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THE UNIVERSITY OF ALBERTA

SYNTHETIC APPLICATIONS OF PHENYL DICHLOROPHOSPHATE AND SYNTHETIC STUDIES ON PHYLLANTHOCIN

BY

VIRGINIA WISZNIEWSKI

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1989

ISBN 0-315-52977-6

THE UNIVERSITY OF ALBERTA

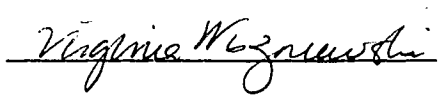
RELEASE FORM

NAME OF AUTHOR: VIRGINIA WISZNIEWSKI

TITLE OF THESIS: SYNTHETIC APPLICATIONS OF PHENYL DICHLOROPHOSPHATE AND SYNTHETIC STUDIES ON PHYLLANTHOCIN

DEGREE FOR WHICH THIS THESIS WAS PRESENTED: Ph. D.

YEAR THIS DEGREE GRANTED: 1989



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SYNTHETIC APPLICATIONS OF PHENYL DICHLOROPHOSPHATE AND SYNTHETIC STUDIES ON PHYLLANTHOCIN

submitted by VIRGINIA WISZNIEWSKI in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Chemistry.

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Date: March 10, 1989

Dedicated to my family

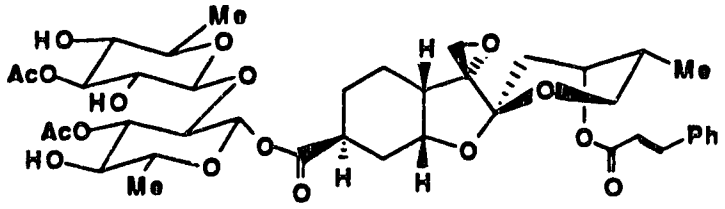
Abstract

The first chapter of this thesis describes the cleavage of acyclic aliphatic ethers with phenyl dichlorophosphate and sodium iodide in refluxing xylenes or acetonitrile, resulting in the formation of alkyl iodides.

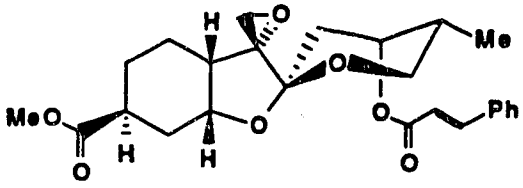
The second chapter of this thesis describes a simple and mild procedure for the conversion of thioacetals to the corresponding carbonyl compounds using the combination of phenyl dichlorophosphate, dimethylformamide and sodium iodide in acetonitrile.

In the third chapter of this thesis, studies towards the synthesis of phyllanthocin (**57**), the aglycone of the potent antineoplastic agent phyllanthoside (**56**) are described. The key intermediate (**130**) was prepared in 11 steps from m-methoxybenzoic acid. The AB ring system was formed by a [2+2] photocycloaddition reaction of enone ester **96** with vinyl acetate, to give keto-ester **121**. Removal of the ketone carbonyl was achieved in a two step sequence involving thioacetalization followed by Raney nickel reduction. Transesterification with isopropyl alcohol and anhydrous hydrogen chloride provided hydroxy-ester **123**. Oxidation using PCC on alumina yielded the two epimeric keto-esters **119** and **120**. Although only isomer **119** possessed the correct stereochemistry required for the target molecule, isomer **120** could be epimerized into isomer **119** by treatment with sodium isopropoxide. Isomer **119** was treated

with MCPBA to provide butyrolactone **125**. Oxidation of this compound to the α-keto-butyrolactone molecule was accomplished in three steps by treatment of the enolate with benzaldehyde, followed by dehydration to form the α-benzilidine-butyrolactone **129**. Ozonolysis of this compound provided the desired α-keto-lactone **130**.



56



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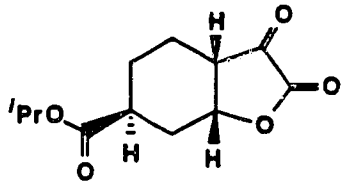


130

Acknowledgements

I would like to express my sincerest thanks to Professor H. J. Liu for the unfailing support, guidance, interest, assistance he has willingly given to me throughout my degree. Needless to say his patience, wisdom and humor, all helped to pave the way. His interest and assistance in the preparation of this thesis are also appreciated. Thanks are also extended to Professor J. Hooz for allowing me to use the Macintosh in the preparation of this thesis.

Thanks are also extended to the excellent technical staff of the department. Not only did they do their work well they did so with a smile: Dr. A. M. Hogg, L. Harrower, D. Morgan, J. Olekszyk and A. Jodhan in the Mass Spectromety Laboratory, R. Swindlehurdst, D. Formanski and J. Hoyle in the Spectral Services Laboratory, D. Mahlow and A. Dunn in the Microanalytical Laboratory, T. T. Nakashima, T. Brisbane, G. Bigam, L. Kong, and G. Aarts in the NMR Spectroscopy Laboratory, as well as all the personnel in the Electronic, Glass Blowing and Machine Shops. I would also like to thank the University of Alberta for financial support.

I would particulary like to thank all the people who I have have had the pleasure getting to know over the years. Although many have come and gone, they are nonetheless remembered fondly and missed. These friendships have helped me, supported me, and made me laugh. I would like to thank Milan Ralitsch for proofreading the entire thesis. His helpfulness throughout the years was always appreciated. I would like to thank Mirna Cerda

for her friendship especially during difficult times. I would also like to thank Claude Dufresne for his friendship and support.

My parents, Lily, Judy and Eddy deserve special mention for the support and help they have given me over the years. Judy especially, has been there for me many times, to share the good and help shoulder the bad, in spite of the many miles between us.

Finally, last but not least, a very special thanks to Richard Fisette for his friendship, support, strength, humor and especially understanding. He never failed to make the difficult times easier and the good times better.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Bn	benzyl
Bu	butyl
cims	chemical ionization mass spectrum
MCPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPC	diethyl phosphorocyanidate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
eq	equivalent

eqn	equation
Et	ethyl
h	hour
HMPA	hexamethylphosphoramide
hrms	high resolution mass spectrum
i	iso
ir	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
m	meta
Me	methyl
MEM	methylethoxymethyl
min	minutes
MoOPH	oxadiperoxymolybdenum(pyridine)-hexamethyl-phosphoramide
m.p.	melting point
Ms	methanesulfonyl

nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDCP	phenyl dichlorophosphate
Ph	phenyl
Pr	propyl
py	pyridine
r.t.	room temperature
t	tert
TBDMS	*tert*-butyldimethylchlorosilane
TEA	triethylamine
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran

tlc	thin layer chromatography
TMS	trimethylsilyl
Ts	p-toluenesulfonyl

CHAPTER I

CLEAVAGE OF ALIPHATIC ETHERS

Introduction

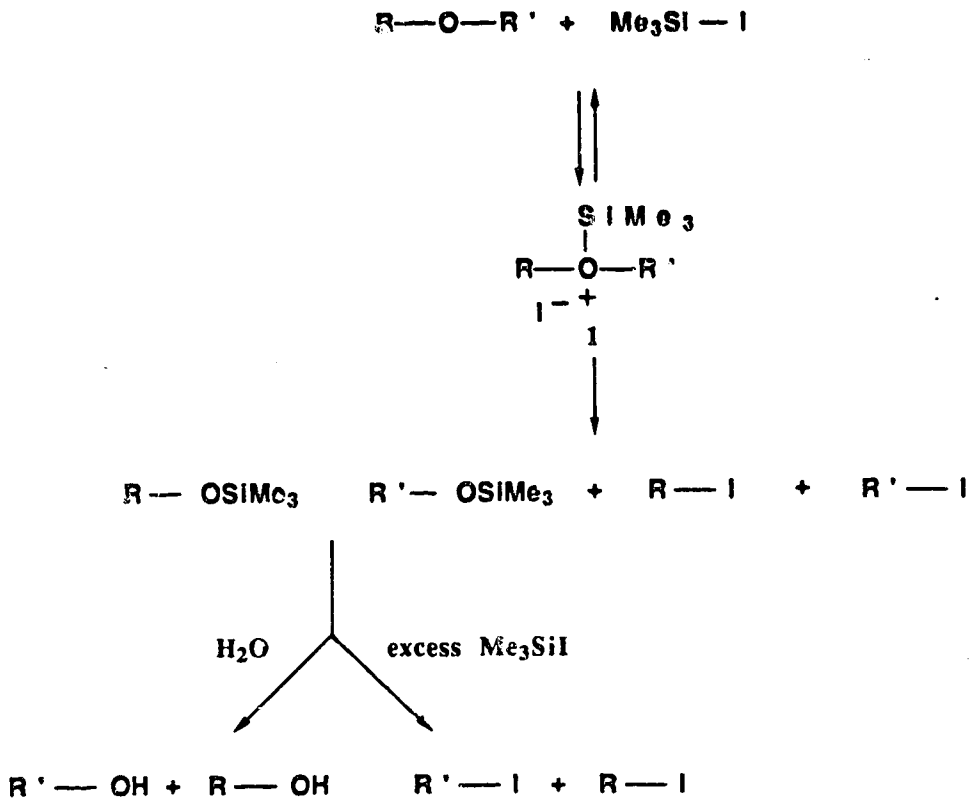
The ether functionality to date has been of limited synthetic utility. It is at first glance an attractive protecting group for the alcohol because it is easy to prepare in good yield, and is stable under a wide variety of reaction conditions. This inherent stability becomes a hindrance however when it comes to deprotection. Forcing conditions, which may not be compatible with other functionalities in the molecule, are often required. As a result, there exists a need to develop methods which would increase the reactivity of the ether linkage under mild reaction conditions. It is also desirable to convert the ether group directly into a more reactive functionality which can be used for subsequent transformations. One such functionality is the halide group.

Alkyl halides are useful synthetic intermediates: they can be metallated, eliminated, and can be substituted by carbon, oxygen, sulfur, nitrogen, and phosphorus nucleophiles, among others. Thus replacement of the halogen by another group is a very important reaction accessing a wide range of functionalized compounds. Although there are many different methods available for the preparation of alkyl halides,[1] the direct transformation of non-activated alkyl ethers to alkyl halides is not so common.[2]

Most methods invariably employ strongly acidic or forcing conditions. Less commonly, ethers have been cleaved by strong bases such as alkyl and aryllithium reagents,[3] and alkali metals.[4] Those methods which avoid the use of such drastic conditions, particularly the presence of strong acids or bases, are relatively few in number.

Silicon based reagents are among the most recently developed methods employing mild reaction conditions. In particular, trimethylsilyl iodide[5] has emerged as an excellent electrophilic agent to activate the carbon-oxygen bond towards cleavage. Jung *et al.*[6] have reported the cleavage of ethers to alcohols or iodides, depending on the quantity of trimethylsilyl iodide used. The reaction is proposed to proceed via a silylated oxonium iodide **1**, which proceeds further to the products. (Scheme 1)

Scheme 1

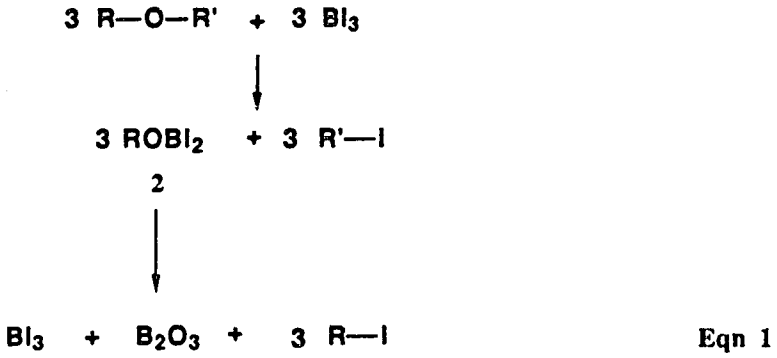


Olah *et al.*[7] and Morita *et al.*[8] report similar results with the combination of trimethylsilyl chloride and sodium iodide (*in situ* formation of trimethylsilyl iodide) in acetonitrile. Other silicon based reagents which have been used include hexamethyldisilane/iodine[9a,b,c] and allyltrimethylsilane/iodine.[9d]

Lewis acids (such as $ZnCl_2$, $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, $SbCl_5$ and BF_3) have been used in conjunction with acid chlorides or anhydrides to cleave ethers. However, the products here are

esters and alkyl halides. Furthermore, problems arise with competing Friedel-Crafts reactions when aromatic substrates are used. There are reports of ether cleavage in the absence of Lewis acids, with the addition of acyl iodides. However, the preparation of these acyl iodides can be difficult and the products formed are still esters and iodides.[10]

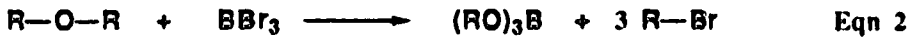
Of all the Lewis acids, the boron trihalides have been the most successful with regard to cleavage of unactivated ethers. Boron triiodide has been used to cleave aliphatic, cyclic, and mixed aliphatic aromatic ethers to iodides in good yields.[11] The reaction proceeds *via* alkoxy diiodoborane **2**, which is itself unstable and decomposes according to Eqn 1.



Eqn 1

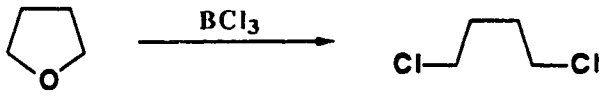
Boron tribromide has been used to cleave diethyl ether, dibutyl ether and diisopropyl ether. Ether cleavage results in the

formation of the alkyl bromide and the orthoboric ester, according to Eqn 2.[12] Hydrolysis of the orthoboric ester provides the alcohol.



Eqn 2

Similarly, boron trichloride has been used to effect ether cleavage, providing (after hydrolysis) alcohols and alkyl chlorides. Interestingly, treatment of tetrahydrofuran with boron trichloride formed a 1:1 complex, which upon pyrolysis gave 1,4-dichlorobutane (Eqn 3).[13]

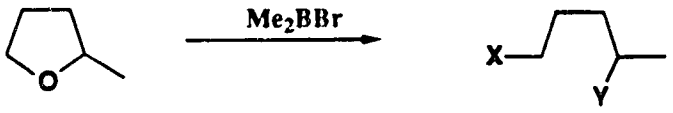


Eqn 3

Boron trifluoride is comparatively inert with regard to ethers, this is evidenced by the fact that it is sold commercially as a 1:1 addition complex with diethyl ether, and this complex is stable enough to be distilled at its boiling point without decomposition. In contrast, the analogous 1:1 addition complex between boron trichloride and diethyl ether decomposes at its melting point. When aliphatic ethers other than methyl or ethyl ethers are used as substrates, boron trifluoride gives alkenes as

products, demonstrating the difficulties faced with regard to product formation.[14]

Dimethylboron bromide has been reported to cleave aliphatic, aromatic and cyclic ethers under mild conditions. Aliphatic methyl ethers were cleanly demethylated to provide the the aliphatic alcohols, and aromatic methyl ethers were cleaved to the corresponding phenols. In the case of cyclic ethers, the corresponding bromo-alcohol was formed in good yield (Eqn 4).[15]



Eqn 4

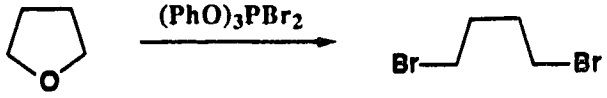
(i) X = Br, Y = OH
(ii) X = OH, Y = Br
i:ii = 3.5:1

In addition, there are a number of other boron based reagents which have been reported in ether cleavage: phenylboron dichloride[16a], 9-bromo-9-borabicyclo[3.3.0]nonane[16b], boron tribromide with sodium iodide and 15-crown-5[16c], diborane/iodine[16d], decaborane/iodine[16e] and sodium borohydride/iodine[16f].

Titanium tetrachloride in conjunction with lithium iodide has been reported to effect the cleavage of a single ether

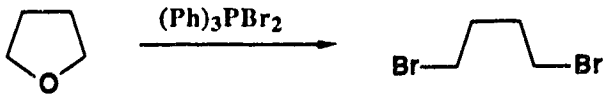
substrate.[56f] Treatment of 1-methoxyheptane with titanium tetrachloride and lithium iodide in dichloromethane at room temperature afforded heptanol in quantitative yield. This report was discovered after the completion of the thesis.

Phosphorus containing reagents have also been reported to effect ether cleavage. There is a single report of the use of triphenoxydibromophosphine in the conversion of tetrahydrofuran to 1,4-dibromobutane (Eqn 5).[17]



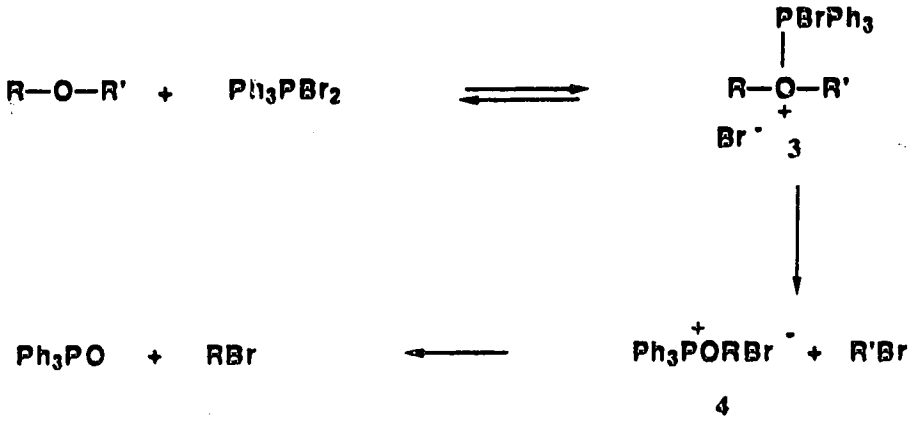
Eqn 5

Triphenyldibromophosphorane, which has been explored more extensively, has been found to generally convert dialkyl ethers to alkyl bromides under essentially neutral conditions,[18] again being capable of forming the dibromide from tetrahydrofuran (Eqn 6). The reaction is proposed to proceed first via oxonium ion **3**, then to quasiphosphonium ion intermediate **4**, resulting in the formation of alkyl bromides (Scheme 2).



Eqn 6

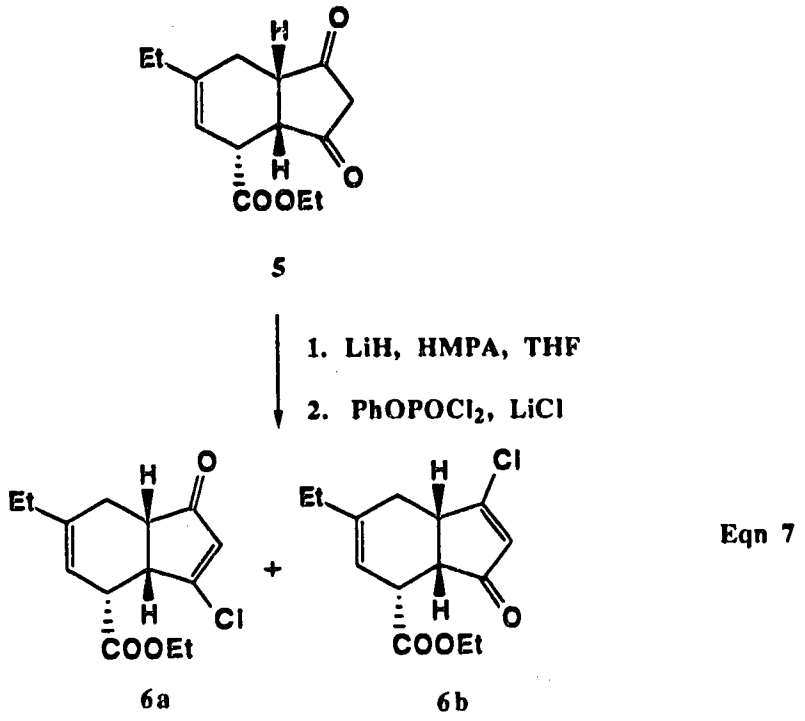
Scheme 2



It is this capacity of phosphorus-containing compounds to act as activating agents to facilitate the cleavage of the ether carbon-oxygen bond, that we sought to explore further. Our interest in this area was fueled by a particular reagent: phenyl dichlorophosphate (PDCP).

The hint that such a transformation would be possible was suggested by an observation during synthetic studies on coronafacic acid. One step of the synthesis involved the conversion of β-diketone **5** to β-chloro-α,β-unsaturated ketones **6a** and **6b** using lithium hydride, phenyl dichlorophosphate and lithium chloride[19] (Eqn 7). Interestingly, when the analogous reaction was carried out with sodium iodide in the place of lithium chloride, in addition to the expected β-iodo analogs of **6a** and **6b**, 1,4-diiodobutane was also unexpectedly formed. This product

apparently resulted from the cleavage of tetrahydrofuran, which was used as the solvent for the reaction.



5

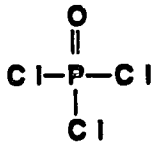
6a 6b

Eqn 7

This unexpected experimental observation can be extrapolated to other cyclic ethers. An investigation was subsequently carried out whereby a number of cyclic ethers varying in size and substitution pattern were treated with the combination of phenyl dichlorophosphate and sodium iodide. This reagent combination was found to cleanly convert these cyclic ethers to their diiodo compounds, regardless of the substitution pattern.[20] During these studies it was found that both phenyl dichlorophosphate and sodium iodide were essential for cleavage

of the tetrahydrofuran ring, whereas lithium hydride was not required. These findings confirmed the earlier observation, and suggested that phenyl dichlorophosphate was indeed acting as an activating agent for the C-O ether linkage. In this way it facilitated C-O replacement with a nucleophile, in this case iodide.

The reagent used for this transformation, phenyl dichlorophosphate, comes from a family of phosphorus reagents related to the well known phosphorus oxychloride (**7**). There are the dichlorophosphates; i.e. those where an alkoxy group has replaced only one of the chlorines, such as methyl dichlorophosphate (**8**), ethyl dichlorophosphate (**9**), and phenyl dichlorophosphate (**10**). Then there are the chlorophosphates, where two alkoxy groups replace two chlorines, such as dimethyl chlorophosphate (**11**), diethyl chlorophosphate (**12**), diphenyl chlorophosphate (**13**), and 1,2-phenylene phosphorochloridate (**14**). There are also compounds related to these esters of phosphoric acids by replacement of chloride by some other leaving group, such as bromide in diethyl bromophosphate (**15**), as cyanide in diethyl phosphorocyanidate (**16**), or as azide in diphenyl phosphoryl azide (**17**). These reagents have been used in many different capacities, such as phosphorylation,[21] halogenation of alcohols,[22] dehydration,[23] cyclization,[24] activation of



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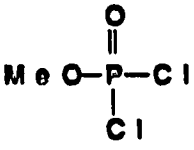

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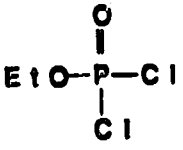

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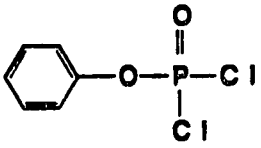

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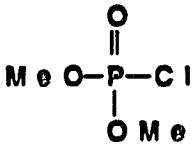

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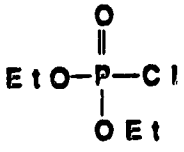

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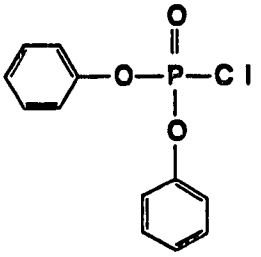

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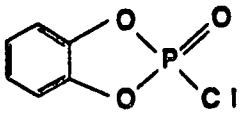

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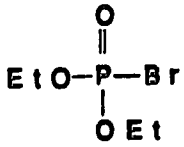

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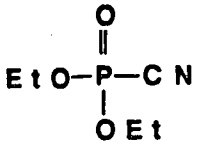

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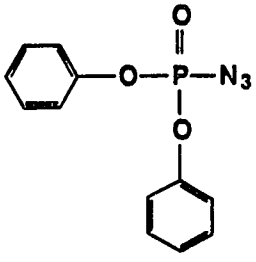
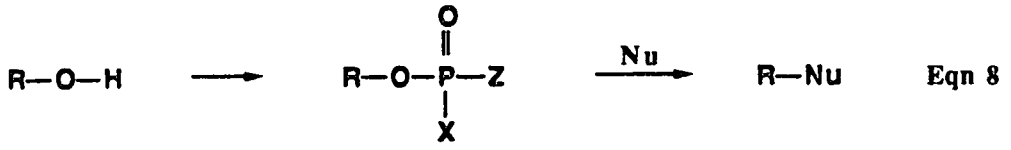


17

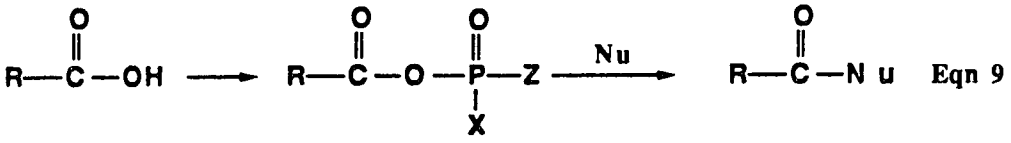
dimethyl sulfoxide in the Pfitzner-Moffatt oxidation,[25] deoxygenation,[26] cyanidation,[27] azidation,[28] and amidation.[29]

In general, these reagents do have a history of carbon-oxygen bond activation. They have been used to activate the carbon-oxygen bond of alcohols[22] and carboxylic acids towards replacement with a variety of nucleophiles (Eqn 8 and Eqn 9, respectively).



X = leaving group
Z = X or OR'

Eqn 8



Eqn 9

The latter function, with regard to acting as a coupling or activating agent for carboxylates has been the most exploited to date. In this capacity, carboxylic acids have been converted to esters,[30] thiol esters,[31] amides,[32] acyl azides,[33] and anhydrides.[30a,34] They have been similarly used in lactonization,[35] formation of β-lactams,[36] peptide bond formation,[37] carbon acylation of active methylene type compounds,[38] and preparation of amino acids.[39] The capacity of these reagents to activate C-O bonds can be further

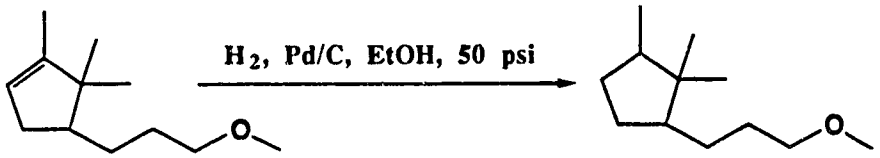
extended to include ethers; indeed the previous results involving cyclic ethers were very encouraging, and the further extension to include acyclic aliphatic ethers looks very promising.

The first part of this thesis describes an investigation of the application of the reagent combination of phenyl dichlorophosphate and sodium iodide towards acyclic aliphatic ethers, and a study examining the requirements and limitations of this reaction. This investigation resulted in the development of a general methodology whereby aliphatic ethers can be converted to aliphatic iodides.

Phenyl dichlorophosphate is the reagent of choice for this study because of success with initial studies,[20] superiority to some other reagents when applied in carboxylate activation and phosphorylation,[40] and the absence of complicating side reactions some other reagents would undoubtedly pose.[41]

Results and Discussion

A number of primary and secondary ethers, **18** to **26**, and a single tertiary ether **27** were used as substrates for the present study (Table 1). The methyl and ethyl ethers were prepared from the corresponding alcohol and methyl iodide or ethyl iodide respectively, according to the Williamson method,[42] using sodium hydride as the base (yields ranged from 58% to 80%). All of the alcohols were commercially available with the exception of those corresponding to ethers **23**, **24** and **27**. Ether **23** was prepared in 50% yield according to Eqn 10, and olefin **28** is available in a few steps from α-pinene oxide.[43] 6-Undecanol was prepared by standard sodium borohydride reduction[44] of 6-undecanone and 6-hydroxy-6-methyl-undecane was prepared by addition of methyl lithium to 6-undecanone (90%).[45]



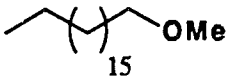
Eqn 10

28 23

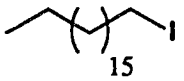
The isopropyl ether **19** was prepared in 80% yield by reacting the corresponding primary bromide (available in 80% yield from treatment of the primary alcohol with PBr_3[46]) with

sodium isopropoxide in isopropyl alcohol.[47] The isopropyl ether **22** was prepared in the same fashion, by treatment of the corresponding primary alcohol with PBr_3 to give the analogous bromide in 90% yield. The bromide was then treated with sodium isopropoxide to give the desired ether in 98% yield.

Initial studies for the transformation of ethers to alkyl halide compounds utilized the long chain ether 1-methoxyoctadecane (**18**) as the starting substrate. Treatment of this compound with phenyl dichlorophosphate (PDCP) (2 eq) and sodium iodide (3 eq) in benzene under refluxing conditions resulted in a very sluggish reaction: after 77 h, only a trace of a less polar product was detected by thin layer chromatography (tlc). In order to increase the reaction rate, the solvent was changed to toluene. By tlc monitoring, we observed that product formation began comparatively earlier, however the reaction was still quite sluggish, with no significant progression or change from 66 h to 85 h. By changing the solvent to xylenes, it was possible to obtain complete conversion of the starting material into product after 84 h, to give 1-iodooctadecane (**29**) in 96% yield.



18

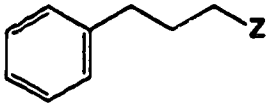


29

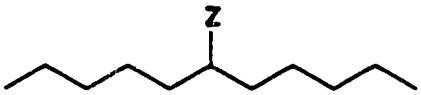
The ^1H nmr spectrum of the product showed a slight upfield shift of the most downfield methylene protons from δ 3.36 (in the starting material) to δ 3.20 (in the product). This change in chemical shift is consistent with the typical values reported for methylene hydrogens alpha to an oxygen (δ 3.40) and those alpha to an iodide (δ 3.15).[48] In addition, the singlet for the methoxy methyl group in the starting material was absent. In the infrared (ir) spectrum the absorption at 1160 cm^{-1} is within the range observed for the CH_2-I absorption (1200-1150 cm^{-1} region[49]). The mass spectrum of the compound was the most informative showing a molecular ion at m/z 380.1942, in agreement with the molecular formula $C_{18}H_{37}I$. Also found was the peak corresponding to loss of the iodine (alpha cleavage) at m/z 253.2893 ($C_{18}H_{37}$). As expected, the rest of the mass spectrum was dominated by the hydrocarbon pattern. The product had a melting point of 33-36°C, in agreement with the literature melting point value of 33-35°C for 1-iodooctadecane.[50]

With this positive result an additional primary methyl ether and a number of secondary methyl ethers were subjected to the same reaction conditions to test the generality of the transformation. The results are summarized in Table 1. The primary ether 1-methoxy-3-phenylpropane (**20**) gave 1-iodo-3-phenylpropane (**30**) in 70% yield in a comparatively short

reaction time of 6 h (Entry 3). Iodide **30** had a molecular ion at m/z 245.9905 in the mass spectrum, in agreement with the formula $C_9H_{11}I$. 6-Methoxyundecane (**24**) was converted into 6-iodoundecane (**31**) in only 35% yield, and required 13 h for the conversion (Entry 7). In the mass spectrum of 6-iodoundecane the molecular ion was observed at m/z 282.0834 in agreement with the formula $C_{11}H_{23}I$.



20 Z = OMe
30 Z = I



24 Z = OMe
31 Z = I

2-Methoxydecahydronaphthalene (**25**) required 4.5 h to be converted to 2-iododecahydronaphthalene (**32**) in 84% yield. The last secondary ether examined, 4-*tert*-butyl-1-methoxycyclohexane (**26**) was more troublesome. When a mixture of the *cis* and *trans* methyl ethers was treated with PDCP and sodium iodide in refluxing xylenes, after 6 h the starting material had been consumed, and a single nonpolar spot (R_f = 0.8 in petroleum ether) was observed by tlc. The ^1H nmr spectrum however indicated that several products had been formed. Four downfield signals were observed: those at δ 5.02 and 4.88 were multiplets, with similar shapes. The additional peaks observed at δ 4.17 and 4.10 were each a triplet of triplets. By ^1H nmr the ratio of the

peaks was found to be 1 : 1.25 : 1.75 : 1.75, respectively. It was determined that besides the formation of the desired alkyl iodides, the additional compounds being observed could be attibuted to the formation of the alkyl chorides. The source of the chloride undoubtedly had to be the PDCP reagent. This is particularly interesting since this was the only ether substrate which led to the formation of an alkyl choride. The peak at δ 5.02 was attributed to the *cis* iodide, and that at δ 4.88 was assigned as the *cis* chloride. The peaks at δ 4.17 and 4.10 were assigned to the *trans* iodide and *trans* chloride, respectively. Normally the trend of chemical shift of the α protons increases as the electronegativity of the attached atom increases. For example the methyl group in methyl chloride is further downfield than that in methyl iodide. This is true if the group is methyl or methylene, however a reversal occurs for methine protons. The α methine proton for an alkyl chloride is now further upfield relative to the corresponding iodide.[51] On the basis of the integration, it was determined that the *cis* and *trans* chloride had a combined isolated yield of 33%, and the *cis* and *trans* iodide had a combined yield of 20%. In this case none of the elimination product, **33c** was observed.

Table 1. Transformation of Ethers to Alkyl Iodides

$$R{-}O{-}R' \xrightarrow[\text{xylenes (A) or acetonitrile (B)}]{PhOPOCl_2,\ NaI} R{-}I$$

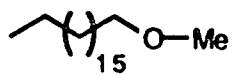
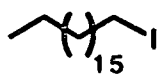
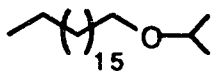
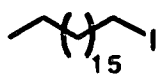
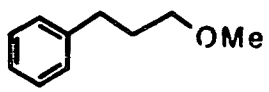
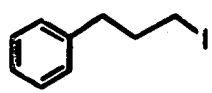
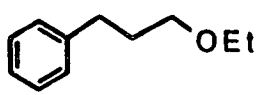
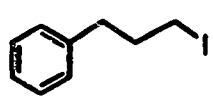
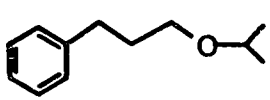
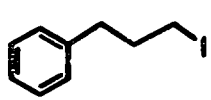
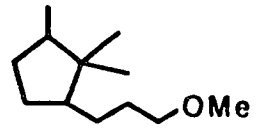
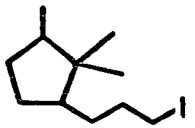
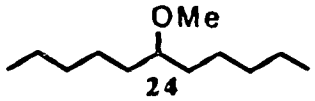
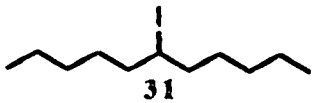
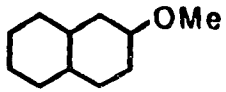
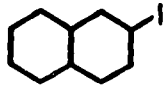
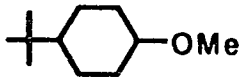
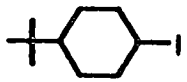
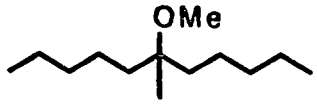
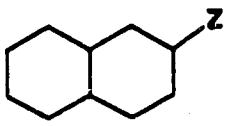
Entry	Ether	Solvent[a]	Time (h)	Product	% Yield
1	 **18**	A B	96 8	 **29**	96 97
2	 **19**	A	75	 **29**	90
3	 **20**	A B	6 2.5	 **30**	70 92
4	 **21**	A B	6.5 2.5	 **30**	60 77
5	 **22**	A B	8.5 5	 **30**	80 83

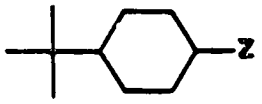
Table 1 (Continued)

Entry	Ether	Solvent[a]	Time (h)	Product	% Yield
6	 23	B	1	 34	85
7	 24	A B	13.5 0.75	 31	35 91
8	 25	A B	4.5 3	 32	84 85
9	 26	A[b] B[c,d]	6 34	 33b	20 18
10	 27	A	8.5	—	

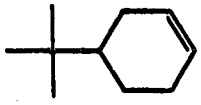
[a] Reactions were carried out at reflux temperature, using 2 eq of $PhOPOCl_2$ and 3 eq of NaI.
[b] Starting material was a mixture of cis and trans isomers.
[c] Starting material was only the trans isomer.
[d] Reaction was carried out at room temperature.



25 Z = OMe
32 Z = I

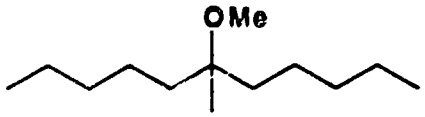


26 Z = OMe
33a Z = Cl
33b Z = I



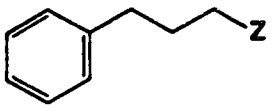
33c

Only one tertiary ether, 6-methoxy-6-methylundecane (**27**) was examined under these reaction conditions. Observations made while monitoring the reaction by tlc showed extensive decomposition and the formation of a complex mixture of products. Consequently studies with this substrate were abandoned.

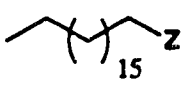


27

It was hoped that we could gain insight into the reaction by variation of the steric requirement of the ethers. Towards this end, we synthesized the ethyl and isopropyl ethers of 3-phenyl-1-propanol, compounds **21** and **22**.



21 Z = OEt
22 Z = O^{i}Pr



18 Z = OMe
19 Z = O^{i}Pr

As the steric requirement of the molecule was increased from the methyl to ethyl to isopropyl ethers (compounds **20** to **21** to **22**, respectively) the iodide was obtained in 70%, 60% and 80% yield, in 6 h, 6.5 h and 8.5 h (respectively) (Entries 3, 4 and 5). Unfortunately there was no clear correlation with steric environment since the yields obtained were variable, and the reaction times were comparable. For methyl and isopropyl ethers based on 1-octadecanol (compounds **18** and **19**, respectively), the corresponding iodide was obtained in 96% and 90% yield (respectively), in 84 h and 75 h (respectively) (Entries 1 and 2). Again the results here were comparable, both in terms of yield and reaction time.

With the successful conversion of various ethers into their iodides, it was demonstrated that the transformation was possible. However, aside from the ethers **18** and **19** based on 1-octadecanol which were converted to the products in very good yield (96% and 90%), most yields ranged from low (20% yield) to good (84% yield). Most reaction times were on the order of 5-14 h. However the ethers based on 1-octadecanol required prohibitively long reaction times: 96 h and 75 h (Entries 1 and 2). The predominant concern was the high temperature requirement (the boiling point of xylenes is 137-144°C) in order to obtain reasonable product formation. In general, in the development of a methodology, it is

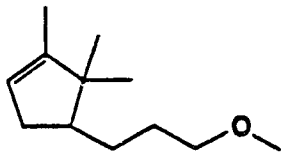
desirable to employ conditions which are as mild as possible. In this regard we hoped that a more polar solvent might better facilitate the reaction, and eliminate the need for high temperatures in order to effect the transformation. In addition, the solvent chosen must not react with the PDCP reagent. Upon first examination, acetonitrile seemed to meet most of our requirements, and this was the solvent we chose to study. Treatment of ether **20** under the same reaction conditions previously employed, however substituting acetonitrile for xylenes, led to the same product in only 2 h (Entry 3, solvent B = acetonitrile) as opposed to the 6 h previously required (Entry 3, solvent A = xylenes). In addition, the yield was increased from 70% to 92%. As a result of this improvement, the remainder of the substrates were also subjected to the same solvent change. In most cases the use of acetonitrile as the reaction solvent generally gave as good or better product yields, in addition to a reduction in reaction time. The most dramatic improvement in reaction time was observed for the conversion of 1-methoxyoctadecane to 1-iodooctadecane. In xylenes the time required was 96 h, whereas when acetonitrile was employed, the time required dropped significantly to only 8 h (Entry 1). The most significant improvement with regard to yield was observed in the conversion of 6-methoxyundecane to its corresponding iodide, in which the

yield was increased from 35% to 91%, an improvement of 56% (Entry 7).

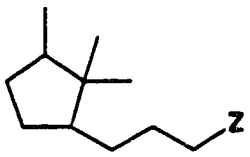
In examining the reaction of ether **26** with the use of acetonitrile as the solvent we decided to use only the *trans* isomer. This would reduce the number of products being formed in the reaction. When the *trans* ether **26** was treated with PDCP and sodium iodide in acetonitrile under refluxing conditions, predominantly elimination occurred. By conducting the same reaction at room temperature, the starting material was consumed within 34 h to give a single spot by tlc. By ^{1}H nmr three products had been formed with peaks at δ 5.70 (m), 5.02 (m) and 4.88 (m) in a ratio of 1.2 : 1 : 1.8. These signals were assigned to olefin (**33c**) the *cis* iodide (**33b**) and the *cis* chloride (**33a**), respectively. From the integration ratio, the yields of the products were determined to be 38% for the olefin, 16% for the alkyl iodide and 45% for the alkyl chloride. When the mixture was submitted for gas chromatography-mass spectrometry (GC-MS), five compounds were found: two alkyl chlorides, two alkyl iodides, and the elimination product. The molecular weights obtained were m/z 266 for the alkyl iodides, m/z 174 and 176 for the alkyl chlorides and the olefin at m/z 138. These are in agreement with the expected molecular weights. Upon reexamination of the ^{1}H nmr at increased receiver gain, small amounts of the additional two

compounds corresponding to the *trans* alkyl iodide (δ 4.17 (tt)) and *trans* alkyl chloride (δ 4.10 (tt)) were also observed.

We decided to try one additional ether which possessed another functionality besides the ether linkage. For this substrate we chose ether **28** which also possesses a double bond. Treatment of this compound under the same reaction conditions consistently led to a complex mixture of products. Due to these complications, we decided to remove the double bond by hydrogenation (Eqn 10). Treatment of the saturated ether **23** under the same conditions gave the corresponding iodide **34** in 85% yield within 1 h. Hence the double bond in this molecule was clearly the functionality that was being problematic. It was later determined that olefin **28** is labile under various reaction conditions, and is not an ideal substrate for this study. Further investigation of other ethers which also possess a double bond remains to be investigated.



28



23 Z = OMe
34 Z = I

Studies were done with regard to the specific requirements of the reaction in terms of ratios/quantities of reagents required,

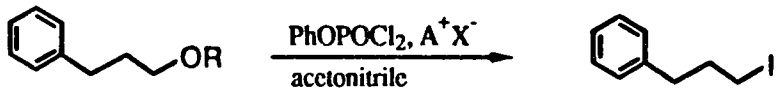
temperature requirements, and variation of the sources of iodide. The results are summarized in Table 2.

For substrates which may be thermally labile, refluxing conditions may not be desirable. It was found that it was possible to conduct these reactions at room temperature in acetonitrile, on the condition that an extended time period was provided, as exemplified in Table 2, Entry 1.

While sodium iodide was the iodide routinely used, lithium iodide was also found to be effective. Both sodium and lithium iodide gave comparable yields and reaction times (Entries 2 and 3). In contrast, potassium iodide (Entry 4) was considerably less effective, requiring a much longer reaction time (26 h), and having a yield inferior by 17%.

The use of a large excess (3 eq) of sodium iodide was found to be essential. Restriction of its quantity resulted in a significant decrease in product formation. When the quantity of iodide was reduced from 3 to 2 to 1 eq, there was a corresponding drop in yield from 92% to 54% to an incomplete reaction respectively, despite extended reaction periods (Entries 2, 6, and 7). Interestingly, when sodium iodide was replaced with sodium chloride, only starting material was recovered (Entry 9).

Table 2. Variation of reaction conditions in iodination reaction



Entry	R	$PhOPOCl_2$ (eq)	A^+X^-	A^+X^- (eq)	Additive	Temp (°C)	Time (h)	% Yield
1	Me	2	NaI	3	—	25	30	84
2	Me	2	NaI	3	—	82	2.5	92
3	Me	2	LiI	3	—	82	5.0	91
4	Me	2	KI	3	—	82	26	75
5	Me	1.1	NaI	3	—	82	1.3	80
6	Me	2	NaI	2	—	82	3.0	54
7	Me	2	NaI	1.1	—	82	16	incomplete
8	Me	2	NaI	3	CaH_2[a]	82	3.5	71
9	Me	2	NaCl[b]	3	—	82	51	—
10	H	2	NaI	3	—	82	3.5	92

[a] 1.1 eq of CaH_2 was added to the reaction mixture.
[b] In this case, only starting material was recovered.

There was not as dramatic an effect on yield when phenyl dichlorophosphate quantities were reduced. When the amount of PDCP was dropped from 2 eq to 1.1 eq, there was only a small (~10%) drop in yield (Entry 5).

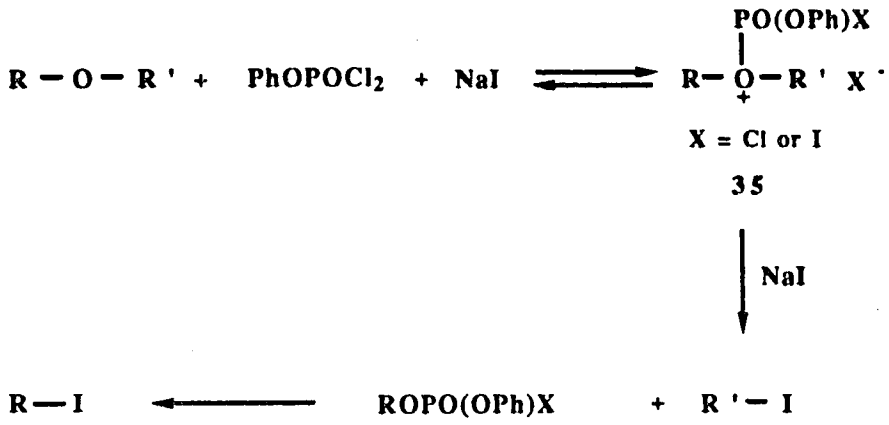
Hydriodic acid is known to cleave ethers to form alkyl iodides.[52] It was a concern at one point, that if there were traces of water present in the reaction mixture that it would be possible to form small amounts of hydriodic acid from the combination of PDCP and NaI, and that it was in fact HI that was catalyzing the reaction, rather than the reagent. This possibility was ruled out by the observation that when CaH_2 was added to the reaction mixture (Entry 8), neither the product yield nor the reaction rate was substantially affected.

The reaction is found to be equally applicable for the direct conversion of alcohols to alkyl iodides: 3-phenyl-1-propanol was converted to 1-iodo-3-phenylpropane in 92% yield, in 3.5 h, as shown by Entry 10.

Mechanistically, it is likely that the reaction proceeds in a similar fashion to the reagents discussed in the introduction, via an oxonium ion, such as **35**. A possible reaction pathway is

outlined in Scheme 3, and it should be pointed out that the exact nature of the phosphorus reagent is not known at this time.

Scheme 3



It is known however that NaI is crucial to the success of the reaction, and the mixture of the combination of PDCP and NaI is observed to result in the formation of some new species, perhaps one such as $PhOPOX_2$ (X = Cl and/or I), and it is likely that this is the true activating agent.

The results just presented can be extrapolated further to include the use of nucleophiles besides iodide. In this respect a limited investigation has been conducted: experiments have been carried out in conjunction with sodium azide in one case and sodium cyanide in another case. The alkyl azide and the alkyl cyanide were formed for each respective reaction, resulting in a

one pot conversion. However this work is not of prime synthetic interest and further work was not continued.

Experimental

General

Melting points were recorded on a Köfler hot stage apparatus and are uncorrected. Combustion elemental analysis were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra were recorded on a Nicolet 7199 spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-400 or Bruker AM-400 spectrometer. Tetramethylsilane (TMS) was used as an internal reference. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet and br = broad. High resolution electron impact mass spectra (hrms) were recorded using A.E.I. model MS-50 mass spectrometers. Chemical ionization mass spectra (cims) were obtained using an A.E.I. MS-12 mass spectrometer, using ammonia as the reagent gas. Data are reported as m/z values. Gas chromatography-mass spectrometry (GC-MS) [Varian Vista 6000 GC oven, DB-5 column - VG-70E, MS-12] was used employing helium as the carrier gas. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 10% ethyl acetate in petroleum ether means 10 parts ethyl acetate by volume to 90 parts petroleum ether by volume.

Materials

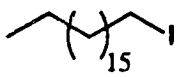
All reactions were carried out under a positive pressure of an inert gas. Anhydrous reaction solvents were distilled under argon before use from the appropriate drying agents. Benzene, toluene, and xylenes used for reactions were freshly distilled from lithium aluminum hydride. Acetonitrile was distilled from calcium hydride. Commercial phenyl dichlorophosphate (Aldrich Chemical Company) was used without further purification unless the material was colored, then it was distilled under reduced pressure. Reactions requiring anhydrous conditions were performed in flame or oven-dried glassware, assembled and allowed to cool while being purged with an inert gas. The term *in vacuo* refers to solvent removal *via* Buchi rotoevaporator at water aspirator pressure.

Nitrogen or argon was passed through a purification train of Fieser's solution,[53] concentrated sulfuric acid and potassium hydroxide pellets. Alternatively it was passed through a column of 4 A molecular sieves, with self indicating silica gel (coarse grained) as the indicator.

Flash chromatography developed by Still[54a] was used routinely for purification and separation of product mixtures using silica gel of 230-400 mesh. Dry column flash chromatography[54b] was conducted according to the procedure of Hardwood on silica gel of 200-450 mesh. Analytical thin layer chromatography (tlc) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt).

Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For tlc the visualization of the chromatograms was completed by dipping with an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%, w/v) in sulfuric acid (3%, v/v), followed by careful charring on a hot plate. Alternatively an ethanol solution of vanillin (5%, w/v) with sulfuric acid (5%, v/v) was used as the dipping solution, followed by hot plate charring.

1-Iodooctadecane (29)



A- Using xylenes as the solvent

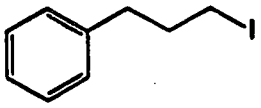
To a solution of 1-methoxyoctadecane (111 mg, 0.39 mmol) and sodium iodide (175 mg, 1.17 mmol, 3.0 eq) in dry xylenes (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (164 mg, 0.78 mmol, 2.0 eq) in xylenes (1 mL). The whole apparatus was then wrapped in aluminum foil to protect it from light. The mixture was heated to reflux with stirring for 96 h, cooled to room temperature, and the xylenes were removed under reduced pressure. The crude product was then subjected to flash chromatography on silica gel. Elution with petroleum ether gave 1-iodooctadecane (143 mg, 96% yield) as a

white solid: mp 33-36°C, literature mp: 33-35°C[50]; ir ($CHCl_3$ cast) 1160 cm^{-1} (CH_2I); ^1H nmr (200 MHz, $CDCl_3$) δ 3.20 (t, 2H, J = 7.5 Hz, $-CH_2CH_2I$), 1.80 (br quintet, 2H, J = 7.5 Hz, $CH_3(CH_2)_{15}CH_2CH_2I$), 1.28 (br s, 30H, $CH_3(CH_2)_{15}CH_2I$) and 0.89 (virtual t, 3H, J = 7.5 Hz, $CH_3(CH_2)_{16}CH_2I$); hrms M^+ 380.1942 (calcd. for $C_{18}H_{37}I$: 380.1942). Also found: $[M-I]^+$ 253.2893 (calcd. for $C_{18}H_{37}$: 253.2897). Anal. calcd. for $C_{18}H_{37}I$: C 56.84, H 9.80, I 33.36; found: C 56.68, H 9.64, I 33.35.

B- Using acetonitrile as the solvent

To a solution of 1-methoxyoctadecane (100 mg, 0.35 mmol) and sodium iodide (159 mg, 1.06 mmol, 3.0 eq) in dry acetonitrile (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (147 mg, 0.70 mmol, 2.0 eq) in acetonitrile (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 8 h, cooled to room temperature, and then subjected to silica gel dry column flash chromatography using petroleum ether as the eluting solvent. Concentration *in vacuo* followed by flash chromatography, eluting with petroleum ether gave 1-iodooctadecane (130 mg, 97% yield).

1-Iodo-3-phenylpropane (30)



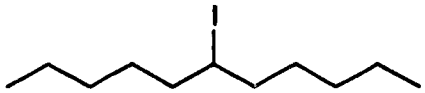
A- Using xylenes as the solvent

To a solution of 1-methoxy-3-phenylpropane (99 mg, 0.66 mmol) and sodium iodide (300 mg, 2.0 mmol, 3.0 eq) in dry xylenes (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (282 mg, 1.34 mmol, 2.0 eq) in xylenes (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 6 h, cooled to room temperature, and the xylenes were removed under reduced pressure. The crude product was subjected to flash chromatography using petroleum ether as the eluting solvent to give 1-iodo-3-phenylpropane (114 mg, 70% yield) as a pale yellow liquid: ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.25 (m, 5H, aromatic hydrogens), 3.16 (t, 2H, J = 7.5 Hz, $Ph(CH_2)_2C\mathbf{H}_2I$), 2.70 (t, 2H, J = 7.5 Hz, $PhC\mathbf{H}_2(CH_2)_2I$) and 2.08 (quintet, 2H, J = 7.5 Hz, $PhCH_2C\mathbf{H}_2CH_2I$); hrms M^+ 245.9905 (calcd. for $C_9H_{11}I$: 245.9906). Also found: $[M-I]^+$ 119.0860 (calcd. for C_9H_{11}: 119.0861) and $[M-CH_2CH_2I]^+$ 91.0548 (calcd. for C_7H_7: 91.0548). Anal. calcd. for $C_9H_{11}I$: C 43.93, H 4.51, I 51.57; found: C 43.87, H 4.45, I 51.70.

B- Using acetonitrile as the solvent

To a solution of 1-methoxy-3-phenylpropane (106 mg, 0.71 mmol) and sodium iodide (317 mg, 2.11 mmol, 3.0 eq) in dry acetonitrile (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (293 mg, 1.39 mmol, 2.0 eq) in acetonitrile (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 2.5 h, cooled to room temperature, and then subjected to dry column flash chromatography using petroleum ether as eluent. Concentration *in vacuo* gave the crude product which was further subjected to flash chromatography. Elution with petroleum ether gave 1-iodo-3-phenylpropane (158 mg, 92% yield).

6-Iodoundecane (31)



A- Using xylenes as the solvent

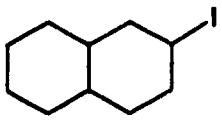
To a solution of 6-methoxyundecane (102 mg, 0.55 mmol) and sodium iodide (250 mg, 1.67 mmol, 3.0 eq) in dry xylenes (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (230 mg, 1.09 mmol, 2.0 eq) in xylenes

(1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 13.5 h, cooled to room temperature, and the xylenes were removed under reduced pressure. The crude product was then subjected to dry column flash chromatography. Elution with petroleum ether gave 6-iodoundecane (74 mg, 35% yield) as a pale yellow liquid: ^{1}H nmr (200 MHz, $CDCl_3$) δ 4.15 (m, 1H, -$(CH_2)_4$C**H**I$(CH_2)_4$-), 1.20-1.95 (complex m, 16H, -$(CH_2)_4$CHI$(CH_2)_4$-) and 0.90 (virtual t, 6H, J = 7.5 Hz, 2 × C**H**$_3$-); hrms M^+ 282.0836 (calcd. for $C_{11}H_{23}I$: 282.0844). Also found: $[M-I]^+$ 155.1799 (calcd. for $C_{11}H_{23}$: 155.1801). Anal. calcd. for $C_{11}H_{23}I$: C 46.82, H 8.22 I 44.97; found: C 46.87, H 8.07, I 45.17.

B- Using acetonitrile as the solvent

To a solution of 6-methoxyundecane (115 mg, 0.62 mmol) and sodium iodide (277 mg, 1.85 mmol, 3.0 eq) in dry acetonitrile (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (260 mg, 1.23 mmol, 2.0 eq) in acetonitrile (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 0.75 h, cooled to room temperature, and then subjected to dry column flash chromatography using petroleum ether as the eluting solvent. Concentration *in vacuo* gave 6-iodoundecane (159 mg, 91% yield) as a yellow liquid.

2-Iododecahydronaphthalene (32)



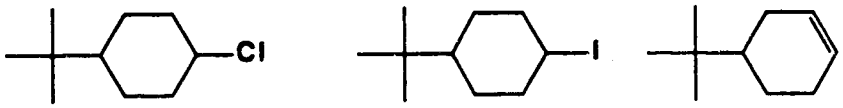
A- Using xylenes as the solvent

To a solution of 2-methoxydecahydronaphthalene (104 mg, 0.62 mmol) and sodium iodide (280 mg, 1.87 mmol, 3.0 eq) in dry xylenes (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (261 mg, 1.24 mmol, 2.0 eq) in xylenes (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 4.5 h, cooled to room temperature, and the xylenes were removed under reduced pressure. The crude product was then subjected to dry column flash chromatography. Elution with petroleum ether gave 2-iododecahydronaphthalene (136 mg, 84% yield) as a pale yellow liquid: ^{1}H nmr (200 MHz, $CDCl_3$) δ 4.94, 4.66, 4.20 (1:3:5), (each m, combined 1H, -CH_2C**H**ICH_2-) and 1.00-2.28 (br m, 16H); hrms M^+ 264.0376 (calcd. for $C_{10}H_{17}I$: 264.0376). Also found: $[M-I]^+$ 137.1329 (calcd. for $C_{10}H_{17}$: 137.1330). Anal. calcd. for $C_{10}H_{17}I$: C 45.47, H 6.49, I 48.04; found: C 45.75, H 6.45, I 48.13.

B- Using acetonitrile as the solvent

To a solution of 2-methoxydecahydronaphthalene (103 mg, 0.61 mmol) and sodium iodide (277 mg, 1.85 mmol, 3.0 eq) in dry acetonitrile (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (257 mg, 1.22 mmol, 2.0 eq) in acetonitrile (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 3 h, cooled to room temperature, and then subjected to dry column flash chromatography using petroleum ether as the eluting solvent. Concentration *in vacuo* gave 2-iododecahydronaphthalene (139 mg, 85% yield) as a yellow liquid.

4-*tert*-Butyl-1-chlorocyclohexane (33a), 4-*tert*-butyl-1-iodocyclohexane (33b) and 4-*tert*-butylcyclohex-1-ene (33c),



33a 33b 33c

A- Using xylenes as the solvent

To a solution of 4-*tert*-butyl-1-methoxycyclohexane (104 mg, 0.61 mmol) (as a mixture of *cis* and *trans* isomers) and sodium iodide (275 mg, 1.83 mmol, 3.0 eq) in dry xylenes (1 mL) under an

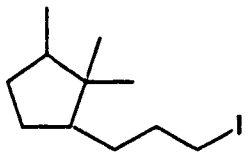
atmosphere of argon, was added a solution of phenyl dichlorophosphate (270 mg, 1.28 mmol, 2.1 eq) in xylenes (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 6 h, cooled to room temperature, and the xylenes were removed under reduced pressure. The crude product was then subjected to dry column flash chromatography. Elution with petroleum ether followed by concentration *in vacuo* gave the product which was further subjected to Kugelrohr distillation (0.05 mm Hg, 50°C) to give a mixture of compounds *cis*-**33a**, *trans*-**33a**, *cis*-**33b** and *trans*-**33b** (67.35 mg) in a ratio of 1.25 : 1.75 : 1 : 1.75, respectively (by nmr). This translates into yields of 33% for both the *cis* and *trans* alkyl chloride, and 20% for the *cis* and *trans* alkyl iodide. ^{1}H nmr (200 MHz, $CDCl_3$) [only the most downfield signals are reported] δ 5.02 (m), 4.88 (m), 4.17 (tt, $J_t = 4$, $J_t' = 12$ Hz) and 4.10 (tt, $J_t = 4$, $J_t' = 12$ Hz) (1.25 : 1.75 : 1 : 1.75), (-CH_2C**H**ICH_2-).

B- Using acetonitrile as the solvent

To a solution of *trans*-4-*tert*-butyl-1-methoxycyclohexane (313 mg, 1.84 mmol) and sodium iodide (842 mg, 5.61 mmol, 3.0 eq) in dry acetonitrile (3 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (777 mg, 3.68 mmol, 2.0 eq) in acetonitrile (3 mL). The whole apparatus was then wrapped in aluminum foil, and the reaction was stirred at room temperature for 34 h. The mixture was then subjected to dry column flash chromatography, eluting with petroleum ether.

Concentration *in vacuo* gave a mixture of *cis*-**33a**, *cis*-**33b** and **33c** (319 mg) (1.8 : 1 : 1 : 1.2) This translates into a yield of 45% for *cis*-**33a**, 16% for *cis*-**33b** and 38% for **33c**. ^{1}H nmr (200 MHz, $CDCl_3$) [only the most downfield peaks are reported] δ 5.70 (m, 2H, -**H**C=C**H**-), 5.02 (m, 1H, -CH_2C**H**ICH_2-) and 4.88 (tt, 1H, J_t = 4, J_t' = 12 Hz, -CH_2C**H**ICH_2-), respectively. GC-MS (DB-5) showed five compounds with molecular ions at m/z 138, 174 and 176, 174 and 176, 266 and 266.

2-(3-Iodopropyl)-1,1,5-trimethylcyclopentane (34)



To a solution of ether **23** (71 mg, 0.39 mmol) and sodium iodide (173 mg, 1.15 mmol, 3.0 eq) in dry acetonitrile (1 mL) under an atmosphere of argon, was added a solution of phenyl dichlorophosphate (163 mg, 0.77 mmol, 2.0 eq) in acetonitrile (1 mL). The whole apparatus was then wrapped in aluminum foil. The mixture was heated to reflux with stirring for 1 h, cooled to room temperature, and then subjected to dry column flash chromatography using petroleum ether as the eluting solvent. Concentration *in vacuo* gave iodide **34** (93 mg, 85% yield) as a pale pink liquid: ^{1}H nmr (200 MHz, $CDCl_3$) δ 3.24 and 3.22 (each t,

each 1H, each J = 7 Hz, -C**H**$_2$I), 1.05-2.00 (br m, 10H), 0.90 (s, 3H, -C**H**$_3$), 0.85 (d, 3H, J = 7 Hz, -CHC**H**$_3$) and 0.55 (s, 3H, -C**H**$_3$); hrms M^+ 280.0691 (calcd. for $C_{11}H_{21}I$: 280.0689). Also found $[M-I]^+$ 153.1647 (calcd. for $C_{11}H_{21}$: 153.1644). Anal. calcd. for $C_{11}H_{21}I$: C 47.15, H 7.55, I 45.29; found: C 47.40, H 7.39, I 45.68.

CHAPTER II

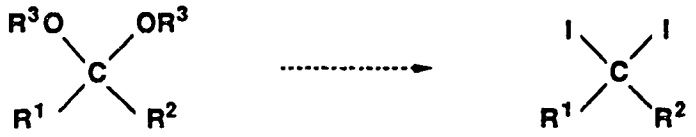
CLEAVAGE OF THIOACETALS

Introduction

With the successful application of PDCP and sodium iodide to cleave the normally inert carbon-oxygen bond of ethers as demonstrated by the direct conversion of alkyl ethers to alkyl iodides (Eqn 11), the capability of this reagent combination to cleave the carbon-oxygen bond of other compounds became the next concern.

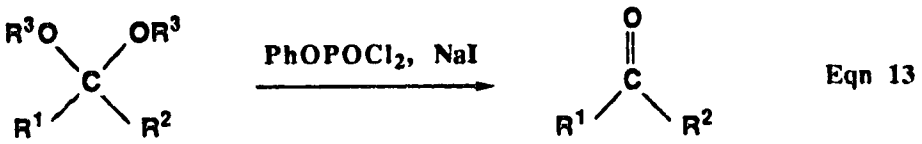
$$R-O-R' \xrightarrow{PhOPOCl_2,\ NaI} R-I + R'-I \qquad \text{Eqn 11}$$

Indeed, since a carbon with one ether linkage resulted in the formation of the mono iodo compound, then by analogy related compounds in which a carbon bears two ether linkages such as acetals, should in principle form the diiodo compound, as illustrated in Eqn 12.



Eqn 12

Experimentally, Liu and Yu[55] found that by treatment of acetals with PDCP and sodium iodide in refluxing acetonitrile,* rather than the diiodo compounds, the products formed were the corresponding carbonyl compounds. The reaction was found to be general, resulting always in deprotection of the acetal (Eqn 13).



Eqn 13

Standard conditions to effect this transformation involves the use of aqueous hydrolysis under acid catalysis. In some cases these conditions may prove to be problematic, particularly for those substrates which cannot withstand acidic conditions. This new reaction in contrast, is carried out under unusually mild and nearly neutral conditions, and thus constitutes a particularly important and novel alternative method to effect deacetalization. There are relatively few methods which circumvent the use of strong acids or aqueous conditions.[56]

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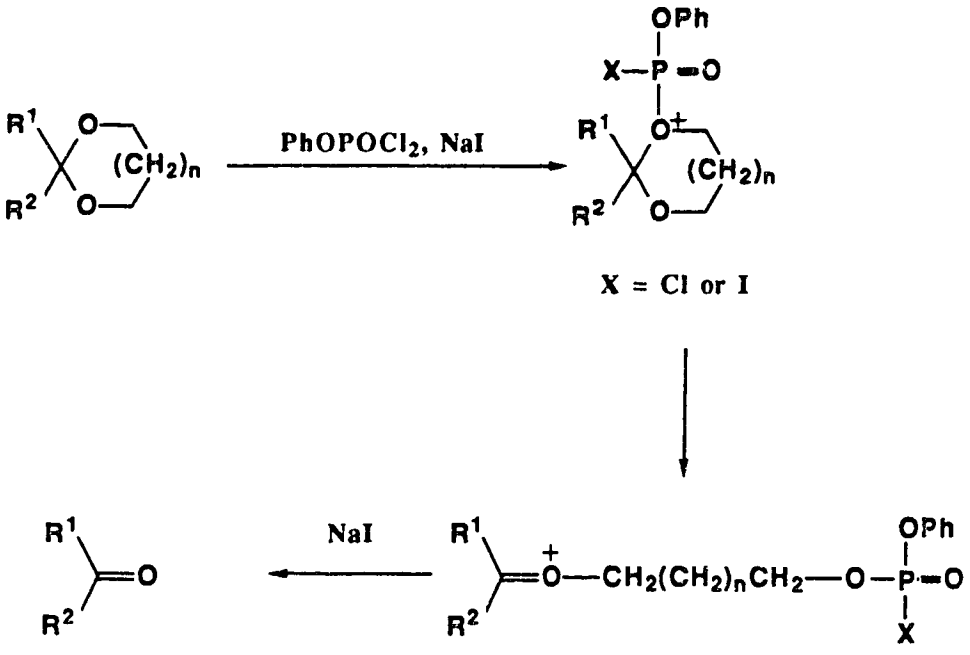
* Originally, benzene was used as the solvent in this study. It was later found however, that acetonitrile served as a better solvent by dramatically decreasing the reaction time required to effect the transformation.

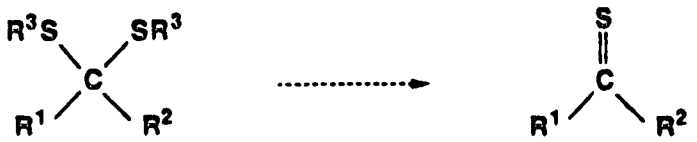
The mechanism which was forwarded to account for the deprotection is proposed to proceed *via* the pathway outlined in Scheme 4. "PDCP" activation of the acetal oxygen, in a manner similar to that suggested for the ether oxygen activation (Scheme 3), is followed by cleavage of first one carbon-oxygen bond. Subsequent cleavage of the second carbon-oxygen bond releases the carbonyl group.

Scheme 4



Based on this mechanism, it seemed that the heteroatom present in the final product was the same as the heteroatom originally involved in the acetal functionality. Then perhaps

substitution of the oxygen atoms in the acetal functionality with sulfur atoms, would in principle yield a product also possessing a sulfur atom. In other words, treatment of thioacetals could possibly lead to the formation of thiones (Eqn 14).



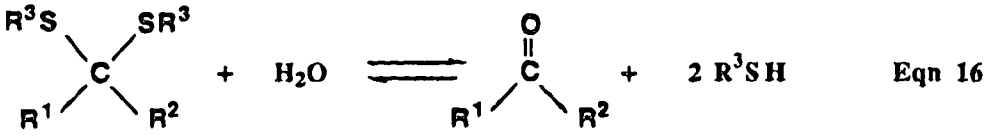
Eqn 14

However, during the course of these studies exploring the feasibility of such a transformation, a new method was discovered whereby thioacetals could be converted to their parent carbonyl compounds (Eqn 15), that is, effecting dethioacetalization.

Eqn 15

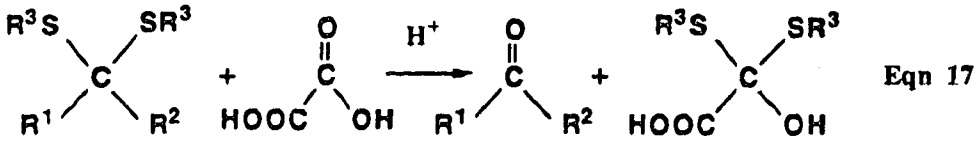
Currently there are a large number of dethioacetalization procedures available in the literature.[57,58] Hydrolytic dethioacetalization (Eqn 16) is an equilibrium reaction. The irreversible removal of either the thiol or the carbonyl compound can be used to push this equilibrium to the right. Normally the irreversible removal of the thiol compound is the most commonly employed method to facilitate this reaction, and this has been accomplished in a number of different ways. The thiol may be removed by transacetalization to a highly reactive carbonyl

derivative, by the formation of a transition metal thiolate, by oxidation to a higher oxidation state of sulfur, or by alkylation to a sulfide. Volatile low molecular weight thiols can be removed by taking advantage of their volatility. In accordance, the methods employed for dethioacetalization can be grouped into four categories: transacetalization, transition metal induced hydrolysis, oxidative hydrolysis and alkylative hydrolysis.



Eqn 16

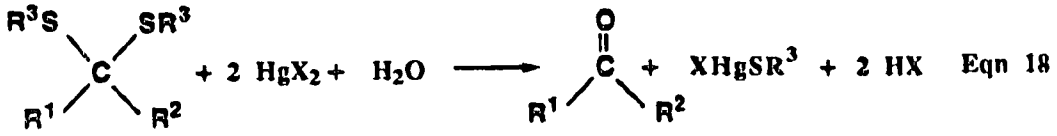
In the transacetalization method, the mercaptan unit is transferred irreversibly to the highly reactive carbonyl group of glyoxylic acid (Eqn 17).



Eqn 17

Transition metal-induced hydrolysis utilize salts involving metals such as titanium, copper, silver, cadmium and mercury. Among these the mercury (II) salts (as the perchlorate, chloride, or oxide) have been the most widely used in spite of their toxicity. As indicated in Eqn 18, another consideration is the fact that acid is released during the reaction; consequently basic additives must be included to maintain neutrality. Other metals with less

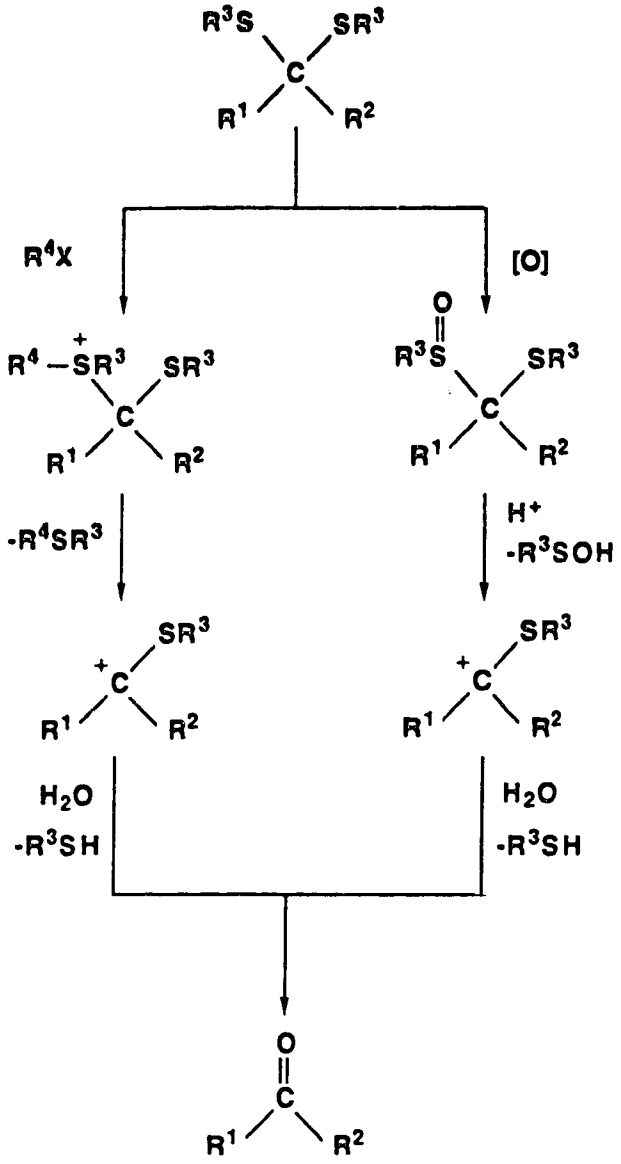
poisonous properties than mercury have been used: such as silver(I) (as the nitrate, perchlorate or oxide), titanium(IV) chloride and copper(II) chloride.



Both the oxidative and alkylative methods of hydrolysis function on the same principle. First the sulfur moiety in the acetal is rendered a better leaving group, and second, the thiol is removed irreversibly by converting it to some other sulfur derivative (Scheme 5).

Oxidative methods rely on the oxidation of sulfur to a higher oxidation state, followed by hydrolysis of the S-oxide under mildly acidic conditions to give the disulfide and the carbonyl compound. Those reagents which utilize this mode of cleavage, i.e., oxidation of sulfide to sulfoxide, include chlorine, bromine, iodine, t-butyl hypochlorite, N-chloro- and N-bromosuccinimide, benzoyl peroxide, chloramine-T, hydrogen peroxide, mesitylsulfonyl-hydroxylamine, oxygen, sodium periodate, thallium (III) trifluoroacetate, thallium (III) nitrate, lead (IV) acetate, and cerium (IV) ammonium nitrate.

Scheme 5


R3S
SR3
C
R1
R2
R4X
[O]
R4 —SR3
SR3
C
R1
R2
O
R3S
SR3
C
R1
R2
-R4SR3
H+
-R3SOH
SR3
C
R1
R2
SR3
C
R1
R2
H2O
-R3SH
H2O
-R3SH
O
C
R1
R2

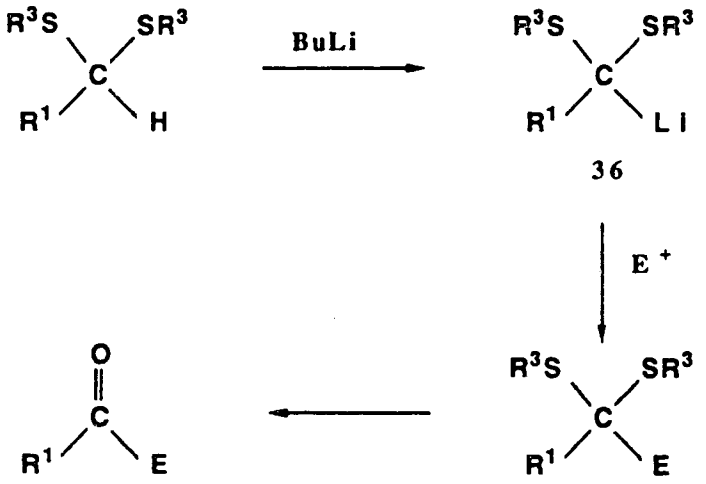
In the alkylative hydrolysis method, a better leaving group is formed by alkylation to the sulfonium salt, followed by hydrolysis to yield the carbonyl compound and a sulfide. Typical reagents employed in alkylative hydrolysis include methyl iodide, methyl fluorosulfonate (magic methyl), trimethyl- or triethyloxonium tetrafluoroborate (Meerwein's reagent), bromo dimethylsulfonium bromide, pyridinium bromide perbromide, sulfuryl chloride, nitrosyl sulfate, nitronium tetrafluoroborate, and isoamyl nitrite. Acylative acetal hydrolysis has also been reported using acetyl chloride, acetic anhydride or trifluoroacetic anhydride.

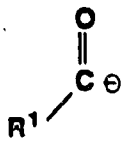
In spite of this extensive list of reagents and methods which have been developed to effect dethioacetalization, the thioacetal is still used to a somewhat limited extent as a carbonyl protecting group. The excellent yields and the ease with which the thioacetal can be rapidly prepared,[59] in conjunction with its tolerance under a wider range of reaction conditions renders the thioacetal functionality a particularly promising protecting group when compared to the acetal group. Equally attractive is its high stability: thermally, towards bases and acids alike, and towards chromatographic purification. These features allow the thioacetal functionality to be carried easily through multistep operations. However, in spite of these apparent advantages, applications of the thioacetal group in a protection-deprotection scheme have been somewhat hampered by the problems associated with its

deprotection, and consequently has not achieved the same widespread use that is common to the acetal group.

With regard to the utility of the thioacetal functionality, it should also be pointed out that this functional group has emerged as an excellent acyl carbanion equivalent, as aptly demonstrated by Seebach,[57] and outlined in Scheme 6. Thioacetals derived from aldehydes can be converted to their lithio derivatives by treatment with *n*-butyllithium, followed by reaction with an electrophile and then hydrolysis of the thioacetal to the carbonyl compound, resulting in carbon-carbon bond formation. Importantly, the lithiated thioacetal **36** can be viewed as the synthetic equivalent for synthon **37**.

Scheme 6





37

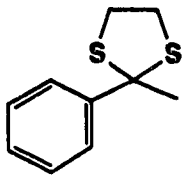
Keeping in mind the utility of the thioacetal as an acyl carbanion equivalent, as well as a carbonyl protecting group, it is indeed desirable to develop methods for deprotection which are simple, high yielding, and yet safe.

In this chapter of the thesis the results for a new dethioacetalization procedure using phenyl dichlorophosphate will be described.

Results and Discussion

The thioacetals employed in this study were a number of 1,3-dithiolane compounds prepared from the corresponding carbonyl compounds in the standard manner with 1,2-ethanedithiol and boron trifluoride etherate in dichloromethane.[59] The carbonyl compounds were commercially available with the exception of dihydroisophorone (**46**) and 4-cyclohexylcyclohexanone (**45**). Dihydroisophorone was obtained in 81% yield by reduction of isophorone using hydrogen and 5% Pd/C in ethyl acetate. 4-Cyclohexylcyclohexanone was obtained in 88% yield from a mixture of *cis* and *trans* isomers of 4-cyclohexylcyclohexan-1-ol.

The first compound examined, 2-methyl-2-phenyl-1,3-dithiolane (**38**) was subjected to PDCP (2 eq) and sodium iodide (3 eq) in acetonitrile at room temperature, in a manner similar to that utilized in the deacetalization reaction. It was found that even after an extended reaction time of 44 h, the starting material remained intact. When the reaction temperature was increased to reflux temperature, a complex mixture was formed as observed by tlc.

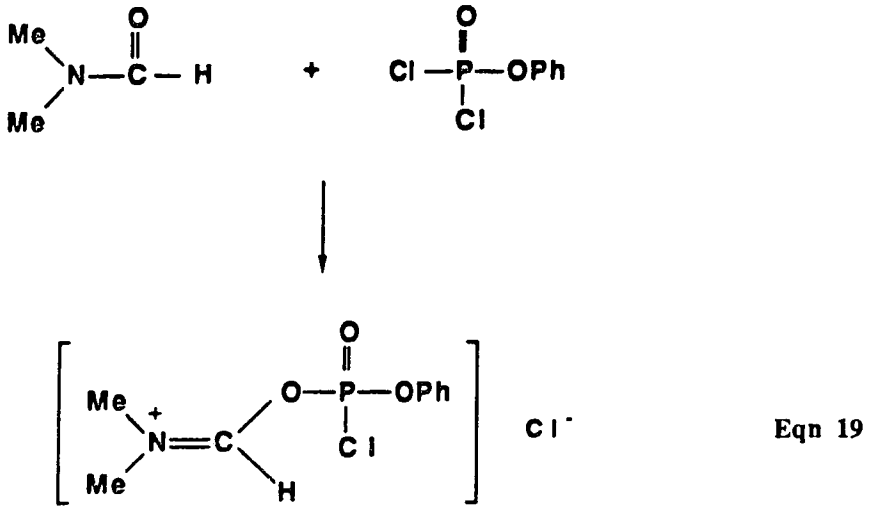


38

These results thus posed a problem with respect to the reactivity balance of the reagent. At room temperature the reagent was not reactive enough leaving the starting substrate unaffected, whereas reacting at reflux temperature led to a complex mixture of products, implying undesired side reactions were taking place. Consequently we searched a way of increasing the reactivity of the reagent enough to cause a reaction preferably at or below room temperature, but not at the expense of complicating side reactions.

Upon examining the literature, some reports were found with regard to activated forms of both phenyl dichlorophosphate and diphenyl phosphorochloridate. The earliest reports came from Cramer and Winter,[60] in which they described the formation of a yellow precipitate when PDCP was mixed with N,N-dimethylformamide (DMF) in an inert solvent (note that both PDCP and DMF are clear and colorless liquids). It was further found that the "complex" was stable enough to be kept for extended periods of time provided anhydrous conditions were maintained. A yellow complex was similarly formed in the case of diphenyl phosphorochloridate. With phosphorus oxychloride

however, they reported having some difficulty in getting such a complex. The structure of the complex formed from the reaction of PDCP and DMF was depicted as **39**, in Eqn 19.



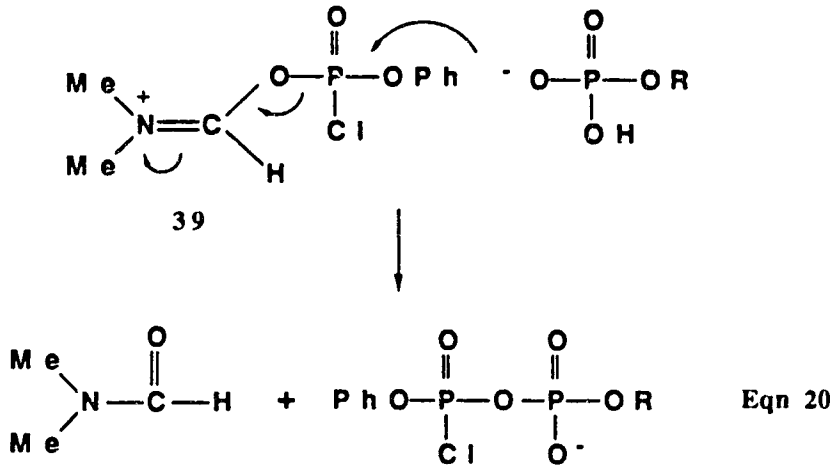
Eqn 19

39

The belief that the reaction of these chlorophosphates with DMF results in the formation of a more "activated" phosphorus reagent is substantiated by several observations. The "new" reagent displays particularly enhanced reactivity in two regards: hydrolysis and ester formation. In terms of hydrolysis, it is known that the reaction of these phosphorochloridates with water is relatively slow. However when the complex with DMF is formed first, hydrolysis is extremely rapid resulting in an almost explosive reaction with water. Ester formation from carboxylic acids and alcohols with these phosphorochloridates can occur in the absence of DMF, however high temperatures are required and

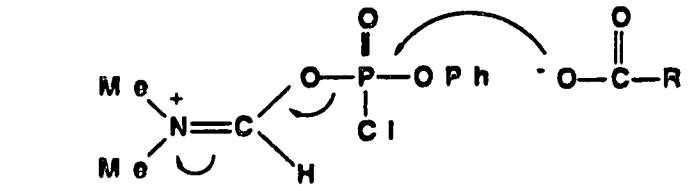
yields are usually low. In contrast, by carrying out the same reaction with the addition of DMF, these esters are usually formed at 0°C, in many cases quantitatively and within a few minutes.

Cramer and Winter reported the use of this complex in two types of reactions. The first involves the reaction of **39** with phosphates to form pyrophosphates (Eqn 20), and the second involves the reaction of **39** with carboxylic acids to result in the formation of a more active carboxylate **40** (Eqn 21).



39

Eqn 20



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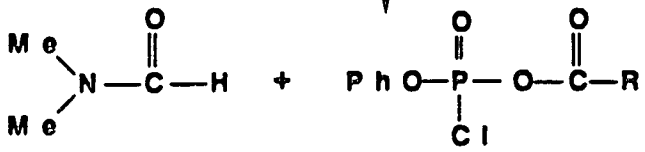
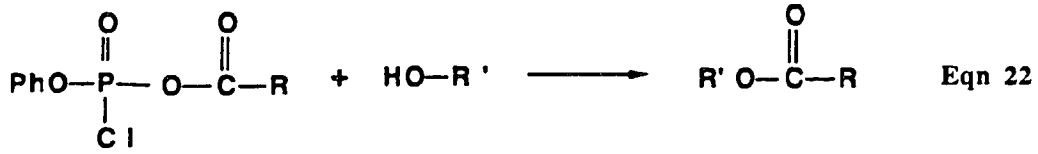


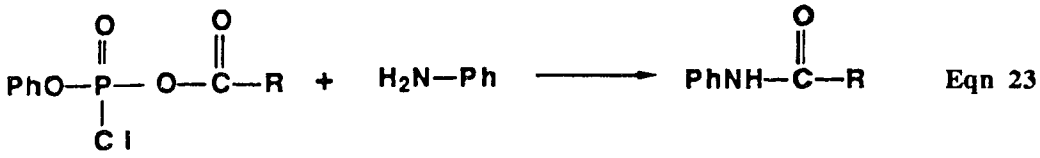
40

Eqn 21

The mixed anhydride **40** was used in subsequent reactions with alcohols or amines to form esters (Eqn 22) or amides (Eqn 23), respectively. Peptide bond formation has been effected in a similar manner.



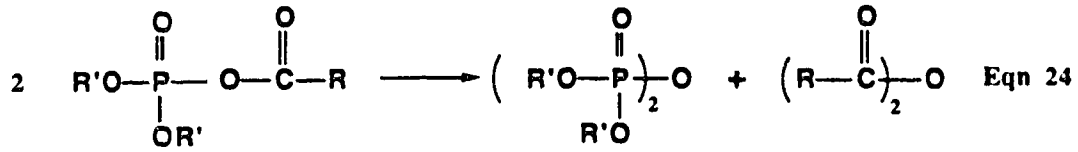
Eqn 22



Eqn 23

Since these reports, the use of these phosphorus reagents in conjuction with DMF had basically remained stagnant, until this area was revived some 20 years later in 1982 by Palomo and his group in Spain. Liu *et al.* had reported the preparation of esters

from carboxylic acids and alcohols by the use of PDCP and a tertiary organic base.[30b] Palomo and coworkers[61] reported that when they used the conditions reported by Liu, in one case rather than getting the desired ester, they got disproportionation products. Interestingly, disproportionation of the mixed anhydride# derived from a related phosphorus reagent has also been reported independently by Masamune[62] in accord with Eqn 24.

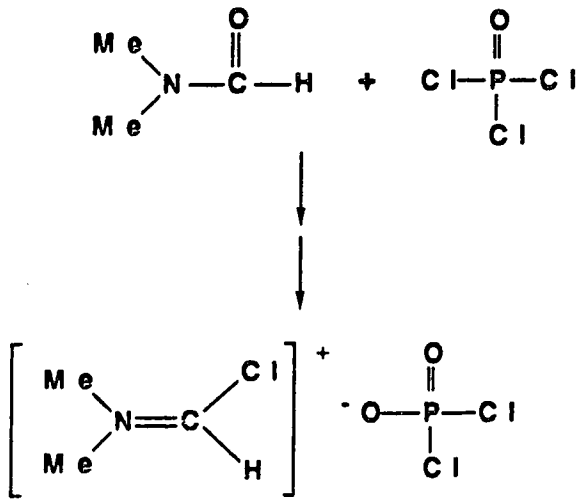


Eqn 24

Palomo solved this problem by adding DMF to the reaction to form the PDCP-DMF complex first. The carboxylic acid was then added, followed by the alcohol, and finally the base to yield the desired compound in good yield. With the success of this complex with regard to the optimization of ester formation, they subsequently applied the complex as a coupling agent in other reactions involving carboxylic acids. It has been used in β-lactam formation,[63] anhydride,[64] and thiol ester formation.[64]

This intermediate mixed anhydride was rather labile to both heat and base, and was prone to disproportionation.

As illustrated by the cases above, complex **39** has been used primarily in the area of carboxylate activation. This complex however is not so novel, since it is closely related to the well established Vilsmeier-Haack reagent: complex **41** derived from phosphorus oxychloride and DMF (Eqn 25).



Eqn 25

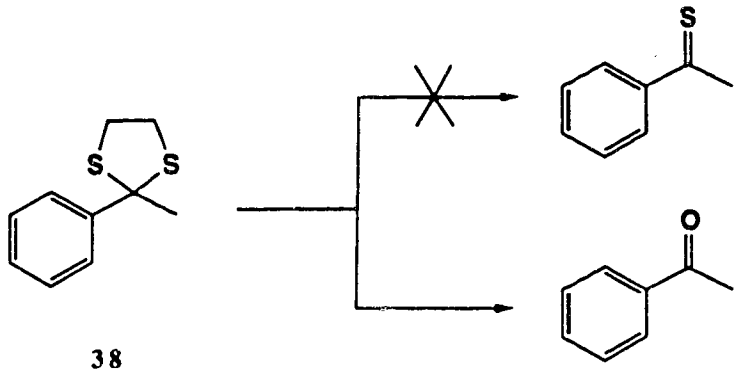
41

The Vilsmeier-Haack reagent, first reported in 1927,[65] has been extensively used primarily for formylation of aromatic compounds, but it has also been applied to olefins[66] and acetylenes,[67] as well as being applied in other contexts.[68]

In the hopes that this activated form of phenyl dichlorophosphate had the enhanced reactivity we required, we applied this complex to the same substrate we had first examined. 2-Methyl-2-phenyl-1,3-dithiolane (**38**) was treated with PDCP

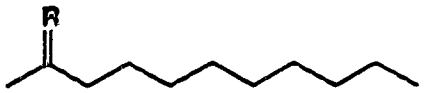
(1.1 eq), DMF (1.1 eq), and sodium iodide (4.4 eq). The mixture was stirred at room temperature for 2 h, at which point all the starting material was consumed. To our delight, a single product was formed, which upon isolation was found by tlc, ir, nmr, and ms to be identical to acetophenone (**42**). Interestingly then, the reaction did not result in thione formation, but rather dethioacetalization (Scheme 7).

Scheme 7



38 42

With this success in hand we attempted the reaction on another substrate, namely 2-methyl-2-nonyl-1,3-dithiolane (**43**). Treatment of this compound with PDCP, DMF and sodium iodide in acetonitrile gave 2-undecanone (**44**) in 94% yield (Table 3, Entry 1).



43 R = -SCH_2CH_2S-

44 R = O

Treatment of a number of thioacetals in the same manner gave the deprotected carbonyl compounds in good yields. These results are summarized in Table 3. 4-Cyclohexylcyclohexanone (**45**) was obtained from its thioacetal in 77% yield (Entry 2), dihydroisophorone (**46**) was recovered in 90% yield from its thioacetal (Entry 3). Treatment of 2,2-diphenyl-1,3-dithiolane in the same manner gave benzophenone (**47**) in 92% yield (Entry 5). 1-Indanone (**48**), isophorone (**49**), and cinnamaldehyde (**50**) were recovered from their respective thioacetals in 76%, 73% and 73% yield, respectively (Entries 6, 7, and 8 respectively).

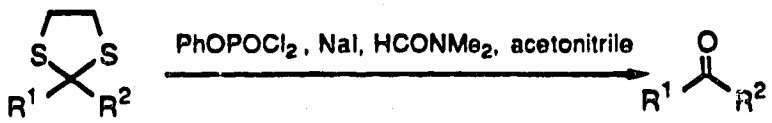
The reaction was found to be generally applicable to a range of substrates such as cyclohexyl thioacetals (Entries 2, 3, and 7), cyclopentyl substrates (Entry 6), as well as aliphatic acyclic cases (Entries 1 and 8). Furthermore the reaction was successful for aromatic substrates (Entries 4-6). Allylic cases such as Entries 7 and 8 were found to give the desired conjugated carbonyl functionality. Notably, the reaction could also be applied to recover the aldehyde carbonyl (Entry 8) without complications.

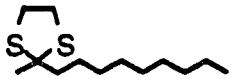
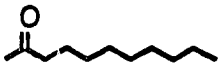
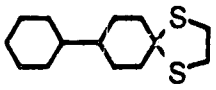
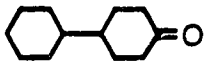
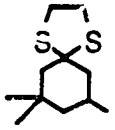
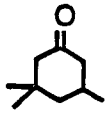
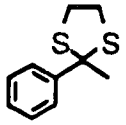
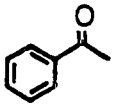
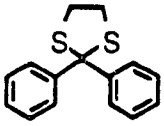
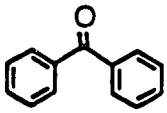
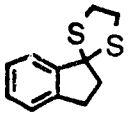
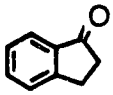
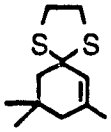
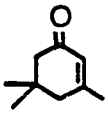
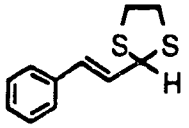
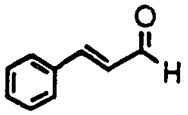
Reaction times were generally short, ranging from 1-17 h. The yields obtained were all satisfactory, being very high in some cases (Entries 1, 3 and 5). In some cases (Entries 2, 4, 6, 7, and 8) the product yield was not excellent, however all the reactions were very clean by tlc: the reaction always proceeded to give the desired compound as the only detectable product. Although reasonable precautions were taken, the small amount of material loss may be occurring during the work up procedure.

A number of reactions were carried out to examine the limitations of this new method. In order to see whether sodium iodide was really essential to carry out the transformation, 2-methyl-2-nonyl-1,3-dithiolane (**43**) was treated with PDCP and DMF in acetonitrile, in the absence of sodium iodide. The reaction was found to be extremely slow: within 28 h there was a trace of the carbonyl compound as detected by tlc, however despite an extended reaction time of 70 h, the reaction did not advance any further.

The applicability of the Vilsmeier-Haack-type reagent was examined by conducting the same reaction as previously described with DMF and sodium iodide, but with substitution of phosphorus oxychloride for PDCP. In this case phosphorus oxychloride was also effective, albeit somewhat inferior in terms of yield. The importance of including sodium iodide was again confirmed when

Table 3. Transformation of thioacetals to carbonyl compounds



Entry	Thioacetal	Time (h)	Product	% Yield
1	 **43**	1	 **44**	94
2		17	 **45**	77
3		2	 **46**	90
4	 **38**	1	 **42**	71
5		10	 **47**	92
6		2	 **48**	76
7		2	 **49**	73
8		2	 **50**	73

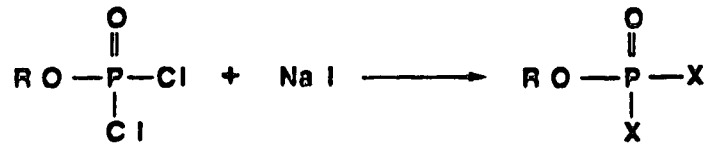
the reaction was carried out with just phosphorus oxychloride and DMF. Here again the reaction was found to be extremely sluggish: only traces of product were detected after 24 h.

In addition, as emphasized by the earliest studies, DMF is crucial to effect this transformation since the reaction does not occur in its absence.

A number of observations are noteworthy with regard to the complex formation. In our hands, in accordance with the literature, a yellow preciptate was formed when PDCP and DMF were mixed, and this preciptate was readily hydrolyzed upon exposure to air. Furthermore it was observed that by mixing PDCP (a clear and colorless liquid) and sodium iodide (a white granular solid) in acetonitrile at room temperature, a new pale yellow precipitate was formed within a few minutes. Addition of DMF to this mixture resulted, within five minutes, in the formation of a different precipitate which was darker yellow in color (compound **51**), and a more viscous suspension. Preforming the complex in this manner for the reaction, rather than arbitrarily mixing the reagents generally resulted in an optimization of yields and reaction times.

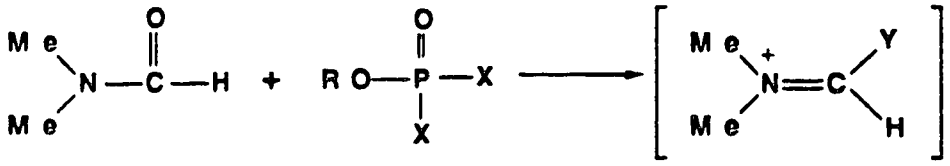
In terms of the details of the reaction, because of the observations made upon mixing of the reagents, sodium iodide and

PDCP must combine to form a new reagent in which either only one or both of the chlorines have been replaced (Eqn 26). This new compound must then react with DMF to perhaps form a compound such as **51** (Eqn 27).



Eqn 26

X = Cl or I



Eqn 27

Y = Cl or I or OP(O)Cl(OR) or OP(O)I(OR)

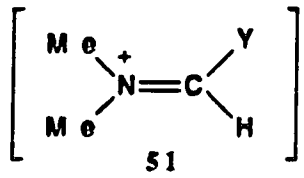
51

The exact mechanism of the reaction is yet to be determined, however it is likely that an intermediate such as **51**, similar to the Vilsmeier-Haack reagent serves as the activating agent. What is very clear however, is that PDCP, sodium iodide and DMF are all necessary to efficiently promote the transformation.

Outlined in Scheme 8 is a possible pathway by which the starting material could be converted to the product. Attack of one

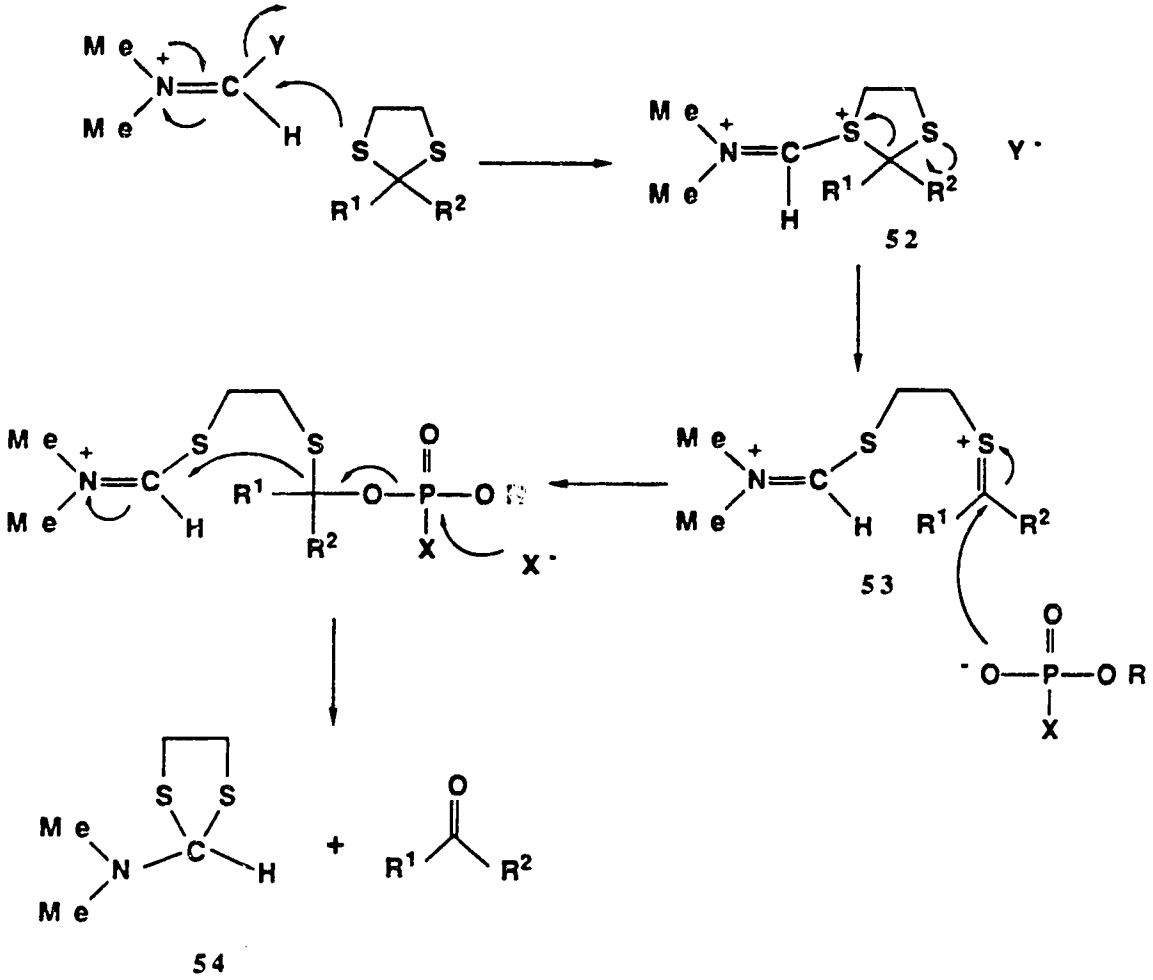
of the sulfur atoms of the thioacetal on complex **51**, substituting for the ligand Y yields the sulfonium salt **52**. Cleavage of one of the sulfur-carbon bonds of the acetal yields the new sulfonium salt **53**. Attack by some oxygenated species, such as a phosphorus reagent forms the first requisite carbon-oxygen bond, followed by attack of some nucleophile on the central phosphorus atom, results in formation of the double bond between the carbon and the oxygen, while cleaving the final carbon-sulfur bond, and neutralizing the postive charge on the nitrogen. Interestingly, besides the unprotected carbonyl compound, this pathway would also form the thioacetal of DMF, compound **54**. Although a byproduct such as **54** has never been detected by tlc or isolated, in one reaction a compound **55** was isolated. This could be related to compound **54**, by the pathway formulated in Scheme 9, and would be subjected to the conditions used while working up the reaction.

Scheme 8



51

Y = Cl or I or OP(O)Cl(OR) or OP(O)I(OR)



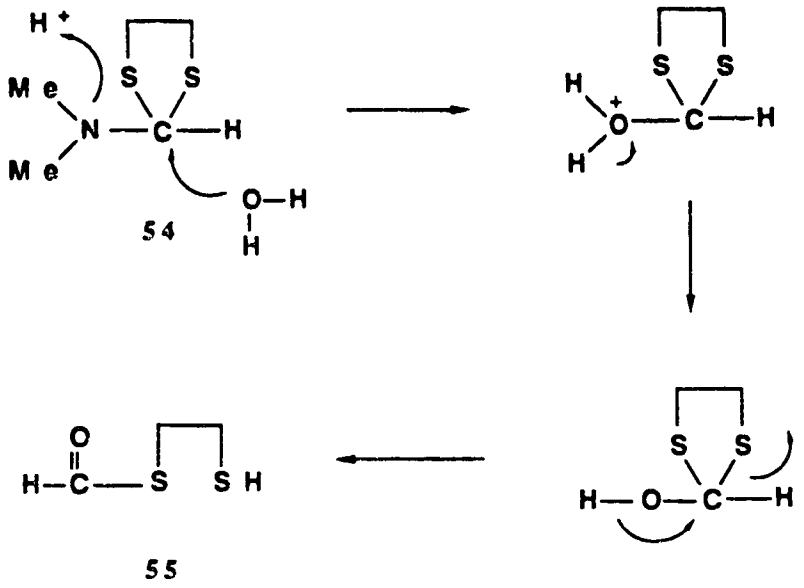
52

53

54

If this is indeed the operative mechanism, then overall the reaction seems to involve a transthioacetalization: that is transfer of the thioacetal group from the dithioacetal compound to DMF.

Scheme 9



Besides the obvious synthetic applications resulting from the ether cleavage and the dethioacetalization projects previously described, there are implications which extend beyond the simple transformations they represent. The first point involves the use of sodium iodide as a simple, facile way with which to activate certain reagents by halogen exchange, and the second involves the use of the combination of sodium iodide and DMF for reagent activation.

Enhanced reactivity by halogen exchange with sodium iodide has been reported although only to a limited extent. Besides the phosphorochloridates previously mentioned, it has also been used in the formation of acyl iodides from acyl chlorides,* and the generation of the trimethylsilyl iodide reagent from trimethylsilyl chloride.[69] The combined use of boron tribromide with sodium iodide and 15-crown-5 has been found to be superior to boron tribromide alone for the cleavage of the ether linkage.[16c] Titanium tetrachloride has been used in combination with lithium iodide in the conversion of acetals to carbonyl compounds. The addition of lithium iodide resulted in an improvement in the reaction rate.[56f]

DMF has a long history of reagent activation, which has been effectively applied. Besides the phosporochloridate reagents, it has been utilized with other related reagents such as phosporus pentachloride,[70] thionyl chloride,[71] phosgene,[72] and oxalyl chloride.[73] In most of these reactions addition of DMF has led to various improvements such as a more facile reaction, better yields, or a reduction in temperature requirements. Although these latter

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* In contrast to the acyl chlorides, these acyl iodides are active enough to cleave ethers in the absence of Lewis acids (see reference 11).

reagents have not been used in conjunction with sodium iodide, this is another area of activation which has yet to be explored.

In most of the cases mentioned above, either sodium iodide or DMF have been used for reagent activation. Extension one step further is the use of sodium iodide and DMF together for activation. As illustrated by the dethioacetalization methodology just described, a collaborative effort between DMF and sodium iodide could have a synergistic effect, resulting in an enhanced reactivity greater than that capable by each individual compound. With further study, this area of activation may prove to be useful in the future .

As a result of the work just described, the capability of the phenyl dichlorophosphate reagent has been extended from deacetalization as reported by Liu and Yu,[55] to include the dethioacetalization. This is particularly interesting in light of the fact that the trimethylsilyl iodide reagent which has also been used in deacetalization, could not be extended further to effect dethioacetalization.[74]

Thus a new, facile, and direct procedure has been developed to effect dethioacetalization under mild, and virtually neutral conditions. This method is a non-toxic alternative to popular methods such as those involving methyl iodide or mercury salts.

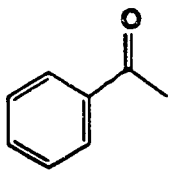
Another very important advantage is that this is the only other method besides beneneseleninic anhydride[58b] which obviates the need for aqueous conditions in order to effect dethioacetalization.

Experimental

Remarks

Dimethylformamide was stored over magnesium sulfate and syringed out as required. For other general remarks and details about materials see Part I of this thesis.

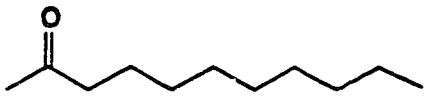
Acetophenone (42)



To a mixture of 2-methyl-2-phenyl-1,3-dithiolane (619 mg, 3.16 mmol) and sodium iodide (2.09 g, 13.9 mmol, 4.4 eq) in acetonitrile (10 mL) was added PDCP (0.52 mL, 3.48 mmol, 1.1 eq), followed by DMF (0.27 mL, 3.49 mmol, 1.1 eq) after a few minutes. The apparatus was wrapped in aluminum foil to protect the reaction from light, and allowed to stir for 1 h at room temperature under an atmosphere of argon. The reaction mixture was concentrated and partitioned between hexanes and water. The hexanes layer was washed successively with 10% aqueous

sodium thiosulfate solution (2 × 15 mL) and water (2 × 15 mL). The hexanes extracts were dried over magnesium sulfate and then filtered. The hexanes were removed by distillation at atmospheric pressure using a 10 cm Vigreux column, and the residual solvent was removed *in vacuo*. The crude product was subjected to Kugelrohr distillation (0.5 mm Hg, 50°C) to give acetophenone (270 mg, 71% yield) as a clear colorless oil: ir (CH_2Cl_2 cast) 1687 cm^{-1} (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 7.94 (m, 2H, C-2H and C-6H) and 7.50 (m, 3H, C-3H, C-4H, and C-5H) and 2.53 (s, 3H, -C(O)C**H**$_3$); hrms M^+ 120.0576 (calcd. for C_8H_8O: 120.0575).

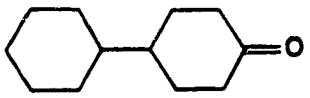
2-Undecanone (44)



To 2-methyl-2-nonyl-1,3-dithiolane (232 mg, 0.94 mmol) and sodium iodide (630 mg, 4.20 mmol, 4.5 eq) in dry acetonitrile (3 mL) under an atmosphere of argon, was added PDCP (0.16 mL, 1.07 mmol, 1.1 eq). After a few minutes DMF (0.08 mL, 1.03 mmol, 1.1 eq) was added. The apparatus was then wrapped in aluminum foil and allowed to stir at room temperature for 1 h. The reaction mixture was then concentrated and subjected to

flash chromatography. Elution with 20% diethyl ether in petroleum ether gave 2-undecanone (151 mg, 94% yield) as a yellow oil: ir ($CHCl_3$ cast) 1719 cm^{-1} (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 2.38 (t, 1H, J = 7.5 Hz, $CH_3C(O)CH_2CH_2$-), 2.09 (s, 3H, $CH_3C(O)CH_2CH_2$-), 1.51 (m, 2H, $CH_3C(O)CH_2CH_2CH_2$-), 1.22 (s, 12H, -$CH_2(CH_2)_6CH_3$) and 0.83 (t, 3H, J = 7.5 Hz, -CH_2CH_3); hrms M^+ 170.1670 (calcd. for $C_{11}H_{20}O$: 170.1672).

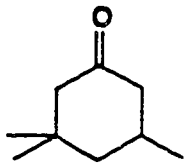
4-Cyclohexylcyclohexanone (45)



To a mixture of 4-cyclohexyl-1,1-ethylenedithiocyclohexane (197 mg, 0.77 mmol) and sodium iodide (460 mg, 3.07 mmol, 4.0 eq) in dry acetonitrile (5 mL), under an atmosphere of argon, was added PDCP (0.12 mL, 0.80 mmol, 1.0 eq), followed by the addition of DMF (0.06 mL, 0.76 mmol, 1.0 eq) after a few minutes. The apparatus was wrapped in aluminum foil, and allowed to stir at room temperature for 17 h. The reaction mixture was concentrated and partitioned between hexanes and water. The hexanes layer was washed successively with 10% aqueous sodium

thiosulfate solution (2 × 10 mL) and water (2 × 10 mL). The hexanes extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography using 5% ethyl acetate in petroleum ether as the eluent to give 4-cyclohexylcyclohexanone (107 mg, 77% yield) as an oil: ir (CH_2Cl_2 cast) 1718 cm^{-1} (C=O); ^1H nmr (400 MHz, $CDCl_3$) δ 2.33 (m, 4H, -C**H**$_2$C(O)C**H**$_2$-), 2.02 (m, 2H), 1.60-1.80 (m, 5H), 1.47 (m, 3H), 1.20 (m, 3H), 1.13 (dt, 1H, J_d = 19, J_t = 3 Hz) and 1.00 (m, 2H); hrms M^+ 180.1512 (calcd. for $C_{12}H_{20}O$: 180.1515).

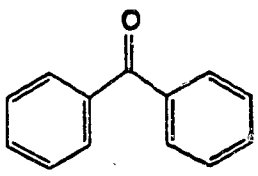
Dihydroisophorone (46)



To a mixture of 3,3,5-trimethyl-1,1-ethylenedithiocyclohexane (279 mg, 1.29 mmol) and sodium iodide (850 mg, 5.67 mmol, 4.4 eq) in dry acetonitrile (4 mL), under an atmosphere of argon, was added first PDCP (0.21 mL, 1.41 mmol, 1.1 eq), followed by DMF (0.11 mL, 1.42 mmol, 1.1 eq) after a few minutes. The apparatus was wrapped in aluminum foil, and allowed to stir at room temperature for 2 h. The reaction mixture was concentrated and partitioned between hexanes and water.

The hexanes layer was washed successively with 10% aqueous sodium thiosulfate solution (2 × 10 mL) and water (2 × 10 mL). The hexanes extracts were dried over magnesium sulfate and then filtered. The hexanes were removed by distillation at atmospheric pressure using a 10 cm Vigreux column, and the residual solvent was removed *in vacuo*. The crude product was subjected to Kugelrohr distillation (0.5 mm Hg, 50°C) to give dihydroisophorone (163 mg, 90% yield) as a clear colorless oil: ir (CH_2Cl_2 cast) 1711 cm^{-1} (C=O); ^1H nmr (400 MHz, $CDCl_3$) δ 2.30 (d quintet, 1H, J_d = 13, $J_{quintet}$ = 2 Hz, C-6Hβ), 2.13 (d, 1H, J = 13 Hz, C-2Hα), 2.01 (dt, 1H, J_d = 13, J_t = 2Hz, C-2Hβ), 1.96 (m, 1H, C-5H), 1.83 (t, J = 13 Hz, C-6Hα), 1.55 (d quintet, 1H, J_d = 13, $J_{quintet}$ = 2 Hz, C-4Hβ), 1.26 (t, 1H, J = 13 Hz, C-4Hα), 1.02 (s, 3H, -CH_3), 0.95 (d, 3H, J = 6.5 Hz, -CHCH_3) and 0.83 (s, 3H, -CH_3); hrms M^+ 140.1199 (calcd. for $C_9H_{16}O$: 140.1202).

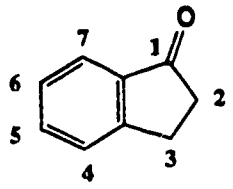
Benzophenone (47)



To a mixture of 2,2-diphenyl-1,3-dithiolane (107 mg, 0.42 mmol) and sodium iodide (250 mg, 1.67 mmol, 4.1 eq) in

acetonitrile (2 mL) was added PDCP (0.13 mL, 0.87 mmol, 2.1 eq), followed by DMF (0.07 mL, 0.90 mmol, 2.2 eq) after a few minutes. The apparatus was wrapped in aluminum foil and allowed to stir for 10 h at room temperature under an atmosphere of argon. The reaction mixture was then concentrated, and the crude product was subjected to flash chromatography using 5% ethyl acetate in hexanes as the eluent to give benzophenone (270 mg, 92% yield) as a pale yellow solid: mp 46-48°C; ir (CH_2Cl_2 cast) 1660 cm^{-1} (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 7.82 (m, 4H, C-2H and C-6H) and 7.50 (m, 6H, C-3H, C-4H, C-5H); hrms M^+ 182.0729 (calcd. for $C_{13}H_{10}O$: 182.0732).

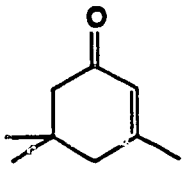
1-Indanone (48)



To a mixture of 1,1-ethylenedithioindane (132 mg, 0.63 mmol) and sodium iodide (390 mg, 2.60 mmol, 4.1 eq) in acetonitrile (2 mL) was added PDCP (0.10 mL, 0.67 mmol, 1.1 eq), followed by DMF (0.06 mL, 0.78 mmol, 1.2 eq) after a few minutes. The apparatus was wrapped in aluminum foil and allowed

to stir for 2 h at room temperature under an atmosphere of argon. The reaction mixture was concentrated, and partitioned between hexanes and water. The hexanes layer was washed successively with 10% aqueous sodium thiosulfate solution (2 × 10 mL) and water (2 × 10 mL). The hexanes extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was subjected to flash chromatography using 10% ethyl acetate in hexanes as the eluent. This afforded 1-indanone (64 mg, 76% yield) as a yellow oil: ir (CH_2Cl_2 cast) 1711 cm^{-1} (C=O); ^1H nmr (400 MHz, $CDCl_3$) δ 7.75 (br d, 1H, J = 7.5 Hz, C-7H), 7.58 (dt, 1H, J_d = 1.5, J_t = 7.5 Hz, C-5H), 7.47 (dt, 1H, J_d = 7.5, J_t = 1 Hz, C-4H), 7.37 (dt, 1H, J_d = 1, J_t = 7.5 Hz, C-6H), 3.15 (m, 2H, -C(O)C**H**$_2$CH$_2$-) and 2.70 (m, 2H, -C(O)CH$_2$C**H**$_2$-); hrms M^+ 132.0575 (calcd. for C_9H_8O: 132.0575).

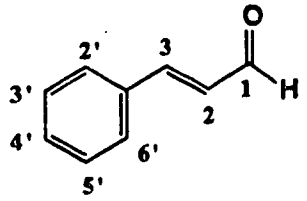
Isophorone (49)



To a mixture of 1,5,5-trimethyl-3,3-ethylenedithiocyclohexene (218 mg, 1.02 mmol) and sodium iodide (675 mg, 4.50 mmol, 4.4 eq) in acetonitrile (4 mL) was added

PDCP (0.17 mL, 1.14 mmol, 1.1 eq), followed by DMF (0.09 mL, 1.16 mmol, 1.1 eq) after a few minutes. The apparatus was wrapped in foil and allowed to stir for 2 h at room temperature under an atmosphere of argon. The reaction mixture was subjected to dry column flash chromatography using 20% ethyl acetate in hexanes as the eluent. The solvent was distilled at atmospheric pressure using a 10 cm Vigreux column, and the residual solvent was removed *in vacuo*. The crude product was subjected to Kugelrohr distillation (1 mm Hg, 50°C) to give isophorone (101 mg, 73% yield) as a pale yellow liquid: ir (CH_2Cl_2 cast) 1669 cm^{-1} (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 5.85 (br s, 1H, -C(O)C**H**=C(CH_3)CH_2-), 2.20 (s, 2H, -C**H**$_2$C(O)-), 2.15 (s, 2H, -C(O)HC=C(CH_3)C**H**$_2$-), 1.90 (s, 3H, -C(O)HC=C(C**H**$_3$)CH_2-) and 1.00 (s, 6H, -C(C**H**$_3$)$_2$); hrms M^+ 138.1034 (calcd. for $C_9H_{14}O$: 138.1045).

Cinnamaldehyde (50)



To a mixture of 3,3-ethylenedithio-1-phenylpropene (276 mg, 1.33 mmol) and sodium iodide (800 mg, 5.33 mmol, 4.0 eq) in acetonitrile (3 mL) was added PDCP (0.22 mL, 1.47 mmol,

1.1 eq), followed by DMF (0.11 mL, 1.42 mmol, 1.1 eq) after a few minutes. The apparatus was wrapped in foil and allowed to stir for 2 h at room temperature under an atmosphere of argon. The reaction mixture was subjected to dry column flash chromatography using 20% ether in hexanes as the eluent. The solvent was removed *in vacuo* to yield cinnamaldehyde (128 mg, 73% yield) as a pale yellow oil: ir (CH_2Cl_2 cast) 1677 (C=O); ^1H nmr (200 MHz, $CDCl_3$) δ 9.72 (d, 1H, J = 8 Hz, -C**H**O), 7.56 (m, 2H, C-2'H, C-6'H), 7.43 (m, 4H, C-3'H, C-4'H, C-5'H and -**H**C=CHCHO) and 6.73 (dd, 1H, J = 8, J' = 16 Hz, -HC=C**H**CHO); hrms M^+ 132.0570 (calcd. for C_9H_8O: 132.0575).

CHAPTER III

SYNTHETIC STUDIES TOWARDS PHYLLANTHOCIN

Introduction

In the early 1960's, as part of a programme initiated by the National Cancer Institute (NCI) in the United States, Kupchan and coworkers became involved with the search for tumor inhibitors of plant origin. During the course of their investigation, Kupchan found that the crude ethanol extract obtained from the roots of the Central American tree *Phyllanthus acuminatus* Vahl (Euphorbiaceae)* possessed anti-cancer properties. It exhibited potent antitumor activity against lymphocyte leukemia P-388 in mice. These significant pharmacological properties were traced to a bisabolane sesquiterpene glycoside, (+)-phyllanthoside (**56**).[75]

Methanolysis (Scheme 10) of phyllanthoside gave two crystalline compounds: a disaccharide **61** and the aglycone methyl

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*The tree was originally assigned as *Phyllanthus braseliens* Muell (Euphorbiaceae), however this category was later corrected by Pettit and coworkers.

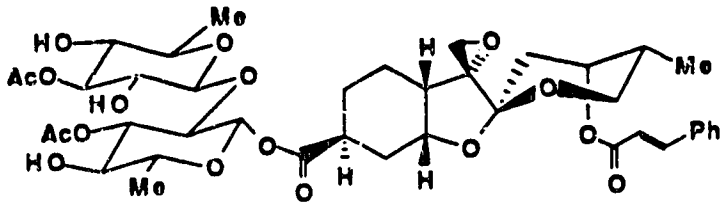
ester phyllanthocin (**57**).# The aglycone structure was elucidated by Kupchan and coworkers from a single-crystal X-ray diffraction study. The authors do point out however that "with the radiation used ... (monochromatic M_O K_α) ... anomalous dispersion effects are too small to allow a determination of absolute configuration, and none has been made." The absolute configuration of the series remained unknown until years later when it was established by total synthesis.[76]

Although there have not been any biosynthetic studies of phyllanthoside or its relatives, as a bisabolane sesquiterpene it must be biogenetically derived from *trans,cis*-farnesyl pyrophosphate (FPP), itself derived from *trans,trans*-farnesyl pyrophosphate (Scheme 11). Cyclization to form ring A yields γ-bisabolene via the intermediacy of the bisabolyl cation. Without labelling studies however, the sequence of oxidations, and cyclization simply remain speculative. What is evident however is that due to the high oxidation level of the molecule, a number of oxidations are required, followed by cyclizations to construct the B, C and oxirane rings of the molecule. As illustrated in Figure 1

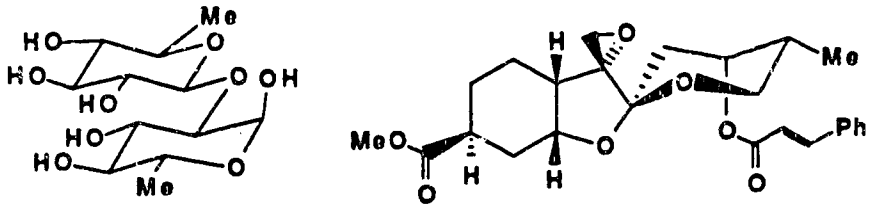
#Unlike phyllanthoside, phyllanthocin is reported to be devoid of any antileukemic activity.

the carbon framework of γ-bisabolene is easily transposed towards phyllanthocin.

Scheme 10



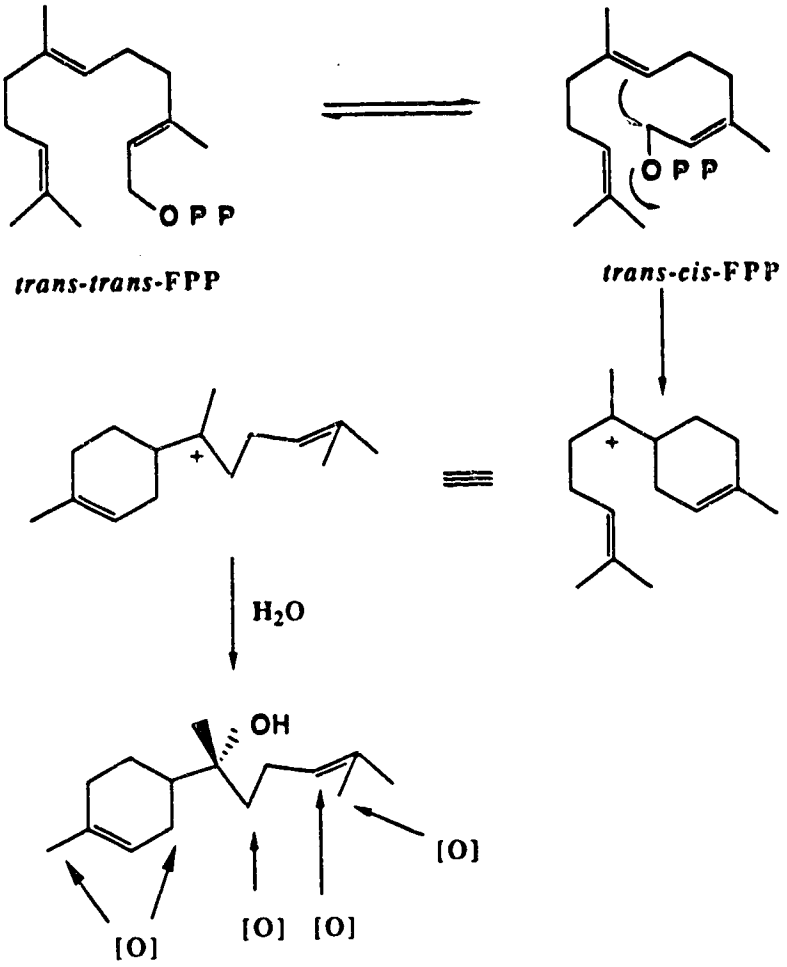
56



61 57

Following the death of Dr. Kupchan in 1976, the work on the isolation of biologically active compounds from *P. acuminatus Vahl* was transferred into the hands of Dr. G. R. Pettit and his coworkers at Arizona State University.[77] It was not until 1982 however that the first papers on the subject appeared.

Scheme 11



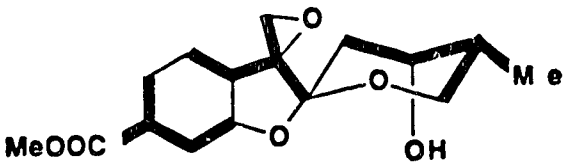
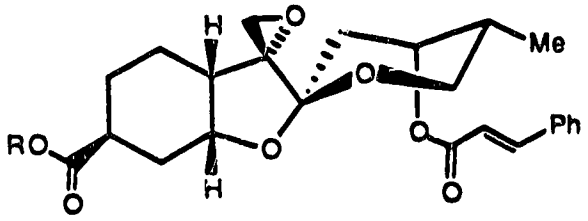


Figure 1. Outline of isoprene units in phyllanthocin skeleton

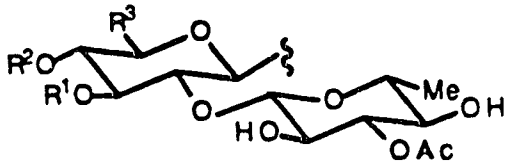
Further investigation by Pettit of other constituents present in the same tree roots, resulted in the discovery of a small family of antileukemic sesquiterpene glycosides, closely related in structure to phyllanthoside and named phyllanthostatin 1[77] (**58**), 2[78] (**59**), and 3[78] (**60**). The complete structural assignment of these principal *P. acuminatus* glycosides was based on both chemical degradation and spectroscopic evidence, and was confirmed by X-ray crystallographic analyses. The structure of phyllanthose (**61**), the disaccharide resulting from the methanolysis of phyllanthoside was likewise reported.[79]

Phyllanthoside, phyllanthostatin 1, and phyllanthostatin 2 were all found to possess a common aglycone moiety, differing only in the position of the acetates in the disaccharide portion of the molecule. On the other hand, phyllanthostatin 3 possesses a different aglycone moiety, with a disaccharide unit which is identical to that found in phyllanthoside. Methanolysis of phyllanthostatin 3 gave the methyl ester phyllanthocindiol (**62**).

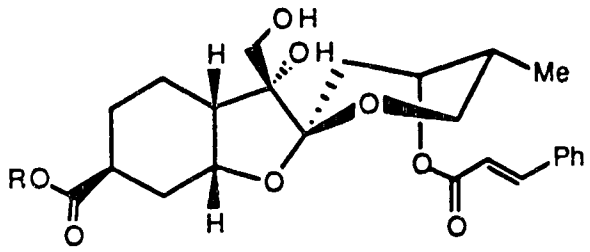
During structural studies on this family of glycosides, it was discovered that they displayed a strong tendency to undergo both O-acetyl migration and solvolysis under mildly acidic or basic conditions. Interestingly this tendency was discovered during the challenging isolation and purification of these compounds, where which silica gel chromatography was extensively employed. It was



R =



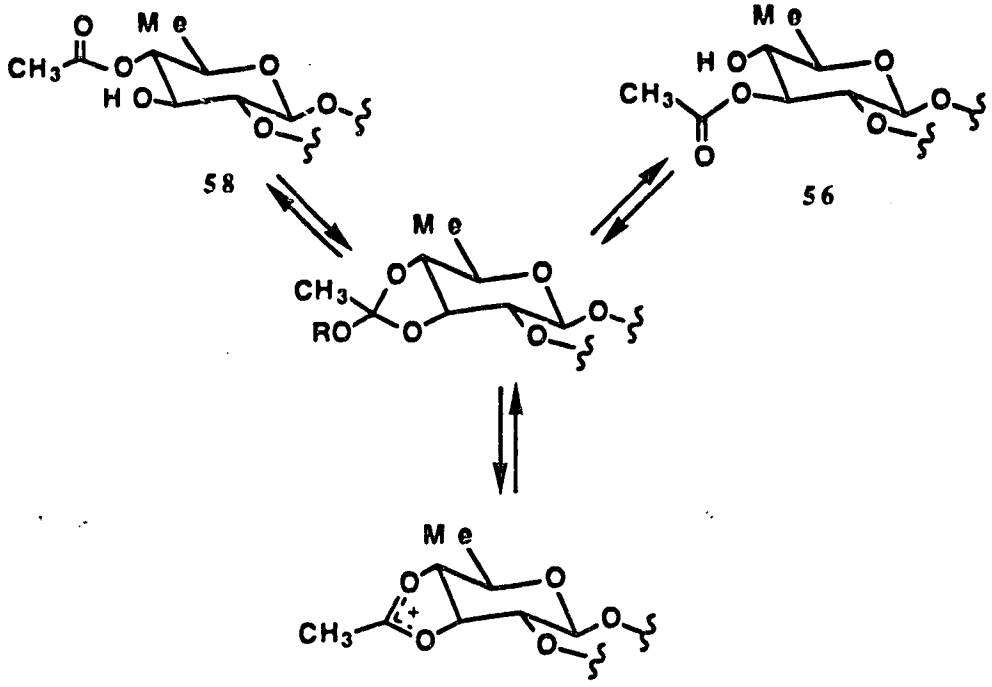
		R^1	R^2	R^3
58	phyllanthostatin 1	H	$COCH_3$	CH_3
59	phyllanthostatin 2	$COCH_3$	H	CH_2OH
56	phyllanthoside	$COCH_3$	H	CH_3
57	phyllanthocin	R = CH_3		



60	phyllanthostatin 3	R as in 56
62	phyllanthocindiol	R = CH_3

observed that the relative amounts of phyllanthoside and phyllanthostatin 1 varied markedly, depending on the time used for the chromatographic procedures. It was subsequently shown that phyllanthoside and phyllanthostatin 1 were interconvertible via O-3 / O-4 acetyl migrations in neutral aqueous solution, eventually undergoing solvolysis to a mixture of about ten other components. These intramolecular acyl group migration of the orthoacid type, involve neighboring group participation *via* acetoxonium ion intermediates (Scheme 12).

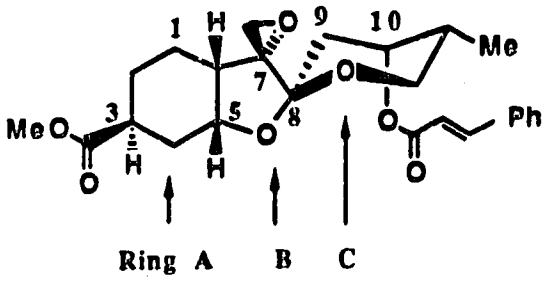
Scheme 12



As mentioned earlier, all the phyllanthostatins exhibit pronounced antineoplastic activity. Of the relatively small number (<5%) of higher plants that receive even superficial examination for anticancer constituents, the phyllanthostatins are tremendously encouraging. Most notably, phyllanthoside has emerged as a particularly promising candidate for cancer chemotherapy. As a result, phamaceutical interest in this compound has escalated. The significant level of inhibition by phyllanthoside of the NCI murine B16 melanoma and the human myeloma cell line has led to extensive pre-clinical testing. More recently NCI has advanced phyllanthoside from the level of pre-clinical to clinical trials, where it will undergo human testing. This tremendous chemotherapeutic potential, in combination with its intriguing and challenging structure renders phyllanthoside an attractive synthetic target.

Since the first published synthesis in 1982 there has been a flurry of synthetic activity directed towards this family of glycosides. However most of the work has been directed towards phyllanthocin. To date there have been four syntheses of (+)-phyllanthocin, one of (+)-phyllanthoside, one of (+)-phyllanthocindiol, and one of (+)-phyllanthostatin 2. Common to all the syntheses reported is convergency: there is a basic dissection of the molecule into a left and right side. The approaches differ however with respect to which key

carbon-carbon bond of the target molecule is constructed (C7-C8, C8-C9, or C9-C10), and the order in which the rings are formed.



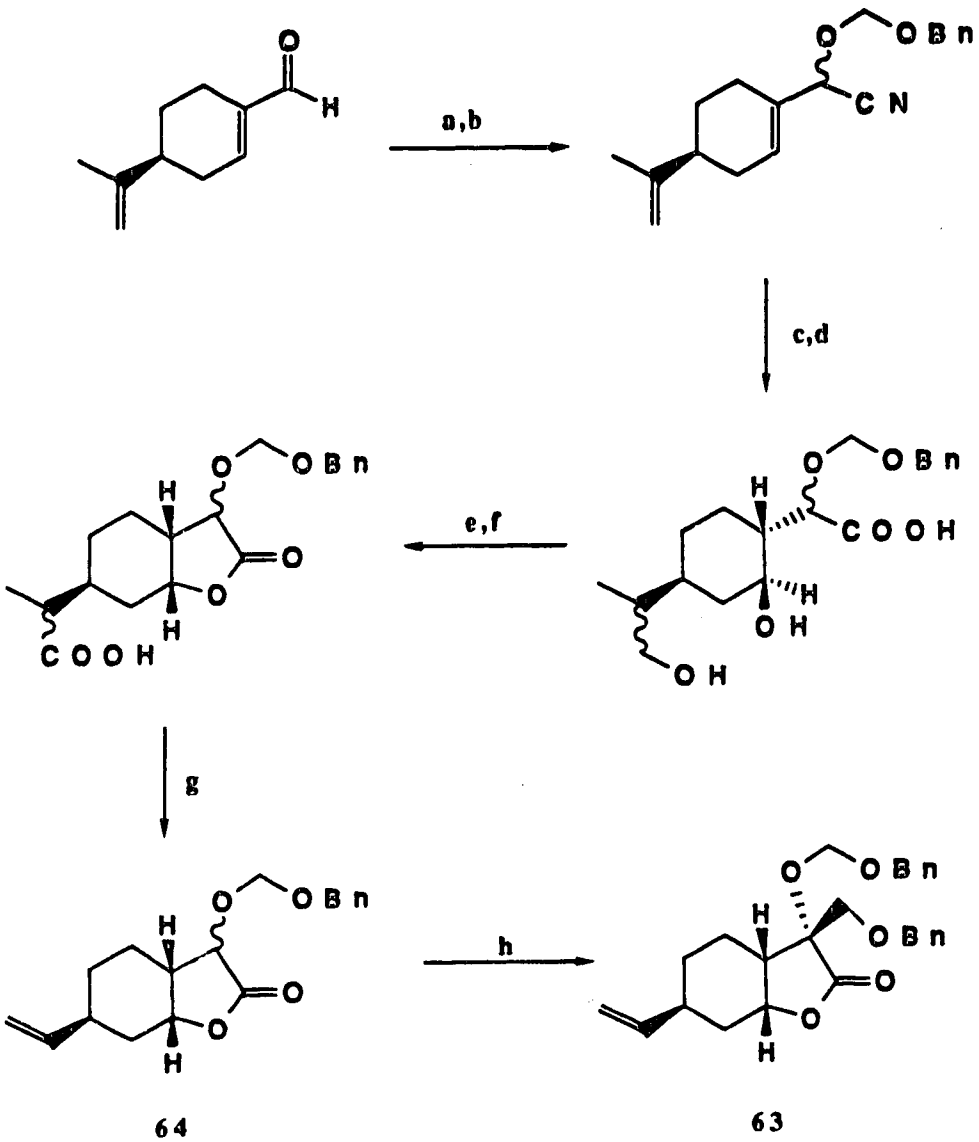
In the McGuirk and Collum[76] approach, the AB bicyclic butyrolactone ring system was built first, followed by attachment of a carbon chain to form the C8-C9 bond, and which was eventually cyclized to form ring C. Both Williams and coworkers[80] and Smith and coworkers[82] had similar approaches: ring A was first prepared, a side chain was coupled to it to make the C7-C8 bond, and in one simultaneous step, rings B and C were formed. Burke and coworkers[81] on the other hand were more sequential: ring A was formed, then ring B, and finally ring C. Martin and coworkers[83] used a novel sequence in which ring A was formed, the appropriate appendage was attached to form the C9-C10 linkage, and this was followed up by cyclization to create ring C. Ring B, achieved by a rearrangement, was the last to be formed.

In 1982, McGuirk and Collum[76] reported the first total synthesis of (+)-phyllanthocin. This synthesis also established the absolute configuration of the series, which up to this point was

unknown. Not long afterwards, they also reported the synthesis of phyllanthocindiol, along with its absolute configuration. The details of their work are outlined in Schemes 13 and 14.

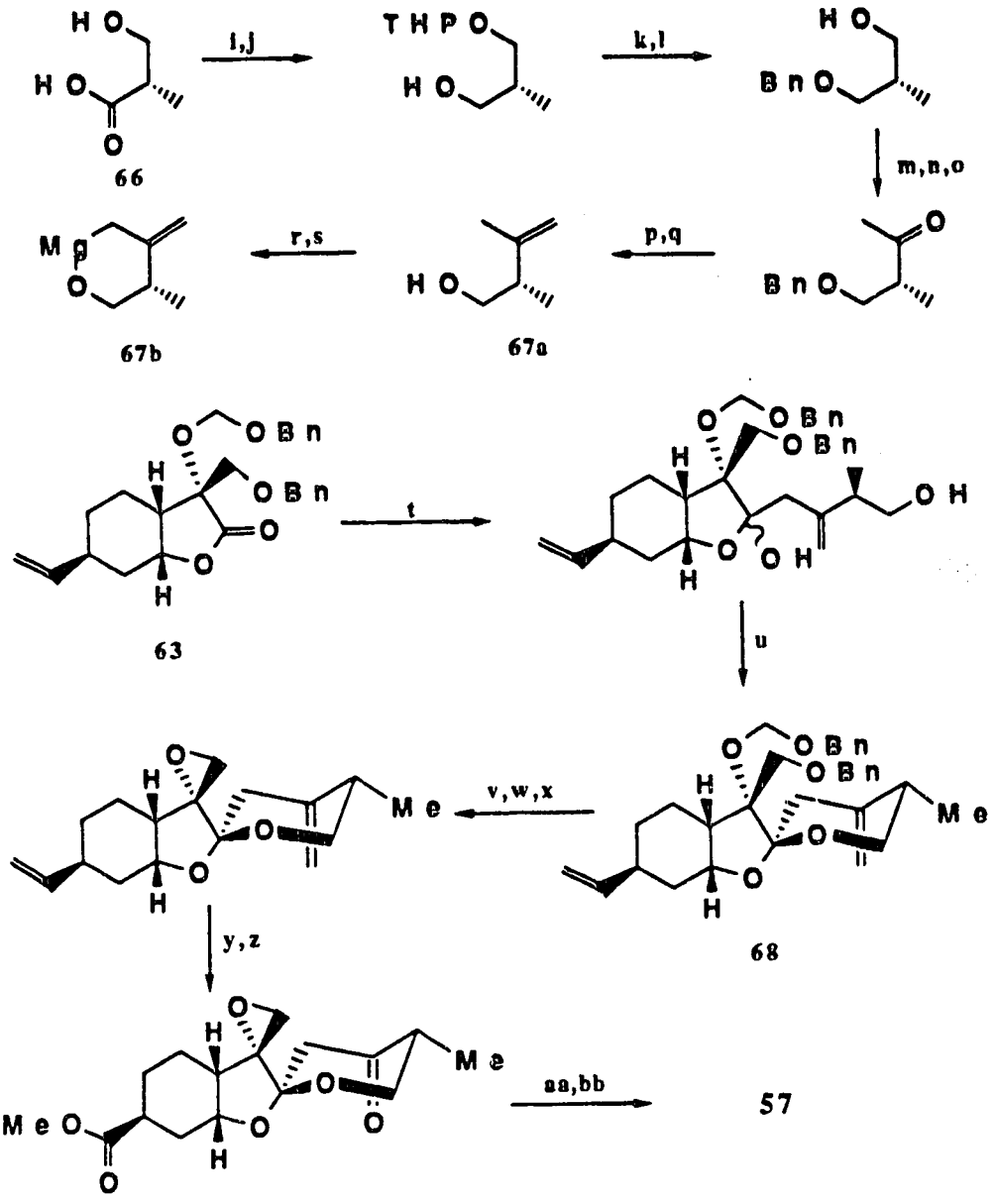
Since the absolute configuration of phyllanthocin had yet to be established, a starting material was required of which both antipodes were available so that either enantiomeric series could be readily entered. (S)-(-)-Perilla aldehyde was chosen as the starting material: it already possessed the six membered ring of the bicyclic AB ring system, and was suitably functionalized to allow further elaboration. The one chiral center already present in the starting material was used to establish the ring juncture stereochemistry of butyrolactone **63**. This was achieved by a cyclic stereoselective oxidative hydroboration modelled after one achieved by Brown. Although this reaction was successful at establishing the requisite 1,4-*trans* stereochemical relationship in the cyclohexane ring system with concomitant oxygenation, the alcohol stereochemistry was incorrect. This was easily remedied at a latter stage, during a phosphonium salt induced lactonization, which also served to invert this stereocenter. The isopropenyl group was eventually degraded into the C3 methyl ester, and the aldehyde functionality was treated with cyanide to provide the additional carbon required for the construction of the butyrolactone system. The stereochemistry of the spiroepoxide at

Scheme 13



a. KCN, HOAc, diethyl ether, 25°C; b. $PhCH_2OCH_2Cl$, C_5H_5N, 60°C;
c. thexylborane, H_2O_2, NaOAc, THF, -40°C; d. KOH, ethanol, 100°C;
e. EtOOCN=NCOOEt, PPh_3, THF, -20°C; f. Jones reagent, acetone 0°C;
g. $Pb(OAc)_4$, $Cu(OAc)_2$, C_5H_5N, benzene, 80°C;
h. LDA, THF, -78°C, then $PhCH_2OCH_2Cl$, THF, HMPA, -60°C

Scheme 13 (cont'd)



i. Dihydropyran, CH_2Cl_2, *p*-TsOH, 0°C; j. $LiAlH_4$, THF, 0°C; k. KH, $PhCH_2Br$, THF, 23°C

l. *p*-TsOH, ethanol, reflux; m. $CrO_3 \cdot H_2SO_4$, acetone, 23°C; n. $(COCl)_2$, benzene, 50°C;

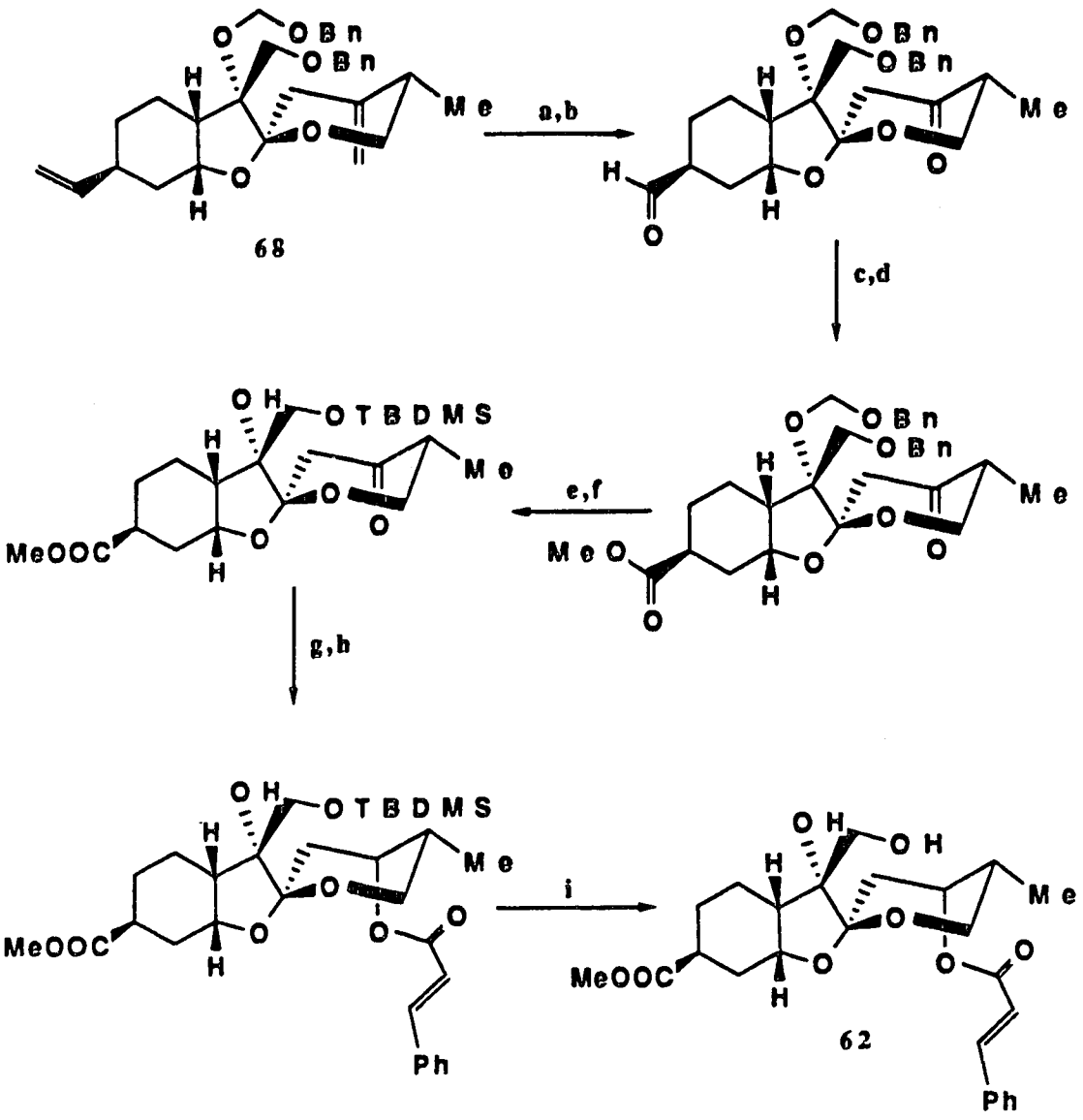
o. $(Me)_2CuLi$, THF, -78°C; p. $Ph_3P=CH_2$, THF, 0°C; q. Li, NH_3, -78°C;

r. *t*-BuOK, *n*-BuLi, hexane, 0°C; s. $MgBr_2$, THF; t. 67b, Et_2O, -60°C; u. $ZnCl_2$, CH_2Cl_2, -20°C;

v. Li, NH_3; w. MsCl, TEA; x. DBU, benzene; y. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2O, CH_3CN, CCl_4;

z. CH_2N_2; aa. KS-Selectride, THF, 0°C; bb. *trans*-PhCH=CHCOCl, CH_2Cl_2, C_5H_5N, DMAP

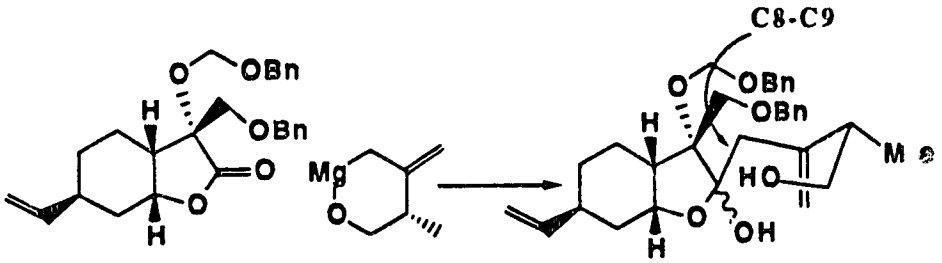
Scheme 14



a. O_3, CH_2Cl_2, -78°C; b. Me_2S, 23°C; c. Jones reagent, acetone, -10°C; d. CH_2N_2, ether, 0°C;
e. 10% Pd/C, H_2; f. *t*-butyldimethylsilyl chloride; g. KS-Selectride, THF, 0°C;
h. *trans*-PhCH=CHCOCl, CH_2Cl_2, C_5H_5N, DMAP; i. tetra-*n*-butylammonium fluoride, THF

C7 was established at this stage in the synthesis during a highly stereoselective benzyloxymethylation of the enolate derived from butyrolactone **64** to form the key intermediate **63**.

The crucial intermediate alcohol **67a**, containing the carbon framework for ring C, was prepared in enantiomerically pure form from the optically active alcohol **66**. With some difficulties, dianion **67b** was prepared from alcohol **67a**, and then coupled with lactone **63**, containing the AB ring system. This constructed the key C8-C9 bond of the target, to form the hemiacetal (Eqn 28).



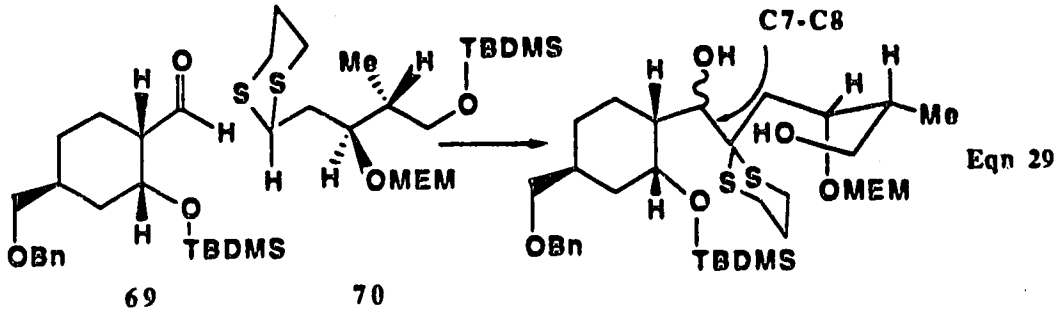
63 67b Eqn 28

Lewis acid induced spirocyclization afforded spiroketal **68** without stereochemical complications at C8. This intermediate **68** was especially pivotal since by one route it led to phyllanthocin, (Scheme 13) and by another route led to phyllanthocindiol (Scheme 14). Conversion of intermediate **68** to phyllanthocin was achieved first by deprotection to yield the vicinal diol, mesylation of the primary alcohol, followed by base induced oxirane ring closure to afford the spiroepoxide. An additional series of steps including oxidative cleavage, esterification, reduction and finally

cinnamoylation provided phyllanthocin. The reduction served to establish the final chiral center with high stereoselectivity.

Besides the basic difference of having C7 as a vicinal diol as opposed to a spiroepoxide, the phyllanthocindiol synthesis was conducted employing the same reaction sequence until spiroketal **68**. From this point, the synthesis of the diol with a sequence that was less efficient than that achieved for the epoxide due to complications with reagents and functional groups, which required an alteration of the reaction sequence.

Another synthesis of (+)-phyllanthocin was reported in 1984, by Williams and Sit (Scheme 15).[80] Crucial to their strategy was the use of lithio dithiane chemistry to serve both as a carbanion in the construction of a carbon-carbon bond and as a latent carbonyl group. The functionalized cyclohexyl aldehyde derivative **69** was used for ring A (similar to McGuirk and Collum), and dithiane **70** carried the remainder of the carbon skeleton for rings B and C. These two key fragments were coupled to form the C7-C8 bond of the target (Eqn 29).

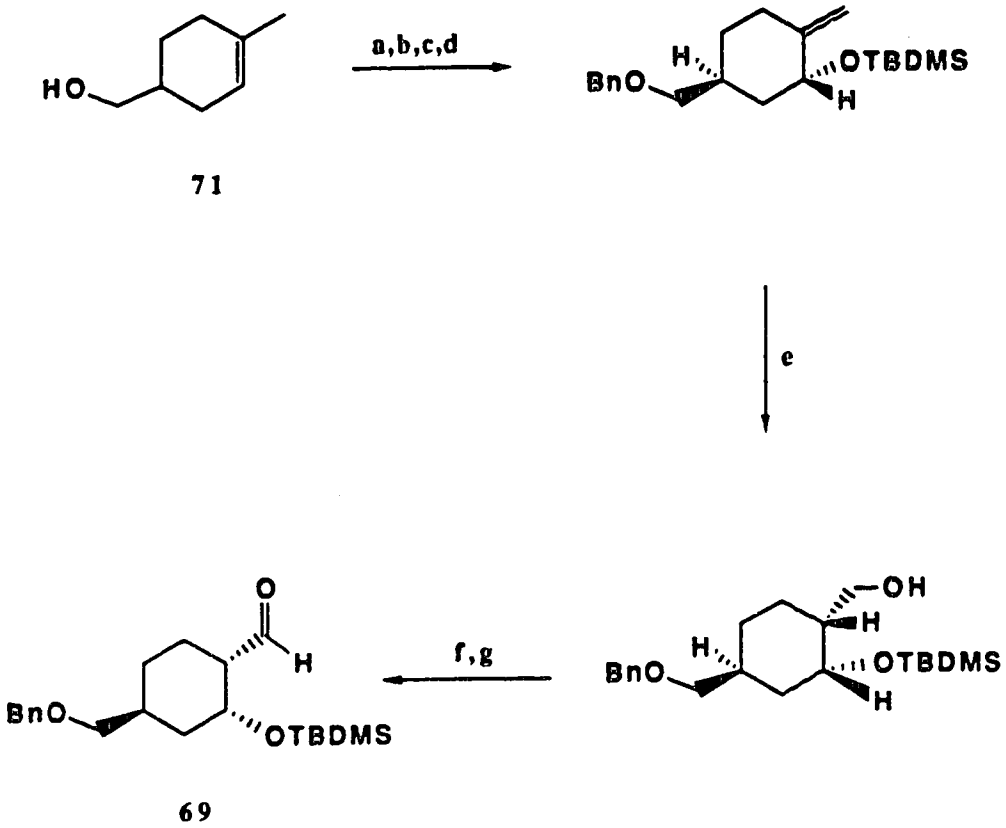


69 70

The optically active aldehyde **69** was prepared from the racemic alcohol **71**. The relative 1,3-*trans* relationship of the two substituents was achieved by epoxidation ($\alpha : \beta = 1 : 1$), elimination and protection of the alcohol, followed by separation of the undesired 1,3-*cis*-fused product. The stereochemistry at the third chiral center was established with slightly better stereoselectivity (2.3:1) by an oxidative hydroboration to form the required 1,4-*trans* stereochemical relationship. Due to the racemic nature of the starting material, a resolution had to be effected. This was carried out at the alcohol stage, and was followed by an oxidation to yield aldehyde **69**.

The optically active dithiane component **70** was prepared from natural tartaric acid which possessed all but one of the backbone carbons required for rings B and C. The chiral epoxide derived from diethyl tartrate was used as the starting material and was converted to epoxide **72** in nine steps. The additional carbon was added by treatment of epoxide **72** with lithio-1,3-dithiane.

Scheme 15



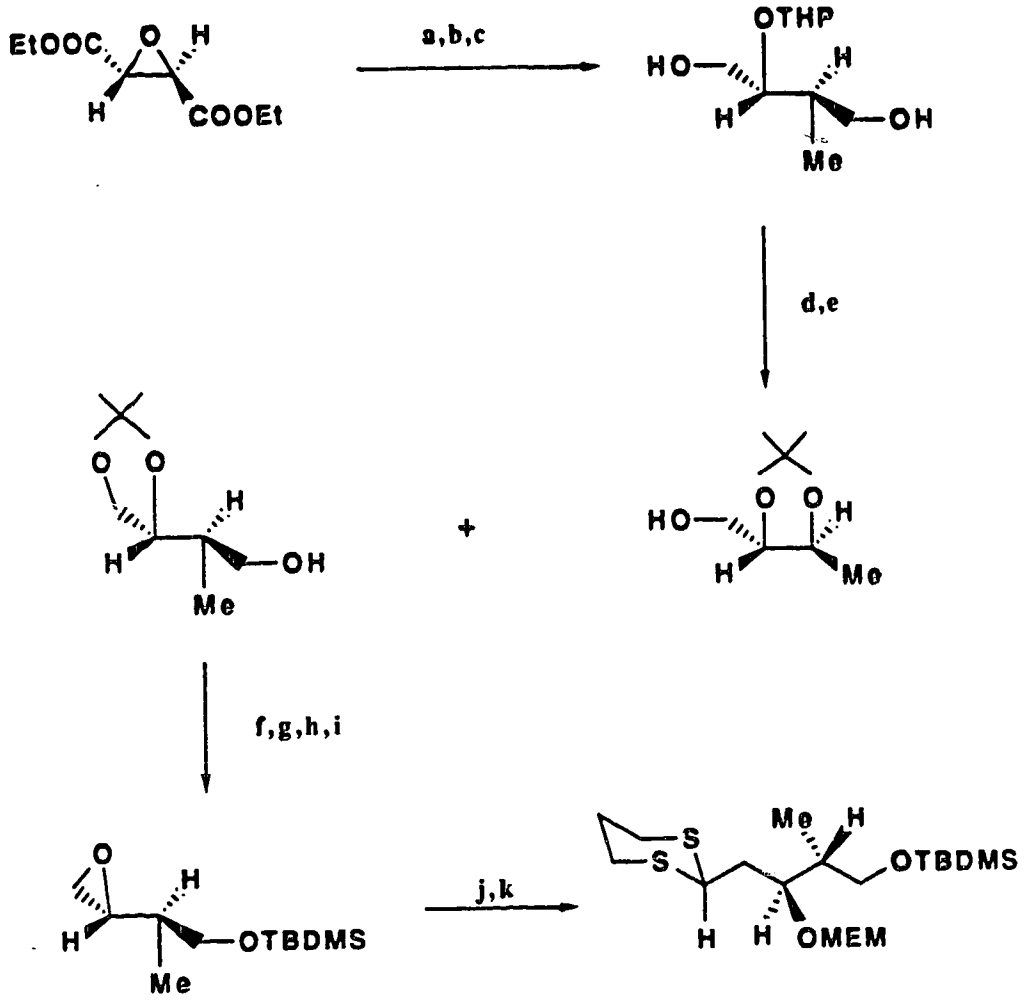
a. benzylation; b. MCPBA, CH_2Cl_2, 10°C → room temperature;

c. Lithio-2,6-dimethylpiperidide, ether, 50°C, Carius tube;

d. *t*-$BuMe_2SiCl$, DMF, DMAP, 22°C; e. Borane, THF, 22°C, then H_2O_2, HO^-;

f. resolution with (-)-camphanic acid, then KOH, aq. MeOH; g. PCC, CH_2Cl_2, 22°C

Scheme 15 (cont'd)



72 70

a. $LiMe_2Cu$, ether, -78°C; b. Dihydropyran, ether, catalytic *p*-TsOH;

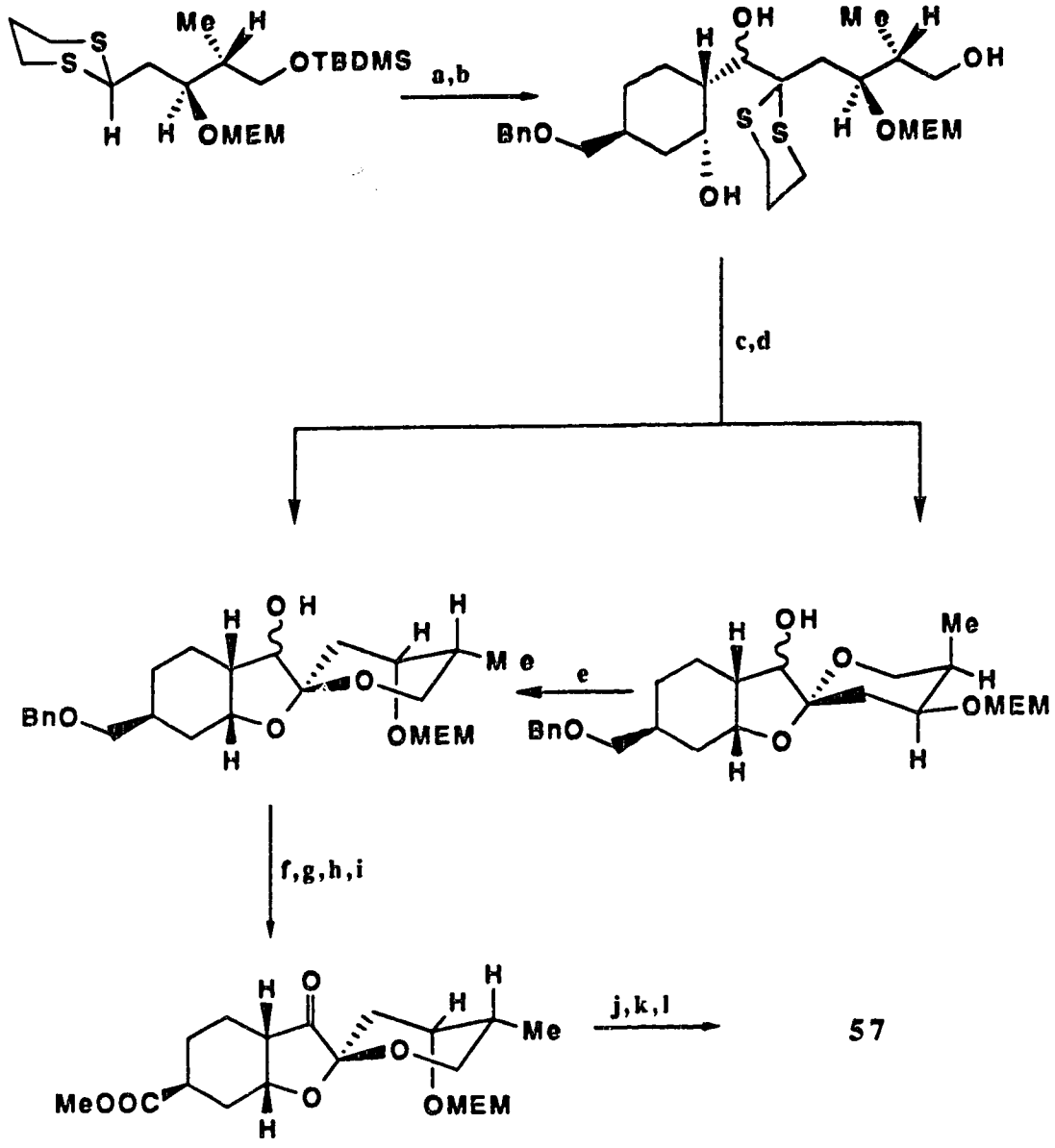
c. $LiAlH_4$, ether, 22°C; d. *p*-TsOH, methanol, 22°C; e. Acetone, *p*-TsOH;

f. *t*-$BuPh_2SiCl$, DMAP, CH_2Cl_2, 22°C; g. Ethanedithiol, $CHCl_3$, *p*-TsOH;

h. TsCl, TEA, CH_2Cl_2; i. NaH, THF, 0°C → room temperature;

j. 2-Lithio-1,3-dithiane, THF, -25°C; k. MEM-Cl, DMAP, diisopropylethylamine

Scheme 15 (cont'd)



a. *t*-butyllithium, THF, HMPA, -78°C, followed by addition of aldehyde 69;

b. *n*-$Bu_4N^+F^-$, THF, 22°C; c. $HgCl_2$, HgO, aqueous CH_3CN; d. TFA, CH_2Cl_2, 0°C;

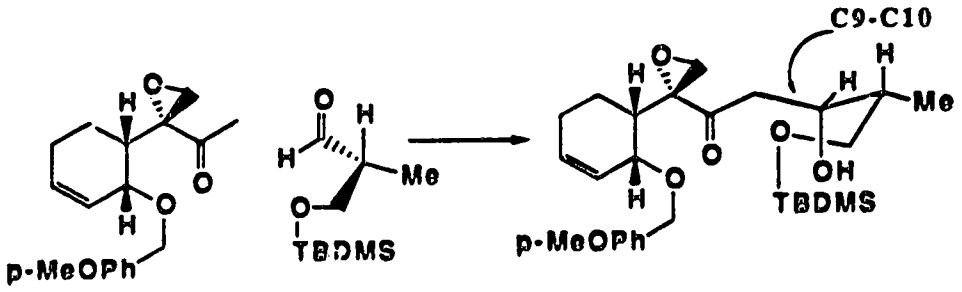
e. TFA, methyl magnesium chloride, THF, 0°C; f. H_2CrO_4, aqueous acetone, 22°C;

g. H_2, 5% Pd/C, MeOH h. Jones' reagent, 22°C; i. CH_2N_2, ether; j. $ZnBr_2$, CH_2Cl_2, 22°C;

k. methyleneoxysulfurane, DMSO, THF, 22°C; l. *trans*-PhCH=CHCOCl, CH_2Cl_2, DMAP, 40°C

Carbon 2 of the dithiane unit would eventually become C8 in the final product. The dithiane **70** resulting from this reaction was used in yet another carbon-carbon forming reaction, this time with aldehyde **69** to form the coupled product. Unmasking of the protected carbonyl resulted in the formation of the keto triol as well as a mixture of spirocyclized products. This resulted in some difficulties regarding stereochemical control at the C8 center. The conditions used to effect the internal spirocyclization were found to influence the stereochemical consequences at C8. Protic conditions as opposed to Lewis acid catalysis favored the formation of the unnatural configuration at the critical C8 spirocenter. Despite these difficulties, the situation was remedied to form the desired stereoisomer. The spiroepoxide was formed with good stereoselectivity from the carbonyl at C7 and methyleneoxysulfurane.

In 1985, a third synthesis of (+)-phyllanthocin appeared by Burke and coworkers,[81] using an approach which was both convergent and sequential (Scheme 16). Once ring A was formed, an appendage was attached and cyclization was effected to form ring B, then ring C was formed last. The critical bond formation occurred by the use of a Cram cyclic stereoselective aldol coupling of the enolate derived from epoxy ketone **73** and aldehyde **74** to construct the C9-C10 bond (Eqn 30).



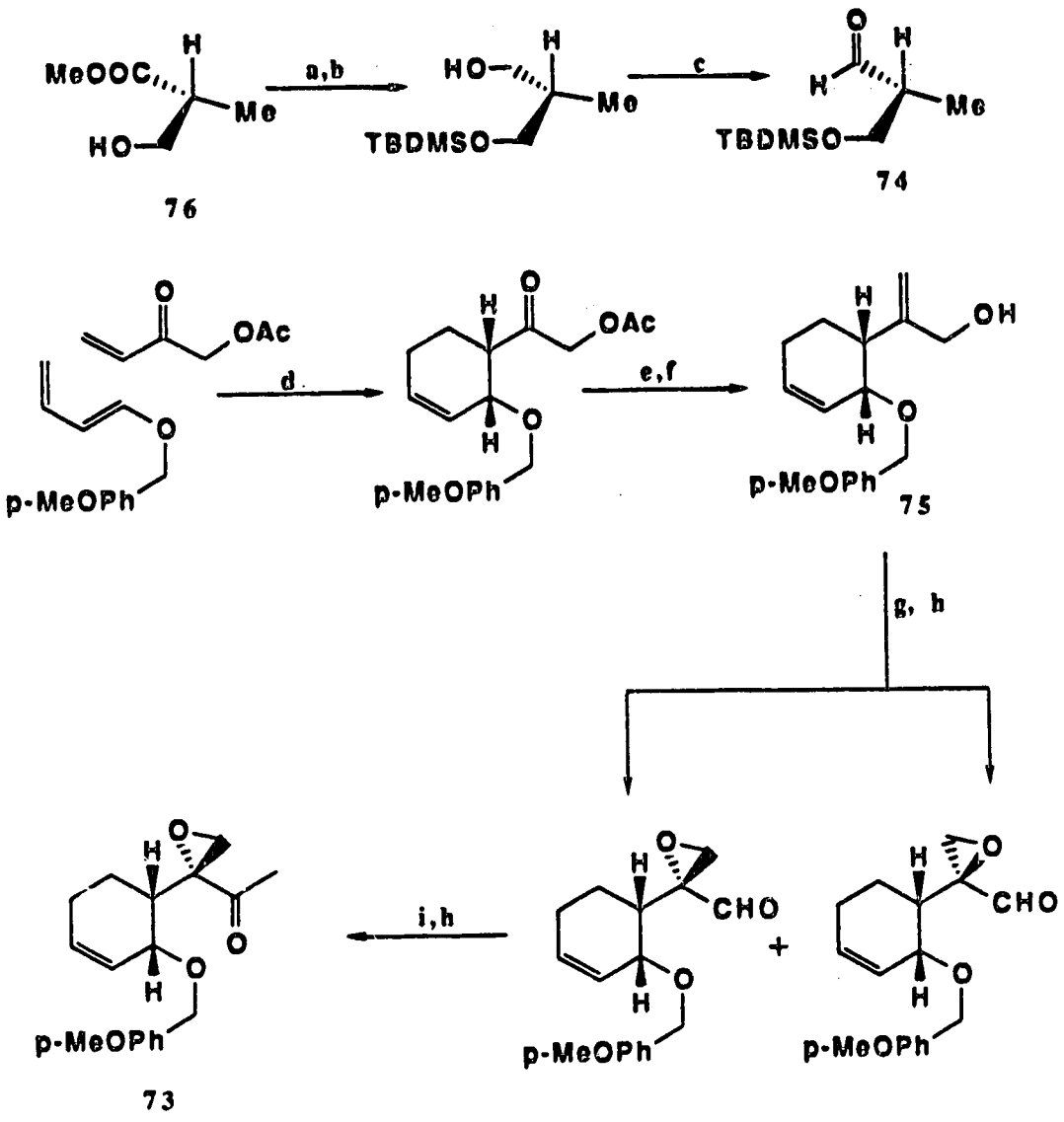
73 74

Eqn 30

Unlike Collum and Williams, who used a starting material already containing a six-membered ring, Burke constructed ring A via a Diels-Alder reaction. This also served to establish the 1,2-*cis* stereochemical relationship of the substituents on the cyclohexane ring. The C3-C4 double bond formed during the reaction was the only handle provided for the introduction of the required C3 methoxycarbonyl substituent. The postponement of the introduction of this ester group until a later stage in the synthesis eventually proved to be particularly risky, in light of the difficulties that were eventually encountered.

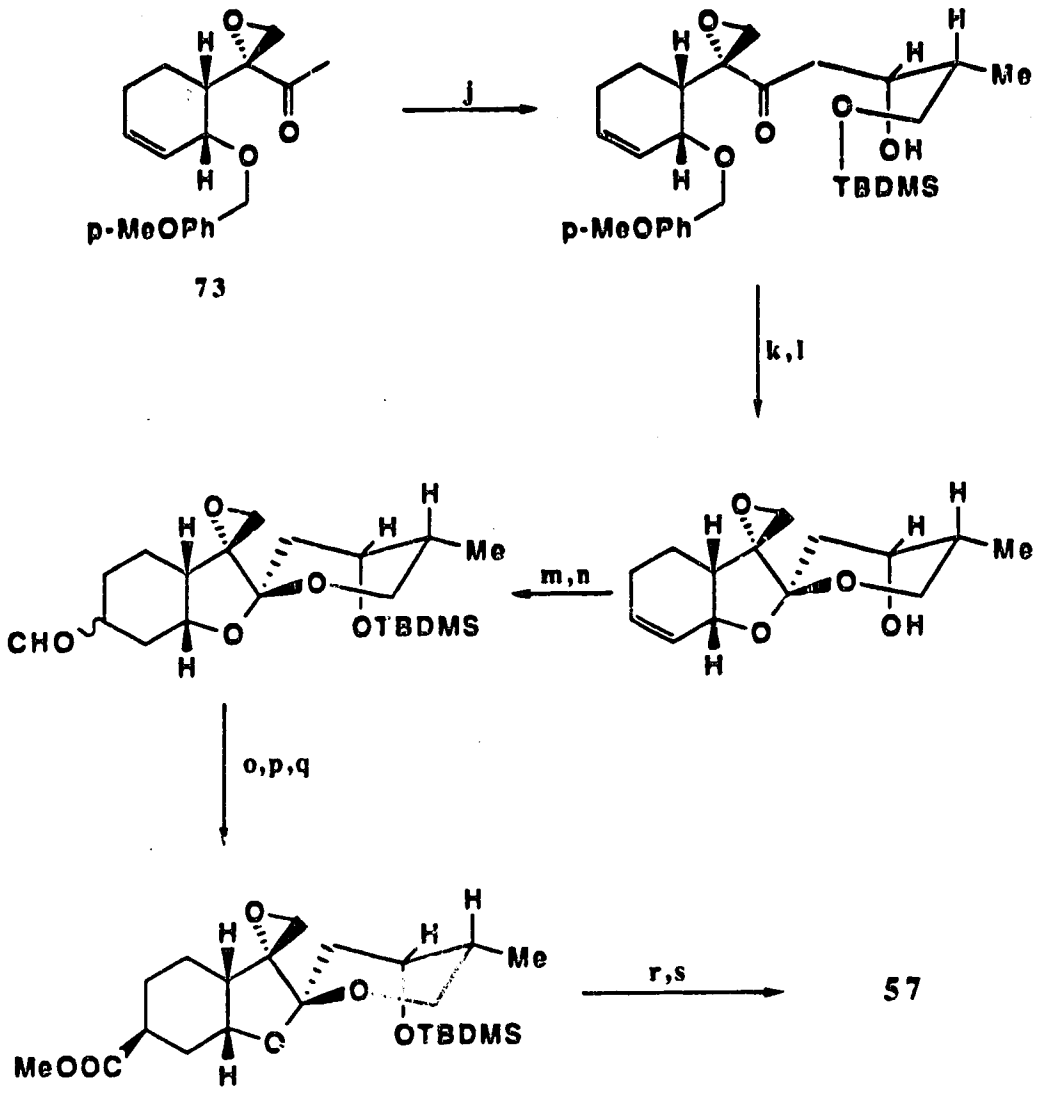
The Diels-Alder adduct was converted into alcohol **75**, and the spiroepoxide was formed at a comparatively early stage of the synthesis, by a Sharpless asymmetric epoxidation reaction. This resulted in the formation of an approximately equal mixture of epoxy alcohols, the correct isomer of which was carried through to the methyl ketone **73**.

Scheme 16



a. *t*-Butyldimethylsilyl chloride, imidazole, DMF; b. *i*-Bu_2AlH, CH_2Cl_2, -23°C;
c. Swern oxidation; d. cycloaddition; e. $Ph_3P{=}CH_2$, THF, -100°C; f. K_2CO_3, MeOH, 25°C;
g. *t*-BuOOH, (+)-diethyl tartrate, $Ti(O\text{-}t\text{-}Bu)_4$, CH_2Cl_2, -23°C;
h. Me_2SO, oxalyl chloride, TEA, CH_2Cl_2, -60°C; i. MeLi, THF, -78°C;

Scheme 16 (cont'd)



j. LDA, THF -78°C, then aldehyde 74; k. DDQ, CH_2Cl_2, H_2O (19:1), 25°C;

l. 5% aqueous HF, CH_3CN, 25°C; m. *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0°C;

n. 8 mol% $[(COD)RhOAc]_2$, PhH, 1:1 CO/H_2 (560 psi), 76°C; o. NaOMe, MeOH, 25°C

p. $H_2Cr_2O_7$, aqueous acetone, 0°C; q. CH_2N_2, Et_2O, 0° → 25°C;

r. 5% aqueous HF, CH_3CN, 0°C, s. *trans*-PhCH=CHCOCl, CH_2Cl_2, DMAP, 40°C

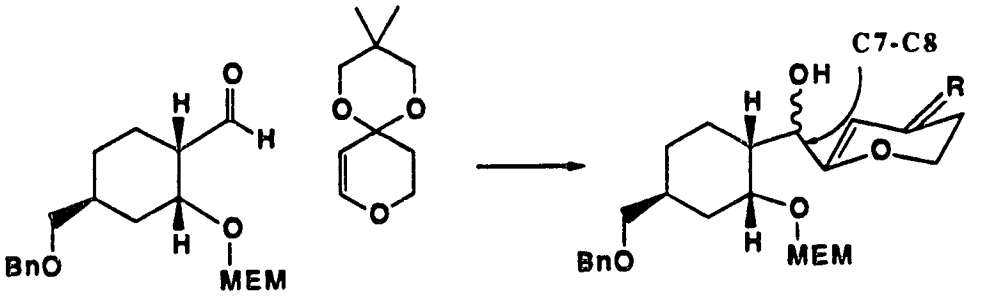
The coupling partner for ketone **73** was derived from the optically active alcohol **76** through a number of steps to aldehyde **74**. This aldehyde was problematic since it had a tendency towards racemization during purification procedures. Consequently, it was coupled with **73** without purification. The formation of rings B and C was achieved sequentially via the hemiacetal, eventually to provide the spiroketal. Notably, the silyl ether cleavage (aqueous HF) gave the spiroketal with complete stereoselectivity at C8. This is especially interesting when compared to the work of Williams and Sit who experienced problems when other protic acids were used in this step.

The introduction of the C3 methoxycarbonyl group proved to be the most problematic step, regardless of the methodology employed. Hydroformylation, the method eventually used required forcing conditions and resulted in the formation of a mixture of C3α, C3β and C4 formyl products, in modest yields. However, once this substituent was introduced, the remaining transformations to the target molecule were all routine.

In 1987, Smith and coworkers[82] were the next to report the total synthesis of (+)-phyllanthocin. They were the first to synthesize the disaccharide unit, and consequently were the first to report the total synthesis of (+)-phyllanthoside as well as

(+)-phyllanthostatin 2. Since our concern is primarily with the aglycone portion phyllanthocin, we will focus strictly upon that synthesis, rather than the disaccharide chemistry.

Smith's approach (Scheme 17) to phyllanthocin is somewhat reminiscent of that achieved by Williams, some three years earlier. Both employ a convergent strategy in which the key bond of the target formed is the C7-C8 bond. Both employ a functionalized cyclohexyl aldehyde as the electrophile in the key carbon-carbon forming reaction, and both generate a carbanion at what will eventually become C8 in the target. For Williams the carbanion was generated from a 1,3-dithiane type compound, whereas for Smith the carbanion was derived from a dihydropyran. (Eqn 31; compare to Eqn 29)



Eqn 31

77 75 R = $OCH_2C(CH_3)_2CH_2O$

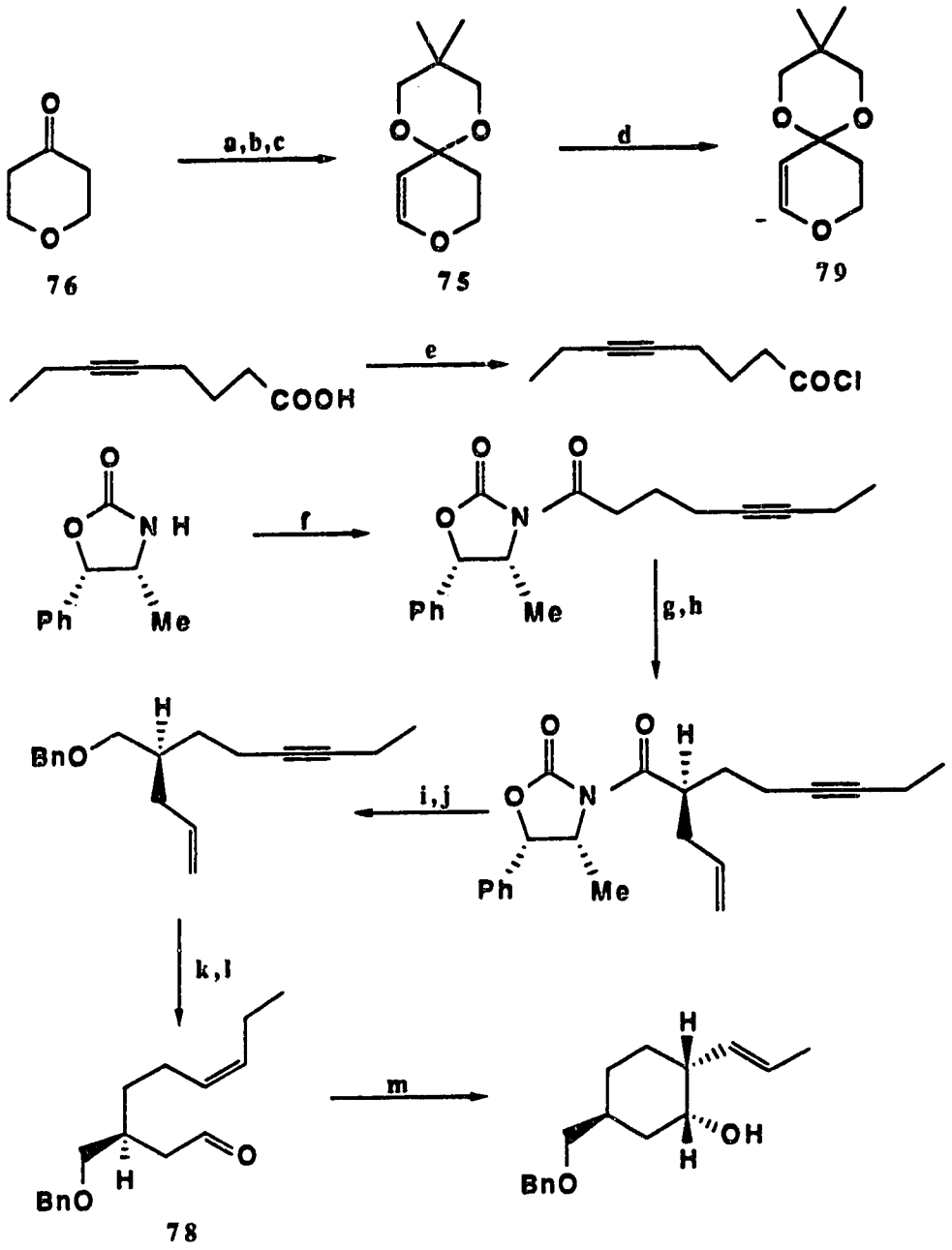
Dihydropyran **75**, required for the construction of the spiroketal, was prepared from the tetrahydropyran **76** in three steps. The optically pure aldehyde **77** was constructed using

Evans' oxazolidone methodology to prepare **78** with the correct absolute stereochemistry at C3. Aldehyde **77** was constructed from aldehyde **78** by a stereoselective intramolecular ene reaction. This reaction established correctly the stereochemistry of the three chiral centers of ring A .

Coupling of the two key intermediates, aldehyde **77** and the carbanion **79** (generated from dihydropyran **75**), followed by oxidation led to the substituted dihydropyran **80**. Spirocyclization to ketal **81** was successfully effected with camphorsulfonic acid, and similar to Williams, spiroepoxidation was achieved by the use of dimethylsulfoxonium methylide to give only the correct stereoisomer.

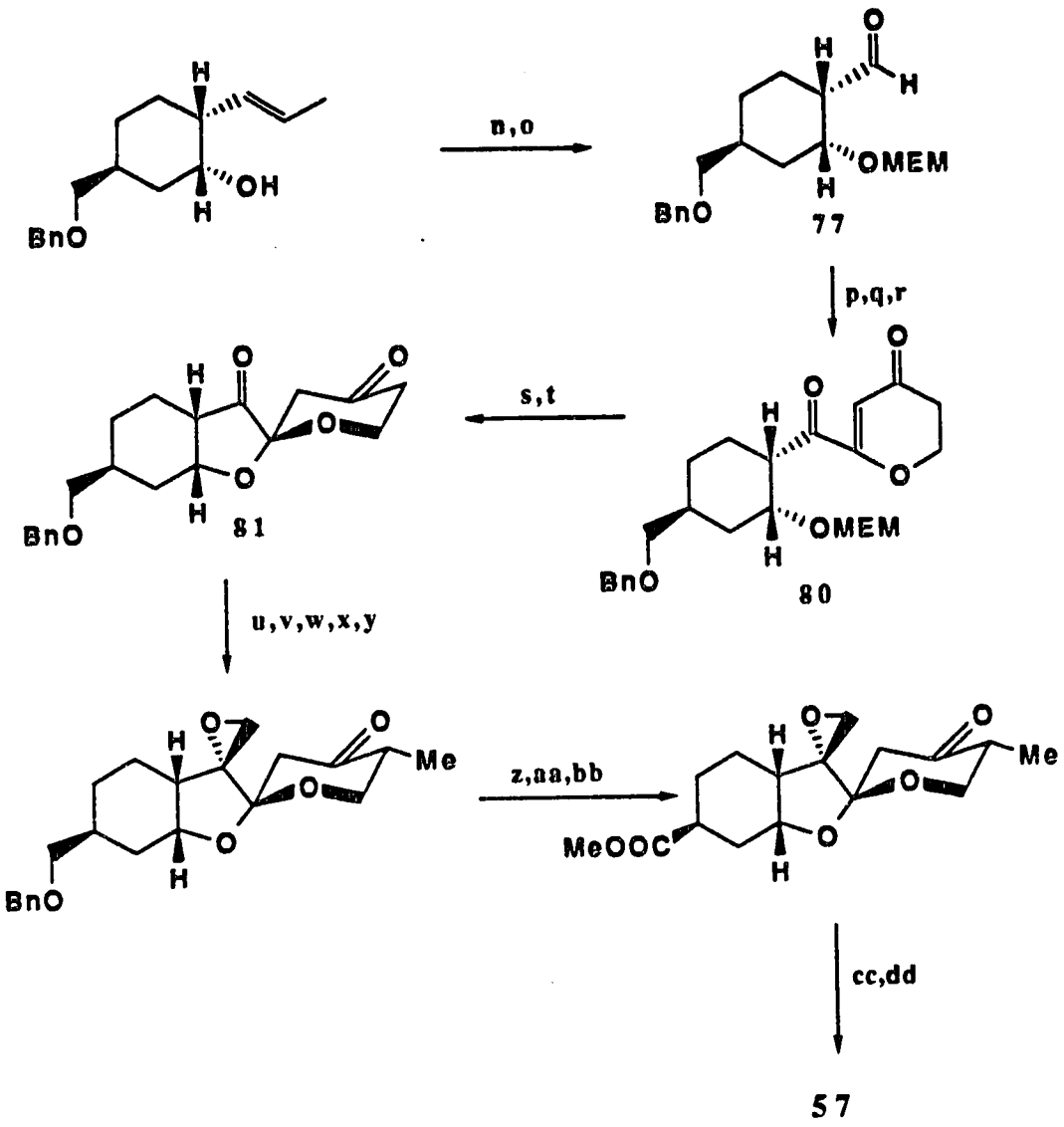
Introduction of the methyl group at C11 was problematic. Both mono- and di- alkylations at the C9 position resulted when standard kinetic conditions were employed. Eventually Corey's procedure employing silyl enol ether chemistry was utilized, with good regiochemical control. Although a mixture of C11 stereoisomers resulted, these were readily equilibrated to yield the desired stereoisomer. The synthesis was completed by a series of routine steps to eventually form the C3 methoxycarbonyl, the C10 axial alcohol (using Collum's precedent) and finally cinnamoylation.

Scheme 17



a. 1,3-dihydroxy-2,2-dimethylpropane, H^+, benzene; b. py·HBr_3, THF;
c. *t*-BuOK, DMSO; d. *t*-BuLi, THF; e. $(COCl)_2$; f. *n*-BuLi, THF, then the acid chloride;
g. $(Me_3Si)_2NLi$, THF, -78°C; h. allyl bromide, THF, -78 → 0°C; i. $LiAlH_4$, THF;
j. KH, BnBr, THF; k. O_3, CH_2Cl_2; l. H_2, 5% $Pd/CaCO_3$, quinoline, hexane;
m. Me_2AlCl, CH_2Cl_2

Scheme 17 (cont'd)



n. MEM-Cl; o. O_3; p. anion 79, THF/HMPA (2:1); q. H_3O^+; r. Swern oxidation;

s. $ZnBr_2$, CH_2Cl_2 t. CSA, benzene;

u. sodium dimethylsulfoxonium methylide, DMSO-THF (1:1)

v. LDA; w. Me_3SiCl; x. $PhCH_2Me_3NF$, -78°C, MeI; y. DBU, THF;

z. H_2, 10% Pd/C, MeOH; aa. RuO_4-$NaIO_4$, $CH_3CN/CCl_4/H_2O$ (6:6:9); bb. CH_2N_2;

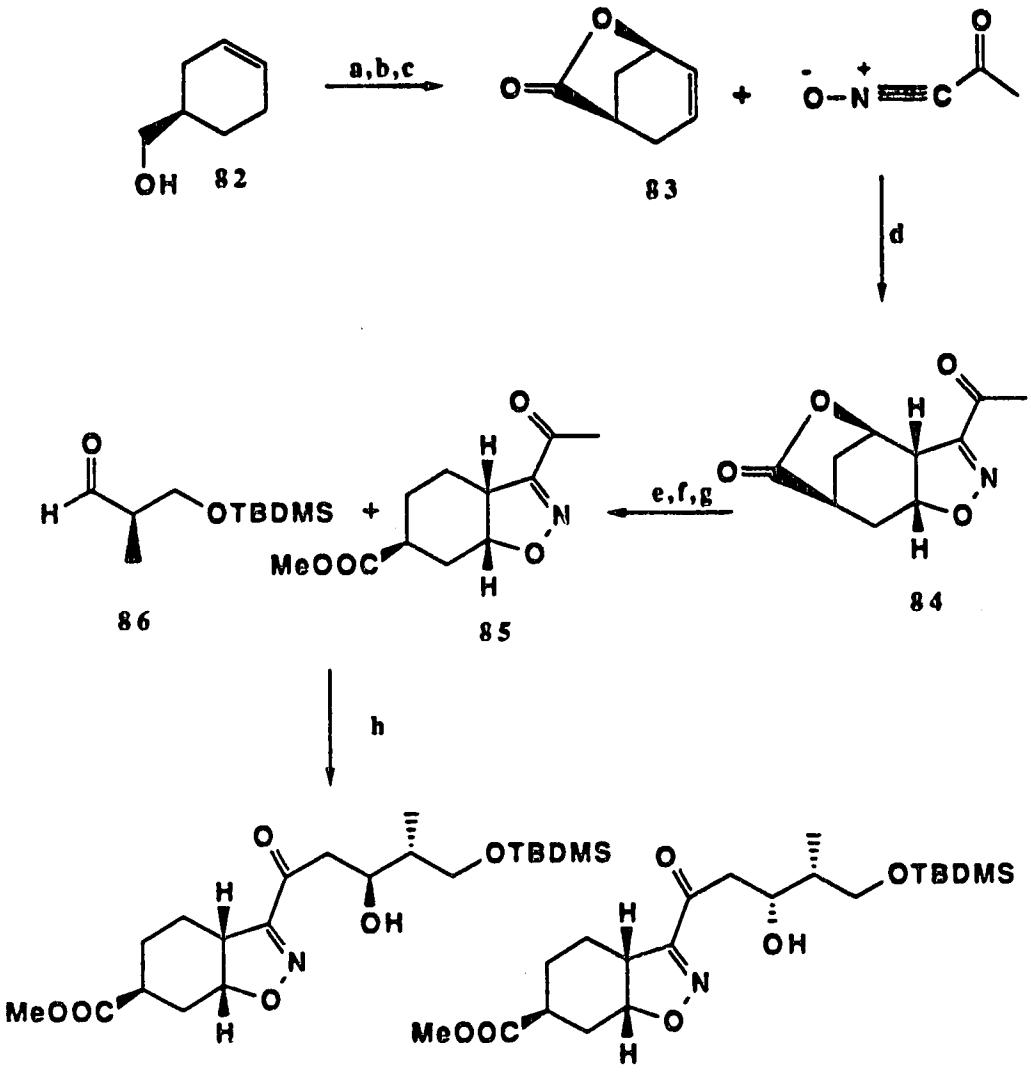
cc. $NaBH_4$; dd. *trans*-PhCH=CHCOCl, DMAP, py

The most recent synthesis of (+)-phyllanthocin reported was that by Martin and coworkers in 1987 (Scheme 18).[83] Although this approach is also highly convergent, it differed significantly from those previously reported by the use of a dipolar cycloaddition to construct an isoxazoline ring, synthetically equivalent to a β-hydroxy ketone moiety.

The optically active carbinol **82**, utilized as starting material, was converted into lactone **83** by a number of steps that included an iodolactonization. This unsaturated lactone was utilized in a dipolar cycloaddition reaction to give the desired cycloadduct **84** in somewhat moderate yield. The one chiral center present in the starting material was utilized as a stereocontrol element in establishing the three chiral centers about the cyclohexane ring. Having served its purpose, the lactone ring was opened followed by excision of the C1 hydroxyl group.

The key reaction involved the coupling of the two optically active subunits **85** and **86** thereby forming the C9-C10 bond. Attempts at a Lewis acid chelation controlled reaction to achieve a high level of stereochemical efficiency during this aldol reaction were low yielding. In order to obtain high yields, standard enolate chemistry had to be employed for this bond construction, although this was at the expense of stereoselectivity. The incorrect

Scheme 18

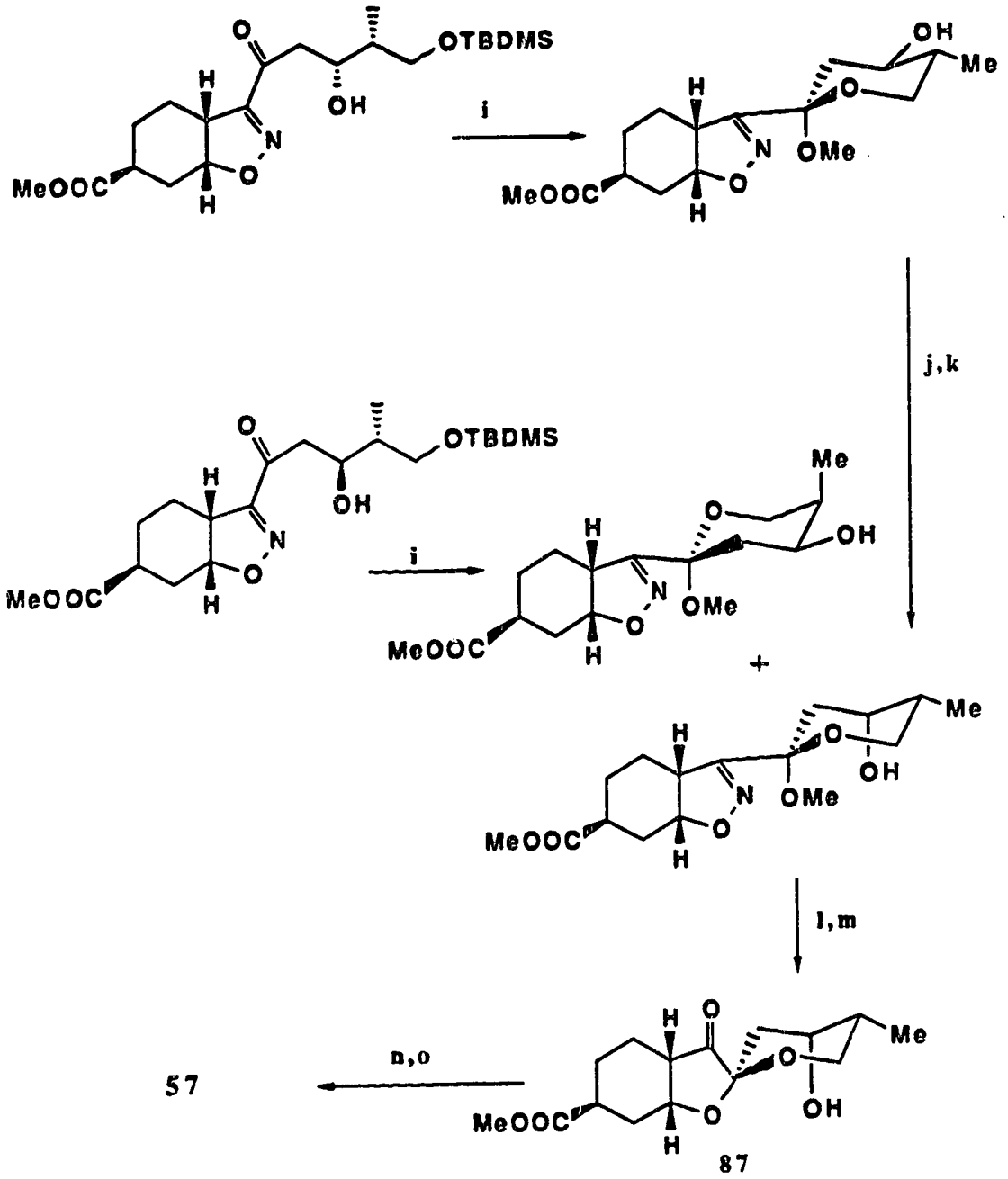


a. PDC, DMF, room temperature; b. $NaHCO_3$, I_2, KI, H_2O, 25°C; c. DBU, THF;

d. toluene, reflux; e. K_2CO_3, MeOH, 25°C; f. ClCSOPh, DMAP, CH_2Cl_2, 25°C;

g. Bu_3SnH, catalyst AIBN, benzene, reflux; h. LDA, THF, -78°C;

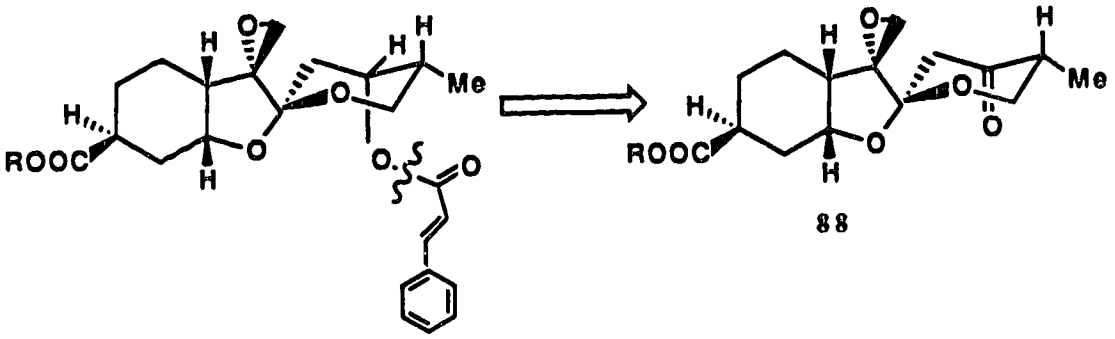
Scheme 18 (cont'd)



l. 5% aq. HF, MeOH, 25°C; J. Py-SO_3, Me_2SO, TEA, 25°C;
k. L-Selectride, THF, -78°C
l. H_2, 55 psi, W-2 Raney Ni, $B(OH)_2$, 15 % aq. MeOH, 25°C;
m. CF_3SO_3H, CH_2Cl_2, 25°C; n. $Me_2S(O)=CH_2$, THF, 0°C;
o. *trans*-PhCH=CHCOCl, DMAP, CH_2Cl_2, reflux

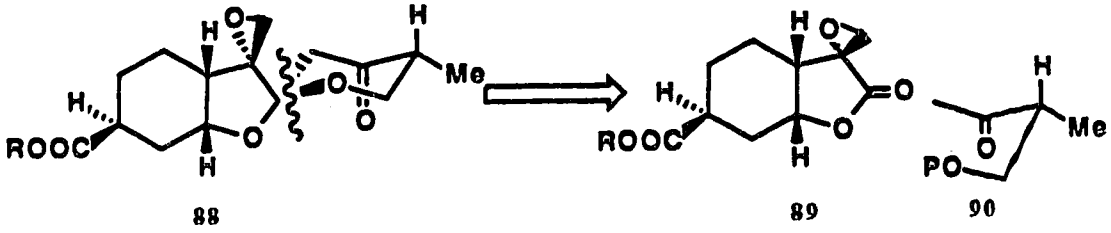
stereoisomer was epimerized at a later stage. Removal of the terminal hydroxyl protecting group, liberation of the β-hydroxy ketone array from the isoxazoline ring, and kinetically controlled, acid-catalyzed spiroketalization formed spiroketal **87**, an intermediate identical to that achieved by Williams.

When our work on (+)-phyllanthocin was initiated, only a few syntheses were reported of this novel, biologically potent compound. We also chose to employ a convergent approach to the syntheis of phyllanthocin. First, dissection of the ester functionality at C10 would give ketone **88**.



88

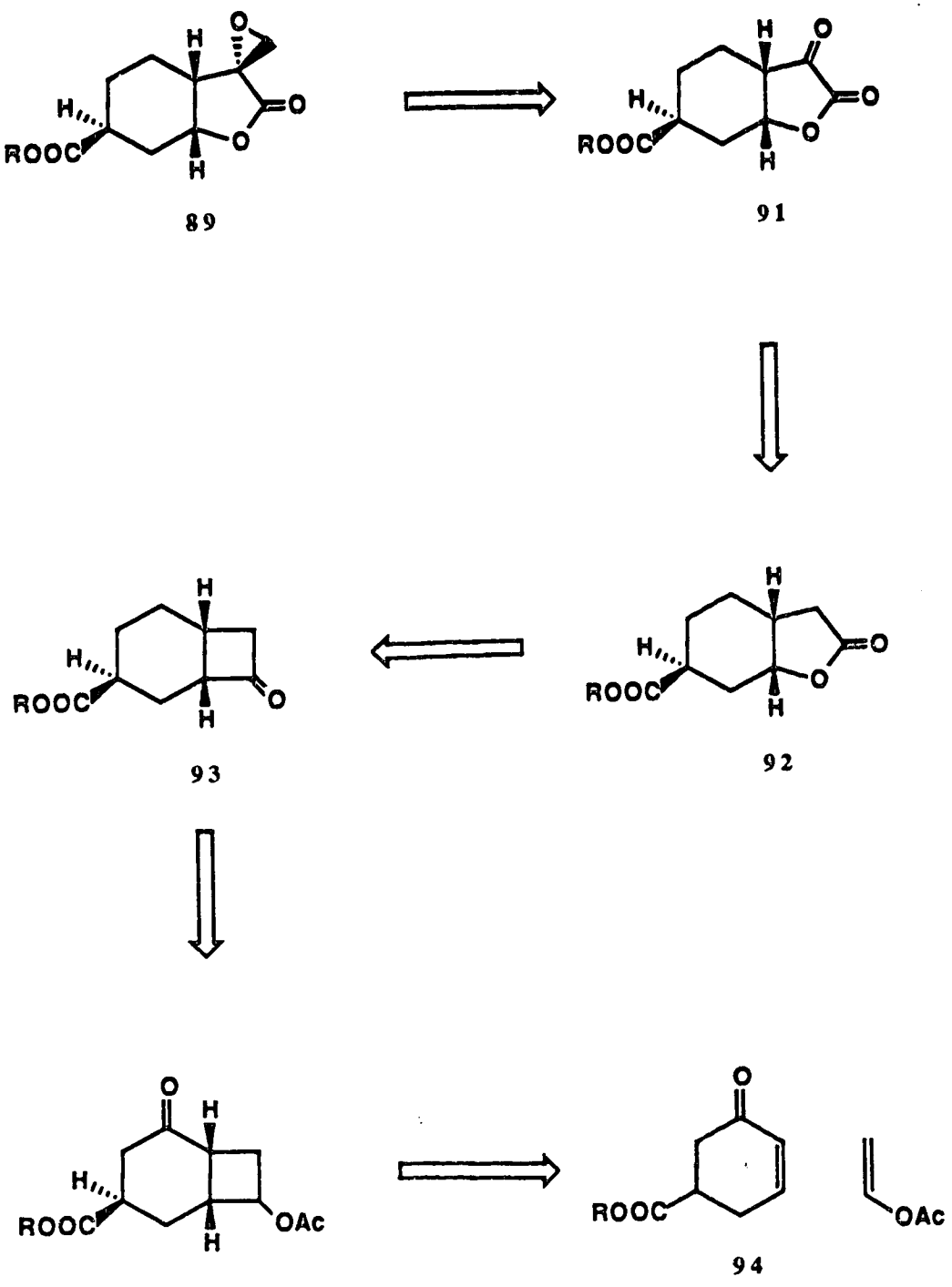
The key dissection at the C8-C9 bond, would yield two crucial sub-target molecules, a spiroepoxybutyrolactone **89** and the protected (P) keto-alcohol **90**.



Our approach differs predominantly in the construction of the bicyclic AB ring system, as outlined in Scheme 19. In order to obtain the correct stereochemistry at the C7 position, the spiroepoxide would have to be derived from addition of a sulfonium ylide to the carbonyl group from the least hindered side The required precursor would then be keto-lactone **91**. This compound in turn would have to be prepared by oxidation of butyrolactone **92**. Further retrosynthetic analysis renders the bicyclic cyclobutanone **93** as a key intermediate. We envisioned its preparation via a [2+2] photocycloaddition reaction, and so consequently enone **94** was the important precursor. In contrast to previous reported syntheses, our approach employed a starting material which already possessed the desired functionality at the C3 position.

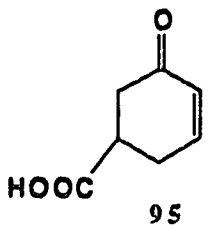
Based on the strategy outlined above, an advanced key intermediate towards the synthesis of phyllanthocin has been achieved. The details of this work are described in the last chapter.

Scheme 19

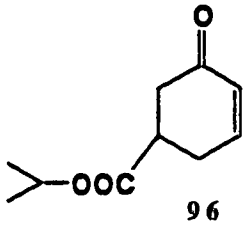


Results and Discussion

Enone **95** or **96** was envisioned as a good precursor for ring A of phyllanthocin for several reasons. First, it was suitably functionalized with the enone system such that ring B could be constructed onto it. Second, the appendage at C-5 (numbering of enone **95** or **96**) was already at the correct oxidation level, and third, this appendage at C-5 could hopefully be used to influence the relative stereochemistry of the ring juncture positions (C-1, C-6 of bicyclic system) to this appendage (C-4, of bicyclic system).



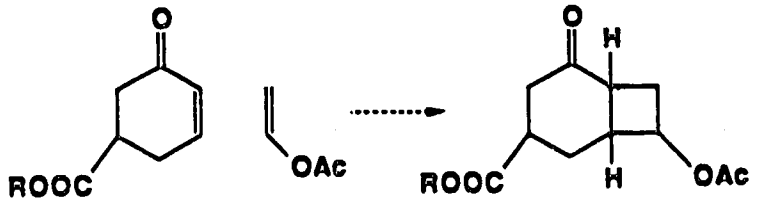
95



96

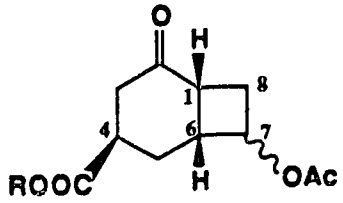
The bicyclo[4.2.0]octane ring system could be rapidly constructed by the photocycloaddition of enone **95** or **96** with vinyl acetate (Eqn 32). Vinyl acetate was chosen as the enone counterpart because it adds regioselectively in a head-to-tail fashion to enones. This would yield a photoadduct with an oxygenated functionality at the C-7 position as desired, rather than at C-8 (numbering of bicyclic ketone **97**). 1,1-Dialkoxyethenes have also been used in photocycloaddition reactions to provide head-to-tail adducts oxygenated at C-7. However, their

preparation is difficult, whereas vinyl acetate is commercially available.



Eqn 32

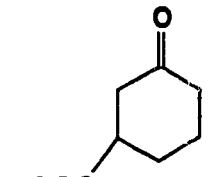
Although a mixture of stereoisomers should result from the photocycloaddition step, the stereoisomer that is required is that in which the appendage at C-4 is *cis* to the ring juncture hydrogens, as depicted in **97**. It was thought that by the use of a suitable functionality in the enone molecule, that is the acid enone **95** or the ester enone **96**, it would be possible to influence the relative stereochemistry of critical stereocenters (C-1, C-4, and C-6) in the photoadduct either on the basis of hydrogen bonding or steric effects. Although a mixture of isomers will also result at the C-7 position, this is of no consequence since this stereocenter will be destroyed at a later stage.



97

Biffin, Moritz and Paul[84] have reported the preparation of enone **95** in 73% yield by Birch reduction of m-methoxybenzoic

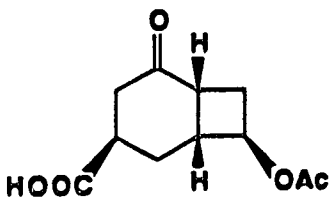
acid using sodium metal, methanol, and liquid ammonia, followed by treatment with 1N aqueous hydrochloric acid to effect hydrolysis. Enone **95** was prepared according to this procedure with the only modification being the use of THF as the solvent for the acidic hydrolysis step. In this manner the enone acid was obtained in 70% yield. In addition, the tetrahydro reduction product, cyclohexanone **98** was obtained in 20% yield. This compound displayed a hydroxyl absorption (O-H, 3150 cm^{-1}), and carbonyl absorptions for the acid (1733 cm^{-1}) and the ketone (1712 cm^{-1}). In the ^1H nmr, the signal at δ 2.88 which appeared as a multiplet, was assigned to the methine proton α to the acid. Peaks at δ 2.59 and 2.38 were observed for those methylene protons α to the carbonyl group in the cyclohexanone. In the mass spectrum, the molecular ion was observed at m/z 142.0630, in agreement with the molecular formula $C_7H_{10}O_3$.



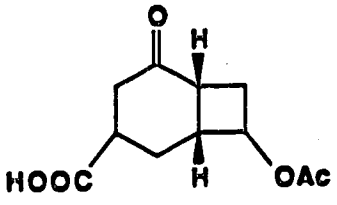
98

With the enone in hand, the next step was the photocycloaddition step. A degassed solution of enone **95** in benzene containing an excess of vinyl acetate, was irradiated for 12 h (450-W Hanovia medium pressure mercury lamp, quartz immersion well, pyrex filter) at 0°C. The crude product from this

reaction was subsequently treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene under reflux for 48 h. Treatment of the crude product in this manner serves two purposes. First, it serves to epimerize the stereocenter α to the ketone carbonyl (C-1 of the bicyclic ring system **97**). Thus the initial photoadducts can be converted from *trans* fused at the ring juncture position to *cis* fused. Secondly, it serves to eliminate those photoadducts which possess the undesired regiochemistry, i.e. those resulting from head-to-head addition of vinyl acetate to the enone. At this point the crude product consisted of two spots by tlc. After separation it was found that the less polar spot consisted of a single stereoisomer, isolated in 27% yield. On the basis of the following discussion of its spectral data, this compound was assigned structure **99**. The more polar spot, isolated in 35% yield, consisted of a mixture of three stereoisomers. The ir spectrum for this mixture **100** displayed a hydroxyl absorption (br, 3000 cm^{-1}), and two carbonyl absorptions (1734 cm^{-1} for the acid and acetate, 1707 cm^{-1} for the ketone). The ^1H nmr displayed only two methine protons in the acetate region (δ 5.08, m and δ 4.68, m), however in the region of 2 ppm, where the methyl group of the acetate appears, three singlets were observed indicating this was a mixture of three compounds. The molecular ion was not observed in the mass spectrum for the mixture, however the base peak at m/z 166.0630 corresponded to that formed by the loss of acetic acid $[M - 60]^+$, as is readily possible for these compounds.



99



100

In the infrared spectrum of compound **99** there appeared a hydroxyl absorption (br, 3200 cm^{-1}) for the O-H of the carboxylic acid. There was another absorption at 1737 cm^{-1} for both the acid and the acetate carbonyl, and one at 1715 cm^{-1} corresponding to the ketone carbonyl. The chemical ionization mass spectra (cims) using ammonia showed an $[M + 18]^+$ peak at m/z 244, consistent with the molecular formula $C_{11}H_{14}O_5$.

Since distinctive resonances were displayed by single protons in the ^1H nmr, the spectrum of this compound was very informative with regard to its structure. By conducting a number of experiments, it was possible to achieve the complete proton assignment and to determine all the coupling constants. First, extensive decoupling experiments were carried out. For example, by irradiation of the signal at δ 4.80, H-7 (dddd, J = 1.5, $J' = J'' = J''' = 7.5$ Hz) it was determined that this proton was coupled to the signal at δ 2.80, H-1 (dddd, J = 1.5, J' = 2.5, $J'' = J''' = 10$ Hz) by 1.5 Hz, and by 7.5 Hz to each of the signals at δ 3.10, H-6 (ddddd, J = 1, J' = 2.5, J'' = 6, J''' = 7.5, J'''' = 9.5 Hz), δ 2.65, H-8α (dddd, J = 1, J' = 2.5, J'' = 7.5, J''' = 11 Hz), and δ 2.22, H-8β (ddd, J = 7.5, J' = 10, J'' = 11 Hz). Similarly, by

irradiation of the signal at δ 3.10, H-6, it was determined that this proton was coupled to H-8α (δ 2.65) by 1 Hz, to H-5α (δ 2.22) by 2.5 Hz, to H-5β (δ 1.90) by 6 Hz, to H-7 (δ 4.80) by 7.5 Hz, and to H-1 (δ 2.80) by 10 Hz. By carrying out this type of decoupling similarly for each of the signals, that is decoupling first one proton of a coupled pair and then the other, it was possible to discern and confirm coupling values and coupling partners. In this manner it was possible to determine the coupling constants associated with each proton, and fully assign the spectrum. Although these experiments led to an unambiguous assignment of the six membered ring protons, this was not true for the assignment of C-7 and C-8 protons of the four membered ring.

The determination of the stereochemistry at C-7, as well as the assignment of each of the methylene hydrogens at C-8 were more challenging. It is known that four membered rings may adopt a planar or a puckered conformation. In the puckered conformation, substituents or hydrogens may have two different orientations with respect to the ring, namely *pseudo-axial* or *pseudo-equatorial*, and the population of these conformers will influence the nmr characteristics of the compound. For these reasons, the use of proton-proton vicinal coupling constants for the assignment of relative configuration of protons in a cyclobutane ring is unreliable. Values of reported vicinal coupling constants for J_{cis} and J_{trans} may be quite different , and the ranges often overlap. Values for J_{cis} range from 4.6 to 11.5 Hz, whereas values for J_{trans}

vary from 2.0 to 10.7 Hz.[85] Nuclear Overhauser enhancement difference spectroscopy (nOeds) has been used to determine whether substituents are relatively close in space.[86] A nuclear Overhauser effect would be expected to occur between *cis* protons even when the ring is not planar; the distance between *cis* protons remains small and this should result in a detectable nOe which would not be the case with *trans* oriented protons.

An nOe study on compound **99** provided evidence for the exo orientation of the acetate group at C-7. By saturation of the signal at δ 3.00 (H-4), an enhancement of 11% was observed at δ 4.80 (H-7). When the complementary experiment was carried out, that is when δ 4.80 (H-7) was saturated, an enhancement of 6% was observed at δ 3.00 (H-4). This experiment indicated that the methine protons of the acid and acetate were in close proximity, and consequently established the exo orientation of the acetate group. When H-7 was saturated, besides the enhancement at H-4, a 6% enhancement was also observed for the signal at δ 2.65 (H-8α). This established the *cis* relationship between the signals at δ 4.80 (H-7) and 2.65 (H-8α). Saturation of the signal at δ 3.10 (H-6) resulted in an enhancement of 2% to the signal at δ 2.80 (H-1), 3% to the signal at δ 1.90 (H-5β) and finally a 6% enhancement for the signal at δ 2.10 (H-8β). This established the *cis* relationship between these protons around the four membered ring, i.e. that H-6 and H-1 are *cis*, H-6 and H-8β are *cis*, as well as H-6 and H-5β.

A two dimensional nOe (NOESY) was carried out on this stereoisomer, and the results are illustrated in Figures 2 and 3. From this experiment, the nOe previously observed between the signal at δ 4.80 (H-7) and that at δ 3.00 (H-4) was confirmed. Correlations for the following signals: δ 2.70 (H-3α) with that at 2.47 (H-3β), the signal at δ 2.65 (H-8α) with the one at 2.22 (H-8β), and finally the signal at δ 2.22 (H-5β) with 1.88 (H-5α) confirmed the previous assignment of these pairs of signals as geminal partners.

A COSY-90 (^{1}H-^{1}H correlation spectrum) was carried out to further confirm the assignment. These results are illustrated in Figure 4, with the expansion in Figure 5.

The most notable features in the ^{1}H nmr spectrum is the long range coupling (^{4}J) between signals. In the cyclohexane portion of the molecule, the signals at δ 2.70 (H-3α) and δ 2.22 (H-5α) exhibited a 1 Hz coupling. This type of four bond coupling is typically observed for those protons diequatorially disposed to one another and oriented in a "W" fashion,[87] as illustrated in Figure 6.

In addition, a long range four bond coupling of 1.5 Hz was also observed between H-1 and H-7. By inspection of Dreiding models, it was not obvious how this coupling comes about since

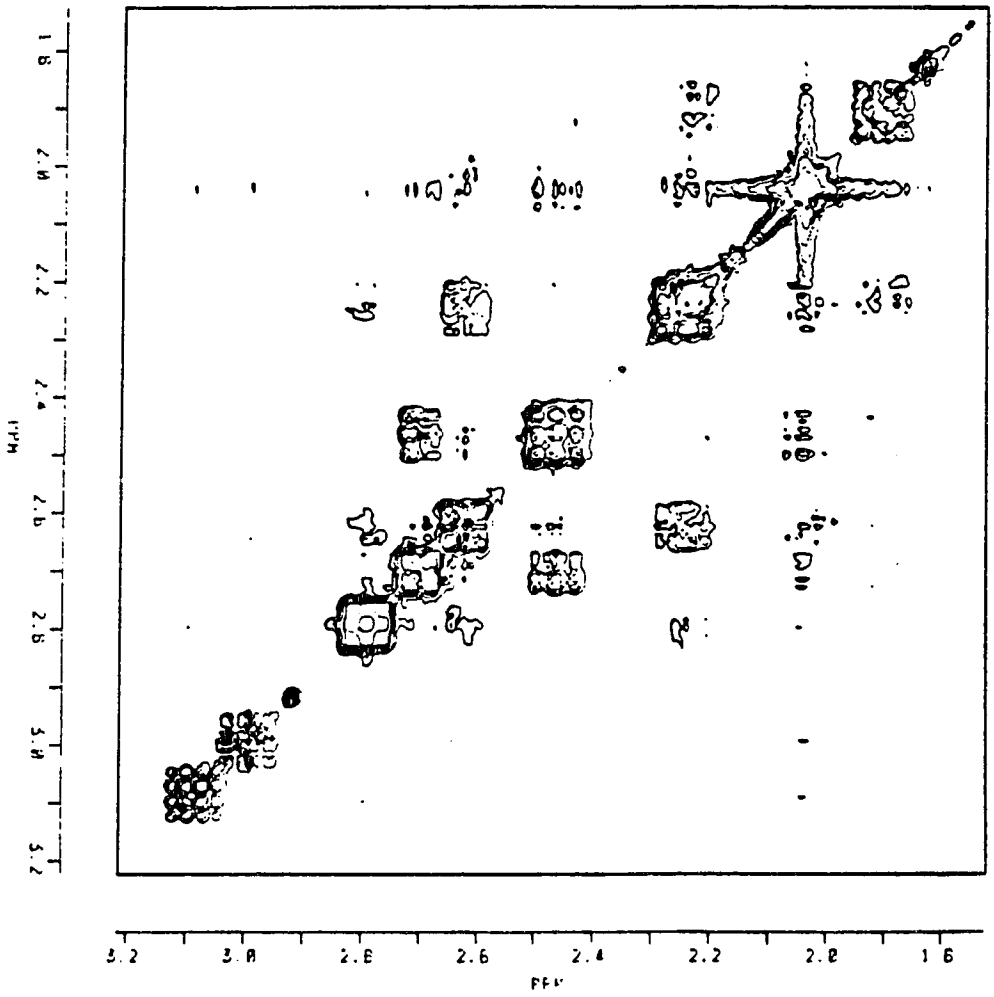


Figure 2. NOESY Spectrum of compound **99**.

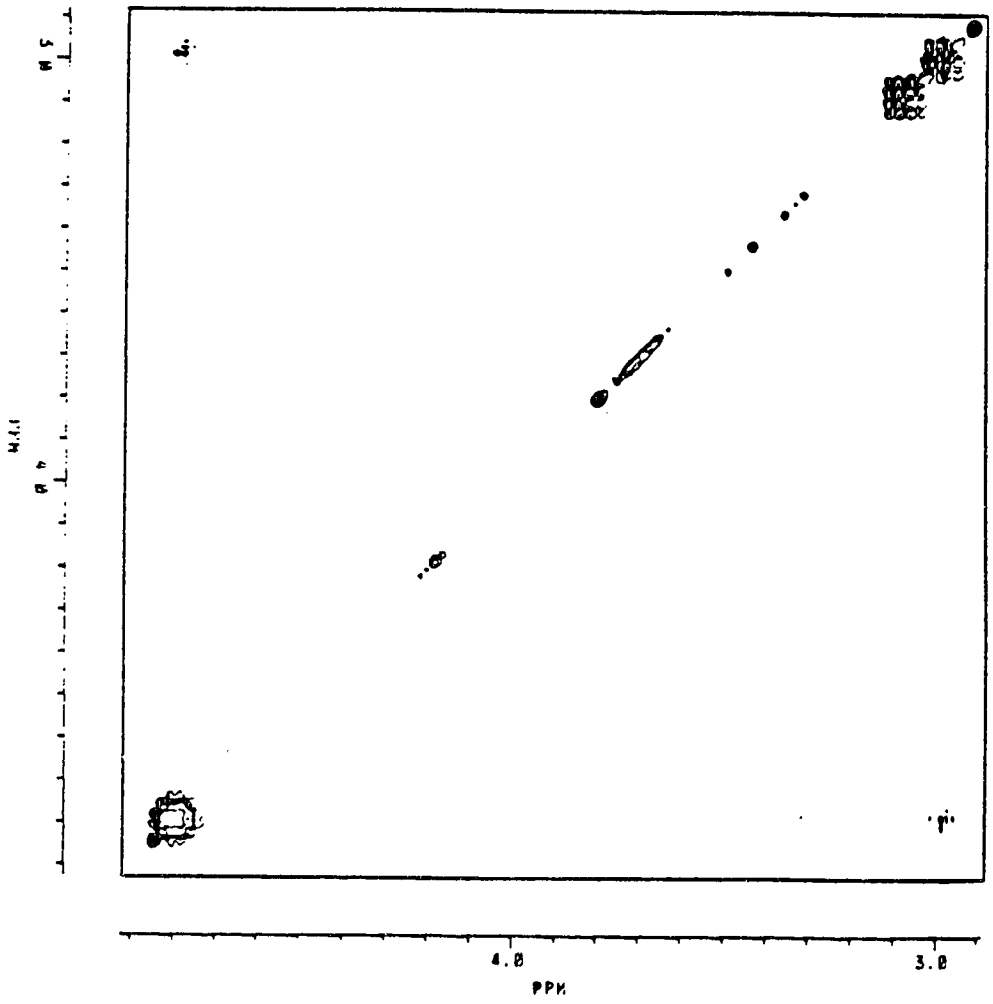


Figure 3. NOESY Spectrum of compound **99**. (continued)

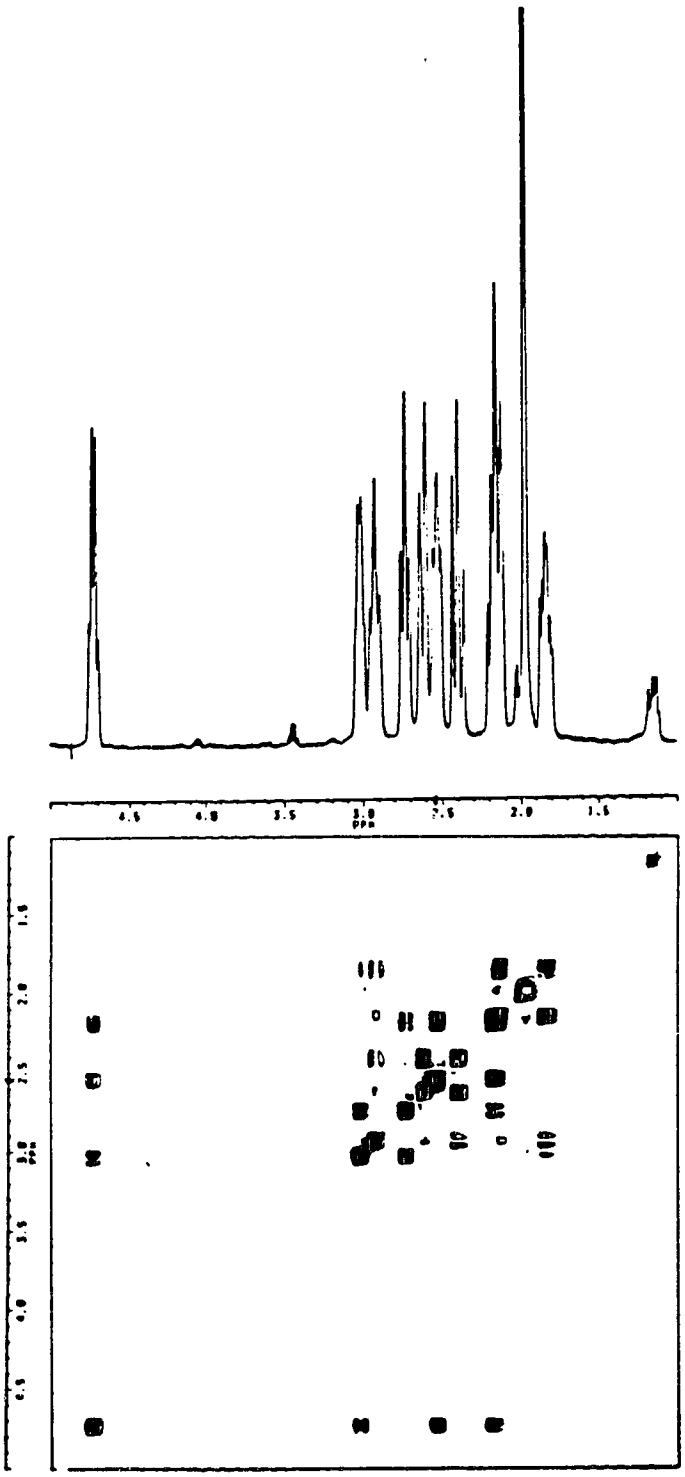


Figure 4. COSY-90 Spectrum of compound **99**.

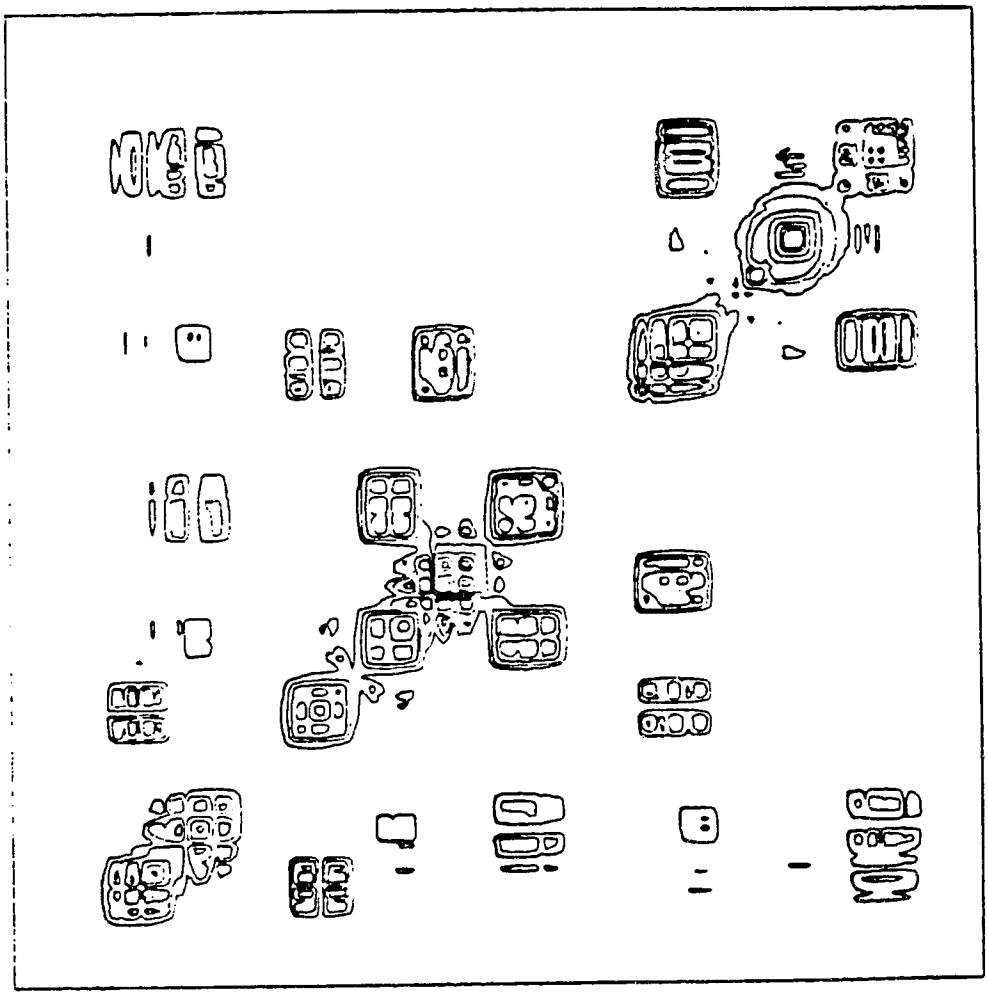


Figure 5. Expansion of COSY-90 Spectrum of compound **99.**

Table 4. 400 MHz ^{1}H nmr data for compound **99**

Proton	Chemical Shift (δ)	Number of Hydrogens	Multiplicity (coupling constant in Hz)
H-7	4.80	1	dddd (1.5, 7.5, 7.5, 7.5)
H-6	3.10	1	ddddd (1, 2.5, 6, 7.5, 9.5)
H-4	3.00	1	dddd (3.5, 3.5, 12, 12)
H-1	2.80	1	dddd (1.5, 2.5, 10, 10)
H-3 α	2.70	1	ddd (1, 3.5, 15)
H-8 α	2.65	1	dddd (1, 2.5, 7.5, 11)
H-3 β	2.47	1	dd (12, 15)
H-8 β	2.22	1	ddd (7.5, 10, 11)
H-5 α	2.22	1	dddd (1, 2.5, 3.5, 14)
H-11	2.02	3	s
H-5 β	1.90	1	ddd (6, 12, 14)

these two protons are not oriented in a W fashion. This is similarly true for H-6 and H-8a, for which a 1 Hz coupling was observed.

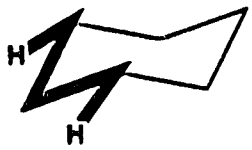


Figure 6. Long range hydrogen coupling in cyclohexane systems

The results of these experiments are summarized in Table 4. Figure 7 shows the structure of the compound for correlation with proton spin systems outlined in Scheme 20. This scheme illustrates the spin systems between coupled partners. The solid lines between protons indicate the three bond couplings (^3J) and the dashed lines indicate long range four bond couplings (^4J).

The ^{13}C results are summarized in Table 5. The assignment was achieved with both an APT spectrum, as well as a two dimensional ^1H-^{13}C correlation spectrum (Figure 8)

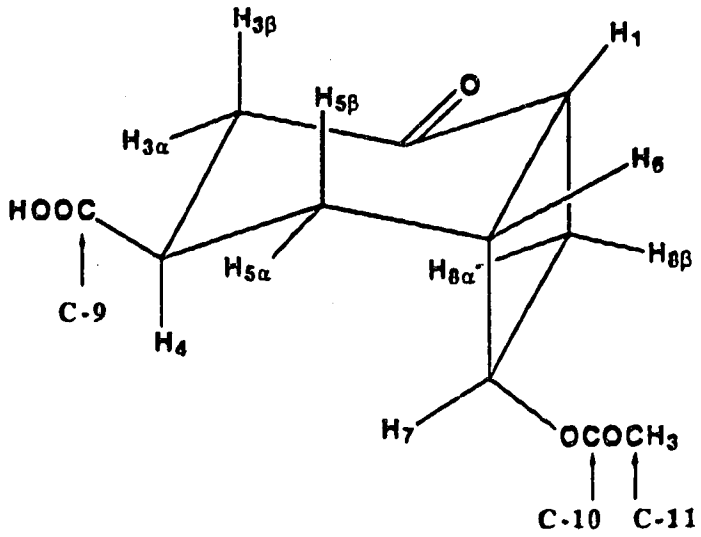
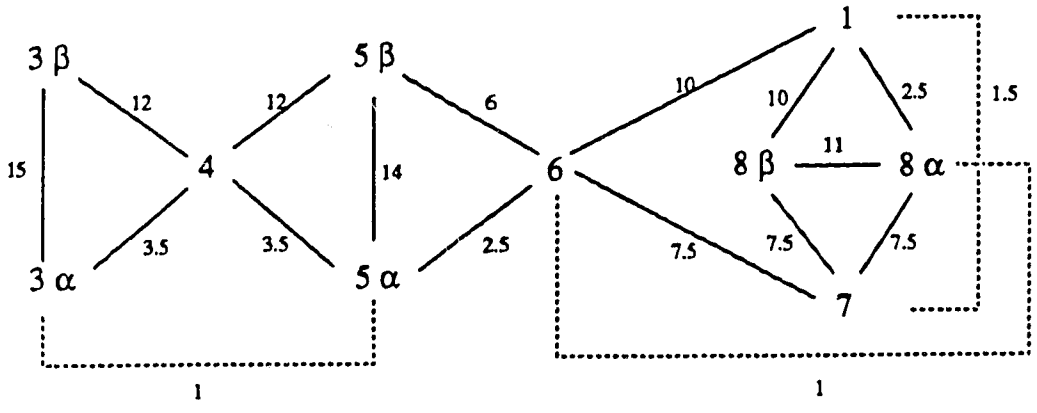


Figure 7. Structure of compound **99**

Scheme 20



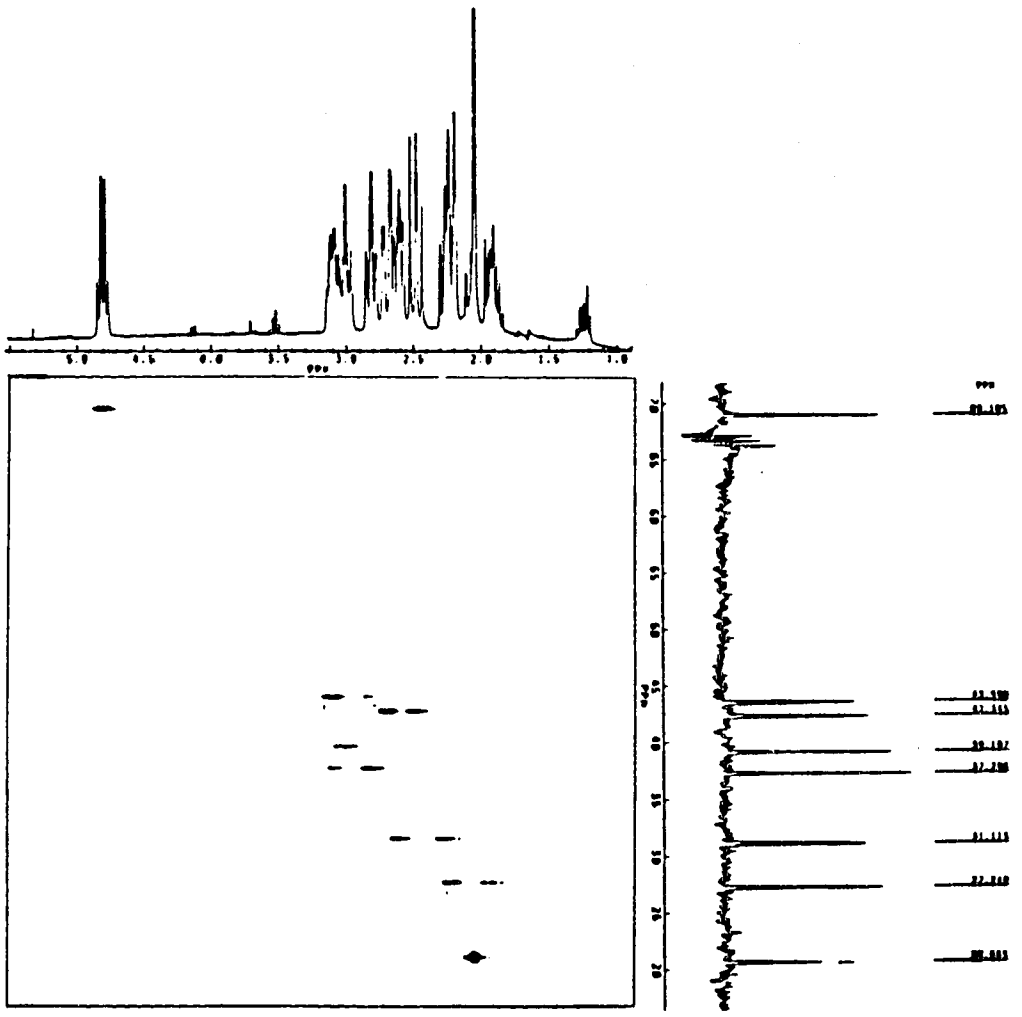


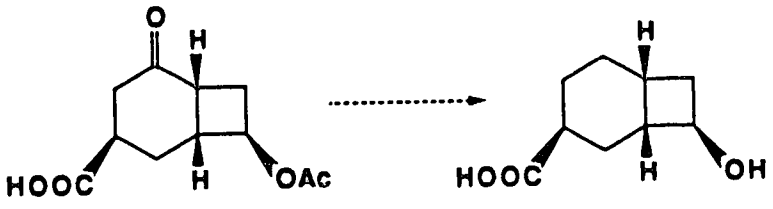
Figure 8. ^{1}H-^{13}C Correlation Spectrum of compound **99**

Table 5. ^{13}C nmr data for acid **99**

Carbon	Chemical Shift (δ)	Multiplicity
C-2	210.8	s
C-9	178.6	s
C-10	170.5	s
C-7	69.2	d
C-6	43.9	d
C-3	42.6	t
C-4	39.4	d
C-1	37.5	d
C-8	31.3	t
C-5	27.5	t
C-11	20.9	q

Having constructed the bicyclo[4.2.0]octane ring system, the next step involved the conversion of the ketone carbonyl into a methylene unit. Although there are a number of multistep methods[88] which could serve to effect such a transformation, there are only two reactions which involve direct single step operations: the Clemmenson[89] and the Wolff-Kishner reactions.[90] Of the two, the Wolff-Kishner reduction was preferable because in principle not only could it effect reduction, but under the strongly basic reaction conditions, deacetylation could also be effected (Scheme 21). Towards this end, keto-acetate **99** was treated with hydrazine and potassium hydroxide in ethylene glycol at 200°C. These conditions disappointingly resulted in extensive decomposition.

Scheme 21



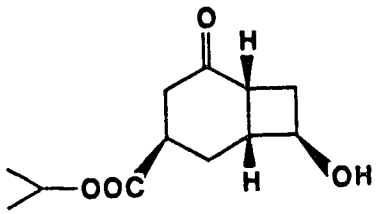
99

We thus turned our attention towards milder methods for the complete reduction of the carbonyl group. One method which involves the overall conversion of a ketone to a methylene unit under mild conditions first involves the conversion of the ketone to its thioacetal,[58] followed by treatment with Raney nickel.[91] In

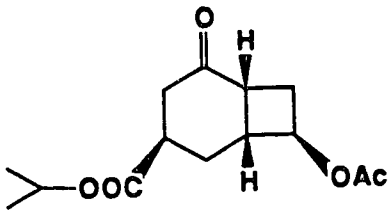
addition, for convenience we decided to work with the ester rather than the acid.

Esterification can be effected by a number of different methods.[92] Among those available, acidic conditions had the added advantage that besides esterification, deacetylation to the alcohol could be effected *via* transesterification. This would effectively combine two steps into one, since a deacetylation step would eventually have to be carried out. We decided to employ the Fisher esterification method[93] in which the carboxylic acid is treated with a large excess of an alcohol in the presence of a mineral acid.

Acid-acetate **99** was dissolved in dry isopropyl alcohol through which anhydrous hydrogen chloride was bubbled. This resulted in the formation of two products in 56% yield and 11% yield, assigned structures **101** and **102**, respectively.



101



102

The major compound **101**, was that in which both esterification and deacetylation had taken place. This compound displayed three significant absorption bands in the ir spectrum:

one at 3440 cm^{-1} for the O-H stretch of the alcohol, and two carbonyl stretches, one at 1727 cm^{-1} and another at 1708 cm^{-1} for the ester and ketone carbonyls respectively. The ^1H nmr spectrum displayed a septet at δ 5.03 for the methine proton of the isopropyl ester, as well as a doublet at δ 1.25 for the methyl groups of the isopropyl ester. This indicated that the isopropyl ester had indeed been formed. The combination of an upfield shift for the quartet for the methine C-7 proton from δ 4.80 (in the acetate) to δ 4.00, as well as the absence of the acetate methyl singlet at δ 2.04 confirmed that deacetylation had taken place. The mass spectrum of this compound showed a molecular ion at m/z 226.1205, consistent with the formula $C_{12}H_{18}O_4$.

The minor compound **102** was that in which only esterification had taken place, while leaving the acetate group intact. The ir spectrum for this compound had two carbonyl absorptions, one at 1731 cm^{-1} for both the ester and acetate, and one at 1713 cm^{-1} for the ketone. The mass spectrum of this compound displayed a molecular ion at m/z 268.1311 consistent with the molecular formula $C_{14}H_{20}O_5$.

The ^1H nmr spectrum for ester **102** compared very closely to that previously obtained for acid **99**. The chemical shifts and the coupling patterns observed for each proton were almost identical. Besides those signals common to the acid, ester **102**

also had the signals indicative of the isopropyl ester: a septet at δ 5.02 and the two doublets, one at δ 1.25 and one at δ 1.27. Interestingly, in comparing the spectra of **99** and **102**, the only two protons which had the same chemical shift in the acid, H-8β and H-5α each at δ 2.22, were now resolved in the ester: H-8β was at δ 2.23, and H-5α was at δ 2.14. Furthermore, the two protons H-3α and H-8α which had coalesced at δ 2.63 in the ester were distinct in the acid: H-3α at δ 2.70 and H-8α at δ 2.65. Thus the complete spectral assignment was achieved only with the ^{1}H nmr spectra of both the acid and the ester. The assignment of individual protons in ester **102** was achieved by both comparison with those results previously obtained for the acid, and with the same type of extensive decoupling experiments previously described that were conducted on the acid. The ^{1}H nmr results obtained for this compound are summarized in Table 6.

Table 6. 400 MHz ^{1}H nmr data for ester **102**

Proton	Chemical Shift (δ)	Number of Hydrogens	Multiplicity (coupling constant in Hz)
H-10	5.02	1	septet (6.5)
H-7	4.78	1	dddd (1.5, 7.5, 7.5, 7.5)
H-6	3.06	1	dddd (2.5, 6, 7.5, 9.5)
H-4	2.88	1	dddd (3.5, 3.5, 12, 12)
H-1	2.77	1	dddd (1.5, 2.5, 10, 10)
H-3 α	2.63	1	dd (3.5, 15)
H-8 α	2.63	1	ddd (2.5, 7.5, 11)
H-3 β	2.45	1	dd (12, 15)
H-8 β	2.23	1	ddd (8, 10, 11)
H-5 α	2.14	1	ddd (14, 3, 3)
H-9	2.04	3	s
H-5 β	1.86	1	ddd (6, 12, 14)
H-12	1.27	3	d (6.5)
H-11	1.25	3	d (6.5)

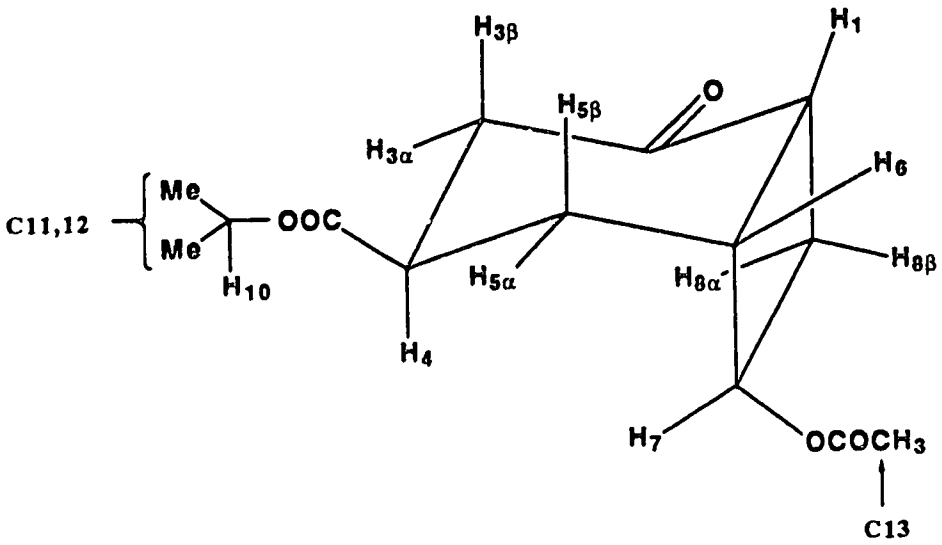
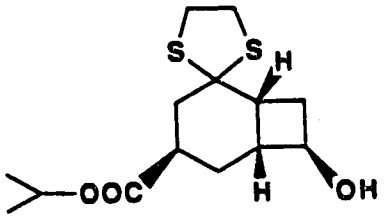


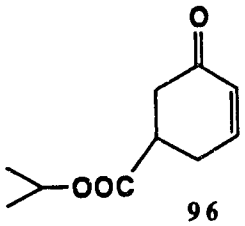
Figure 9. Structure of compound **102**

With keto-alcohol **101** in hand, we set out to prepare the thioacetal. Treatment with boron trifluoride etherate and 1,2-ethanedithiol in methylene chloride at 0°C afforded thioacetal **103** in 95% yield. The ir spectrum of this compound showed absorbances at 3400 cm^{-1} (hydroxyl group) and 1724 cm^{-1} (ester carbonyl). The ^1H nmr spectrum showed the presence of the thioacetal group by the multiplet at δ 3.26 for the methylene protons adjacent to the sulfur. The isopropyl ester was intact (δ 5.00, septet; δ 1.23 and δ 1.25 each doublet), as was the cyclobutanol moiety (δ 4.28, ddd, $J = J' = J'' = 7.5$ Hz).



103

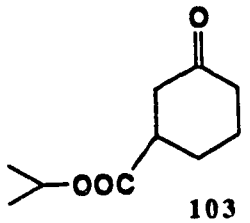
Treatment of thioacetal **103** with Raney nickel in benzene at room temperature for 10 h, led to a complex mixture of products. Examination of the crude products by ^1H nmr indicated that the cyclobutanol portion of the molecule had been cleaved. Consequently we decided to attempt the desulfurization while still at the acetate stage. In this regard we required keto-ester **102**. Rather than using acidic conditions to prepare this compound, the ester could be formed under basic conditions from acid-acetate **99** using potassium carbonate and isopropyl iodide in refluxing acetone.[94] In this manner keto-ester **102** was prepared in 94% yield.



96

Keto-ester **102** can also be prepared by the photocycloaddition of enone-ester **96** with vinyl acetate. This was a more appealing route towards the preparation of this compound, since it bypassed compound **99** altogether, along with the

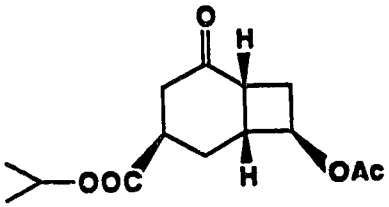
difficulties associated with the preparation of compound **99** in terms of solubility and purification. Towards this end we decided to prepare the isopropyl ester-enone **96** from enone-acid **95**. Treatment of the acid **95** with potassium carbonate and isopropyl iodide in refluxing acetone for 71 h gave **96** in 65% yield. Due to the length of time required for this reaction, and in the hopes that the yield could be optimized, we attempted the esterification using the Fisher conditions previously described. Treatment of enone-acid **95** with anhydrous hydrogen chloride in the presence of an excess of isopropyl alcohol resulted in the disappearance of the starting material by tlc within 3 h. However the short reaction time turned out to be at the expense of yield; enone-ester **96** was isolated in only 41% yield. The ir spectrum of ester **96** displayed absorbances at 1728 cm^{-1} for the ester carbonyl and at 1683 cm^{-1} for the carbonyl of the enone system. The ^1H nmr spectrum confirmed the formation of the ester by the signals at δ 5.02 (septet), and the doublets at δ 1.21 and δ 1.23. The presence of the enone system was indicated by the signals at δ 6.95 (ddd, J = 10, J' = J'' = 5 Hz) and δ 6.05 (ddd, J = 10, J' = J'' = 2 Hz) for the β and α enone protons, respectively. The remaining signal at δ 2.63 was assigned to the two methylene units, α and γ to the enone carbonyl.



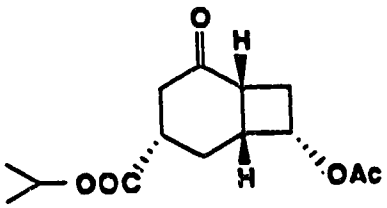
103

Alternatively, enone **96** could be prepared more directly by modification of the Birch reduction. Treatment of m-methoxybenzoic acid with sodium metal and liquid ammonia in isopropyl alcohol, followed by hydrolysis in isopropyl alcohol using anhydrous hydrogen chloride afforded enone **96** in 30% yield overall, along with the overreduced compound, ester **103**, isolated in 11% yield. When the reaction was conducted in the same fashion using lithium metal instead of sodium, enone **96** was isolated in 43% yield, along with 13% of compound **103**. The advantage of this sequence is that it involves one less step in the preparation of enone **96**. Cyclohexanone **103** displayed the following spectral data: in the ir spectrum it displayed a single absorption at 1727 cm^{-1} (br) for the carbonyls of the ester and the ketone. In the ^1H nmr spectrum, the ester functionality was present as indicated by the peaks at δ 4.96 (septet) for the methine proton of the isopropyl group and at δ 1.17 (d) for the methyl groups of the isopropyl functionality. The rest of this spectrum displayed signals very similar to those observed for compound **98**. In the mass spectrum, the molecular ion was observed at m/z 184.1099, in agreement with the formula $C_{10}H_{16}O_3$.

Irradiation of enone ester **96** in the presence of an excess of vinyl acetate for 11 h in benzene at 0°C, in the same manner as previously described for the acid, led to a mixture of photoadducts, which was subsequently refluxed with DBU in benzene for 48 h. The mixture resulting from this photocycloaddition consisted of four diastereomers in a 3 : 1.4 : 1 : 2.7 ratio (by ^{1}H nmr) and in a combined yield of 63%. As found for the photoadducts derived from the enone acid, the tlc of this mixture also consisted of two spots. Separation revealed the less polar spot consisted of a single stereoisomer, with identical spectral data as that found for compound **102**. The second spot consisted of the three stereoisomers. By careful chromatographic separation some of each stereoisomer was obtained pure. These compounds were tentatively assigned the structures **104**, **105**, and **106**, on the basis of a combination of spectral data and subsequent chemical manipulation. These assignments will be presented later. For ease of discussion, the compounds will be referred to as isomers 1 (**102**), 2 (**104**), 3 (**105**), and 4 (**106**) respectively, on the basis of order of elution. Compounds **102** (isomer 1) and **106** (isomer 4) were later found to be epimeric at the acetate, as were compounds **104** (isomer 2) and **105** (isomer 3).



102



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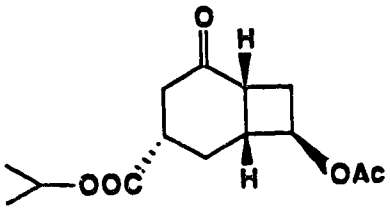
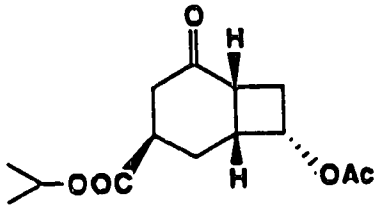


105



106

In the ir spectrum, compound **104** (isomer 2) displayed carbonyl absorptions at 1730 cm^{-1} (ester and acetate) and 1707 cm^{-1} (ketone). The ^1H nmr spectrum displayed a peak at δ 5.05 (m) for the methine protons of both the ester and the acetate. The acetate methyl absorbed at δ 2.07 (s) and the methyl groups of the ester appeared as a doublet at δ 1.25. The cims of compound **104** showed an $[M + 18]^+$ peak at m/z 286, in agreement with the formula $C_{14}H_{20}O_5$.

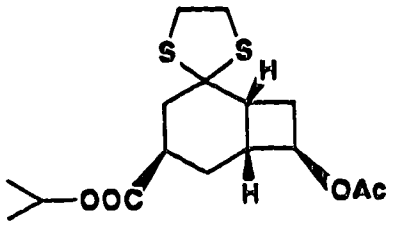
Compound **105** (isomer 3) displayed only one broad carbonyl absorption at 1729 cm^{-1}. The ^1H nmr spectrum of this compound showed the presence of the ester with the signals at δ 5.02 (septet) and δ 1.24 (d). In addition, the acetate methine proton appeared at δ 4.68 (m), and the acetate methyl group appeared at δ 2.04 (s). The cims of this compound shows an $[M + 18]^+$ peak at m/z 286, in agreement with the formula $C_{14}H_{20}O_5$.

Compound **106** (isomer 4) had a broad carbonyl absorption in the ir spectrum at 1726 cm^{-1} for the three carbonyl groups in the molecule. The ^1H nmr spectrum displayed the methine proton of the acetate relatively downfield compared to the other isomers, at δ 5.10 (m), and the acetate methyl group absorbed at δ 2.06 as a singlet. However this signal overlapped with another proton which absorbed as a multiplet. The isopropyl group methine proton absorbed at δ 5.00 (septet) and the isopropyl methyl groups appeared at δ 1.24 (d). The mass spectrum of this compound displayed the molecular ion at m/z 268.1310, which corresponds to the formula $C_{14}H_{20}O_5$.

With each of the four pure stereoisomers in hand, we set about towards the conversion of the ketone carbonyl to a methylene unit, particularly while still at the acetate stage. Thioacetalization of keto-acetate **102** (1,2-ethanedithiol and boron trifluoride etherate in methylene chloride at 0°C), afforded thioacetal **107** in 98% yield.

The ir spectum of thioacetal **107** showed absorptions at 1736 and 1727 cm^{-1} for the ester and acetate carbonyls. The ^1H nmr spectrum of this compound displayed a signal at δ 3.20-3.36 (br m) corresponding to the methylene protons of the thioacetal functionality. The ester was still intact as shown by the signals at δ 5.00 (septet) and at δ 1.22 and 1.24 (each d). The acetate

functionality was also still present as indicated by the absorptions at δ 5.06 (m) and δ 2.04 (s). The mass spectum of compound **107** showed a molecular ion at m/z 344.1119, consistent with the chemical formula $C_{16}H_{24}O_4S_2$.



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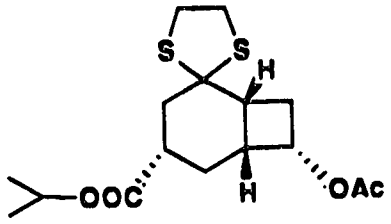

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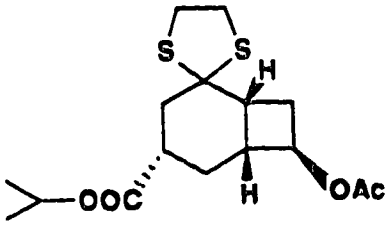

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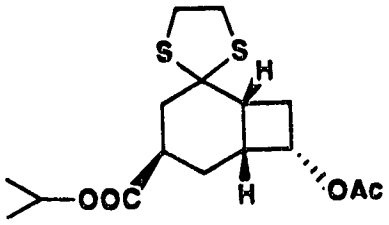


110

Treatment of keto-acetate **104** (isomer 2) in the same manner gave thioacetal **108** in 95% yield. The ir spectrum of this compound displayed a carbonyl absorption at 1725 cm^{-1} due to the ester and acetate. The ^1H nmr spectrum indicated the ester was still intact (δ 5.00 (septet), and δ 1.23, 1.21 (each (d)), as was the acetate (δ 4.78 (m) and δ 2.02 (s)). The thioacetal functionality was present as indicated by the multiplet at δ 3.29. The mass spectum showed a molecular ion at m/z 344.1120 consistent with the chemical formula $C_{16}H_{24}O_4S_2$.

Thioacetalization of keto-ester **105** (isomer 3) gave thioacetal **109** in 81% yield. This compound displayed the ester and acetate carbonyl absorption at 1729 cm^{-1} in the ir spectrum. The ^1H nmr spectrum showed the presence of the ester (δ 4.99 (septet) and δ 1.22 (d)), the acetate (δ 4.51 (d, J = 5.5 Hz) and δ 2.02 (s)), and the thioacetal unit (δ 3.29 (m)). The molecular ion for this thioacetal was observed at m/z 344.1117, in agreement with $C_{16}H_{24}O_4S_2$.

Keto-ester **106** (isomer 4) was similarly treated to provid thioacetal **110** in 73% yield. This compound displayed a singl carbonyl absorption at 1726 cm^{-1} in the ir spectrum for both the ester and the acetate. The ^1H nmr spectrum showed absorptions corresponding to the ester (δ 5.00 (septet) and δ 1.22 (d)), acetate (δ 4.95 (m) and δ 2.02 (s)) and thioacetal (δ 3.25 (m)). The molecular ion for this compound was found at m/z 344.1128 ($C_{16}H_{24}O_4S_2$).

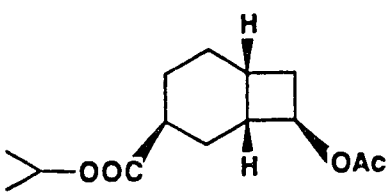
Interestingly, upon thioacetalization, the acetate methine proton of isomer 1 experienced a downfield shift of approximately 0.28 ppm from δ 4.78 to δ 5.06. This is in contrast to the trend observed for the other acetates: upon thioacetalization, isomers 2, 3, and 4 experienced an upfield shift of 0.20, 0.17 and 0.15 ppm, respectively. This may be an indication that the acetate methine

hydrogen is in the shielding region of the ketone carbonyl in compound **102**.

Having the four pure thioacetals in hand, we next set out to effect reduction using Raney nickel. Treatment of thioacetal **107** in benzene with Raney nickel (W-2) provided ester-acetate **111** in 75% yield.

Compound **111** displayed a single carbonyl absorption in the ir spectrum at 1731 cm^{-1} (ester and acetate). In the ^1H nmr spectrum, the loss of the signals at δ 3.20-3.36 (thioacetal functionality) indicated desulfurization had been effected. Both the ester (δ 4.96 (septet) and δ 1.15 (d)) and the acetate (δ 4.94 (q) and δ 1.96 (s)) were intact. The mass spectrum showed a molecular ion at m/z 254.1517 ($C_{14}H_{22}O_4$).

Treatment of thioacetals **108**, **109** and **110** in the same manner led to compounds **112**, **113** and **114** in 91%, 78% and 93% yield, respectively.



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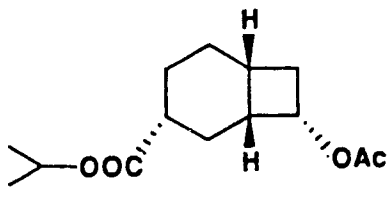

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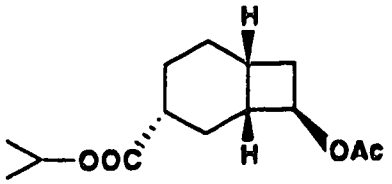

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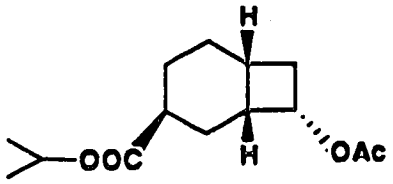


114

Ester-acetate **112** (isomer 2) showed a carbonyl absorption at 1731 cm^{-1} for both the ester and acetate in the ir spectrum. By examination of the ^1H nmr spectrum, it was evident the thioacetal functionality was removed (loss of the signal at δ 3.29) while the ester (δ 4.94 (septet) and δ 1.16 (d)) and acetate (δ 4.79 (m) and δ 2.00 (s)) were intact. The molecular ion of this compound was displayed in the mass spectrum at m/z 254.1522, consistent with the formula $C_{14}H_{22}O_4$.

Ester-acetate **113** (isomer 3), displayed a single carbonyl absorption at 1731 cm^{-1} in the ir spectum. In the ^1H nmr spectrum of this compound, the thioacetal had been removed (loss of the multiplet at δ 3.29), while the ester (δ 4.95 (septet) and δ 1.17 (d)) and acetate (δ 4.71 (ddd, J=4, J'=6, J''=8 Hz) and δ 2.00 (s)) were intact. The molecular ion of this compound was displayed in the mass spectrum at m/z 254.1518, in agreement with the formula $C_{14}H_{22}O_4$.

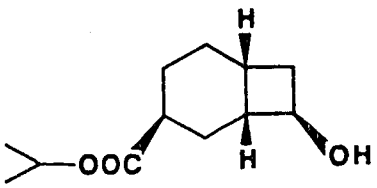
Ester-acetate **114** (isomer 4) displayed two carbonyl absorptions in the ir spectum at 1734 cm^{-1} (acetate) and 1728 cm^{-1} (ester). The ^1H nmr spectrum of this compound

showed no peaks in the 3.3 ppm region, indicating the thioacetal had been removed. It displayed signals for the ester (δ 4.95 (septet) and δ 1.16 (d) and the acetate (δ 4.88 (ddd, $J = J' = J'' = 7.5$ Hz) and δ 2.00 (s)). The mass spectrum displayed a molecular ion at m/z 254.1515, in agreement with the chemical formula $C_{14}H_{22}O_4$.

Having reduced the compound to the methylene analog, we next turned our attention towards the elaboration of the four membered ring. The next key intermediate was the keto-ester corresponding to compound **93** (see Introduction). Deacetylation to the alcohol followed by oxidation to the cyclobutanone should provide the desired keto ester. During the deacetylation step, it was necessary to form the alcohol while leaving the ester functionality intact. Transacetylation using the same alcohol as that involved in the ester functionality of the molecule should effect the desired transformation. We were encouraged by the deacetylation which had been effected earlier during the esterification of acid **99**. Treatment of ester acetate **111** in an excess of isopropyl alcohol with anhydrous hydrogen chloride, formed the desired hydroxy-ester **115** in 79% yield after 24 h. The ir spectrum of this compound showed a hydroxyl absorption (br, 3400 cm^{-1}) and a carbonyl absorption (1727 cm^{-1}) for the ester. In the ^1H nmr spectrum, the isopropyl ester was still present (δ 4.95 (septet) and δ 1.17 (d)). Two features, namely the

upfield shift of 0.84 ppm from δ 4.94 to δ 4.10 for the methine proton, as well as the absence of a singlet at δ 2.00 associated with the acetate methyl group indicated deacetylation had occurred. In the mass spectrum of this compound, the molecular ion was observed at m/z 212.1410, consistent with the formula $C_{12}H_{20}O_3$. Ester-acetates **112** (isomer 2), **113** (isomer 3), and **114** (isomer 4) were similarly treated to give hydroxy-esters **116**, **117**, and **118** in 62%, 74% and 68% yield, respectively.

In the ir spectrum, compound **116** (isomer 2) had a hydroxyl (br, 3400 cm^{-1}) and a carbonyl absorption (1727 cm^{-1}). The ^1H nmr spectrum showed the presence of the ester functionality (δ 5.00 (septet) and δ 1.28 (d)). The acetate was deacetylated to the alcohol as indicated by both the upfield shift of the methine proton by 0.69 ppm from δ 4.79 to δ 4.16, as well as the absence of the singlet at 2 ppm. In the mass spectrum of this compound, the molecular ion was observed at m/z 212.1413, consistent with the formula $C_{12}H_{20}O_3$.



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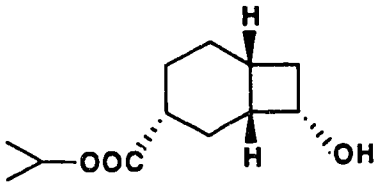

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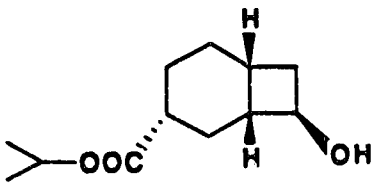

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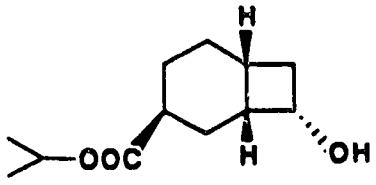


118

The ir spectum of alcohol **117** (isomer 3) showed a hydroxyl absorption (br, 3440 cm^{-1}) as well as a carbonyl absorption for the ester (1726 cm^{-1}). The ^1H nmr spectrum of this compound showed the ester signals (δ 5.00 (septet) and δ 1.22 (d)). The deacetylation was successful as indicated by the methine hydrogen shift of 0.63 ppm upfield from δ 4.71 to δ 4.08. Furthermore there was no singlet around δ 2 ppm, confirming the loss of the acetate. The molecular ion for this compound was observed at m/z 212.1406, in agreement with the formula $C_{12}H_{20}O_3$.

Alcohol-ester **118** (isomer 4), showed a hydroxyl absorption (br, 3440 cm^{-1}) and a carbonyl absorption (1726 cm^{-1}) in the ir spectum. The ^1H nmr spectrum showed the ester (δ 5.00, (septet) and δ 1.20 (d)). The methine hydrogen was shifted from δ 4.88 to δ 4.23, an upfield shift of 0.63 ppm, and there was no singlet at δ 2 ppm. This compound displayed a molecular ion at m/z 212.1417 ($C_{12}H_{20}O_3$.)

In order to accomplish the oxidation of the cyclobutanol moiety to a cyclobutanone, we chose to employ the Swern oxidation.[95] Alcohol **118** was added to a solution of oxalyl chloride

and dimethylsulfoxide in methylene chloride at -20°C. After stirring for 15 min, triethylamine was added, and 5 min later the ice bath was removed. The mixture was allowed to stir at room temperature for 6 h, during which time the starting material was consumed. From this reaction only a small amount of material was obtained, which could not be identified as the required keto ester. Although the methine proton of the alcohol had disappeared in the ^1H nmr spectrum, in the ir spectrum there was no carbonyl absorption in the region of 1780 cm^{-1}, where the carbonyl group in cyclobutanone absorbs.[96]

Pyridinium dichromate (PDC)[97] has been used for the oxidation of alcohols under nearly neutral conditions. When a mixture of alcohols **116-118** was treated with PDC (1.1 eq) in methylene chloride with stirring at room temperature the reaction was observed to be very sluggish; after 21 h mostly starting material remained.

The next alternative was to use pyridinium chlorochromate (PCC). Sometimes however, mixtures of products also result when PCC has been used as the oxidizing agent. This problem has been alleviated in some cases by the use of a superior form of PCC. Cheng and coworkers have reported the use of PCC adsorbed on alumina[98] for the mild oxidation of alcohols. Reagents which have been adsorbed onto solid supports may offer several advantages

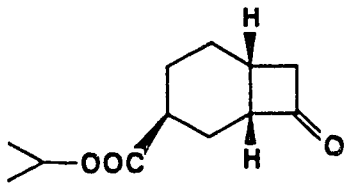
over unsupported reagents.[99] Often the effectiveness of the reagent is increased due to the higher surface area which is available for the reaction. In addition, the reactions are usually clean, rapid, high yielding and offer mild conditions. They have been a useful alternative to those reagents which fail or give a mixture of products if the reagents are unsupported. When alcohol **115** in hexanes was treated with PCC on alumina, keto-ester **119** was isolated in 61% yield.

The ir spectrum of compound **119** displayed a carbonyl absorption at 1778 cm^{-1} for the cyclobutanone carbonyl, as well as an absorption at 1728 cm^{-1} for the ester carbonyl. In the ^1H nmr spectrum, the methine proton at δ 4.10 had disappeared, but the ester functionality was still present (δ 5.00 (septet) and δ 1.22 (d)). Typically, the protons on the α carbon in cyclobutanone appear distinctively at 3.03 ppm.[100] The nmr spectrum of keto-ester **119** two proton absorped above 3 ppm. H-1 appeared at δ 3.44 (br dd, $J = J' = 8$ Hz) whereas one of the C-7 protons appeared at δ 3.20 (ddd, $J = 2$, $J' = 8$, $J'' = 15$ Hz). The other C-7 proton appeared at δ 2.42 (d, $J = 15$ Hz). The fourth proton on the four membered ring, H-6 appeared as a multiplet at δ 2.50. Decoupling experiments confirmed the geminal relationship between the two C-7 protons. Upon irradiation of the signal at δ 3.20, the signal at δ 2.42 lost its 15 Hz coupling. When the signal at δ 2.42 was irradiated, the absorption at δ 3.20 lost its 15 Hz coupling.

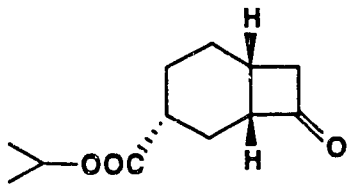
Furthermore irradiation of H-6 resulted in the loss of an 8 Hz coupling to H-1 (δ 3.44) as well as an 8 Hz coupling to H-7 (δ 3.20). This established the spin system around the cyclobutanone moiety. Although further decoupling experiments were conducted to assign the rest of the structure, with the overlap of some signals, this was difficult to do unambiguously.

There were 11 signals in the ^{13}C nmr spectrum of keto-ester **119**. The peaks at δ 208.3 and 174.8 corresponded to the ketone and ester carbonyl carbons respectively. For cyclobutanone, the carbonyl carbon absorbs at δ 208, and the α carbons absorb at δ 46.[101] There were three absorptions around 50 ppm for compound **119**: δ 67.4 for the carbon adjacent to the oxygen in the ester (this carbon typically appears at δ 66.8[102]) and those at δ 56.4 and 52.2 corresponding to C-1 and C-7, respectively.

The cims of this compound shows an $[M + 18]^+$ peak at m/z 228, in agreement with the molecular formula of $C_{12}H_{18}O_3$.



119



120

Treatment of alcohol **116** (isomer 2) in the same manner provided a single compound in 50% yield after 60 h. This

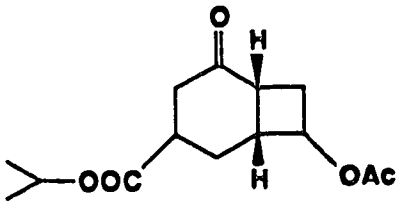
compound was found to be different from the one derived from compound **115** (isomer 1) and was assigned structure **120**. The ir spectrum of this compound displayed an absorption at 1778 cm^{-1} (cyclobutanone carbonyl) and 1724 cm^{-1} (ester carbonyl).

The ^{1}H nmr spectrum of this compound was different from that obtained for compound **119**. The ester functionality was present (δ 4.94 (septet) and δ 1.23 and 1.25 (each d)), and there were three signals around 3 ppm for the three protons α to the four membered ring carbonyl: δ 3.15 (m) for H-1, δ 2.98 (ddd, $J = 4$, $J' = 9$, $J'' = 17$ Hz) for one of the H-7 protons and δ 2.81 ($J = 3$, $J' = 7$, $J'' = 17$ Hz) for the other H-7 proton. Decoupling experiments confirmed that the signals at δ 2.98 and 2.81 were a geminal pair, coupled to each other by 17 Hz.

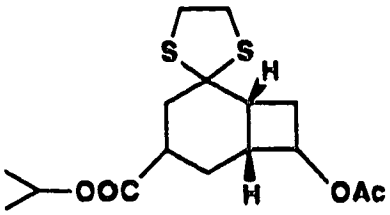
The ^{13}C nmr spectrum of this compound exhibited 11 signals. The ketone carbonyl carbon appeared at δ 209.1, whereas the ester carbonyl carbon appeared at δ 174.9. The three absorbances above 50 ppm at δ 67.8, 55.2, and 50.1 were assigned to the carbon attached to the oxygen in the ester, C-1 and C-7, respectively. In the mass spectrum of this compound, the molecular ion was observed at m/z 210.1262, consistent with the molecular formula $C_{12}H_{18}O_3$.

Oxidation of compound **117** (isomer 3) in the same manner afforded the keto-ester **120** in 58% yield after 19 h. When compound **118** (isomer 4) was subjected to the same conditions, the product was keto-ester **119** in 52% yield, after 30 h. As a result of this oxidation step, it was demonstrated that isomers 1 and 4 were epimers at the acetate/alcohol center, as were isomers 2 and 3.

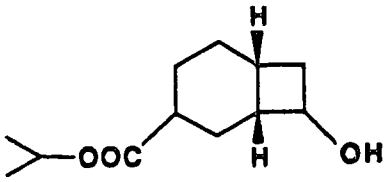
It should be noted that each stereoisomer was subjected individually to the four step reaction sequence described above. However once the identities of the stereoisomers was established, it was more convenient to carry the four compounds through the four steps as a mixture until the keto ester stage. Thus treatment of a mixture of the four photoadducts **121** with 1,2-ethanedithiol and boron trifluoride etherate formed the thioacetal **122** in 72% yield. Reduction of the thioacetal with Raney nickel in benzene gave the ester-acetate in 80% yield. Transesterification of the acetate with isopropyl alcohol and anhydrous hydrogen chloride provided hydroxy-ester **123** in 89% yield. Oxidation of the alcohols in hexanes with PCC on alumina gave a mixture of the two keto-esters **124** in 52% yield.



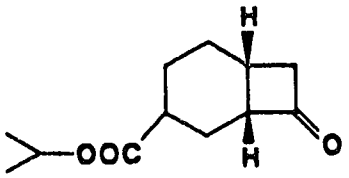
121



122



123



124

Although the undesired keto-ester **120** was obtained as a minor product from the oxidation, the C3 stereocenter which needs to be corrected is α to an ester functionality, and therefore in principle is epimerizable. If keto-ester **120** could be epimerized into keto-ester **119**, this would convert the undesired compound into the desired one, thereby conserving material. In order to investigate this possibility, we subjected keto-ester **120** to treatment with sodium isopropoxide in isopropyl alcohol at room temperature for 5 days. In this manner it was possible to epimerize keto ester **120** to form **119** in 33% yield with no trace of **120** evident (by ^{1}H nmr). The low yields obtained for this epimerization reaction as well as the oxidation of the four stereoisomeric alcohols is due to the volatility of these keto-esters, resulting in loss of material.

Having clearly established the identity of the four stereoisomers, we also were interested in investigating the stereoselectivity of the photocycloaddition reaction, particularly with regard towards influencing the ratio of stereoisomers to favor the formation of isomers 1 and 4 (leading to keto-ester **119**), versus isomers 2 and 3 (leading to keto-ester **120**). It is known that in the photocycloaddition reaction, the enone and olefin are "associated" in the form of an exciplex prior to bond formation.[103] It was hoped that by the use of enone **95** which possesses an acid functionality at C-5, that this "sticky" appendage may exert some hydrogen bonding effects which could influence the ratio of stereoisomers. On the other hand, by use of an enone with a bulky appendage at C-5, such as the isopropyl ester-enone **96**, that stereoselectivity could be influenced on the basis of steric congestion. In the ester case, the isomers 1, 2, 3, and 4 were formed in a ratio of 3 : 1.4 : 1 : 2.7, respectively (by ^{1}H nmr). This translates into a ratio of $\beta : \alpha = 2.4 : 1$; (isomers 1,4) : (isomers 2,3).

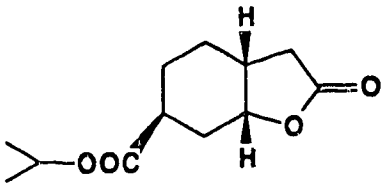
In order to determine the stereoisomeric ratio derived from the acid photoadducts, these compounds were esterified using potassium carbonate and isopropyl iodide in refluxing acetone to provide a mixture of esters **121** in 61% yield. In this case the isomers 1, 2, 3, and 4 were formed in a ratio of 3.4 : 1.4 : 1 : 2, respectively (by ^{1}H nmr). This translates into a ratio of $\beta : \alpha = 2.3 : 1$. Although some stereoselectivity in favor of the desired products was obtained for both the acid and the ester case, the

difference between them was not meaningful. In order to establish some trend, a number of other substrates would have to be investigated. In this regard, perhaps by the use of an olefin with a greater steric requirement than vinyl acetate, such as vinyl pivalate, in conjunction with a bulky ester group on the enone molecule would result in even greater stereoselectivity.

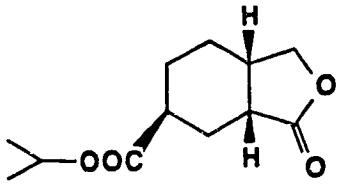
The next key compound required was butyrolactone **125**. This could be prepared from keto-ester **119** by a Baeyer-Villiger rearrangement, and the standard reagent used for it is MCPBA.[104] When keto-ester **110** in chloroform was treated with MCPBA at room temperature for 7 days, only starting material remained with no detectable product formation. Stotter has found that Baeyer-Villiger reactions which are very slow may be accelerated by the addition of sodium bicarbonate.[105] However even after stirring for an addititional 24 h with the addition of an excess of sodium bicarbonate (6 eq), there was still no reaction and only the starting material was recovered intact.

Peroxytrifluoroacetic acid[106] is a particularly good reagent to effect the Baeyer-Villiger rearrangement, and the reaction has been applied often to cyclic ketones to give lactones. Reactions are usually rapid, clean, and give high yields of product. Often it is necessary to add a buffer such as disodium hydrogen phosphate to prevent transesterification of the product with the trifluoroacetic acid formed in the reaction.[107] Keto-ester **119** in methylene

chloride was treated with peroxytrifluoroacetic acid in the presence of disodium hydrogen phosphate at room temperature for 2 h. From this reaction, butyrolactone **125** was obtained in 69% yield. The ir spectrum of the compound formed showed an absorption at 1726 cm^{-1} corresponding to the ester carbonyl. The new carbonyl absorption observed at 1782 cm^{-1} is within the typical range for the carbonyl stretch of γ-lactones (1760-1795 cm^{-1}).[108] In the ^1H nmr spectrum, the ester was intact (δ 4.95, septet; δ 1.15 and 1.17 (each d)). Typically, the γ proton in butyrolactone appears at δ 4.38 in the ^1H nmr.[109] In the nmr spectrum of this compound, a new signal appeared at δ 4.55 (br dd, J = 4.5, J' = 6 Hz) which integrated for one proton. This indicated that the rearrangement proceeded as anticipated to give lactone **125** rather than lactone **126** which would have two γ protons. In the mass spectrum the molecular ion was observed at m/z 226.1205, which is consistent with the molecular formula $C_{12}H_{18}O_4$.



125



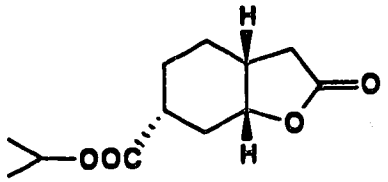
126

Treatment of keto-ester **120** with peroxytrifluoroacetic acid in the same manner gave butryolactone **127** in 72% yield within 2 h. This compound had two carbonyl absorptions in the ir

spectrum, one at 1780 cm^{-1} (butyrolactone carbonyl) and the other at 1726 cm^{-1} (ester). In the ^1H nmr spectrum, the ester functionality was still intact (δ 5.02, septet; δ 1.24 and 1.26 (each d). The γ hydrogen of the lactone ring appeared at δ 4.56 (ddd, $J = 9$, $J' = J'' = 5.5$ Hz). A molecular ion observed at m/z 226.1205 in the mass spectrum is consistent with the molecular formula $C_{12}H_{18}O_4$.

It was later found that MCPBA was an effective reagent for the Baeyer-Villiger rearrangement provided methylene chloride was used as the solvent. Treatment of keto-ester **119** with MCPBA at room temperature for 44 h provided butyrolactone **125** in 92% yield. This reaction notably was achieved in the absence of sodium bicarbonate.

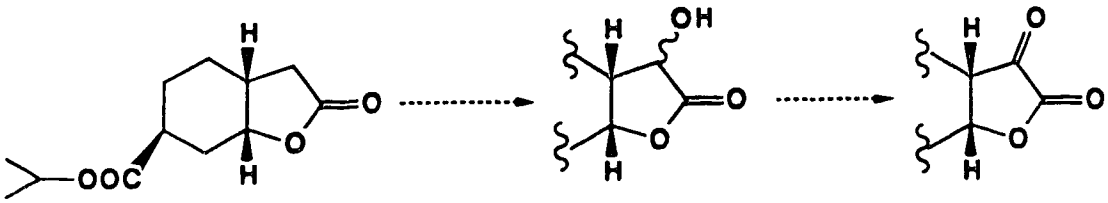
With these two lactone epimers **125** and **127** in hand, we wanted to check first whether these compounds were separable by tlc, and if so whether the undesired epimer could be converted into the desired one. Although a number of solvent systems were examined, one was not found in which the separation could be effected. Consequently, both the separation and the epimerization steps had to be left at the keto-ester stage.



127

Having butyrolactone **125** in hand, the next task involved the oxidation to the α-keto form. Our intention was to form the α-hydroxy compound, followed by oxidation to the keto form (Scheme 22).

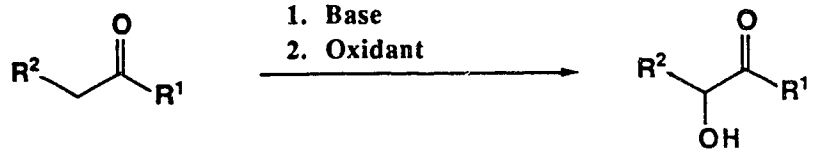
Scheme 22



125

Introduction of an oxygen functionality adjacent to a carbonyl has been a long standing problem in synthesis. There are a number of single step procedures reported to effect the direct oxidation of an enolate to the α-hydroxy compound (Scheme 23).

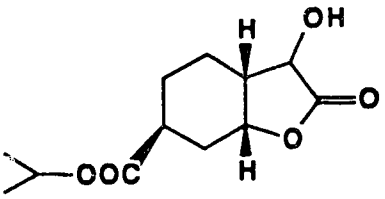
Scheme 23



Included among the reagents capable of this transformation are molecular oxygen (O_2),[110] the Vedejs' reagent molybdenum peroxide-pyridine-hexamethylphosphoramide (MoOPH),[111] 2-(phenylsulfonyl)-3-phenyl-oxaziridine,[112] and iodoso benzene deivatives.[113] Of these available methods both the MoOPH and the oxaziridine reagents required preparation. The molecular oxygen method had the advantage that it was a direct oxidation method, was simple and practical, and that did not involve preparation of the oxidant. This method used to be plagued with problems such as α-carbon cleavage or further oxidation to the α-dicarbonyl compound, however with addition of triethylphosphite for the *in situ* reduction of the hydroperoxide (Gardner modification) this method has since improved. Further encouraging us in this direction was a recent publication by Yoshii which described the α-oxidation of a similar butyrolactone moiety.[114]

Butyrolactone **125** was treated with lithium diisopropylamide (LDA) in a solution of THF containing hexamethylphosphoramide (HMPA) to form the lithium enolate. The enolate was then transferred to a solution of triethylphosphite in THF which had been saturated with dry oxygen for 25 min. The combined solutions were stirred at -78°C for 30 min with continuous bubbling of oxygen gas. The mixture was warmed up to room temperature over 1.5 h, under continued introduction of dry oxygen. In addition to some starting material which was recovered (23% yield), an additional compound, assigned

structure **128**, was isolated in 20% yield. This compound showed a hydroxyl absorption (3400 cm^{-1}) and carbonyl absorptions for the butyrolactone (1780 cm^{-1}) and the ester (1728 cm^{-1}) in the ir spectrum. The ^1H nmr spectrum showed the ester still intact (δ 5.06 (septet); δ 1.19 and 1.21 (each d)), the γ proton of the butyrolactone at δ 4.76 (ddd, J = 10, J' = J'' = 7 Hz) and a new signal at δ 4.16 (dd, J = 2, J' = 6 Hz). In addition, the broad singlet at δ 3.10 (D_2O exchangeable) indicated the α-hydroxy compound had been formed. In the mass spectrum, although a molecular ion was not obtained, the base peak corresponded to M^+ with loss of the isopropyl ester, as is typically observed for these compounds. The $[M - 87]^+$ peak at m/z 155.0714 corresponded to the molecular formula $C_8H_{11}O_3$.



128

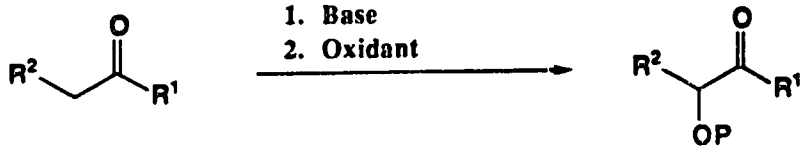
In an attempt to characterize the alcohol as its acetate alcohol, **128** was treated with acetic anhydride and pyridine. However, only the starting material was recovered. When alcohol **128** was treated with acetic anhydride, pyridine and

dimethylaminopyridine under refluxing conditions, disappointingly, extensive decomposition resulted.

In the oxidation of esters and lactones involving the MoOPH reagent as reported by Vedejs, the reactions were typically carried out at -78°C, and the oxidation was typically complete within 2 h. When the lithium enolate of butyrolactone **125** (using LDA, -78°C), was treated with MoOPH, and then allowed to stir at -78°C for 3 h, only starting material was recovered intact, with no trace of the hydroxylated compound. When the enolate was formed in the same manner, treated with MoOPH, followed by warming up to -22°C and stirred for 3 h, again only starting material was recovered. Interestingly, a publication by Stork[115] reported the α-oxidation of a substituted butyrolactone by addition of MoOPH to the enolate (LDA, -78°C), followed by stirring at 0°C. When the reaction was carried out in this manner, involving enolate formation at -78°C, addition of MoOPH, then stirring at 0°C for 4.5 h, a complex mixture was observed by tlc. The ^{1}H nmr spectrum of the crude products showed the hydroxy-lactone as a minor product.

Other methods reported which involve direct oxidation of an enolate, utilize oxidants such as acyl peroxides[116] and peroxydicarbonates.[117] The products from these reactions are typically a protected form of the α-hydroxy compound (Scheme 24).

Scheme 24



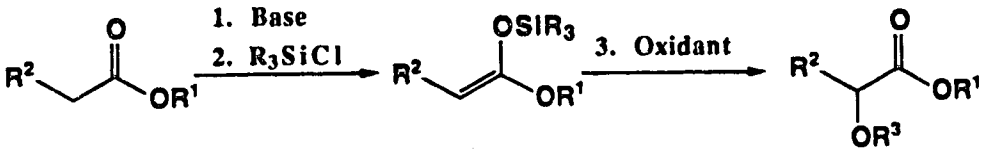
P = protecting group

Although acyl peroxides have been used for the preparation of α-acyloxy products, reports have been limited to oxidation of β-dicarbonyl compounds. Dibenzyl peroxydicarbonate on the other hand, is not so limited and has been used in the preparation of carbonate derivatives of α-hydroxy compounds. Oxygenation attempts on the model compound γ-butyrolactone with dibenzylperoxydicarbonate using potassium hexamethyldisilazide (KHMDS) as the base, only resulted in recovery of the starting material.

In general, the oxidation of ketones has been achieved in a less direct fashion by the intermediacy of a silyl enol ether. Although this involves multistep operations, this method has the advantage that the oxidation is conducted under amine free conditions. In this manner, additional oxidizing agents such as osmium tetroxide, MCPBA, lead tetraacetate can be employed. In the case of esters and lactones, preparation of the O-silyl ketene acetals followed by oxidation, is an alternative mode of α-oxidation. Typically either the α-hydroxy compound or a protected form of it,

such as the α-O-silylated compound, or as the α-O-acetylated compound, is the product (Scheme 25).

Scheme 25



R^3 = H or

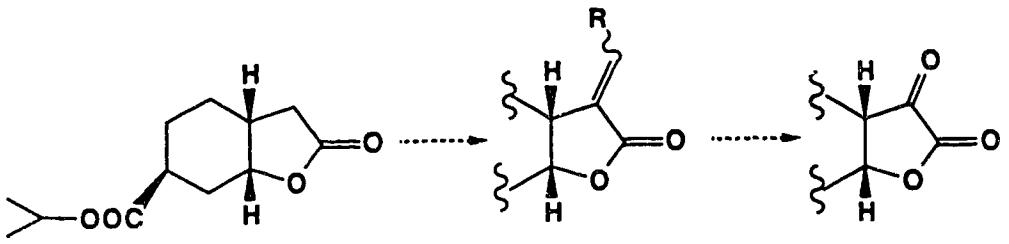
= protecting group

Oppolzer has reported the oxidation of alkyl trimethylsilyl ketene acetals with lead tetraacetate to give the α-O-acetyl compounds.[118a] Rubottom has reported similar oxidations using lead tetrabenzoate as well as lead tetraacetate[118b]. Alternatively, treatment of alkyl trimethylsilyl ketene acetals first with MCPBA then triethylamine hydrofluoride provided α-hydroxy esters, rather than a protected form.[119] This latter method was the procedure we chose to investigate. However, we decided to employ the method of Rathke[120] for the preparation of the ketene acetals. This procedure involves the use of lithium *N*-isopropylcyclohexylamide (LICA) as the base due to its increased solubility over LDA, and *tert*-butyldimethylsilyl (TBDMS) chloride as the silylating agent for its greater resistance to hydrolysis, when compared to acetals derived from trimethylsilyl (TMS) chloride. He also found that addition of hexamethylphosporamide (HMPA) to the reaction mixture led to better yields of ketene acetals.

To the enolate derived from butyrolactone **125** (LICA, HMPA) was added TBDMSCl. Within 30 min the starting material was consumed, and the crude alkyl silyl ketene acetal was subjected to MCPBA with stirring for 30 min, followed by the addition of triethylamine hydrofluoride and stirring for an additional 30 min. From this reaction, along with the recovered starting material (57%) a mixture of products resulted, none of which corresponded to the desired α-hydroxy compound.

With these disappointing results we turned to an alternative method to achieve the oxidation. It was thought that carrying out an aldol type condensation would form the α-methylene-γ-butyrolactone compound. Ozonolysis of such a compound would then provide the desired α-keto lactone (Scheme 26).

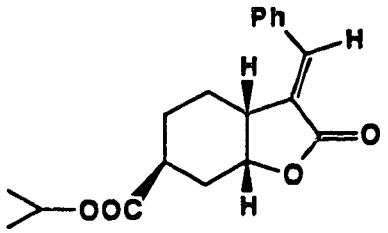
Scheme 26



123

Benzaldehyde was added to the enolate derived from butyrolactone **125** (LICA, HMPA, -78°C) followed by stirring at -78°C for 5 h. There was no evidence of product formation, so the

reaction was allowed to slowly warm up to room temperature, and then allowed to stir for an additional 24 h. When the ^1H nmr of the crude products derived from this reaction was examined, peaks for the ester (δ 5.00, septet; δ 1.25 and 1.27, each d) and the butyrolactone (δ 5.10, m) as well as the benzene ring (δ 7.30, m) were present. In addition the presence of a peak at δ 4.05 as well as a hydroxyl absorption (3450 cm^{-1}) in the ir spectrum indicated that the aldol product did not completely dehydrate. The crude products were thus dissolved in carbon tetrachloride and refluxed in the presence of copper(II) sulfate adsorbed on silica[121] to effect dehydration. From this reaction, 25% of the starting material recovered, and the β–phenyl-α-methylene-butyrolactone **129** was isolated in only 14% yield (18% based on consumed starting material). Further investigation into this reaction is required in order to improve the yield. Lactone **129** displayed carbonyl absorptions in the ir spectrum at 1755 cm^{-1} for the lactone carbonyl and at 1725 cm^{-1} for the ester. The butyrolactone carbonyl stretch shifted from 1782 cm^{-1} for the starting material to 1755 cm^{-1} for the product. This is a reasonable trend since conjugation causes a decrease in the frequency of absorption of a carbonyl group.[122] For example for γ-butyrolactone, the carbonyl stretch is at 1770 cm^{-1}, and for α,β-unsaturated-γ-butyrolactone the carbonyl stretch has moved to 1750 cm^{-1}. In the mass spectrum, the molecular ion was observed at m/z 314.1512 in agreement with the formula $C_{19}H_{22}O_4$.

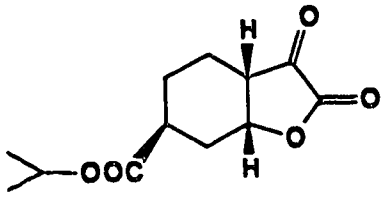


129

In the ^1H nmr spectrum, the compound displayed signals for the ester (δ 5.04 (septet), δ 1.25 and 1.27, (each d)) and the butyrolactone γ proton (δ 4.60, ddd (J = 1, J' = 4, J'' = 5 Hz)) were present. Furthermore the peaks around 7.4 ppm indicated the benzene ring was attached. The aromatic protons were present at δ 7.50 (m, 2H) and δ 7.42 (m, 4H), which accounts for the 5 aromatic protons and the vinylic proton. On the basis of the downfield position of the single olefin proton, which would normally have a shift below 7 ppm, the product was tentatively assigned as the *trans*-α-benzilidene-γ–lactone.[123] This would position the olefinic proton proximate to the carbonyl group of the lactone, which would account for its downfield shift.

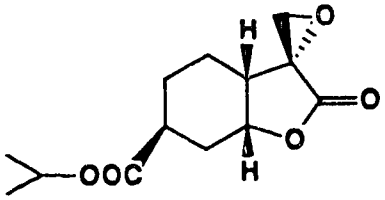
With the α-methylene derivative in hand, the next step was ozonolysis. Treatment of lactone **127** in methylene chloride with ozone at -78°C, followed by treatment with dimethylsulfide at -20°C overnight provided α-keto-butyrolactone **130** in quantitative yield. In the ir spectrum of this compound, two carbonyl peaks were present at 1761 cm^{-1} (lactone) and at 1722 cm^{-1} (ketone and

ester). In the mass spectrum, the molecular ion was observed at m/z 240.0959, corresponding to the formula $C_{12}H_{16}O_5$.



130

In the ^1H nmr spectrum, the ester functionality was present (δ 5.08 (quintet), δ 1.25 and 1.27 (each d)) as was the lactone (δ 4.98). In addition the presence of protons around 3 ppm corresponding to protons α to a carbonyl group indicated that oxygenation had taken place.



131

In order to complete the synthesis of the left hand portion of the molecule, the key intermediate spiroepoxide **131** has yet to be prepared. This can be achieved by treatment of compound **130** with Corey's reagent, dimethyloxosulfonium methylide.[124] This work is still in progress. In addition, in order to complete the synthesis of phyllanthocin, the right hand portion of the molecule, such as compound **90**, has yet to be prepared.

Experimental

General

Proton nuclear magnetic resonance spectra (^{1}H nmr) were obtained on the Bruker AM-300 spectrometer besides those mentioned in Part 1. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-200 (50.3 MHz), Bruker WH-400 (100.6 MHz), or Bruker AM-400 (100.6 MHz), and were obtained as solutions in deuteriochloroform as the internal standard setting the central peak at 77.0. Carbon-13 multiplicities were derived from off-resonance or Carr-Purcell-Meiboom-Gill spin echo J-modulated experiments (APT).[125,126] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. Nuclear Overhauser Enhancement (nOe) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for nOe measurements were deoxygenated with helium gas for 5-10 min prior to use. Two dimensional (2D) homonuclear and heteronuclear correlation spectra (COSY and HCCORR) experiments were performed using

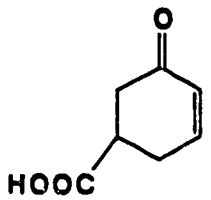
the BRUKER DISNMR software package. Ozone was generated using a Welsbach ozonator (80V).

Materials

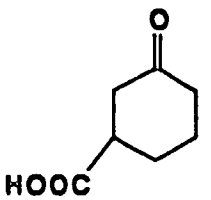
For details of other materials used see Part 1 of this thesis. Solvents were purified by distillation under an argon atmosphere: Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from a blue solution of sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Isopropyl alcohol was distilled first from calcium oxide and then from calcium hydride. Acetone was distilled from potassium permanganate, and then from potassium carbonate. Liquid ammonia was freshly distilled over sodium metal just prior to use. Diisopropyl amine, isopropyl cyclohexyl amine and hexamethylphosphoramide (HMPA) were obtained by distillation from calcium hydride. Dimethylsulfoxide (DMSO) was distilled from calcium hydride at reduced pressure. Triethylphosphine was distilled from sodium metal. *Tert*-butyldiphenylsilyl chloride was subjected to Kugelrohr distillation just prior to use. Pyridinium chlorochromate adsorbed onto alumina was prepared in accordance with the procedure described by Cheng and coworkers.[98] Oxodiperoxymolybdenum(pyridine)-hexamethyl-phosphoramide (MoOPH) was prepared according to the procedure of Vedejs.[111] Dibenzylperoxydicarbonate was prepared according to the procedure of Vederas.[117] Triethylamine

hydrochloride was prepared by the procedure of Hunig.[127] Copper sulfate adsorbed onto silica gel was prepared according to the procedure of Nishiguichi.[128]

5-Oxo-3-cyclohexene-1-carboxylic acid (95) and
3-Oxocyclohexane-1-carboxylic acid (98)



95



98

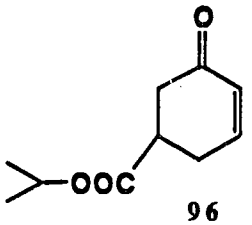
At -78°C, a solution of m-methoxybenzoic acid (10.07 g, 66.25 mmol) in methanol (90 mL) was added over a period of 30 min to freshly distilled liquid ammonia (200 mL) under an argon atmosphere. Sodium metal (7.20 g, 0.31 g-atom) was added in small portions over 5 min, and the mixture was stirred very rapidly using a mechanical stirrer for an additional 5 min. Then ammonium chloride (30 g, 53.49 mmol) was added with vigorous stirring. The mixture was allowed to warm up to room temperature, and stirred for 7 h, allowing the ammonia to evaporate. The residue was dissolved in ice water and the solution was cooled to 0°C. The pH of the solution was adjusted to pH 7 using 2N aqueous HCl and extracted with cold methylene chloride to remove dark colored byproducts. The solution was gradually

adjusted to pH 4 at 0°C with frequent extractions into cold methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to afford the crude reduced product. To a solution of the crude product (1.05 g) dissolved in THF (5 mL) was added 1N aqueous HCl (20 mL). The mixture was heated under reflux for 1 h. The solution was concentrated *in vacuo* to remove all the THF and water, leaving a yellow oil. Chloroform (200 mL) was added which dissolved most of the oil. The small amount of residue which was insoluble was removed and discarded. The chloroform solution was dried over magnesium sulfate, filtered and concentrated to afford the crude product which was subjected to flash column chromatography. Elution with acetic acid and ethyl acetate in petroleum ether (1:40:59) afforded cyclohexanone **98** (212 mg, 20% yield): ir ($CHCl_3$ cast) br 3150 (O-H), 1733 (C=O, acid) and 1712 cm^{-1} (C=O, ketone); ^1H nmr (200 MHz) δ 6.50 (br s, 1H, -COO**H**), 2.88 (m, 1H, -C**H**(COOH)), 2.59 (m, 2H), 2.38 (m, 2H), 2.15 (m, 2H) and 1.87 (m, 2H); hrms M^+ 142.0630 (calcd. for $C_7H_{10}O_3$:142.0630).

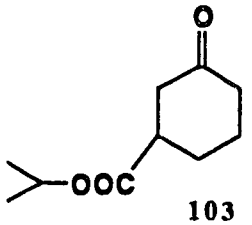
Furthier elution with acetic acid and ethyl acetate in petroleum ether (1:50:49) gave enone **95** (636 mg, 70% yield): ir (CH_2Cl_2 cast) br 2750 (O-H), 1725 (C=O, acid) and 1677 cm^{-1} (C=O, enone); ^1H nmr (200 MHz) δ 10.95 (br s, 1H, -COO**H**), 6.98 (ddd, 1H, J = 4, J' = 5, J'' = 10 Hz, COCH=C**H**), 6.05 (ddd, 1H, J = 10, J' = J'' = 2 Hz, COC**H**=CH), 3.15 (m, 1H, -C**H**(COOH)) and

2.70 (m, 4H); hrms M^+ 140.0473 (calcd. for $C_7H_8O_3$: 140.0473). Anal. calcd. for $C_7H_8O_3$: C 60.00, H 5.75; found: C 59.90, H 5.86.

Isopropyl 5-oxo-3-cyclohexene-1-carboxylate (96) and **Isopropyl 3-oxocyclohexane-1-carboxylate (103)**



96



103

From acid **95** using basic conditions

To a solution of enone-acid **95** (235 mg, 1.68 mmol) in acetone (4 mL) was added potassium carbonate (0.700 g, 5.07 mmol) and isopropyl iodide (1.25 mL, 2.13 g, 12.5 mmol). The mixture was allowed to reflux under an atmosphere of argon for 71 h. The reaction mixture was then cooled to room temperature, and the solvent was removed by distillation using a Vigreux column. The residue was then cooled, dissolved in ice water and extracted with methylene chloride (3 × 10 mL), and dried over magnesium sulfate and filtered. The bulk of the solvent was removed by distillation using a Vigreux column, and the residual solvent was removed by concentration *in vacuo*. Kugelrohr distillation (0.20 mm Hg, 60°C) gave enone-ester **96** (198 mg, 65% yield): ir (CH_2Cl_2 cast) 1728 (C=O, ester) and 1683 (C=O, enone); ^1H nmr (200 MHz) δ 6.95 (ddd, 1H, J = 10, J' = J'' = 5 Hz,

COCH=C**H**)), 6.05 (ddd, 1H, J = 10, J' = J'' = 2 Hz, COC**H**=CH), 5.02 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 3.02 (m, 1H, C**H**COOCH$(CH_3)_2$), 2.63 (m, 4H), 1.21 and 1.23 (each d, each 3H, each J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 182.0945 (calcd. for $C_{10}H_{14}O_3$: 182.0943). Anal. calcd. for $C_{10}H_{14}O_3$: C 65.91, H 7.74; found: C 65.63, H 7.54.

From acid **95** using acidic conditions

At 0°C, through a solution of enone-acid **95** (16.75 g, 0.120 mol) dissolved in isopropyl alcohol (300 mL) was bubbled anhydrous hydrogen chloride for 30 min, until saturated. The ice bath was removed, and the solution was allowed to stir at room temperature for 3 h. The bulk of the isopropyl alcohol was removed by distillation using a Vigreux column. The remainder of the solution in the distilling flask was cooled in an ice bath, and a slurry of ice and water (100 mL) was added. The solution was extracted with methylene chloride (3 × 150 mL). The combined organic extracts were washed with water (2 × 25 mL), 5% aqueous sodium carbonate (2 × 25 mL), and water (2 × 25 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was subjected to Kugelrohr distillation (0.6 mm Hg, 60°C) to provide enone-ester **95** (8.91 g, 41% yield).

Birch reduction using sodium metal

At -78°C, a solution of m-methoxybenzoic acid (1.00 g, 6.49 mmol) in isopropyl alcohol (9 mL) was added over a period of 5 min to freshly distilled liquid ammonia (20 mL) under an argon atmosphere. Sodium metal (0.72 g, 0.031 g-atom) was added in small portions over 5 min, and the mixture was stirred very rapidly using a mechanical stirrer for an additional 5 min. Then ammonium chloride (6.00 g, 112 mmol) was added with vigorous stirring. The dry ice bath was removed and the mixture was allowed to stir at room temperature, allowing the ammonia to evaporate. Isopropyl alcohol (20 mL) was added to the residue, and the mixture was cooled to 0°C. Anhydrous hydrogen chloride was slowly bubbled through the solution until the mixture reached a pH of 1 (using pH paper). The solution was then allowed to stir at room temperature for 1.5 h, cooled and water was added to dissolve the solid residue. The solution was then extracted with methylene chloride (3 × 20 mL). The combined organic solvents were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude enone-ester. The crude product was subjected to flash chromatography. Elution with 20% ethyl acetate in petroleum ether gave cyclohexanone **103** (130 mg, 11% yield): ir (neat) br 1727 cm^{-1} (C=O, ketone and ester); ^1H nmr (200 MHz) δ 4.96 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 2.55-2.75 (m, 1H, -C**H**COOCH$(CH_3)_2$), 2.46 (d, 2H, J = 7 Hz), 2.26 (m, 2H), 1.90-2.12 (m, 2H), 1.60-1.85 (m, 2H) and 1.17 (d, 6H,

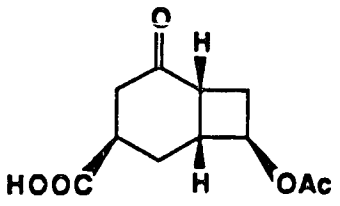
J = 6.5 Hz, -COOCH(CH_3)$_2$); hrms M^+ 184.1099 (calcd. for $C_{10}H_{16}O_3$: 184.1100). Further elution gave cyclohexenone **96** (356 mg, 30% yield).

Birch reduction using lithium metal

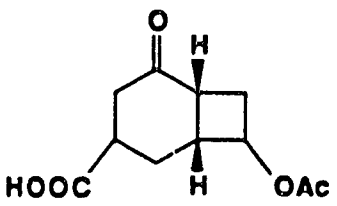
At -78°C, a solution of m-methoxybenzoic acid (5.00 g, 32.90 mmol) in isopropyl alcohol (45 mL) was added over a period of 30 min to freshly distilled liquid ammonia (100 mL) under an argon atmosphere. Lithium metal (1.24 g, 0.18 g-atom) was added in small portions over 5 min, and the mixture was stirred very rapidly using a mechanical stirrer for an additional 5 min. Then ammonium chloride (15 g, 26.75 mmol) was added with vigorous stirring. The mixture was allowed to stir at room temperature, allowing the ammonia to evaporate. Isopropyl alcohol (200 mL) was added to the residue, and the mixture was cooled to 0°C. Anhydrous hydrogen chloride was slowly bubbled through the solution until the mixture reached a pH of 1 (using pH paper). The solution was then allowed to stir at room temperature overnight. The bulk of the isopropyl alcohol was removed by distillation, and the residue in the distilling flask was cooled. Methylene chloride (50 mL) and water (25 mL) were added and the solution was extracted with methylene chloride (4 × 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was then subjected to flash chromatography. Elution with 15%

ethyl acetate in petroleum ether gave cyclohexanone **103** (61 mg, 1% yield). Further elution gave a mixture (3.02 g) of compounds **96** and **103** in a ratio of 3:1 (by nmr). Continued elution with 20% ethyl acetate in petroleum ether gave pure enone (300 mg, 5% yield). This translates into yields of 43% yield for compound **96**, and 13% yield for compound **103**.

(1R*, 4R*, 6R*, 7R*)- (99) and the mixture of **(1R*, 4R*, 6R*, 7S*)- , (1R*, 4S*, 6R*, 7R*)-** and **(1R*, 4S*, 6R*, 7S*)-7-Acetoxy-4-carboxy-bicyclo[4.2.0]octane-2-one (100)**



99



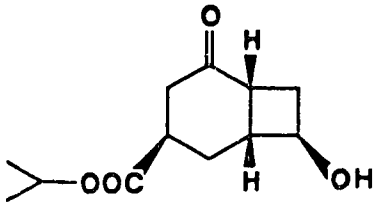
100

A degassed benzene (200 mL) solution of cyclohexenone **95** (using argon) (2.21 g, 9.80 mmol) and vinyl acetate (24 mL, 22.4 mg, 0.260 mol, 26 eq) in a quartz photochemical immersion well was suspended in a large Dewar flask. An ice-water slush mixture was added to the Dewar flask, and the reaction mixture was allowed to cool to 0°C. The solution was irradiated using a 450-W Hanovia high pressure mercury lamp, through a Pyrex filter for 12 h. The solvent was removed *in vacuo*, and the a yellow viscous oily residue was then dissolved in benzene (150 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (3.0 mL, 3.0 g, 20 mmol,

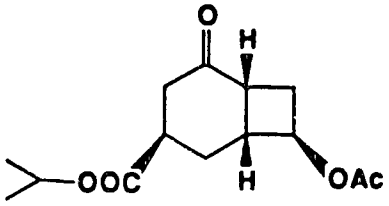
2.0 eq) was added and the mixture was heated to reflux for 48 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo* to give a viscous brown oil. This oil was dissolved in methylene chloride (250 mL), washed with 1N aqueous HCl (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude reaction mixture was subjected to flash chromatography. Elution with acetic acid and ethyl acetate in petroleum ether (1:45:54) gave the keto-acid **99** (958 mg, 27% yield) as a white solid: mp 108-109°C; ir (CH_2Cl_2 cast) br 3200 (O-H), 1737 (C=O, acid and acetate) and 1715 cm^{-1} (C=O, ketone); ^1H nmr (400 MHz) δ 4.80 (dddd, 1H, J= 1.5 J' = J'' = J''' = 7.5 Hz, H-7), 3.10 (ddddd, 1H, J = 1, J' = 2.5, J'' = 6, J''' = 7.5, J'''' = 9.5 Hz, H-6), 3.00 (dddd, 1H, J = J' = 3.5, J'' = J''' = 12 Hz, H-4), 2.80 (dddd, 1H, J= 1.5, J' = 2.5, J'' = J''' = 10 Hz, H-1), 2.70 (ddd, 1H, J = 1, J' = 3.5, J'' = 15 Hz, H-3α), 2.65 (dddd, 1H, J = 1, J' = 2.5, J'' = 7.5, J''' = 11 Hz, H-8α), 2.47 (dd, 1H, J = 12, J' = 15 Hz, H-3β), 2.22 (ddd, 1H, J = 7.5, J' = 10, J'' = 11 Hz, H-8β), 2.22 (dddd, 1H, J = 1, J' = 2.5, J'' = 3.5, J''' = 14 Hz, H-5α), 2.02 (s, 3H, -OOCC**H**$_3$) and 1.90 (ddd, 1H, J = 6, J' = 12, J'' = 14 Hz, H-5β); ^{13}C nmr (100.6 MHz) δ 210.8 (p), 178.6 (p), 170.5 (p), 69.2 (a), 43.9 (a), 42.6 (p), 39.4 (a), 37.5 (a), 31.3 (p), 27.5 (p) and 20.9 (a); cims (NH_3) $[M+18]^+$ 244. Anal. calcd. for $C_{11}H_{14}O_5$: C 58.40, H 6.24; found: C 58.27, H 6.35.

Continued elution with acetic acid and ethyl acetate in petroleum ether (1:50:49) afforded a mixture of three photoadducts (**100**) (1.24 g, 35% yield). Only the following distinctive features in the spectra of the mixture are described: ir (CH_2Cl_2 cast) br 3100 (O-H), 1734 (C=O, acid and acetate), 1707 cm^{-1} (C=O, ketone); ^1H nmr (400 MHz) δ 5.08, 4.86 (each m, -CHOAc), 2.10, 2.08 and 2.06 (each s, -OOCC**H**$_3$); hrms (M- HOAc) [M^+- 60] 166.0630 (calcd. for $C_9H_{10}O_3$: 166.0630).

(1R*, 4R*, 6R*, 7R*)-7-Hydroxy-4-Isopropoxycarbonyl-bicyclo[4.2.0]octan-2-one (101) and **(1R*, 4R*, 6R*, 7R*)-7-acetoxy-4-isopropoxycarbonylbicyclo[4.2.0]octan-2-one (102)**



101



102

At 0°C, through a solution of keto-acetate **99** (114 mg, 0.51 mmol) in dry isopropyl alcohol (10 mL) was bubbled anhydrous hydrogen chloride for 5 min. The mixture was then stirred at room temperature for an additional 30 min. The mixture was poured into crushed ice and quickly extracted with methylene chloride (3 × 25 mL). The combined methylene chloride extracts were washed successively with water and brine, then dried over magnesium sulfate, filtered and concentrated *in*

vacuo. The crude product was subjected to flash chromatography. Elution with acetic acid and ethyl acetate in petroleum ether (1:35:64) gave acetate **102** (16 mg, 11% yield): ir ($CHCl_3$ cast) 1731 (C=O, ester and acetate) and 1713 cm^{-1} (C=O, ketone); ^1H nmr (400 MHz) δ 5.02 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$) 4.78 (dddd, 1H, J = 1.5, J' = J'' = J''' = 7.5 Hz, -C**H**OAc), 3.06 (dddd, 1H, J = 2.5, J' = 6, J'' = 7.5, J''' = 9.5 Hz, H-6), 2.88 (dddd, 1H, J = J' = 3.5, J'' = J''' = 12 Hz, H-4), 2.77 (dddd, 1H, J = 1.5, J' = 2.5, J'' = J''' = 10 Hz, H-1), 2.63 (dd, 1H, J = 3.5, J' = 15 Hz, H-3α), 2.63 (ddd, 1H, J = 2.5, J' = 7.5, J'' = 11 Hz, H-8α), 2.45 (dd, 1H, J = 12, J' = 15 Hz, H-3β), 2.23 (ddd, 1H, J = 8, J' = 10, J'' = 11 Hz, H-8β), 2.14 (ddd, 1H, J = 14, J' = J'' = 3 Hz, H-5α), 2.04 (s, 3H, -OOCC**H**$_3$), 1.86 (ddd, 1H, J = 6, J' = 12, J'' = 14 Hz, H-5β), 1.25 and 1.27 (each d, each 3H, each J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 268.1311 (calcd. for $C_{14}H_{20}O_5$: 268.1310). Anal. calcd. for $C_{14}H_{20}O_5$: C 62.67, H 7.51; found: C 62.32, H 7.61.

Further elution with acetic acid and ethyl acetate in petroleum ether (1:60:39) gave alcohol **101** (67 mg, 56% yield) as a pale yellow oil: ir ($CHCl_3$ cast) br 3440 (O-H), 1727 (C=O, ester) and 1708 cm^{-1} (C=O, ketone); ^1H nmr (400 MHz) δ 5.03 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$) 4.00 (dddd, J = 1.5, J' = J'' = J''' = 7.0 Hz, -C**H**OH), 2.88 (m, 1H), 2.79 (dddd, 1H, J = J' = 4, J'' = J''' = 12.5 Hz, H-4), 2.67 (br dd, 1H, J = J' = 10 Hz), 2.59 (m, 2H), 2.44 (dd, 1H, J = 12.5, J' = 14 Hz, H-3β), 2.10 (m, 1H), 2.04 (m, 2H), 1.86 (ddd, 1H, J = 6, J' = 12, J'' = 14.5 Hz,

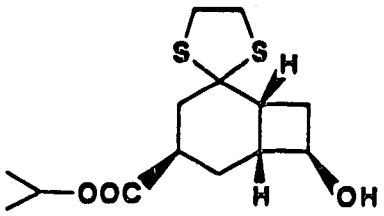
H-5β) and 1.25 (d, 6H, J = 6.5 Hz, -COOCH(CH_3)$_2$); hrms M^+ 226.1205 (calcd. for $C_{12}H_{18}O_4$: 226.1205).

Preparation of compound **102** under basic conditions

To a solution of acid **99** (447 mg, 1.98 mmol) in acetone (30 mL) was added potassium carbonate (1.08 g, 7.78 mmol, 3.9 eq) and isopropyl iodide (1.50 mL, 2.55 g, 15.03 mmol, 7.6 eq). The mixture was stirred under reflux for 26 h under an atmosphere of argon. The mixture was then cooled, the solvent was evaporated *in vacuo*, cold water was added to the mixture, and the mixture was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give ester **102** (501 mg, 94% yield).

Ester **102** has also been prepared by the photocycloaddition of enone **96** with vinyl acetate (*vide infra*).

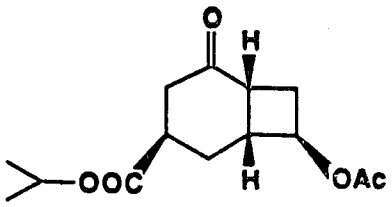
(1R*, 4R*, 6R*, 7R*)-2,2-Ethylenedithio-7-hydroxy-4-isopropoxycarbonylbicyclo[4.2.0]octane (103)



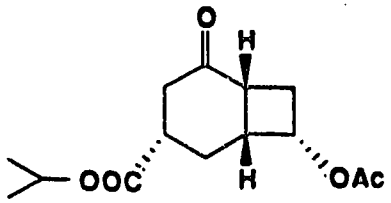
At 0°C, to a solution of keto-alcohol **101** (53 mg, 0.23 mmol) in methylene chloride was added 1,2-ethanedithiol (0.04 mL, 0.49 mmol, 2.1 eq) and boron trifluoride etherate (0.02 mL, 0.16 mmol, 0.70 eq). The mixture was stirred at room temperature under an atmosphere of argon for 40 min. The mixture was poured into cold aqueous 1N sodium hydroxide, and extracted (3 × 20 mL) with methylene chloride. The combined methylene chloride extracts were washed with water, dried over magnesium sulfate, filtered, and then concentrated *in vacuo*. The crude product was then subjected to flash chromatography. Elution with acetic acid, ethyl acetate and petroleum ether (1:20:79) gave thioacetal **103** (67 mg, 95% yield) as a clear colorless oil: ir (CH_2Cl_2 cast) br 3400 (O-H) and 1724 cm^{-1} (C=O); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.28 (ddd, 1H, $J = J' = J''$ = 7.5 Hz, -C**H**OH), 3.26 (m, 4H, -SC**H**$_2$C**H**$_2$S-), 2.70 (m, 1H, -C**H**COOCH$(CH_3)_2$), 2.54 (m, 2H), 2.41 (m, 2H), 2.23 (br s, 1H, -O**H**), 1.99 (m, 3H), 1.63 (ddd, 1H, J = 7, J' = 12, J'' = 15 Hz), 1.23 and 1.25 (each d, each 3H, each J = 6.5 Hz,

-COOCH(CH_3)$_2$); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 174.6, 69.4, 68.8, 67.8, 44.6, 43.6, 40.5, 39.1, 38.3, 35.9, 35.0, 25.4 and 21.7; hrms M^+ 302.1016 (calcd. for $C_{14}H_{22}O_3S_2$: 302.1012).

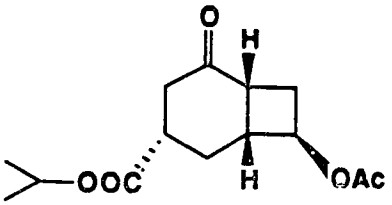
(1R*, 4R*, 6R*, 7R*)- (102) (1R*, 4S*, 6R*, 7S*)- (104) (1R*, 4S*, 6R*, 7R*)- (105) and (1R*, 4R*, 6R*, 7S*)-7-Acetoxy-4-isopropoxycarbonylbicyclo[4.2.0]octan-2-one (106)



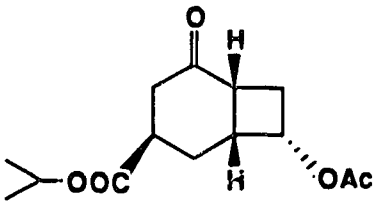
102



104



105



106

To a degassed solution of enone **96** (1.21 g, 6.62 mmol) in benzene (200 mL) was added vinyl acetate (12 mL, 11.2 g, 0.130 mol, 20 eq). The solution was irradiated, in the same manner as previously described for the corresponding acid **95**, for 11 h at 0°C. The solution was then cooled and the solvent was evaporated *in vacuo*. Benzene (50 mL) and DBU (2.5 mL, 2.55 g, 16.72 mmol, 2.5 eq) were added, and the solution was refluxed for 48 h. The solution was then allowed to cool, and the solvent was

removed *in vacuo*. The crude product was then subjected to flash chromatography. Elution with 27% ethyl acetate in petroleum ether afforded ester **102** (194 mg, 11% yield). Continued elution with 30% ethyl acetate in petroleum ether afforded fractions which contained mixtures of isomers. However it was possible to obtain small amounts of each isomer pure. Isomer **106**, the last compound to be eluted was obtained pure (216 mg, 12% yield). The mixtures of isomers had a combined weight of 708 mg (40% yield). The spectral data obtained for isomer **102** has been previously described, while those obtained for the other individual isomers are detailed below.

Isomer **104**: ir (CH_2Cl_2 cast) 1730 (C=O, ester and acetate) and 1707 (C=O, ketone); ^1H nmr (400 MHz) δ 5.05 (m, 2H, -COOC**H**$(CH_3)_2$) and -C**H**OAc), 3.10 (m, 1H, -C**H**COOCH$(CH_3)_2$), 2.58-2.80 (m, 6H), 2.43 (m, 1H), 2.07 (s, 3H, -OOCC**H**$_3$), 1.95 (m, 1H) and 1.25 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3)_2$); cims (NH_3) $[M + 18]^+$ 286.

Isomer **105**: ir (CH_2Cl_2 cast) br 1729 cm^{-1} (C=O, ketone, ester and acetate); ^1H nmr (400 MHz) δ 5.02 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.68 (m, 1H, -C**H**OAc), 2.86-3.02 (m, 3H), 2.73 (ddd, 1H, J = 4, J' = 7.5, J'' = 12 Hz), 2.58 (m, 2H), 2.38 (m, 2H), 2.04 (s, 3H, -OOCC**H**$_3$), 1.78 (ddd, 1H, J = 7.5, J = 10, J' = 14 Hz) and 1.24 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3)_2$); cims (NH_3) $[M + 18]^+$ 286.

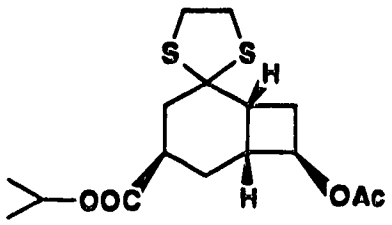
Isomer **106**: ir ($CHCl_3$ cast) 1726 cm^{-1} (C=O, ketone, ester and acetate); ^1H nmr (400 MHz) δ 5.10 (m, 1H, -C**H**OAc), 5.00 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 3.17 (m, 1H), 2.78 (m, 2H), 2.56 (m, 2H), 2.30 (m, 1H), 2.06 (m+s, 4H, -C**H**- + -OOCC**H**$_3$), 2.00 (m, 1H) and 1.24 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 268.1310 (calcd. for $C_{14}H_{20}O_5$: 268.1311). Anal. calcd. for $C_{14}H_{20}O_5$: C 62.67, H 7.51; found: C 62.51, H 7.35.

Determination of stereoselectivity

In order to determine the ratio of the stereoisomers, the photocycloaddition was carried out on a small scale and the ratios were determined by nmr analysis.

To a degassed solution of enone **96** (231 mg, 1.27 mmol) in benzene (10 mL) was added vinyl acetate (10 mL, 9.34 g, 0.108 mol, 85 eq) and the solution was irradiated in the same manner as previously described for 12 h at 0°C. The solution was then cooled and the solvent was evaporated *in vacuo*. The residue was dissolved in benzene (150 mL), then DBU (0.5 mL, 0.51 g, 3.34 mmol, 2.6 eq) was added. The solution was refluxed under an atmosphere of argon for 54 h. The solvent was evaporated, and the crude product was filtered through a dry column, to give the photoadducts (215 mg, 63% yield). The ratio of the four isomers was determined by ^1H nmr (400 MHz) to be 3 : 1.4 : 1 : 2.7 for isomers **102** : **104** : **105** : **106**.

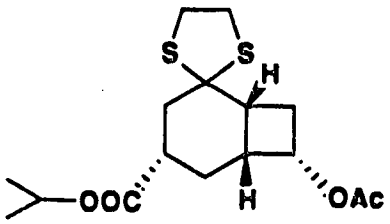
(1R*, 4R*, 6R*, 7R*)-7-Acetoxy-2,2-ethylenedithio-4-isopropoxycarbonylbicyclo[4.2.0]octane (107)



Keto-acetate **102** (501 mg, 1.87 mmol) was dissolved in methylene chloride (15 mL) and cooled to 0°C. To the solution was added 1,2-ethanedithiol (0.50 mL, 6.08 mmol, 3.2 eq) and boron trifluoride etherate (0.11 mL, 0.89 mmol, 0.48 eq). The mixture was stirred under an atmosphere of argon at room temperature for 20 min. The reaction mixture was poured into ice-cold 1N aqueous sodium hydroxide (5 mL) and extracted with methylene chloride (3 × 25 mL). The extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product which was subjected to flash chromatography. Elution using 10% ethyl acetate in hexanes gave thioacetal **107** (630 mg, 98% yield) as white crystals: mp 65-66°C; ir (CH_2Cl_2 cast) 1736 and 1727 (C=O, ester and acetate); ^1H nmr (400 MHz) δ 5.06 (ddd, 1H, $J = J' = J'' = 7$ Hz, -C**H**OAc), 5.00 (septet, 1H, $J = 6.5$ Hz, -COOC**H**$(CH_3)_2$) 3.20-3.36 (m, 4H, -SC**H**$_2$C**H**$_2$S-), 2.66-2.81 (m, 3H), 2.40-2.52 (m, 2H), 1.98-2.20 (m 3H), 2.04 (s, 3H, -OOCC**H**$_3$), 1.70 (m, 1H), 1.22 and 1.24 (each d, each 3H, each $J = 6.5$ Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 344.1119 (calcd. for

$C_{16}H_{24}O_4S_2$: 344.1116). Anal. calcd. for $C_{16}H_{24}O_4S_2$: C 55.79, H 7.02, S 18.62; found: C 55.90, H 6.97, S 18.44.

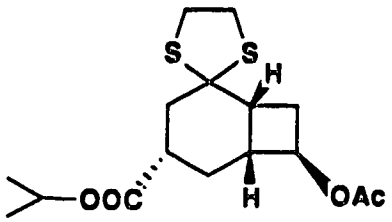
(1R*, 4S*, 6R*, 7S*)-7-Acetoxy-2,2-ethylenedithio-4-isopropoxycarbonylbicyclo[4.2.0]octane (108)



Keto-acetate **104** (59 mg, 0.22 mmol) was dissolved in methylene chloride (2 mL) and cooled to 0°C. To the solution was added 1,2-ethanedithiol (0.05 mL, 0.61 mmol, 2.8 eq) and boron trifluoride etherate (0.025 mL, 0.20 mmol, 0.91 eq). The mixture was stirred under an atmosphere of argon at room temperature for 3 h. The reaction mixture was poured into ice-cold 1N aqueous sodium hydroxide (5 mL) and extracted with methylene chloride (3 × 25 mL). The extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product which was subjected to flash chromatography using 10% ethyl acetate in hexanes as the eluting solvent to give thioacetal **108** (75.20 mg, 95% yield) as a pale yellow oil: ir (CH_2Cl_2 cast) 1725 cm^{-1} (C=O, ester and acetate); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.78 (m, 1H, -C**H**OAc), 3.29 (m, 4H, -SC$\mathbf{H_2}$C$\mathbf{H_2}$S-), 2.82 (m, 1H), 2.31-2.54 (br m, 5H),

2.14 (m, 1H), 2.02 (s, 3H, -C**H**$_3$), 1.84 (m, 1H), 1.70 (m, 1H), 1.21 and 1.23 (each d, each 3H, each J = 6.5 Hz, -COOCH(C**H**$_3$)$_2$); hrms M^+ 344.1120 (calcd. for $C_{16}H_{24}O_4S_2$: 344.1116).

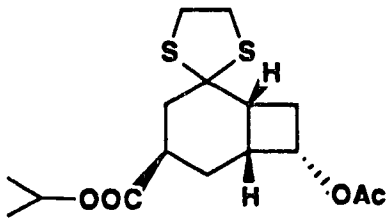
(1R*, 4S*, 6R*, 7R*)-7-Acetoxy-2,2-ethylenedithio-4-isopropoxycarbonylbicyclo[4.2.0]octane (109)



Keto-acetate **105** (187 mg, 0.70 mmol) was dissolved in methylene chloride (10 mL) and cooled to 0°C. To the solution was added 1,2-ethanedithiol (0.13 mL, 1.58 mmol, 2.3 eq) and boron trifluoride etherate (0.05 mL, 0.41 mmol, 0.59 eq). The mixture was stirred under an atmosphere of argon at room temperature for 2.5 h. The reaction mixture was poured into ice-cold 1N aqueous sodium hydroxide (5 mL) and extracted with methylene chloride (3 × 25 mL). The extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product which was subjected to flash chromatography. Elution with 15% ethyl acetate in hexanes gave thioacetal **109** (195 mg, 81% yield) as a white solid: mp 90-93°C; ir ($CHCl_3$ cast) 1729 cm^{-1} (C=O, ester and acetate); ^{1}H nmr (400 MHz) δ 4.99 (septet, 1H, J = 6.5 Hz, -COOC**H**(CH$_3$)$_2$), 4.51 (d, 1H, J = 5.5 Hz,

-CHOAc), 3.29 (m, 4H, -SC**H**$_2$C**H**$_2$S-, 3.12 (ddd, 1H, $J = J' = J'' = 10$ Hz), 2.50 (dddd, 1H, $J = J' = 2.5$, $J'' = J''' = 10$ Hz), 2.42 (m, 2H), 2.33 (dd, 1H, $J = 1.5$, $J' = 11$ Hz), 2.25 (m, 1H), 2.19 (dd, 1H, $J = 10$, $J' = 11$ Hz), 2.09 (ddd, 1H, $J = 3.5$, $J' = 7$, $J'' = 10$ Hz), 2.02 (s, 3H, -OOCC**H**$_3$), 1.45 (ddd, 1H, $J = 8.5$, $J' = 10$, $J'' = 11$ Hz) and 1.20 (d, 6H, $J = 6.5$ Hz, -COOCH(C**H**$_3$)$_2$); hrms M^+ 344.1116 (calcd. for $C_{16}H_{24}O_4S_2$: 344.1116). Anal. calcd. for $C_{16}H_{24}O_4S_2$: C 55.79, H 7.02, S 18.62; found: C 55.87, H 7.28, S 18.25.

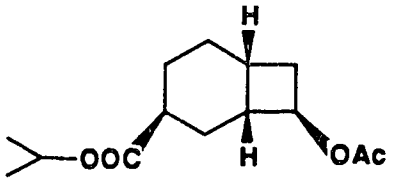
(1R*, 4R*, 6R*, 7S*)-7-Acetoxy-2,2-ethylenedithio-4-isopropoxycarbonylbicyclo[4.2.0]octane (110)



Keto-acetate **106** (199 mg, 0.75 mmol) was dissolved in methylene chloride (10 mL) and cooled to 0°C. To the solution was added 1,2-ethanedithiol (0.15 mL, 1.82 mmol, 2.43 eq) and boron trifluoride etherate (0.05 mL, 0.41 mmol, 0.55 eq). The mixture was stirred under an atmosphere of argon at room temperature for 2.5 h. The reaction mixture was poured into ice-cold 1N aqueous sodium hydroxide (5 mL) and extracted with methylene chloride (3 × 25 mL). The extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the

crude product which was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes gave thioacetal **110** (186 mg, 73% yield) as an oil: ir ($CHCl_3$ cast) 1726 cm^{-1} (C=O, ester and acetate); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.95 (m, 1H, -C**H**OAc), 3.25 (m, 4H, -SCH_2CH_2S-), 3.03 (m, 1H), 2.86 (m, 1H), 2.59 (dd, 1H, J = 5.5, J' = 15 Hz), 2.49 (m, 2H), 2.40 (dd, 1H, J = 7, J' = 15 Hz), 2.14 (m, 1H), 2.02 (s, 3H, -OOCC**H**$_3$), 1.92 (m, 1H), 1.75 (m, 1H) and 1.22 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 344.1128 (calcd. for $C_{16}H_{24}O_4S_2$: 344.1116). Anal. calcd. for $C_{16}H_{24}O_4S_2$: C 55.79, H 7.02, S 18.62; found: C 55.86, H 7.17, S 18.44.

(1R*, 3R*, 6R*, 8S*)-8-Acetoxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (111)



A- Preparation of Raney Nickel (W-2)

At 0°C, to a solution of sodium hydroxide (11.4 g, 285 mmol) in water (45 mL) was added Al-Ni alloy powder (9.0 g) in small portions while stirring, ensuring that the temperature does not exceed 25°C. When the evolution of hydrogen gas had moderated to slow, the suspension was allowed to warm up to room

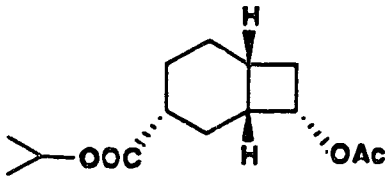
temperature, and then heated on a steam bath until the evolution of hydrogen ceases. The suspension was washed with water until the washings had a pH of 7. The suspension was then washed three times with isopropyl alcohol, and stored as a suspension in isopropyl alcohol.

B- Reduction

To a solution of thioacetal **107** (415 mg, 1.20 mmol) in benzene (20 mL) was added freshly prepared Raney Nickel (W-2, 7 mL). The solution was stirred at room temperature under an atmosphere of argon for 12 h. The mixture was filtered and the residue was washed successively with benzene, and 50% diethyl ether in isopropyl alcohol. The filtrates were combined, concentrated *in vacuo*, then partitioned between water and methylene chloride. The methylene chloride layer was washed with water (2 × 20 mL), and then dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was subjected to flash chromatography and eluted with 10% ethyl acetate in hexanes to afford acetate **111** (230 mg, 75% yield) as a pale yellow oil: ir (CH_2Cl_2 cast) 1731 cm^{-1} (C=O, ester and acetate); ^1H nmr (400 MHz) δ 4.96 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.94 (ddd, 1H, $J = J' = J''$ = 7.5 Hz, -C**H**OAc), 2.44 (ddd, 1H, $J = J' = J''$ = 7.5 Hz), 2.34 (dddd, 1H, $J = J'$ = 4, $J'' = J'''$ = 11 Hz), 1.90-2.10 (m, 5H), 1.96 (s, 3H, -OOCC**H**$_3$), 1.82 (br d, 1H, J = 11 Hz), 1.47 (ddd, 1H, J = 6.5, J' = 12, J'' = 14 Hz) and 1.15

(d+m, 8H, J_d = 6.5 Hz, -COOCH(CH_3)$_2$ + -CH_2-); hrms M^+ 254.1517 (calcd. for $C_{14}H_{22}O_4$: 254.1518). Anal. calcd. for $C_{14}H_{22}O_4$: C 66.12, H 8.72; found: C 66.38, H 8.87.

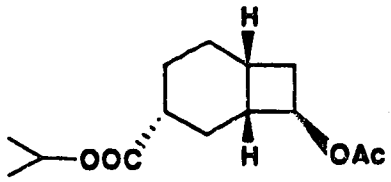
(1R*, 3S*, 6R*, 8R*)-8-Acetoxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (112)



To a solution of thioacetal **108** (69 mg, 0.20 mmol) in benzene (5 mL) was added freshly prepared Raney Nickel (W-2, 2 mL). The solution was stirred at room temperature under an atmosphere of argon for 17 h. The mixture was filtered and the residue was washed successively with benzene, and 50% diethyl ether in isopropyl alcohol. The filtrates were combined, concentrated *in vacuo*, then partitioned between water and methylene chloride. The methylene chloride layer was washed with water (2 × 10 mL), and then dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes afforded acetate **112** (46 mg, 91% yield) as a pale yellow oil: ir (CH_2Cl_2 cast) 1731 cm^{-1} (C=O, ester and acetate); ^1H nmr (400 MHz) δ 4.94 (septet, 1H, J = 6.5 Hz, -COOC**H**(CH_3)$_2$), 4.79 (m, 1H, -C**H**OAc), 2.61 (m, 1H, -C**H**COOCH(CH_3)$_2$), 1.95-2.15 (complex

m, 4H), 2.00 (s, 3H, -OOCC**H**$_3$), 1.65-1.82 (m, 3H), 1.60 (m, 2H), 1.45 (m, 1H) and 1.16 (d, 6H J = 6.5 Hz, -COOCH(C**H**$_3$)$_2$); hrms M^+ 254.1522 (calcd. for $C_{14}H_{22}O_4$: 254.1518).

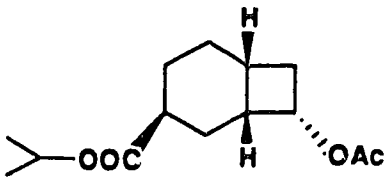
(1R*, 3S*, 6R*, 8S*)-8-Acetoxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (113)



To a solution of thioacetal **109** (186 mg, 0.54 mmol) in benzene (10 mL) was added freshly prepared Raney Nickel (W-2, 4 mL). The solution was stirred at room temperature under an atmosphere of argon for 3 h. The mixture was filtered and the residue was washed successively with benzene, and 50% diethyl ether in isopropyl alcohol. The filtrates were combined, concentrated *in vacuo*, then partitioned between water and methylene chloride. The methylene chloride layer was washed with water (2 × 20 mL), and then dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes afforded acetate **113** (107 mg, 78% yield) as a pale yellow oil: ir (CH_2Cl_2 cast) 1731 (C=O, ester and acetate); ^{1}H nmr (400 MHz) δ 4.95 (septet, 1H, J = 6.5 Hz, -COOC**H**(CH$_3$)$_2$), 4.71 (ddd, 1H, J = 4, J' = 6, J'' = 8 Hz, -C**H**OAc), 2.35 (m, 2H), 2.19 (m, 2H), 2.00

(s, 3H, -OOCC**H**$_3$), 1.91 (m, 2H), 1.73 (m, 2H), 1.59 (m, 2H), 1.43 (m, 1H) and 1.17 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3$)$_2$); hrms M$^+$ 254.1518 (calcd. for $C_{14}H_{22}O_4$: 254.1518). Anal. calcd. for $C_{14}H_{22}O_4$: C 66.12, H 8.72; found: C 66.29, H 8.83.

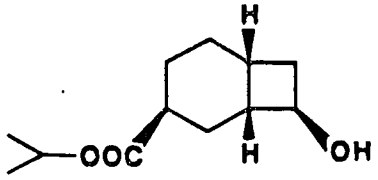
(1R*, 3R*, 6R*, 8R*)-8-Acetoxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (114)



To a solution of thioacetal **110** (135 mg, 1.20 mmol) in benzene (10 mL) was added freshly prepared Raney Nickel (W-2, 3 mL). The solution was stirred at room temperature under an atmosphere of argon for 11 h. The mixture was filtered and the residue was washed successively with benzene, and 50% diethyl ether in isopropyl alcohol. The filtrates were combined, concentrated *in vacuo*, then partitioned between water and methylene chloride. The methylene chloride layer was washed with water (2 × 20 mL), and then dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes afforded acetate **114** (93 mg, 93% yield) as a pale yellow oil: ir ($CHCl_3$ cast) 1734 and 1728 cm^{-1} (C=O, acetate and ester); ^{1}H nmr (400 MHz) δ 4.95 (septet, 1H, J = 6.5 Hz, -COOC**H**(CH$_3$)$_2$), 4.88

(ddd, 1H, $J = J' = J'' = 7.5$ Hz, -CHOAc), 2.76 (m, 1H), 2.61 (m, 1H), 2.24 (ddd, 1H, $J = 3.5$, $J' = 7$, $J'' = 11$ Hz), 2.04 (m, 1H), 2.00 (s+m, 4H, $-OOCCH_3$ + -CH-), 1.81 (m, 2H), 1.72 (ddd, 1H, $J = 5$, $J' = 9.5$, $J'' = 14$ Hz), 1.62 (m, 2H), 1.33 (m, 1H) and 1.16 (d, 6H, $J = 6.5$ Hz, $-COOCH(CH_3)_2$); hrms M^+ 254.1515 (calcd. for $C_{14}H_{22}O_4$: 254.1518). Anal. calcd. for $C_{14}H_{22}O_4$: C 66.12, H 8.72; found: C 66.19, H 8.84.

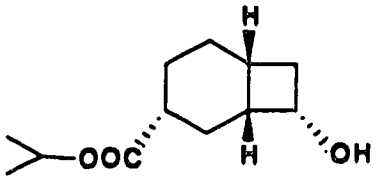
(1R* 3R*, 6R*, 8S*)-8-Hydroxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (115)



To a solution of ester-acetate **111** (350 mg, 1.38 mmol) in isopropyl alcohol (20 mL) was bubbled anhydrous hydrogen chloride for 1 h and stirred for an additional 23 h. The solution was then concentrated *in vacuo* and subjected to flash chromatography. Elution with 20% ethyl acetate in hexanes gave alcohol **115** (230 mg, 79% yield): ir (CH_2Cl_2 cast) br 3400 (O-H) and 1727 cm^{-1} (C=O); ^1H nmr (400 MHz) δ 4.95 (septet, 1H, $J = 6.5$ Hz, $-COOCH(CH_3)_2$), 4.10 (ddd, 1H, $J = J' = J'' = 7.5$ Hz), 2.41 (br s, 1H), 2.25 (m, 2H), 1.97 (m, 3H), 1.90 (dd, 1H, $J = 7$, $J' = 11$ Hz), 1.77 (m, 2H), 1.48 (ddd, 1H, $J = 6.5$, $J' = 12$, $J'' = 14$

Hz) and 1.17 (d+m, J_d = 6.5 Hz, 7H, -COOCH(CH_3)$_2$ + -C**H**-); hrms M^+ 212.1410 (calcd. for $C_{12}H_{20}O_3$: 212.1412).

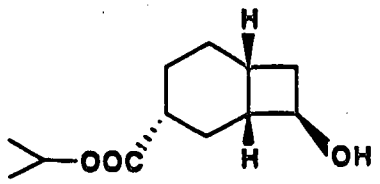
(1R* 3S*, 6R*, 8R*)-8-Hydroxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (116)



At 0°C, to a solution of ester-acetate **112** (41 mg, 0.16 mmol) in isopropyl alcohol (10 mL) was bubbled anhydrous hydrogen chloride for 10 min. The solution was then allowed to warm up to room temperature and stirred for an additional 12 h. The mixture was then poured into crushed ice (10 mL) and quickly extracted with methylene chloride (3 × 20 mL). The combined extracts were washed successively with water, cold 5% sodium bicarbonate, and water, then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then subjected to flash chromatography. Elution with 25% ethyl acetate in hexanes gave alcohol **116** (21 mg, 62% yield): ir (CH_2Cl_2 cast) br 3400 (O-H) and 1727 cm^{-1} (C=O); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J = 6.5 Hz, -COOC**H**(CH_3)$_2$), 4.16 (m, 1H, -C**H**OH), 2.49 (m, 1H), 2.13 (m, 1H), 2.05 (dddd, 1H, $J = J' = 3$, $J'' = J''' = 12$ Hz, -C**H**COOCH(CH_3)$_2$), 1.80-2.00 (m, 6H), 1.67 (d, 1H, J = 7 Hz),

1.48 (m, 2H) and 1.28 (d, 6H, J = 6.5 Hz,-COOCH(CH_3)$_2$); hrms M^+ 212.1413 (calcd. for $C_{12}H_{20}O_3$: 212.1412).

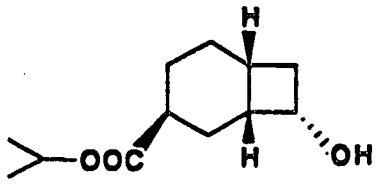
(1R* 3S*, 6R*, 8S*)-8-Hydroxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (117)



At 0°C, to a solution of ester-acetate **113** (81 mg, 0.32 mmol) in isopropyl alcohol (20 mL) was bubbled anhydrous hydrogen chloride for 40 min. The solution was then allowed to warm up to room temperature and stirred for an additional 16 h. The mixture was then poured into crushed ice (10 mL) and quickly extracted with methylene chloride (3 × 25 mL). The combined extracts were washed successively with water, cold 5% sodium bicarbonate, and water, then dried over magnesium sulfate, filtered and concentrated *in vacuo*, and then subjected to flash chromatography. Elution with 30% ethyl acetate in hexanes gave alcohol **117** (50 mg, 74% yield): ir (CH_2Cl_2 cast) br 3440 (O-H) and 1726 cm^{-1} (C=O); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J=6.5 Hz, -COOC**H**(CH_3)$_2$), 4.08 (m, 1H, -C**H**OH), 2.33 (m, 2H), 2.19 (m, 1H), 2.08 (m 1H), 1.80-1.95 (m, 4H), 1.73 (ddd, 1H, J = 4, J' = 7, J'' = 14 Hz), 1.66 (m, 1H), 1.39 (m, 1H) and 1.22 (d+m,

J_d = 6.5 Hz, 7H, -COOCH(CH_3)$_2$ + -C**H**-); hrms M^+ 212.1406 (calcd. for $C_{12}H_{20}O_3$: 212.1412).

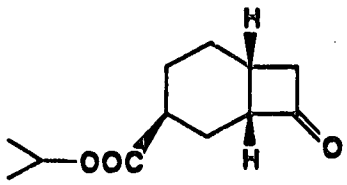
(1R* 3R*, 6R*, 8R*)-8-Hydroxy-3-isopropoxycarbonylbicyclo[4.2.0]octane (118)



At 0°C, to a solution of ester-acetate **114** (91 mg, 0.36 mmol) in isopropyl alcohol (20 mL) was bubbled anhydrous hydrogen chloride for 45 min. The solution was then allowed to warm up to room temperature and stirred for an additional 24 h. The mixture was then poured into crushed ice (10 mL) and quickly extracted with methylene chloride (3 × 25 mL). The combined extracts were washed successively with water, cold 5% sodium bicarbonate, and water, then dried over magnesium sulfate, filtered and concentrated *in vacuo*, and then subjected to flash chromatography. Elution with 25% ethyl acetate in hexanes gave alcohol **118** (52 mg, 68% yield) as white crystals: mp 55-57°C; ir ($CHCl_3$ cast) br 3440 (O-H) and 1726 cm^{-1} (C=O); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J=6.5 Hz, -COOC**H**(CH_3)$_2$), 4.23 (br ddd, 1H, $J = J' = J'' = 7$Hz, -C**H**OH), 2.70 (m, 1H), 2.64 (m, 1H), 2.21 (m, 1H), 1.80-2.00 (m, 5H), 1.70 (ddd, 1H, J = 12, $J' = J''$ = 4 Hz), 1.62 (m, 1H), 1.37 (m, 1H) and 1.20 (d, 6H, J = 6.5 Hz,

-COOCH(CH_3)$_2$); hrms M^+ 212.1417 (calcd. for $C_{12}H_{20}O_3$: 212.1412). Anal. calcd. for $C_{12}H_{20}O_3$: C 67.87, H 9.50; found: C 67.96, H 9.40.

(1R*, 3R*, 6R*)-3-Isopropoxycarbonyl-8-oxobicyclo[4.2.0]octane (119)



A- Preparation of Pyridinium Chlorochromate on Alumina

Pyridine (4.85 mL, 4.75 g, 60 mmol, 1.0 eq) was added slowly at 40°C to a solution of chromium trioxide (6.0 g, 60 mmol) in 6N hydrochloric acid (11 mL, 66 mmol, 1.1 eq). The mixture was cooled down to and maintained at 10°C until a yellow-orange precipitate formed, and then it was reheated to 40°C to redissolve the solid. Neutral active alumina (50 g, Brockmann I, *ca* 150 mesh) was then added to the solution with stirring. After concentration in a rotary evaporator, the solid was dried in a vacuum desiccator overnight at room temperature.

B- Oxidation from alcohol **115**

To a solution of hydroxy-ester **115** (292 mg, 1.38 mmol) in hexanes (25 mL) was added PCC on alumina (4.00 g, 3.72 mmol, 2.7 eq). The suspension was stirred at room temperature for 24 h. The mixture was then filtered through a layer of silica gel, which was then rinsed with ether. The solvent was removed by distillation at atmospheric pressure using a 10 cm Vigreux column, and the residual solvent was evaporated *in vacuo* to give the crude keto ester, which was then subjected to flash chromatography. Elution with 20% ethyl acetate in hexanes gave the keto-ester **119** (177 mg, 61% yield): ir (CH_2Cl_2 cast) 1778 (C=O, ketone) and 1728 cm^{-1} (ester); ^1H nmr (400 MHz) δ 5.00 (septet, 1H, J=6.5 Hz, -COOC**H**$(CH_3)_2$), 3.44 (ddd, 1H, J = 2, J' = J'' = 8 Hz, H-1), 3.20 (ddd, 1H, J = 2, J'=8, J''=15 Hz, -CHC**H**HC(O)CH-), 2.50 (m, 1H), 2.42 (d, 1H, J = 15 Hz, -CHCH**H**C(O)CH-)), 2.31 (m, 1H), 2.23 (m, 2H), 1.87 (br d, 1H, J = 14 Hz), 1.58 (ddd, 1H, J = 8, J' = 12, J'' = 15 Hz), 1.31 (m, 1H), 1.22 (d, 6H, J = 6.5 Hz, -COOCH(C**H**$_3)_2$) and 1.10 (m, 1H); ^{13}C nmr (100.6 MHz) δ 208.3 (p), 174.8 (p), 67.4 (a), 56.4 (a), 52.2 (p), 39.8 (a), 29.0 (p), 25.8 (p), 23.5 (p), 22.0 (a) and 21.7 (a); cims (NH_3) $[M + 18]^+$ 228.

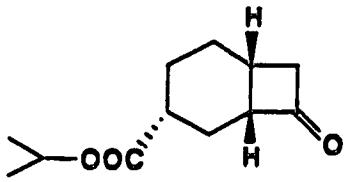
B- Oxidation from hydroxy-ester **118**

To a solution of hydroxy-ester **118** (28 mg, 0.13 mmol) in hexanes (2 mL) was added PCC on alumina (0.33 g, 0.31 mmol, 2.3 eq). The suspension was stirred at room temperature for 30 h. The mixture was then filtered through a layer of silica gel, which was then rinsed with diethyl ether. The solvent was then evaporated *in vacuo* to give the crude keto-ester, which was then subjected to flash column chromatography. Elution with 10% ethyl acetate in hexanes gave the keto-ester **119** (15 mg, 52% yield).

C- Epimerization of keto-ester **120**

To isopropyl alcohol (1 mL) was added sodium hydride (10.45 mg, 50% dispersion in oil, 0.22 mmol), and the mixture was allowed to stir for 30 min. A solution of keto-ester **120** (15.39 mg, 0.07 mmol) in DME (1 mL) was then added, and the solution was stirred for 5 days at room temperature under an atmosphere of argon. The mixture was then partitioned between diethyl ether (40 mL) and water (10 mL). The organic layer was separated, dried over magnesium sulfate and filtered. The bulk of the diethyl ether was removed by distillation at atmospheric pressure using a Vigreux column. The remainder of the solvent was then removed *in vacuo*. This gave keto-ester **119** (4.79 mg, 33% yield).

(1R*, 3S*, 6R*)-3-Isopropoxycarbonyl-8-oxobicyclo[4.2.0]octane (120)



A- Oxidation from hydroxy-ester **116**

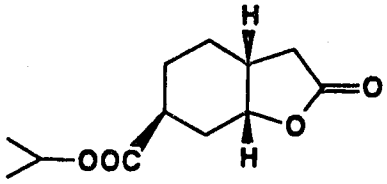
To a solution of hydroxy-ester **116** (14 mg, 0.07 mmol) in hexanes (2 mL) was added PCC on alumina (0.30 g, 0.28 mmol, 4 eq). The suspension was stirred at room temperature for 60 h. The mixture was then filtered through a layer of silica gel, which was then rinsed with diethyl ether. The solvent was then evaporated *in vacuo* to give the crude keto-ester, which was then subjected to flash chromatography. Elution with 30% ether in hexanes gave the keto-ester **104** (6.97 mg, 50% yield): ir (CH_2Cl_2 cast) 1778 (C=O, ketone) and 1724 cm^{-1} (C=O, ester); ^1H nmr (400 MHz) δ 4.94 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 3.15 (m, 1H, -C**H**C(O)CH_2-), 2.98 (ddd, 1H, J = 4, J' = 9, J'' = 17 Hz, -CHC(O)C**H**HCH-), 2.81 (ddd, 1H, J = 3, J' = 7, J'' = 17 Hz, -CHC(O)CH**H**CH-), 2.41 (m, 1H), 2.21 (m, 1H), 1.91 (ddd, 1H, J = 5, J' = 9, J'' = 14 Hz), 1.80 (m, 2H), 1.69 (m, 2H), 1.56 (m, 1H), 1.23 and 1.25 (each d, each 3H, each J = 6.5 Hz, -COOCH$(CH_3)_2$). ^{13}C nmr (100.6 MHz) δ 209.1 (p), 174.9 (p), 67.8 (a), 55.2 (a), 50.1 (p), 38.2 (a), 29.7 (p), 24.8 (p), 23.6 (p), 22.9

(p) and 21.8 (a); hrms M^+ 210.1262 (calcd. for $C_{12}H_{18}O_3$: 210.1256).

B- Oxidation from hydroxy-ester **117**

To a solution of hydroxy-ester **117** (20 mg, 0.095 mmol) in hexanes (2 mL) was added PCC on alumina (0.35 g, 0.33 mmol, 3.5 eq). The suspension was stirred at room temperature for 19 h. The mixture was then filtered through a layer of silica gel, which was then rinsed with ether. The solvent was then evaporated *in vacuo* to give the crude keto-ester, which was then subjected to flash chromatography. Elution with 10% ethyl acetate in hexanes gave the keto-ester **120** (12 mg, 58% yield)

(6R*, 8S*, 9S*)-Hexahydro-6-isopropoxycarbonyl-2(3*H*)-benzofuranone (125)



A- Preparation of peroxytrifluoroacetic acid

Trifluoroacetic anhydride (0.76 mL, 1.13 g, 5.4 mmol) was added slowly to a cold (0°C) suspension of 90% hydrogen peroxide (0.12 mL, 4.4 mmol) in methylene chloride (4.5 mL). After

stirring at 0°C for 15 min the solution was allowed to warm up to room temperature and used for the oxidation step. The reagent was kept stored in the freezer.

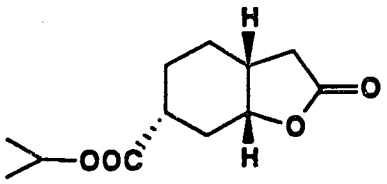
B- Oxidation using peroxytrifluoroacetic acid

Peroxytrifluoroacetic acid solution (2.0 mL, 1.96 mmol, 4.0 eq) was added to a stirred suspenxion of keto-ester **119** (103 mg, 0.49 mmol) and disodium hydrogen phosphate (350 mg, 2.50 mmol, 5.1 eq) in methylene chloride (15 mL). The mixture was stirred at room temperature under an atmosphere of argon for 2 h. The mixture was then filtered, the precipitate was washed with methylene chloride, and the organic extracts were washed with 5% sodium bicarbonate (5 mL), dried over magnesium sulfate, filtered, and concentrated. The crude product was subjected to flash chromatography using 30% ethyl acetate in petroleum ether as the eluent to give lactone **125** (76 mg, 69% yield) as a yellow oil: ir (CH_2Cl_2 cast) 1782 (C=O, butyrolactone) and 1726 cm^{-1} (C=O, ester); ^1H nmr (400 MHz) δ 4.95 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.55 (br dd, 1H, J = 4.5, J' = 6 Hz, -C**H**OOCCH_2-), 2.65 (dd, 1H, J = 7, J = 17 Hz, -CHC**H**HCOO-), 2.42 (m, 2H), 2.31 (m, 1H), 2.19 (d, 1H, J = 17, -CHCH**H**COO-), 1.90 (m, 1H), 1.82 (m 1H), 1.70 (m, 1H), 1.32 (m, 2H) and 1.15 and 1.17 (each d, each 3H, each J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 226.1205 (calcd. for $C_{12}H_{18}O_4$: 226.1205).

C- Oxidation using MCPBA

To a solution of keto-ester **119** (1.30 g, 6.19 mmol) in methylene chloride (25 mL) was added MCPBA (85%) (4.00 g, 19.70 mmol, 3.18 eq). The mixture was allowed to stir at room temperature for 44 h under an argon atmosphere. The mixture was washed with 10% aqueous sodium sulfite solution (3 × 50 mL), saturated aqueous sodium bicarbonate (3 × 50 mL) and water (3 × 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was then subjected to flash chromatography. Elution with 30% ethyl acetate in petroleum ether gave butyrolactone **125** (1.28 g, 92% yield).

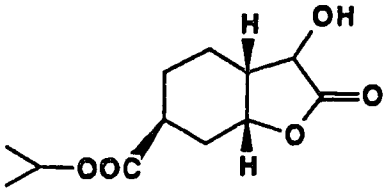
(6R*, 8R*, 9R*)-Hexahydro-6-isopropoxycarbonyl-2(3*H*)-benzofuranone (127)



Peroxytrifluoroacetic acid solution (0.10 mL, 0.098 mmol, 2.3 eq) was added to a stirred suspension of keto-ester **120** (8.96 mg, 0.043 mmol) and disodium hydrogen phosphate (26 mg, 0.183 mmol, 4.3 eq) in methylene chloride (2 mL). The mixture was stirred at room temperature under an atmosphere of argon for

2 h. The mixture was then filtered, the precipitate was washed with methylene chloride, and the organic extracts were washed with 5% sodium bicarbonate (5 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was then subjected to flash chromatography. Elution with 30% ethyl acetate in petroleum ether gave lactone **127** (6.88 mg, 72% yield) as a yellow oil: ir (CH_2Cl_2 cast) 1780 (C=O, butryolactone) and 1726 cm^{-1} (C=O, ester); ^1H nmr (400 MHz) δ 5.02 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.56 (ddd, 1H, J = 9, J' = J'' = 5.5 Hz, -C**H**OOCCH_2-), 2.66 (m, 1H), 2.42 (m, 2H), 2.28 (m, 2H), 1.60-1.90 (m, 5H), 1.20 and 1.22 (each d, each 3H, each J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 226.1205 (calcd. for $C_{12}H_{18}O_4$: 226.1205).

(6R*, 8R*, 9R*)-Hexahydro-3-hydroxy-6-isopropoxycarbonyl-2(3*H*)-benzofuranone (128)

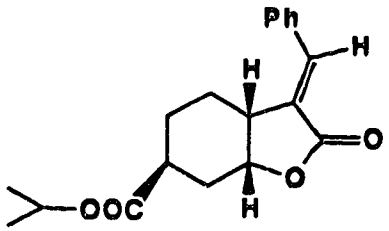


A solution of butyrolactone **127** (111.64 mg, 0.494 mmol) and HMPA (0.086 mL, 0.493 mmol, 1 eq) in dry tetrahydrofuran (0.5 mL) was added dropwise to a cold (-78°C) solution of lithium diisopropylamide [prepared from diisopropylamine (0.076 mL, 0.543 mmol, 1.1 eq) and *n*-butyllithium (2.5 M in hexanes,

0.22 mL, 0.55 mmol, 1.1 eq) in dry tetrahydrofuran (0.5 mL) under an argon atmosphere]. After 30 min, the solution was transferred with a stainless steel double-tipped needle into a cold (-78°C) stirred solution of triethyl phosphite (0.17 mL, 0.99 mmol, 2.0 eq) in dry THF (8 mL) which had been saturated with oxygen for 30 min. The combined solutions were stirred at -78°C for an additional 30 min, then the solution was allowed to warm up to room temperature over 1.5 h and then stirred for an additional 30 min, all under the continued introduction of dry oxygen. The THF was then evaported *in vacuo*, and the solution was neutralized with 5% aqueous HCl, and methylene chloride (50 mL) was added. The organic layer was separated, and washed successively with 5% aqueous HCl (2 × 10 mL), saturated aqueous sodium chloride solution (10 mL) and water (2 × 10 mL). The organic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was then subjected to flash chromatography. Elution with 30% ethyl acetate in petroleum ether as the eluting solvent afforded the starting material (26 mg, 23% yield). Continued elution using 50% ethyl acetate in petroleum ether as the eluting solvent gave alcohol **128** (24 mg, 20% yield) as a yellow oil: ir (CH_2Cl_2 cast) 3400 (O-H), 1780 (C=O, butyrolactone) and 1728 cm (C=O, ester); ^1H nmr (200 MHz) δ 5.00 (septet, 1H, J=6.5 Hz, -COOC**H**$(CH_3)_2$), 4.76 (ddd, 1H, J= 10, J' = J'' = 7 Hz, -C**H**OOCCH_2-), 4.16 (dd, 1H, J = 2, J' = 6 Hz, -C**H**OH), 3.06 (s, 1H, O**H**, D_2O exchangeable), 2.75 (m, 2H), 2.11 (m, 1H), 1.46-1.92 (complex m, 5H), 1.19 and 1.21 (each d, each

J = 6.5 Hz, -COOCH(CH_3)$_2$); hrms [M - 87]$^+$ 155.0714 (calcd. for $C_8H_{11}O_3$: 155.0708).

(6R*, 8S*, 9R*)-3-*Trans*-benzylidene-hexahydro-6-isopropoxy-carbonyl-2(3*H*)-benzofuranone (129)

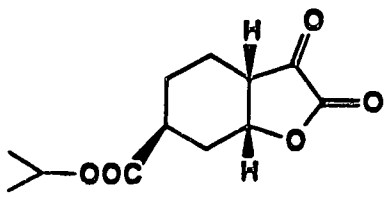


Butyrolactone **127** (276.10 mg, 1.22 mmol) in dry THF was added slowly to a cold (-78°C) solution of lithium isopropylcyclohexylamide [which was prepared at -78°C from *N*-isopropylcyclohexylamine (0.21 mL, 1.27 mmol, 1.0 eq) and *n*-butyllithium (2.5 M solution in hexane, 0.51 mL, 1.28 mmol, 1.1 eq) in THF under an argon atmosphere]. Then HMPA (0.23 mL, 1.32 mmol, 1.1 eq) was added and the mixture was stirred at -78°C for 30 min. Then benzaldehyde (0.13 mL, 1.28 mmol, 1.1 eq) was added. The solution was stirred at -78°C for 7 h, and then allowed to warm up slowly to room temperature. After stirring overnight, the solution was poured into 50% diethyl ether in hexanes (50 mL). The organic layer was washed with water (2 × 20 mL) and 5% aqueous HCl solution (3 × 15 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was dissolved in carbon

tetrachloride (15 mL) and copper sulfate adsorbed onto silica gel (1.33 mmol $CuSO_4$/1g silica gel; 800 mg, 1.06 mmol, 0.87 eq) was added and the mixture was refluxed overnight. The solution was cooled, filtered and concentrated. The residue was then subjected to flash column chromatography. Elution with 22% ethyl acetate in hexanes afforded compound **129** (52.35 mg, 14% yield, or 18% yield based on consumed starting material) as white crystals: mp 95-97°C; ir (CH_2Cl_2 cast) 1755 (C=O, butyrolactone) and 1725 cm^{-1} (C=O, ester); ^1H nmr (400 MHz) δ 7.53 (m, 2H, C=C-**H** aromatic), 7.43 (m, 4H, C=C-**H**, vinylic and aromatic), 5.04 (septet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.60 (ddd, 1H, J = 1, J' = 4, J'' = 5 Hz, H-8), 3.35 (dddd, 1H, J = 1, J' = 5, J'' = 7 J''' = 12 Hz, H-9), 2.55 (m, 2H), 2.20 (ddd, 1H, J = 4, J' = 7, J'' = 10.5 Hz), 2.05 (m, 1H), 1.85 (ddd, 1H, J =4, J' = 13, J'' = 16 Hz), 1.35-1.57 (m, 2H), 1.27 and 1.25 (each d, each J = 6.5 Hz, -COOCH(C**H**$_3)_2$); hrms M^+ 314.1512 (calcd. for $C_{19}H_{22}O_4$: 314.1519).

Elution with 30% ethyl acetate in hexanes afforded the starting material, butyrolactone **125** (69.54 mg, 25% yield).

(6R*, 8S*, 9R*)-Hexahydro-6-isopropoxycarbonyl-3-oxo-2(*3H*)-benzofuranone (130)



At -78°C, a stream of ozone-oxygen gas was allowed to pass through a solution of compound **129** (7.4 mg, 0.024 mmol) in methylene chloride (5 mL) until the gas stream from the reaction vessel caused a discharge of color from a solution of iodine (25 mg) in acetic acid (15 mL), and a pale blue color was observed in the reaction solution. The reaction mixture was further purged with oxygen to remove the excess ozone, and then dimethyl sulfide (0.25 mL) was added. The solution was allowed to stir further overnight at -20°C. The solvent was then removed under reduced pressure. The crude product was subjected to flash column chromatography. Elution with 50% ethyl acetate in hexanes afforded compound **130** (5.65 mg, 100% yield) as a yellow oil: ir (CH_2Cl_2 cast) 1761 (C=O, butryolactone) and 1722 cm^{-1} (C=O, ester and ketone); ^1H nmr (400 MHz) δ 5.08 (quintet, 1H, J = 6.5 Hz, -COOC**H**$(CH_3)_2$), 4.98 (m, 1H), 2.92 (m, 3H), 2.35 (m, 2H), 1.60 (m, 2H), 1.25 and 1.27 (each d, each 6H, J = 6.5 Hz, -COOCH$(C\mathbf{H}_3)_2$); hrms M^+ 240.0959 (calcd. for $C_{12}H_{16}O_5$: 240.0998).

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