous HF. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched and neutralized with saturated aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with saturated aq. NaCl (50 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by dry column flash chromatography (silica gel, 50% ethyl acetate/hexanes) gave 0.65 g of **3.31** as an oil (49% yield). TLC (50% ethyl acetate/CH_2Cl_2) R_f=0.28; GC (210°C, OV-101) t_r=3.5 min; IR (film): 3411, 2936, 2867, 1707, 1422, 1225, 1100, 1011, 972 cm^{-1}; ^1H NMR ($CDCl_3$):δ 5.6 (m, 2H), 4.06 (d, 2 H, J = 3.3 Hz), 1.3-2.6 (m, 10H); ^{13}C NMR ($CDCl_3$):δ 211.3 (C=O), 134.5 (olefinic CH), 128.4 (olefinic CH), 63.0 (OCH_2), 47.0 (ring CH_2), 41.1 (ring CH_2), 41.0 (ring CH), 31.0 (ring CH_2), 24.8 (ring CH_2); MS, *m/e* (relative intensity): 154 (M^+, 3), 136 (15), 124 (10), 113 (19), 97 (40), 79 (42), 67 (45); high resolution *m/e* calcd. for $C_9H_{14}O_2$ 154.0994, found 154.0996.

7-Ethenyl-bicyclo[4.1.0]heptan-2-one (3.37)

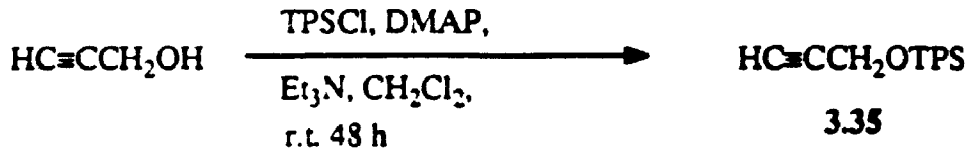


3.31 3.32 3.37

To a solution of ketone **3.31** (0.080 g, 0.52 mmol) in 3 mL of CH_2Cl_2 at 0°C was added 0.060 g (0.52 mmol) of methanesulfonyl chloride and 0.58 g (0.57 mmol) of triethylamine. The reaction mixture was stirred for 30 minutes at 0°C. The reaction was quenched with 20 mL of ice water and extracted with 50 mL of CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was taken up in 4 mL of dry THF and added via syringe to a solution of potassium *t*-butoxide (0.5 mL, 1.0 *M*, 0.5 mmol) in 2 mL of dry THF at 0°C. The reaction mixture was stirred for 30 minutes at 0°C The reaction was quenched with 20 mL of saturated aq. NH_4Cl and extracted with ether (3x25 mL). The combined ether layers were washed with saturated aq. NaCl (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 0.030 g of **3.37** (42%

yield) as an oil. ^{1}H NMR ($CDCl_3$):δ 5.38 (ddd, 1H, *J* = 17, 19, 8.2 Hz), 5.15 (dd, 1H, *J* = 17, 1.5 Hz), 4.98 (dd, 1H, *J* = 19, 1.5 Hz), 1.4-2.5 (m, 9H); ^{13}C NMR ($CDCl_3$):δ 206.9 (C=O), 137.8 (olefinic CH), 114.6 (olefinic CH), 36.9 (ring CH_2), 34.4 (ring CH), 27.5 (CH), 25.1 (CH), 21.0 (ring CH_2), 18.6 (ring CH_2); MS, *m/e* (relative intensity): 136 (M^+, 40), 121 (10), 108 (14), 93 (25), 79 (100), 69 (31), 55 (38); high resolution *m/e* calcd. for $C_9H_{12}O$ 136.0888, found 136.0885.

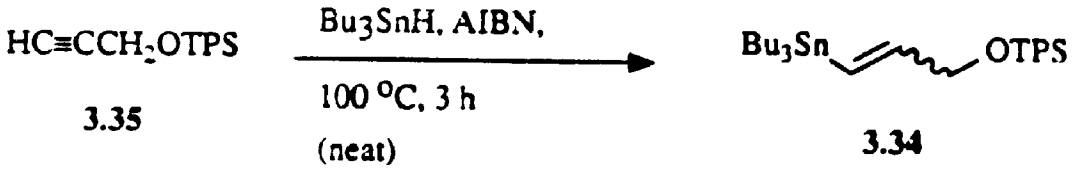
t-butyldiphenylsilylpropargyl ether (**3.35**)



To a solution of *t*-butyldiphenylchlorosilane (10.57 g, 38.4 mmol), 4-dimethylamino pyridine (75 mg, 0.6 mmol), Et_3N (4.07 g, 40 mmol) in 40 mL of CH_2Cl_2 was added a solution of propargyl alcohol (2.06 g, 36.7 mmol) in 10 mL CH_2Cl_2. The cooling bath was removed and the mixture stirred at room temp for 48 h. The reaction was quenched with water (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were washed with saturated aq. NaCl (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Dry column flash chromatography (silica gel, hexanes) yielded 9.9 g of **3.35** as a colourless oil (92% yield). TLC (50% $CHCl_3$/ethyl acetate) R_f=0.77; IR

(film): 3308, 3017, 2860, 2125, 1217, 1111 cm^{-1}; ^1H NMR ($CDCl_3$):δ 7.75 (m, 4H, aromatic), 7.45 (m, 6H, aromatic), 4.36 (d, 2H, J = 2.4 Hz, OCH_2), 2.07 (t, 1H, J = 2.4 Hz, HC≡C-), 1.11 (s, 9H, *tert*-butyl); ^{13}C NMR ($CDCl_3$):δ 135.5 (aromatic CH), 132.9 (aromatic C), 129.8 (aromatic CH), 127.7 (aromatic CH), 81.9 (HC≡C-), 73.1 (OCH_2), 52.4 (HC≡C-), 26.6 (*t*Bu CH_3), 19.1 (CSi); MS, *m/e* (relative intensity): 294 (M^+, 0.6), 207 (100), 237 (85); high resolution *m/e* calcd for $C_{19}H_{22}OSi$ 294.1440, found 294.1442.

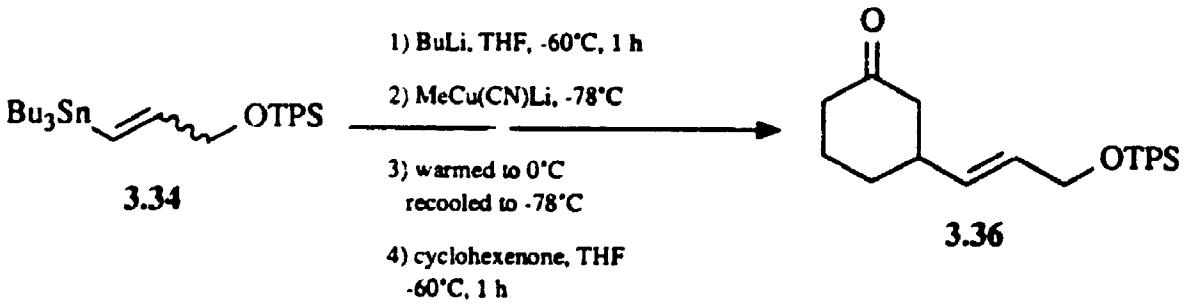
1-(Tributylstannyl)-3-(*tert*-butyldiphenylsiloxy)-1-propene (**3.34**)



To a mixture of *t*-butyldiphenylsilylpropargyl ether (**3.34**, 734 mg, 2.5 mmol) and AIBN (20 mg) was added tributyltin hydride (737 mg, 2.53 mmol). The reaction mixture was stirred at 140°C for 3 h. Purification by dry column flash chromatography (petroleum ether) yielded **3.34** quantitatively as a colourless oil. E/Z=89/11. *E* isomer: TLC (hexanes) R_f=0.2 ; IR (film): 3073, 2926, 2853, 1603, 1464, 1427, 1111, 823, 702 cm^{-1}; ^1H NMR ($CDCl_3$):δ 7.70 (m, 4H, aromatic), 7.41 (m, 6H, aromatic), 6.31 (dt, 1H, J = 19, 1.6 Hz, vinylic H), 6.07 (dt, 1H, J = 19, 3.8 Hz, vinylic H), 4.27 (dd, 2H, J = 1.6, 3.8 Hz, OCH_2), 1.2-1.7 (m, 12H, aliphatic H), 1.09 (s, 9H, *tert*-butyl), 0.7-1.0 (m,

15H, aliphatic); ^{13}C NMR ($CDCl_3$):δ 146.9 (olefinic CH), 135.7 (aromatic CH) 134.1 (aromatic C), 129.7 (aromatic CH), 127.7 (aromatic CH), 126.9 (olefinic CH), 67.1 (OCH_2), 29.0 (aliphatic CH_2), 27.1 (aliphatic CH_2), 26.7 ($SnCH_3$), 19.1 (CSi), 13.5 (*t*Bu CH_3), 9.2 (aliphatic CH_2); MS, *m/e* (relative intensity): 529 (M^+, 100), 317 (13), 291 (10), 197 (52), 161 (51), 135 (38), 119 (48); high resolution *m/e* calcd for $C_{27}H_{41}O^{29}Si^{118}Sn$ (M-C_4H_9), 529.1961, found 529.1913.

E-3-[3-(*tert*-butyldiphenylsilyloxy)-1-propenyl]cyclohexanone (**3.36**)



To a solution of vinyl stannane **3.34** (2.08 g, 3.56 mmol) in 20 mL of THF at -60°C was added 1.4 mL of butyllithium (2.2 M; 2.75 mmol) dropwise via syringe. The reaction mixture was stirred at -60°C for 1 h before being cooled to -78°C. The MeCu(CN)Li was prepared in a separate flask by treatment of a suspension of cuprous cyanide (313 mg, 3.5 mmol) in 5 mL of dry THF at 0°C with methyllithium (2.5 mL; 1.4 M in cyclohexane; 2.73 mmol). The clear

colourless solution was stirred at 0°C for 15 min and cooled to -78°C. It was then transferred via syringe to the vinyllithium solution. The reaction mixture was immediately warmed to 0°C after which it was recooled to -78°C. A solution of cyclohexenone (336 mg; 3.5 mmol) in 4 mL of THF was added via syringe and the reaction mixture was stirred at -60°C for 1 h. The reaction was quenched with water (50 mL), and the aqueous layer was extracted with ether (3x100 mL). The combined organic extracts were washed with water (50 mL) and saturated aq. NaCl (50 mL) before being dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by dry column flash chromatography (silica gel, 10% ethyl acetate/hexanes) yielded 0.92 g of **3.36** as a colourless oil (67% yield). TLC (30% ethyl acetate /hexanes) R_f=0.42; IR (film): 3071,2930, 2855, 1715, 1428, 1113, 702 cm^{-1}; ^1H NMR ($CDCl_3$):δ 7.7 (m, 4H, aromatic H), 7.4 (m, 6 H, aromatic H), 5.6 (m, 2H, vinylic H), 4.2 (d, 2H, J = 3.2 Hz, OCH_2), 1.2-2.5 (m, 9H, aliphatic H), 1.1 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$):δ 211.2 (C=O), 135.6 (aromatic CH), 134.8 (CH), 133.8 (CH), 133.4 (CH), 129.7 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 64.3 (OCH_2), 47.3 (CH_2), 41.3 (CH_2), 41.2 (CH), 31.2 (CH_2), 30.2 (C or CH_2), 26.9 (*t*BuCH_3), 26.6 (CH or CH_3), 25.0 (CH_2), 19.3 (CSi). MS (CI), *m/e* (relative intensity): 393 (M^++H, 5), 355 (M^+-C_4H_9, 100), 315 (10), 305 (15); high resolution *m/e* (CI) calcd for $C_{25}H_{33}O_2Si$ (M^++H) 393.2250, found 393.2213; MS, *m/e* (relative intensity): 335 (M^+-C_4H_9, 83), 257 (20), 225 (8), 199 (100), 181 (17), 139 (15), 77 (29); high

resolution *m/e* calcd for $C_{21}H_{23}O_2Si$ (M^+-C_4H_9) 335.1467, found 335.1466.

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