SYNTHETIC STUDIES WITH 2,5-DIMETHOXYTETRAHYDROFURAN AND RELATED COMPOUNDS

by

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ABSTRACT

The reactions of 2,5-dimethoxytetrahydrofuran and 2,6-dimethoxytetrahydropyran with halotrimethylsilanes have unexpectedly given 1,4-dihalo-1,4-dimethoxybutane and 1,5-dihalo-1,5-dimethoxypentane, respectively. Some features of this reaction were investigated and a mechanism was proposed.

It was shown that 1,4-dichloro-1,4-dimethoxybutane was a mild reagent for the conversion of primary amine and amide to the corresponding N-alkyl and N-acyl pyrroles, respectively. As part of these applications, 2-(2-formylpyrrol-1-yl)-4-methylpentanoic acid, a compound isolated from flue-cured tobacco, was synthesized.

The use of acylpyrroles as active acylating agents was investigated. The preparation of α-substituted derivatives from ethyl 2-(1-pyrrolyl)acetate was achieved by using lithium hexamethyldisilazide as base.

As part of a synthetic study directed toward Nonactin, the bicyclic enol form <u>152</u> and keto form <u>153</u> were obtained by the reaction of 1-methoxy-1,3-*bis*(trimethylsiloxy)-1,3-pentadiene with 2,5-dimethoxytetrahydrofuran.

The configurations at C-4 were determined with the aid of 200 MHz ^{1}H nmr decoupled spectra.

A new rearrangement of α-acyloxy esters into 2-hydroxy-3-keto esters was observed.

ETUDES SYNTHETIQUES DU DIMETHOXY-2,5 TETRAHYDROFURANNE ET DES COMPOSES APPARENTES

RESUME

Cette thèse décrit en premier lieu la réaction du diméthoxy-2,5 tétrahydrofuranne et du diméthoxy-2,6 tétrahydropyranne sur divers halotriméthylsilanes pour fournir les dihalo-1,4 diméthoxy-1,4 butane et dihalo-1,5 diméthoxy-1,5 pentane respectivement. Quelques points caractéristiques à cette réaction ont donc été étudiés et un mécanisme est proposé.

L'utilisation du dichloro-1,4-diméthoxy-1,4 butane pour la transformation d'amines et d'amides primaires en composés N-alkyl et N-acyl pyrroles correspondants est ensuite démontrée. Cette méthodologie est appliquée à la synthèse de l'acide (formylpyrrol-2,yl-1)-2 méthyl-4 pentanoique, un composé isolé des feuilles de tabac.

De même, quelques applications synthétiques à ces noyaux pyrroles ont été développés, soit l'emploi d'acylpyrroles comme agents acylants ainsi que la préparation de dérivés α-substitués d'acides aminés à partir du (pyrrolyl-1)-2 acétate d'éthyle en utilisant le *bis*-(triméthylsilyl)-amidure de lithium comme base.

Ayant aussi comme autre projet une approche à la synthèse de la nonactin, les composés bicycliques <u>152</u> et <u>153</u> ont été obtenus à partir de la réaction du méthoxy-1, *bis*-(triméthylsilyloxy)-1,3 pentadiène-1,3 sur le diméthoxy-2,5 tétrahydrofuranne. Les configurations en C-4 de ces composés ont été déterminés par une étude rmn ^{1}H 200 MHz des spectres découplés.

Finalement, un nouveau réarrangement d'α-acyloxy esters en hydroxy-2 β-cétoesters a été observé.

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TABLE OF CONTENTS

IV 1,4-DICHLORO-1,4-DIMETHOXYBUTANE AS A MILD REAGENT FOR THE CONVERSION OF PRIMARY AMINES TO PYRROLES

V N-ACYLPYRROLE SYNTHESIS AND ITS APPLICATION IN ORGANIC SYNTHESIS

List of Abbreviations

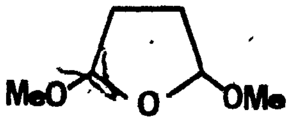
Ac	acetyl
Bn	benzoyl
Bu	butyl
Bz	benzyl
DMSO	dimethylsulfoxide (methylsulfoxide)
Et	ethyl
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
mCPBA	m-chloroperoxybenzoic acid
Me	methyl
MsOH	methanesulfonic acid
Pyr	pyridine
Ra-Ni	Raney-nickel
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl (tetramethylsilane as an internal standard in nmr)
TsOH	toluenesulfonic acid
TLC	thin layer chromatography

CHAPTER I

INTRODUCTION

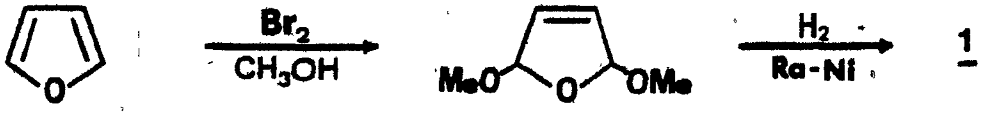
A. Synthesis and Chemistry of 2,5-Dimethoxytetrahydrofuran

Since Clauson-Kaas[1] and his coworkers first prepared 2,5-dimethoxytetrahydrofuran (1) from furan in 1950, compound 1 was used as a valuable intermediate in the synthesis of numerous types of heterocyclic compounds including those of the tropinone series[2]. They obtained 1



2,5-dimethoxytetrahydrofuran (1)

by the reaction of furan with bromine in methanol and then followed by catalytic hydrogenation[1,3]. The product of the first step, 2,5-dimethoxy-2,5-dihydrofuran (2), was often



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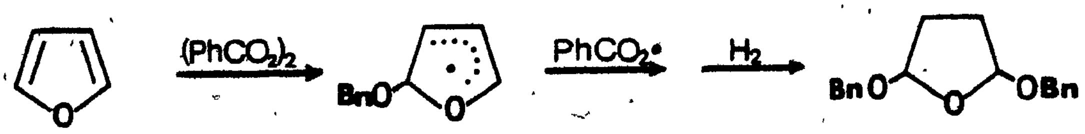
contaminated by a small amount of halogen-containing impurities which may cause the formation of hydrogen halide and therefore greatly influence the stability of the acid-sensitive dimethoxydihydrofuran. This disadvantage was overcome by Clauson-Kaas' discovery of the electrolytic alkoxylation method[4] in an alcoholic solution of ammonium bromide. This reaction gave halogen-free, stable product 2 which could be stored for several years without deterioration.

On the other hand, furan undergoes addition reactions with radicals. When treated with dibenzoyl peroxide[5], furan afforded 2,5-dihydro-2,5-dibenzoyloxy furan and further hydrogenation gave the 2,5-disubstituted tetrahydrofuran 3.



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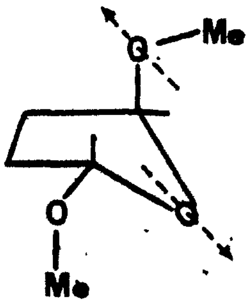
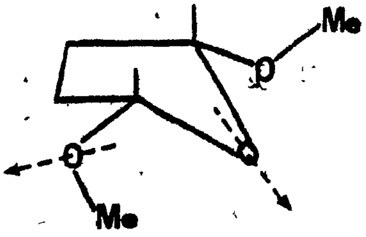
Similarly, Jain *et al.*[6] reported that hydrogenation of 2,5-dimethoxyfuran, obtained from agricultural wastes, over Ra-Ni at room temperature gave directly 2,5-dimethoxytetrahydrofuran.

These 2,5-dialkoxytetrahydrofurans were usually obtained as a mixture of *cis*- and *trans*-isomers. In 1969, Kankaanpera *et al.*[7] reported that the anomeric effect exists not only in 6-membered heterocyclic compounds, but also in 5-membered rings. However, in the case of 2,5-dimethoxy-tetrahydrofuran, the stabilities of the isomers are so much alike that the equilibrium ratios in different solvents were between 40 and 60% and pure isomers could not be isolated.

Riddell[8] has concluded that the anomeric effect is a result of dipole-dipole interactions, which should be weaker in polar solvents as a result of increased solvation of the individual dipoles. Even though the equilibrium composition in several solvents in Kankaanpera's work[7] was not very different between two isomers, it indicated that the *trans* isomer of 2,5-dimethoxytetrahydrofuran was a little more stable than the *cis* isomer in the non-polar solvent benzene (the ratio of *trans*- to *cis*- is about 63:37). In the envelope structure in which the ring oxygen is at the tip of the flap, one of the methoxy groups must be in a nearly axial position in order for the ether dipoles to be nearly anti-parallel. On the contrary, the methoxy dipole in the nearly equatorial position is perpendicular to the endocyclic oxygen dipole and thus the dipolar effect is negligible.

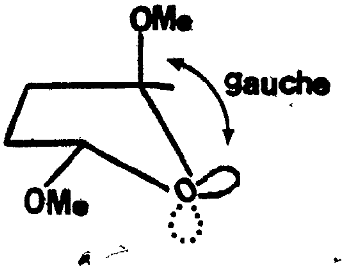


trans-isomer

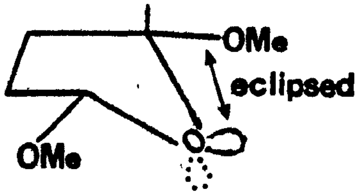


cis-isomer

On the other hand, one might also explain this aspect in terms of the gauche[77] effect. The gauche effect is a tendency to adopt that structure which has the maximum number of gauche interactions between adjacent electron pairs and polar bonds. This effect is ascribed to nuclear-electron attractive forces between the groups and unshared electron pairs. In the *trans*-isomer, one of the methoxy groups must be in a gauche position to one electron-pair of the ring oxygen. In the *cis*-isomer, the methoxy group in the nearly equatorial position is eclipsed to one electron pair of the ring oxygen and thus the *cis*-isomer might be less stable than the *trans*-isomer.



trans-isomer

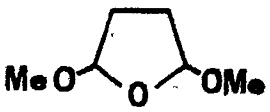


cis-isomer

A well recognized property[8] of the ether linkage, in general, is its unreactivity. This leads to the extensive use of ethers as solvents or as protecting groups for many organic reactions. However, cyclic acetals, for example 2,5-dimethoxytetrahydrofuran, are more reactive than dialkyl ethers. The cyclic acetals serve therefore additional purposes in organic synthesis.

B. The Synthetic Applications with 2,5-Dimethoxy THF

2,5-Dialkoxytetrahydrofurans are normally stable under alkaline and neutral conditions. On acid hydrolysis the ring is opened and 1,4-dicarbonyl compounds are formed[2]. Although Fakstorp *et al.* could isolate succinic aldehyde (4) from 2,5-diethoxytetrahydrofuran in 30% yield[16], the aqueous solutions containing the 1,4-dicarbonyl compounds were, in general, used directly for further reactions without isolation. This is because it is difficult to obtain the 1,4-dicarbonyl compounds resulting from the hydrolysis of dialkoxy THF in a monomeric, water-free state. Therefore, 2,5-dimethoxy THF (1) can be regarded as a stable "depot compound" for the labile 1,4-dicarbonyl compound 4.



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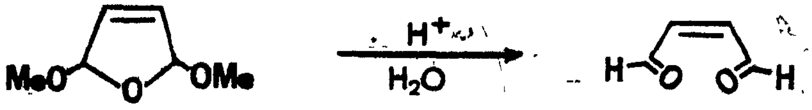
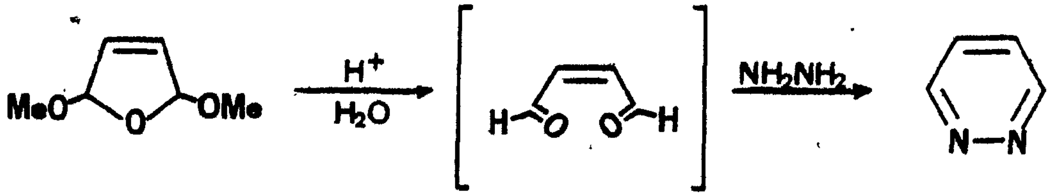
In the same way, malealdehyde (5) could also be obtained from the acid hydrolysis of 2,5-dimethoxy-2,5-dihydrofuran (2)[16].



2 5

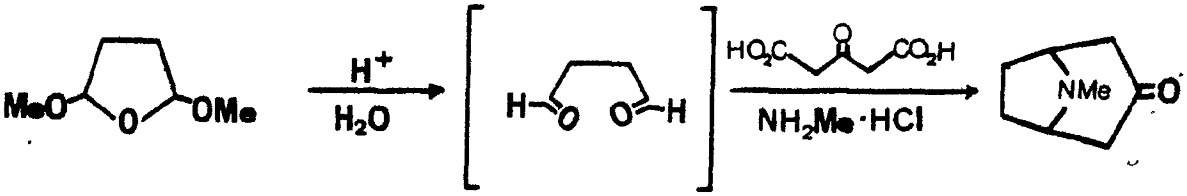
It is clear that dialdehyde compounds as well as the precursor cyclic acetals should have potential for the synthesis of heterocyclic compounds *via* intermolecular and intramolecular condensations.

For examples of intermolecular condensations, we can cite the following: (i) The reaction of hydrazine with malealdehyde (5), obtained by deketalization of 2,5-dimethoxy-2,5-dihydrofuran (2), represents a convenient synthesis of pyridazine[9] (6). (ii) The synthesis of tropinone (7) by the

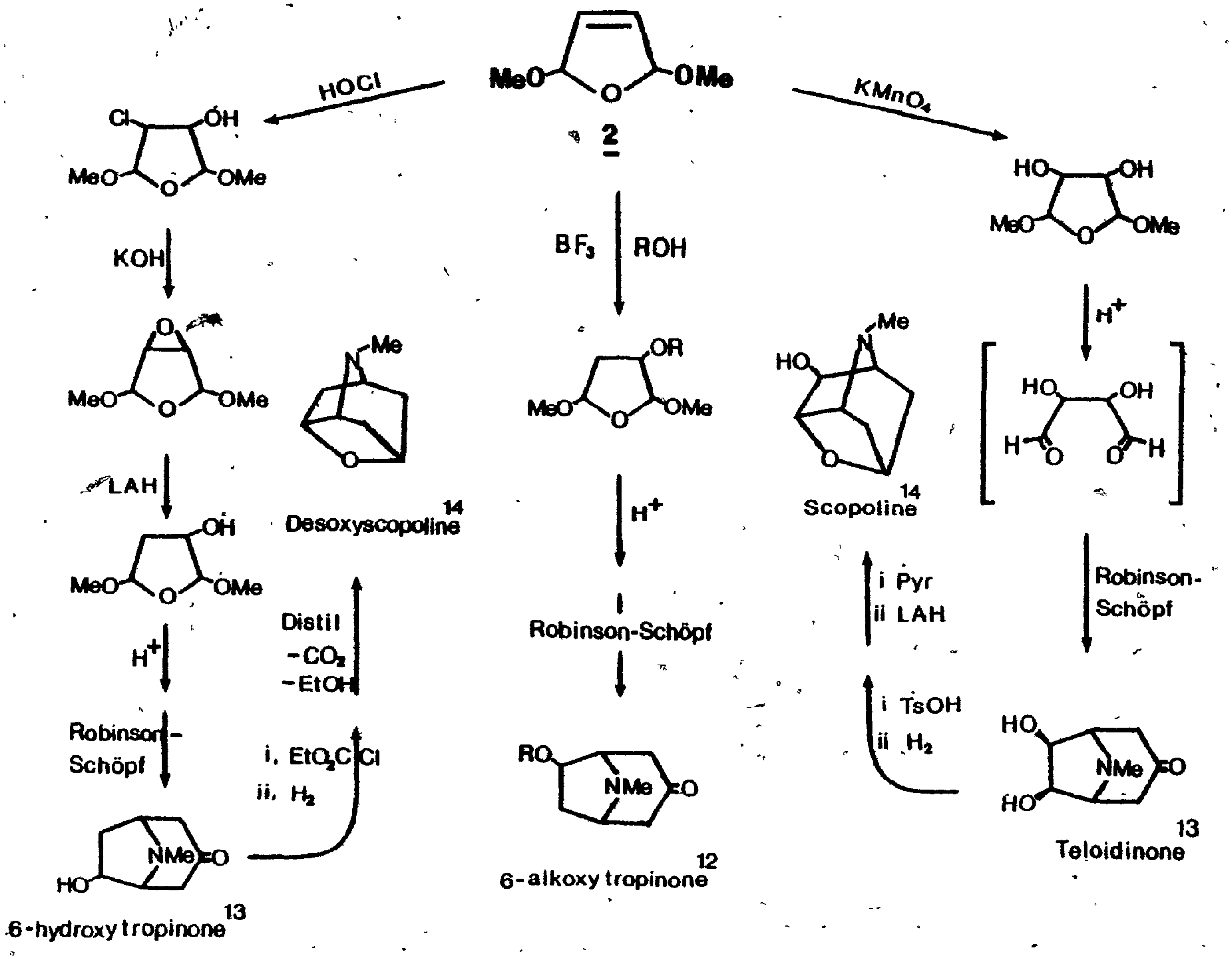


2 5 6

method of Robinson[10] and Schöph[11] involved the condensation of succinic aldehyde (4) with acetonedicarboxylic acid and methylamine hydrochloride to form the tropane skeleton. As shown in Scheme 1, a series of tropinone-type alkaloids

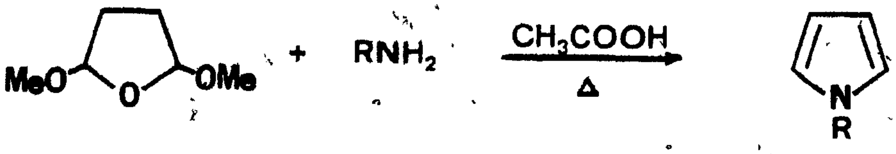


1 4 7



Scheme 1: Intermolecular condensations from 2 into tropinone-type alkaloids

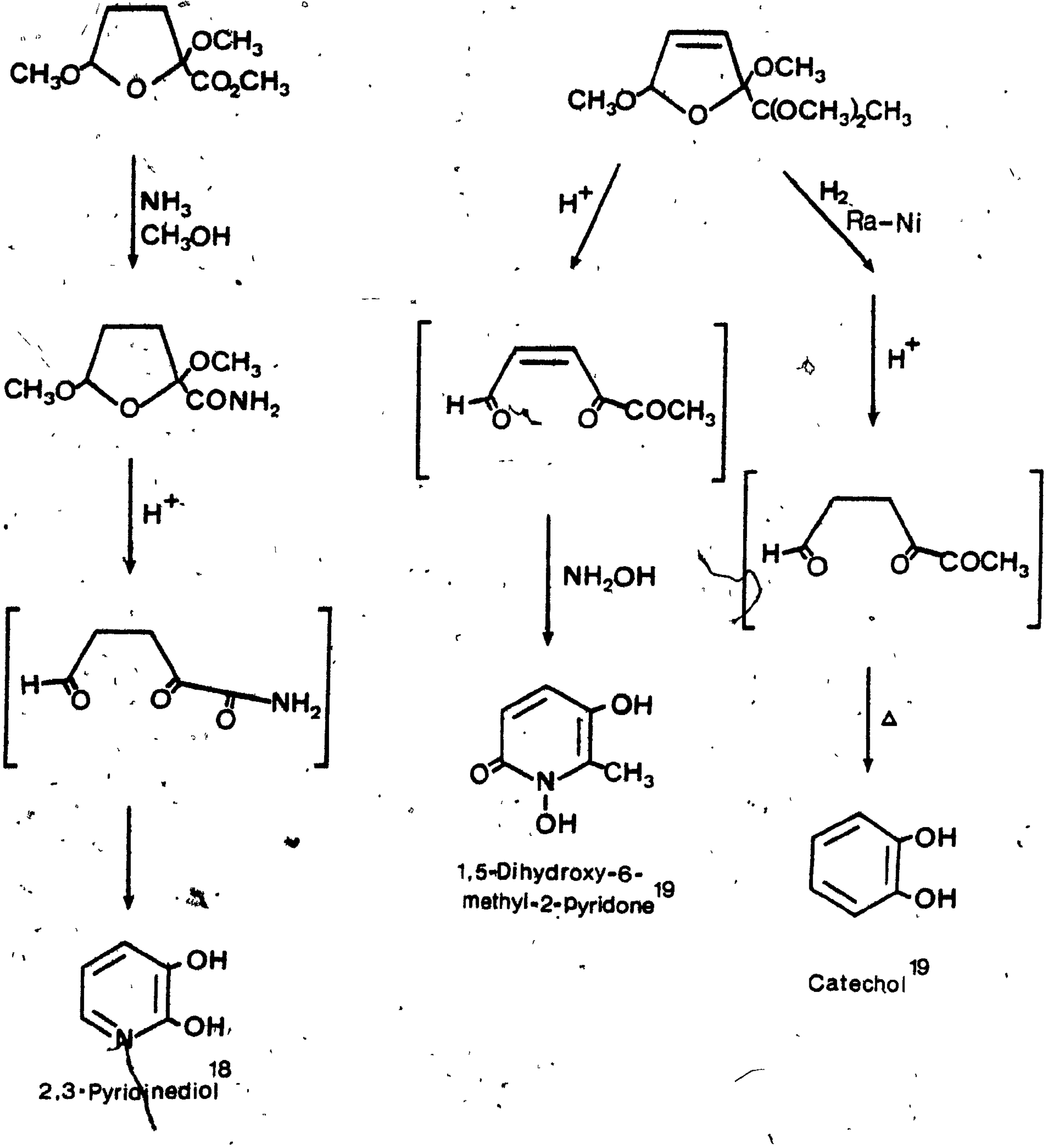
were synthesized[12-14] from a variety of 2,5-dialkoxytetrahydrofurans and acetonedicarboxylic acid/methylamine hydrochloride. (iii) The conversion of primary amines to pyrroles has been achieved by their reaction with 2,5-dimethoxytetrahydrofuran (1) under refluxing acetic acid[15-17]. The reaction is useful for the synthesis of a number of N-substituted pyrroles.



1

Similarly, furans[2] with suitable substituents in the 2-position might be transformed into other cyclic systems by alkoxylation to cyclic acetals of 1,4-dicarbonyl compounds, followed by intramolecular condensation in acid solution. Applications of this reaction had led to the transformation of furans into such substances as pyridine derivatives[18] and benzenoid compounds[19], as shown in Scheme 2.

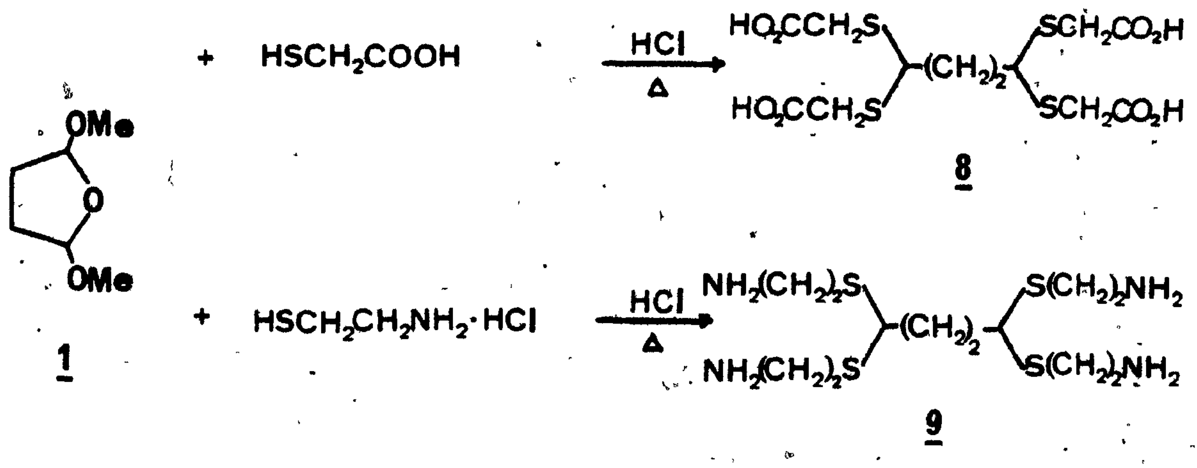
Some of these compounds are quite useful. For example, it was well established that pyridoxine-5-thiol was effective in facilitating the removal of mercury from the central nervous system and across the blood-brain barrier[20]. The success[21] of the polyaminocarboxylic



Scheme 2: Intramolecular condensations of cyclic acetals derivatives

acids (e.g. EDTA) suggests that analogous compounds which were polythio-carboxylic acids might prove very interesting in this respect as well.

Jones[22] reported that (butanediylidenetetrathio)-tetraacetic acid (8) could be prepared by the reaction of mercaptoacetic acid with 2,5-dimethoxytetrahydrofuran (1) in hydrochloric acid solution. Compound 8 is potentially a good chelating agent. In the following year, they prepared butanediylidenetetrathiotetrakis(ethylamine)[23] (9) as a new potentially octadentate chelating agent.



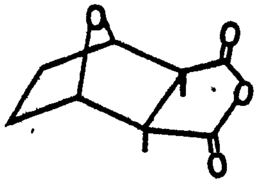
It is obvious from these investigations, that 2,5-dimethoxytetrahydrofuran can be considered as a precursor of succinic aldehyde, which is a good dielectrophile, and thus has great potential for organic synthesis.

CHAPTER II

ATTEMPTED SYNTHESIS OF CANTHARIDIN

A. Previous Syntheses of Cantharidin in the Literature

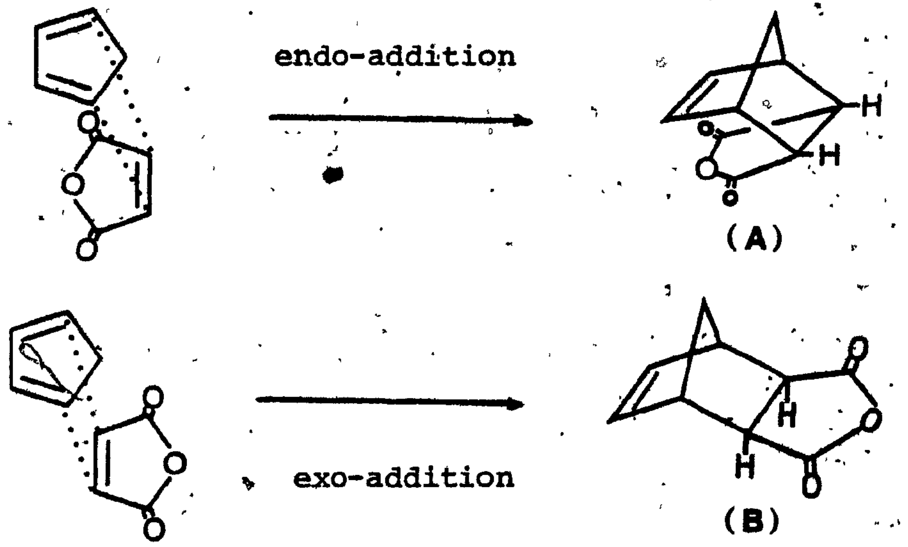
Cantharidin (10), the potent vesicant principle found in various species of cantharides beetles, was first obtained in crystalline form by Robiquet[24] in 1810.



cantharidin (10)

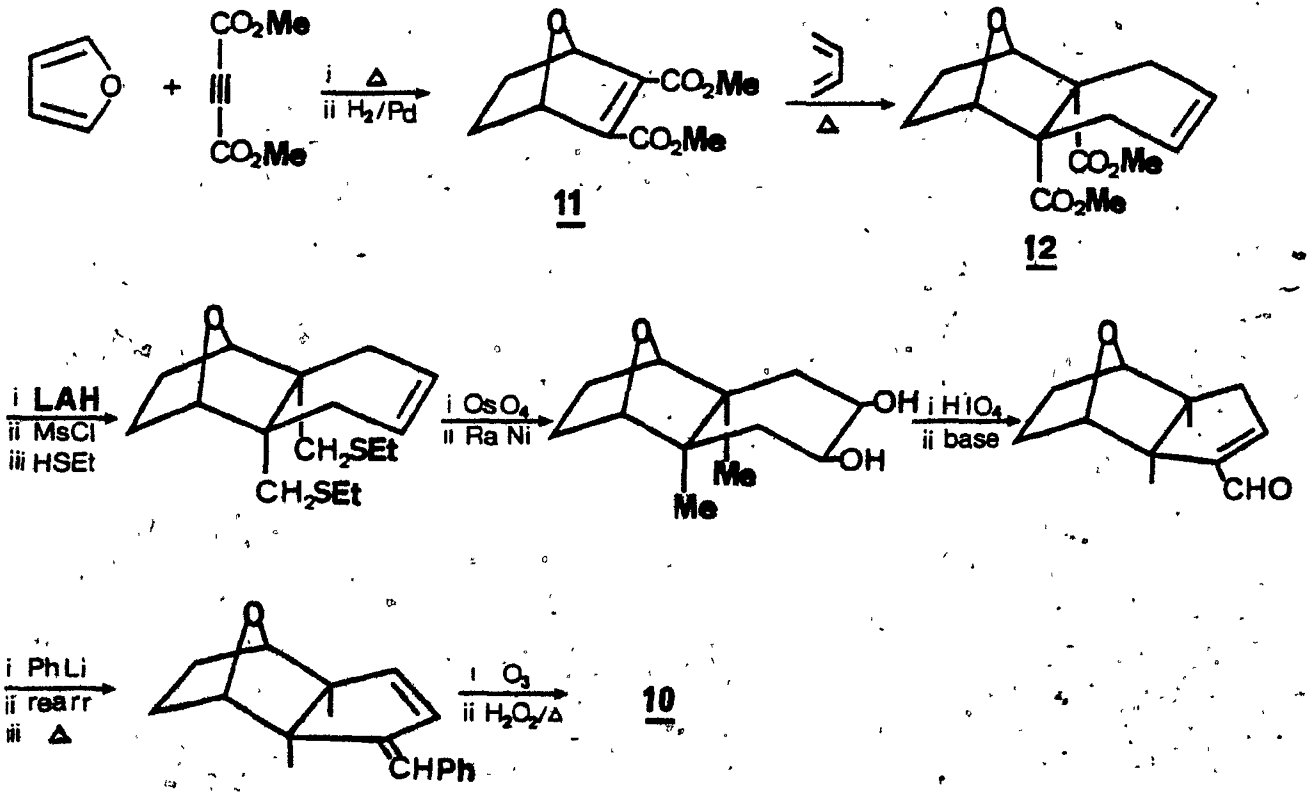
Notwithstanding its notoriety as the putative aphrodisiac in "Spanish fly", cantharidin has found commercial application in the removal of benign epithelial growths (warts[25]). Cantharidin is optically inactive and non-resolvable[26]. Its anhydride ring is therefore *cis* fused and is *cis* to the oxide bridge.

A number of attempts to synthesize cantharidin have been reported in the literature since the early experiments of von-Bruchhausen and Bersch[27] and of Diels and Alder[28] who sought to build up the molecule *via* a diene synthesis between dimethylmaleic anhydride and furan. This straightforward approach, which could well have led to the correct stereochemistry[29], was not successful. During the following 20 years, a variety[30-32] of Diels-Alder reactions for the cantharidin synthesis was attempted but stereospecific synthesis of cantharidin was still unsuccessful. As a matter of fact, these attempts would not be in accord with the Alder rule[33], namely "maximum accumulation of double bonds". For instance, in the reaction of maleic anhydride with a cyclic diene, such as cyclopendadiene, two modes of addition are theoretically possible, leading to the formation of an "endo" product (A) or an "exo" product (B) respectively. Actually, the product (A) was produced selectively[33].



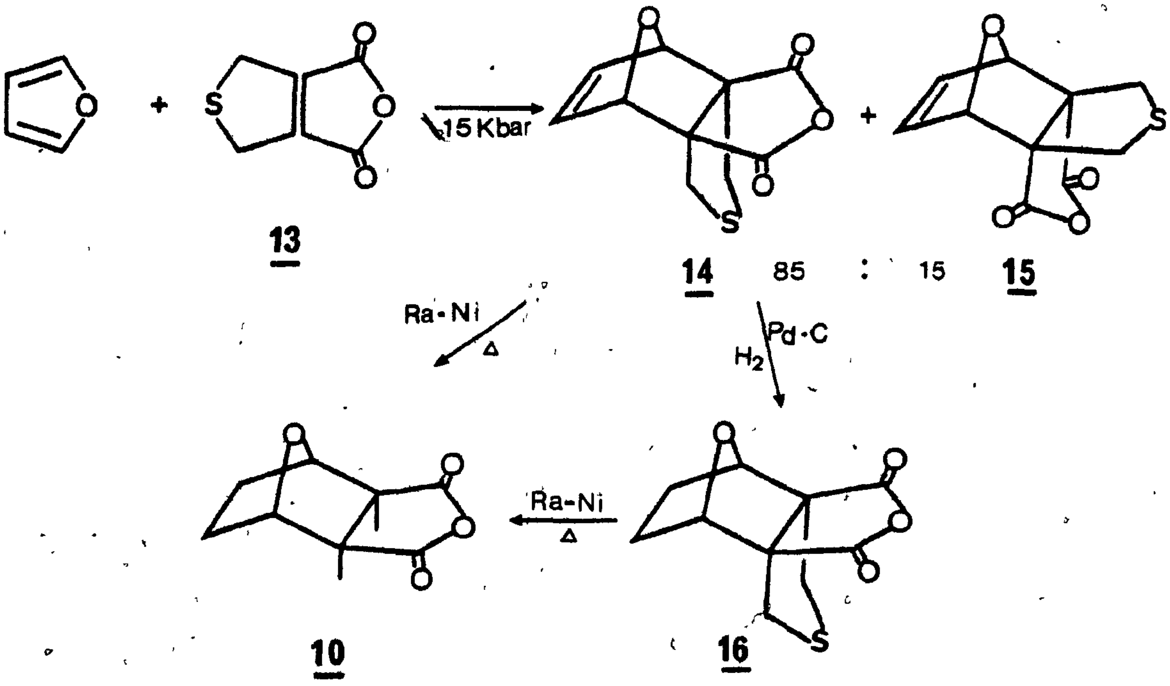
In order to avoid this difficulty, Stork and his coworkers[34] reported a total synthesis of cantharidin (10) from the butadiene adduct (12) of dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate (11) as shown in Scheme 3. The Diels-Alder reaction of 11 with butadiene gave exo-adduct 12 predominantly because the epoxide bridge in 11 offers less hindrance to the approach of the butadiene molecule than does the ethylene bridge. Compound 12 was transformed to

Scheme 3: Cantharidin synthesis by Stork[34]



cantharidin (10) by a series of reactions with defined stereochemistry.

Recently, Dauben *et al.*[35] suggested that the failure of Diels-Alder reaction between furan and dimethylmaleic anhydride, investigated as early as the 1920's, was a result of both electronic and steric factors. The electron-donating methyl groups of dimethylmaleic anhydride decrease its dienophilicity and extra crowding in the transition state given by these same methyl groups should further reduce its reactivity. Furthermore, furan is a poor Diels-Alder diene because of its aromaticity[36], and the cycloadduct is rather sensitive thermally toward reversal to starting materials due to the strain of the bicyclic system[37], so high temperature cannot be used. It has already been shown that high pressures in the range of 10-20 Kbars[35] greatly facilitate Diels-Alder reaction of furan. Although dimethylmaleic anhydride did not add to furan even at 40 Kbar[38], Dauben *et al.*[39] found that reaction of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (13) with furan at room temperature for 6 hrs under 15 Kbar pressure effected quantitative conversion to the cycloadducts 14 and 15 as an 85:15 mixture of isomers. The major isomer 14 was hydrogenated over Pd-C to give 16 in quantitative yield and further desulfurization over Ra-Ni gave 10.

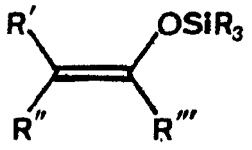


The presence of the sulfur-containing methylene bridge in place of the dimethyl substituents on the maleic anhydride nucleus was anticipated to reduce the electron-donating character of these two alkyl substituents, and it was anticipated that the sulfur-containing ring would reduce the steric demands of the disubstituted maleic anhydride.

In this chapter, we are interested in the possibility of assembling the cantharidin structure in one step by a non-Diels-Alder approach. We will consider the reaction of enol silyl ethers of 2,3-dimethylsuccinic anhydride with 2,5-dimethoxytetrahydrofuran in the presence of a Lewis acid.

B. Chemistry of Enol Silyl Ethers of Acid Anhydride

Since 1958[40a], enol silyl ethers 17 have been known, when the first report of their synthesis appeared in the Russian literature. Following the work of Stork[40b] in 1968, the chemistry of enol silyl ethers has shown them to be very versatile tools[41-43] for organic synthesis. Among other things, a series of 2,5-*bis*(trimethylsiloxy)-furans (18) have been prepared in our laboratory, and they were found to be useful intermediates[44] for the synthesis of lignans, butenolides, hydroquinones and p-quinones.



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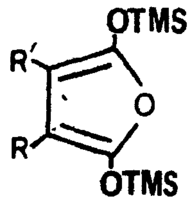

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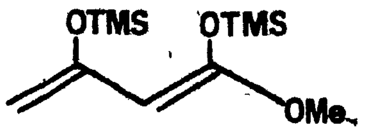
In addition, it was also found in our laboratory[45] that 1,3-*bis*(trimethylsiloxy)-1-methoxybuta-1,3-diene (19) can serve as the equivalent of the dianion of methyl acetoacetate (20).



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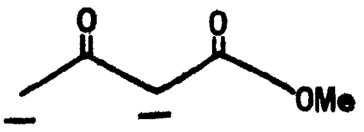

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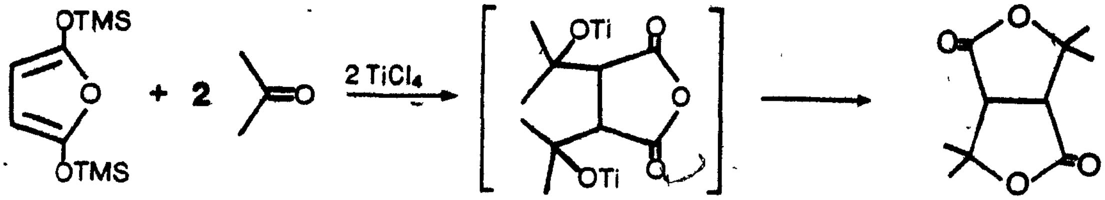
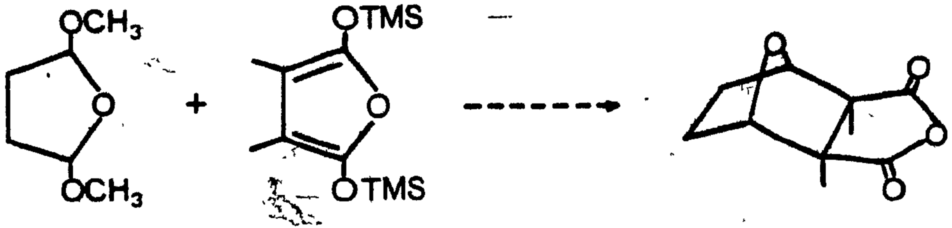
The enol silyl ether 18 with the furan ring skeleton could thus be regarded as the cyclic analogue of 19. In fact, 2,5-*bis*(trimethylsiloxy)furan (21) reacted with acetone, with activation by titanium tetrachloride, to give *bis*-lactone 22 directly in 72% yield[46]. It was suggested that the initial reaction product was 3,4-disubstituted succinic anhydride 23 which then underwent lactonization under the reaction conditions to give 22.



21 **23** **22**

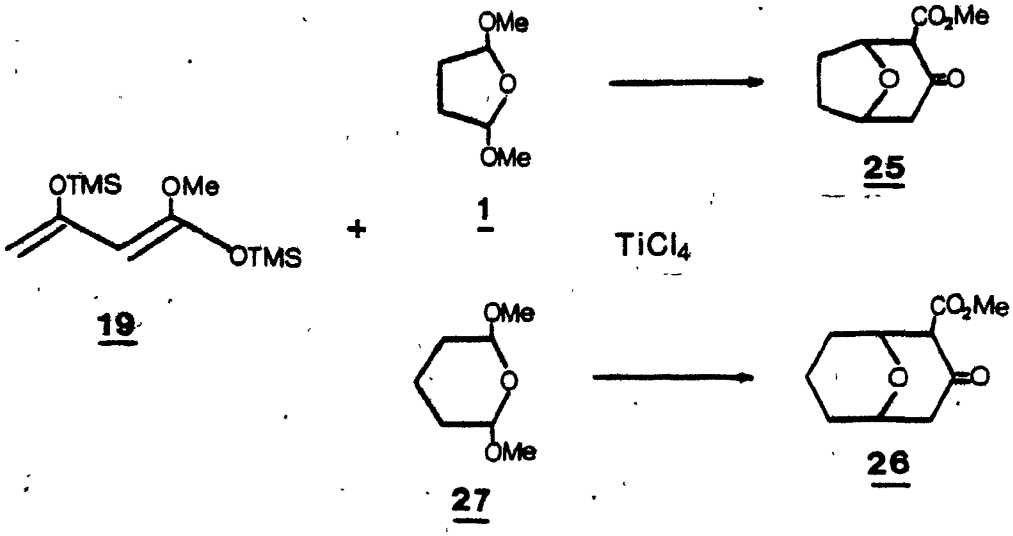
Based on this observation, it seems to us that an alternative approach to cantharidin (10) could start from the enol silyl ether of 3,4-dimethylsuccinic anhydride 24 as nucleophile and 2,5-dimethoxytetrahydrofuran as electrophile in the presence of titanium tetrachloride.



24 **10**

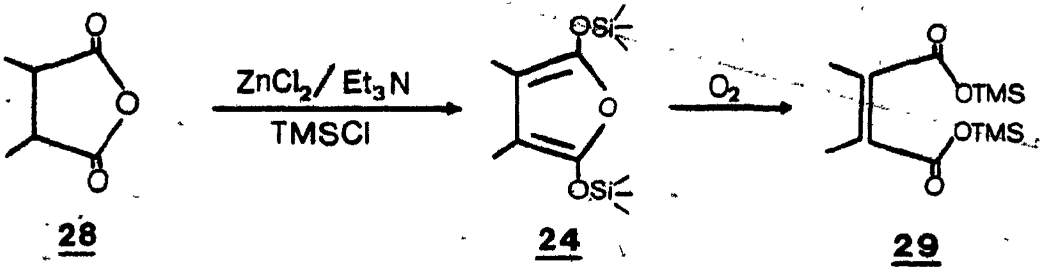
C. Attempted Synthesis of Cantharidin (10) from 2,5-Dimethoxytetrahydrofuran and Enol Silyl Ether 24

As depicted in the above, two molecules of the carbonyl compound reacted at the 3- and 4-positions of 21, resulting in the *bis*-lactone 22. Since it is also known that acetals (*e.g.* $R_1R_2C(OMe)_2$) react with enol silyl ethers under activation by titanium tetrachloride[47], a facile route[45] to the oxabicyclic compounds (25, 26) was developed by the reaction of the enol silyl ether 19 with cyclic acetals such as 1 or 27 (more detailed discussions will be given in Chapter 6).

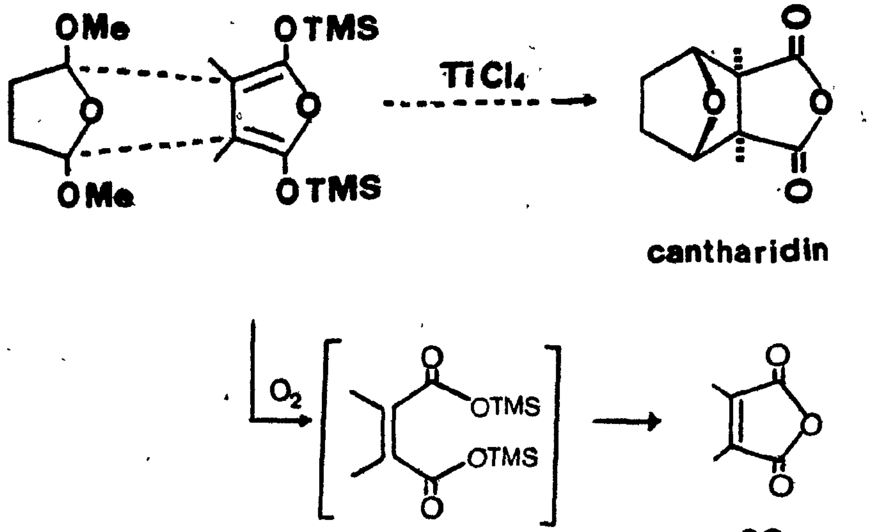


From the above two considerations, it was decided to attempt a one-step synthesis of cantharidin using

3,4-dimethyl-2,5-*bis*(trimethylsiloxy)furan (24) and 2,5-dimethoxytetrahydrofuran (1) in the presence of titanium tetrachloride. 3,4-Dimethylsuccinic anhydride (28), obtained from the dehydration[48] of 3,4-dimethylsuccinic acid, was simply treated[44] with triethyl amine, zinc chloride and trimethylchlorosilane in dry acetonitrile to give the corresponding enol silyl ether 24 (^{1}Hmr ($CDCl_3$) δ: 1.8 (s, 6H), 0.26 (s, 18H, $SiMe_3$)) together with about 20% of 29 (^{1}Hmr ($CDCl_3$) δ: 1.65 (s, 6H), 0.2 (s, 18H, $SiMe_3$)) as impurity according to nmr.



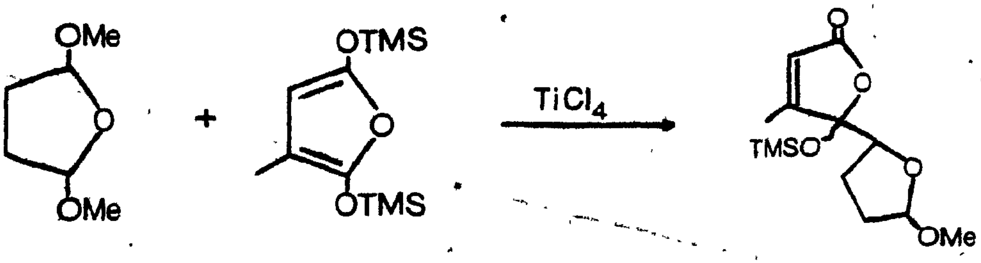
The reaction of 24 with 2,5-dimethoxy THF (1) has not, unfortunately, given us any satisfactory results. As a matter of fact, enol silyl ether 24 is so unstable that it was converted into compound 30 (^{1}Hmr ($CDCl_3$) δ: 2.1 ppm (s, CH_3); ms, m/z (intensity), 126 (M^+, 80.9), 82 (M^+-CO_2, 100); mp, 91 ∿ 93° (lit.[49] 93° ∿ 96°)) within one hour in $CDCl_3$ *via* air oxidation[44].



cantharidin

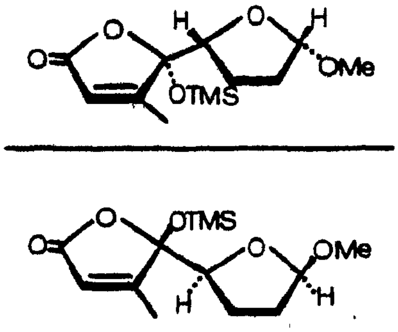
30

On repeating this reaction with 3-methyl-2,5-*bis*(trimethylsiloxy)furan (31) as the nucleophile, the product appeared to be the monosubstituted compound 32.

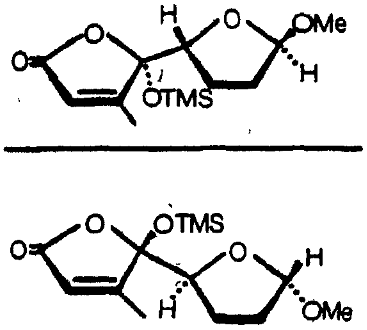


1 31 32

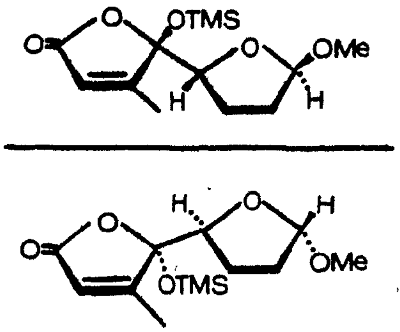
Product 32 has three asymmetric centers and thus four possible diastereoisomers (a-d), each existing as a pair of enantiomers as depicted. Actually, four diastereomers a



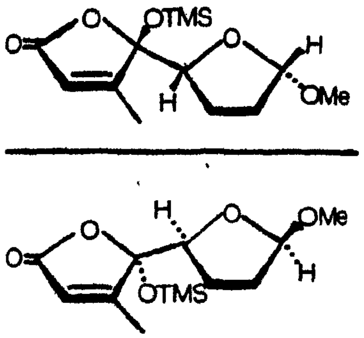
b



c

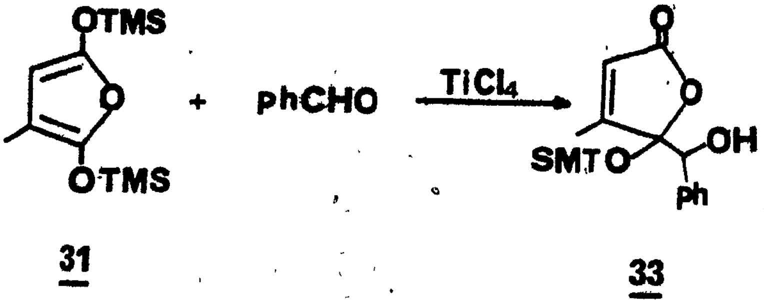


d

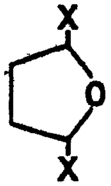


appeared on TLC and they were separated by flash column chromatography[50] on silica gel. Although their stereochemistries were not assigned, the structure of <u>32</u> was confirmed by spectral data; λ_{max} = 217 $\sim$ 220 nm (95% EtOH) for α,β-unsaturated γ-lactone, ν_{max} = 1775 $\sim$ 1755 cm^{-1} for carbonyl stretching and ν_{max} = 1648 $\sim$ 1659 cm^{-1} for olefinic stretching of α,β-unsaturated γ-lactone. Nmr data showed unreacted anomeric proton peaks of the tetrahydrofuran moiety at 4.9 $\sim$ 5.1 ppm, whereas proton peaks in substituted positions showed upfield shifts to 4.0 $\sim$ 4.2 ppm. Vinylic protons appeared at 5.77 ppm, methoxy peaks at 3.16 ∿ 3.3 ppm, vinylic methyl peaks at 2.04 ∿ 2.17 ppm, methylene peaks at 1.95 ∿ 2.05 ppm, and TMS peaks at 0.11 ∿ 0.13 ppm, respectively.

This result seems to suggest that the methyl group of 31 is sufficiently electron-donating to completely control the regioselectivity of the reaction, since none of the alternative 5-substituted product is produced[51]. Such regioselection was previously observed[52] in the reaction of 31 with benzaldehyde to give γ-hydroxybutenolide 33.



A possible approach to overcome the problem of regioselection is to use a more reactive electrophile than 2,5-dimethoxy THF. Some possible candidates are the 2,5-dihalo THF 34. It has been reported[53-54] that photochemical reaction of tetrahydrofuran with chlorine in carbontetrachloride gave compound 34 together with



34

2-chloro- and 2,3-dichlorotetrahydrofuran. The reaction was however very sensitive to temperature and pure 34 could not be obtained. Therefore, we attempted to synthesize compound 34 by the reaction of 2,5-dimethoxytetrahydrofuran with protonic acids (HX) in chloroform but the reaction was not successful. An alternative approach to 2,5-dihalotetrahydrofuran was therefore sought, using halotrimethylsilanes.

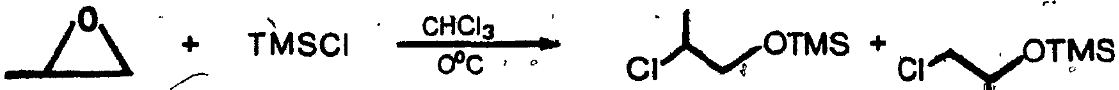
CHAPTER III

REACTION OF 2,5-DIMETHOXYTETRAHYDROFURAN AND RELATED COMPOUNDS WITH HALOSILANES

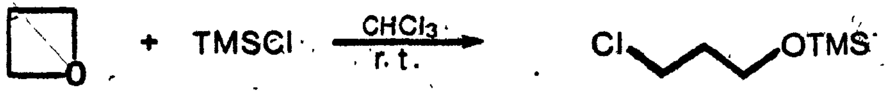
A. Historical Background; halosilanes in the cleavage of ethers and related compounds

Since cleavage of ethers with iodotrimethylsilane was reported by Jung *et al.*[55] in 1977 and Olah *et al.*[56] in 1976, numerous synthetic transformations have been carried out using iodotrimethylsilane. Many alkyl ethers have found extensive use in organic chemistry as protecting groups for alcohols[57]. Foremost among these are t-butyl, trityl and benzyl ethers, all of which can be removed under relatively mild conditions, namely non-aqueous acid, mild aqueous acid and hydrogenation, respectively[58]. However, cleavages of methyl ethers are more difficult, usually requiring rather vigorous acidic conditions. Although the method of dealkylation of ethers using iodotrimethylsilane appears to be straightforward, the handling and the storage of TMSI pose considerable difficulty due to its hydrolytic susceptibility and instability. In view of this, several alternative *in situ* iodotrimethylsilane reagents or their equivalents have recently been reported. These include allyltrimethylsilane/iodine[59], chlorotrimethylsilane/iodine[60], trichloromethylsilane/sodium iodide[61], etc.

In contrast with that, it is known that cyclic ethers such as oxiranes[62], oxetanes[63] and tetrahydrofurans[64] react with bromotrimethylsilane, while non-cyclic ethers are not cleaved. We found[65] that propylene oxide (<u>35</u>) reacted even with chlorotrimethylsilane to give ring opened chloro compounds <u>36</u> (4:1 mixture). Similarly, oxetane (<u>37</u>) reacted with TMSCl to give the chloro compound <u>38</u> in good yield.



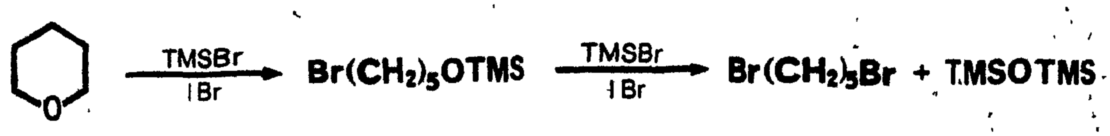
35 **36a** 1 : 4 **36b**



37 **38**

On the other hand, the reaction of tetrahydrofuran or tetrahydropyran even with excess TMSCl for several days was not successful. Whereas the reaction of tetrahydrofuran with TMSBr gave ring-opening product, that of tetrahydropyran with TMSBr did not take place.

Recently, E.C. Friedrich *et al.*[66] have reported interhalogen-catalyzed cleavages of tetrahydropyran and even acyclic ethers by using TMSBr and IBr (catalyst) in the absence of solvent in good yield. This fact was anticipated



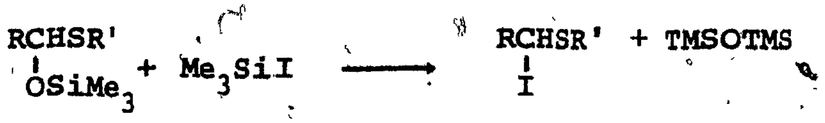
39 **40**

from literature information[67] which was available concerning trihalide formation constants in an equilibrium process.

In addition to these reports[63,68,69], we have done further investigation concerning the effects of ring size and halides on this reaction. Discussion will be given in the next section of this chapter.

B. Unexpected Site Selectivity in the Reaction of 2,5-Dimethoxy THF and 2,6-Dimethoxy THP with TMSX

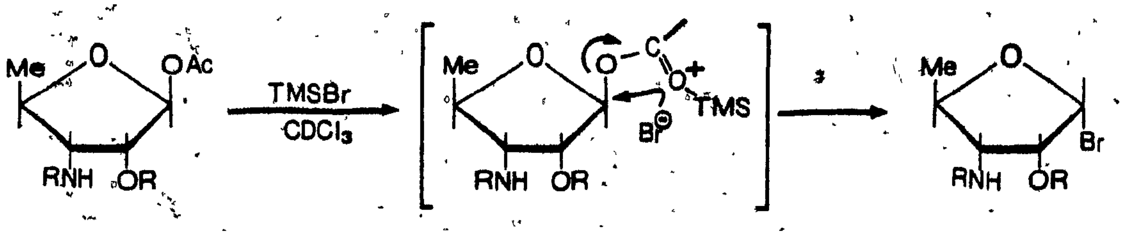
Recently, it has been found in our laboratory that α-iodosulfides[70] (42) can be prepared by the reaction of trimethylsiloxythioacetal 41 with TMSI. In the area of carbohydrates, it was reported that bromotrimethylsilane is a mild, stereoselective anomeric brominating agent.



$$\underset{|\atop \text{OSiMe}_3}{\text{RCHSR}'} + \text{Me}_3\text{SiI} \longrightarrow \underset{|\atop \text{I}}{\text{RCHSR}'} + \text{TMSOTMS}$$

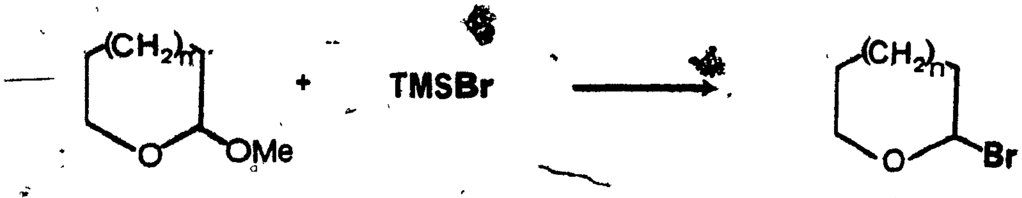
41 **42**

For example[71], stereoselective bromination of anomeric glycosyl acetate (A) was achieved with TMSBr under mild condition which showed inversion (B) of configuration as depicted. In a number of furanosides and pyranosides, reaction with TMSBr led to introduction of bromine at the anomeric carbon with the ring intact.



A **B**

In agreement with this, we observed[72] that 2-methoxy THF (43) or 2-methoxy THP (44) reacted with TMSBr to give the corresponding 2-bromo derivative 45 or 46.

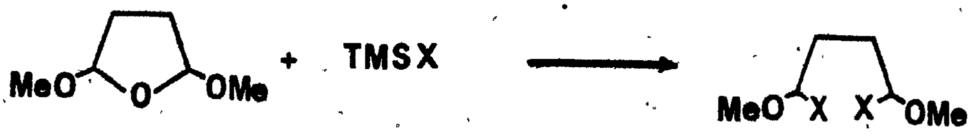


43 n=0 45

44 n=1 46

In the reaction with TMSCl, 2-methoxy THF gave the corresponding 2-chloro compound in 25% yield, while 2-methoxy THP gave no product.

In view of these results, we were therefore quite surprised to find that when 2,5-dimethoxy THF[73] (1) was reacted with TMSBr, the product of reaction was not 2,5-dibromo THF (34) but 1,4-dibromo-1,4-dimethoxybutane (47). The reaction of 1 with TMSI gave similarly



1

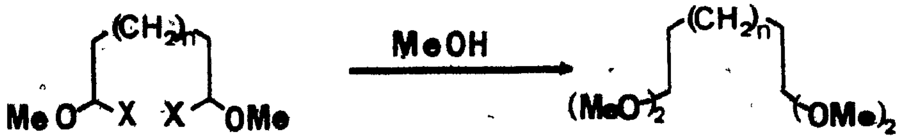
X = Br 47

I 48

Cl 49

1,4-diiodo-1,4-dimethoxybutane (48). The structure of 47 or 48 was quite evident from its spectroscopic data

(Table 1) and also from its chemical transformation to 1,1,4,4-tetramethoxybutane (50a) on reaction with methanol.

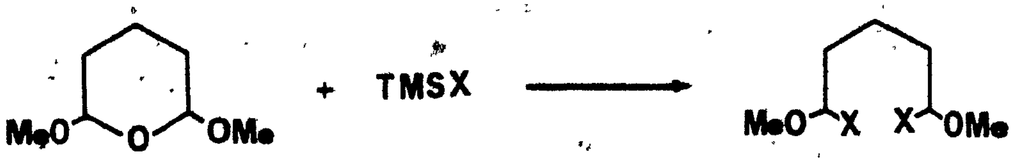


n=0 50a

n=1 50b

This unexpected result led us to examine this reaction in greater detail.

Furthermore, when 2,6-dimethoxy THP (52) was reacted with TMSX, 1,5-dihalo-1,5-dimethoxypentane (53-55) (Table 1) was obtained likewise, again with no evidence for the formation of 2,6-dihalo THP (51).



52

X = Br 53

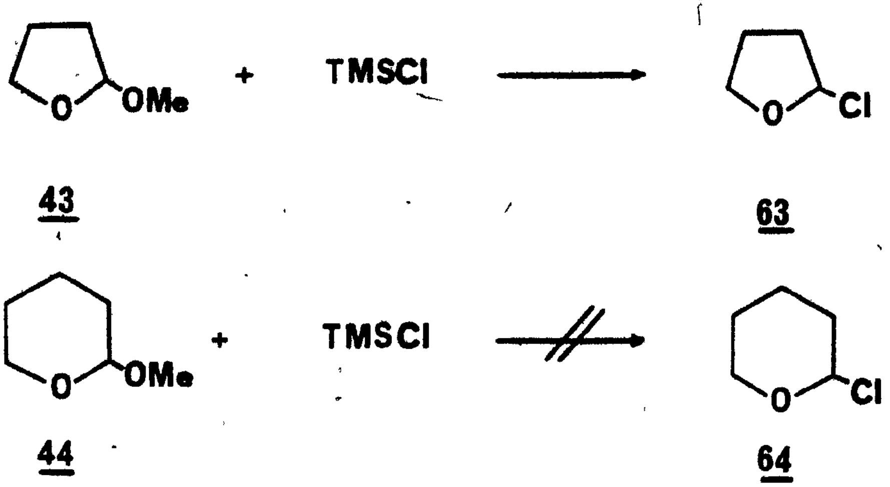
I 54

Cl 55

Table 1: Yields and nmr data of 47-49 and 53-55

compound	% yield	^{1}H nmr data (CDCl$_3$), ppm	^{13}C nmr data (CDCl$_3$), ppm
49 X = Cl	86	5.50 (m, 2H), 3.45 (s, 6H), 2.25 (m, 4H)	99.27, 57.47 (OMe), 34.54
47 X = Br	quant.	5.92 (m, 2H), 3.45 (s, 6H), 2.4 (m, 4H)	97.88, 59.38 (OMe), 36.81
48 X = I	quant.	6.22 (m, 2H), 3.43 (s, 6H), 2.38 (m, 4H)	------
55 X = Cl	84	5.48 (t, 2H), 3.43 (s, 6H), 1.97 (m, 6H)	100.57, 57.63 (OMe), 38.75, 20.46
53 X = Br	quant.	5.85 (t, 2H), 3.40 (s, 6H), 2.10 (m, 4H), 1.70 (m, 2H)	99.10, 59.39 (OMe), 39.97, 22.44
54 X = I	quant.	6.10 (t, 2H), 3.25 (s, 6H), 2.10 (m, 4H), 1.80 (m, 2H)	------

More interestingly, the conversion of 1 or 52 to the corresponding di-halo compounds occurred not only by TMSBr or TMSI, but also with TMSCl, but 5 times the normal amount was required (10 equiv. of TMSCl instead of the usual 2 equiv.). The structures of the dichloro products 49 and 55 were confirmed from their spectroscopic as well as chemical evidence. This result is in contrast to the reaction of TMSCl with the monomethoxy compound 43 (see p. 28).



Another interesting aspect of the reaction is the stereochemical course of the transformation. In the assignment of stereochemistry for the compounds 1 and 52 from its ^{1}H and ^{13}C nmr spectra, 1 was found to be an equal mixture of the *cis*- and *trans*-isomers. Compound 52 was however a mixture of 9:1 of *trans*- to *cis*-isomer.

Aso *et al.*[74] have proposed that the methoxy protons of the *cis*-isomer of 1 are expected to resonate at a lower field than those of the *trans*-isomer because the probability of methoxy protons approaching the other methoxy oxygen is much larger in the *cis*-configuration than in the *trans*-configuration. For compound 52 which was prepared by acid-catalyzed methanolysis of 2-methoxy-3,4-dihydro-2H-pyran, the assignment of stereochemistry was based on the upfield shift of ^{13}C nmr and on the downfield shift of ^{1}H nmr for the *trans*-isomer of 2,6-dihydroxy-1,4-dioxane[75] (Table 2).

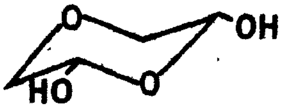
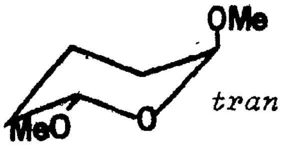
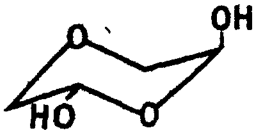
In the transformation of 1 to 47-49 and 52 to 53-55, the relative stereochemistry of the two methoxy groups was however lost, because either 47 or 53 is one single isomer according to its ^{13}C nmr spectrum (Table 1).

As investigated above, several important features of this unexpected site selectivity were revealed as follows:

(1) The change in site selection not only takes place in the tetrahydrofuran system but also in the tetrahydropyran system to give the corresponding terminal-dihalo, dimethoxy alkanes.

(2) The change in site selectivity is somewhat independent of the halosilane used. Thus, TMSCl is also effective in transforming 1 or 52 to dichloro compound (49 or 55) as is TMSBr or TMSI. This is in contrast to the monomethoxy situation

Table 2: Spectral data of anomeric protons and carbons of 52 and related 2,6-dihydroxy-1,4-dioxane[75]

stereochemistry*	^1H nmr, ppm	^{13}C nmr, ppm
 *cis*-52	4.46	100.52
	5.04	103.5
 *trans*-52	4.76	98.09
	5.30	101.7

*The ratio of *trans*-52 to *cis*-52 was about 9:1 by ^1H nmr spectrum

where TMSCl did not react with 44 even after longer heating and reacted sluggishly with 43 to give 2-chloro THF.

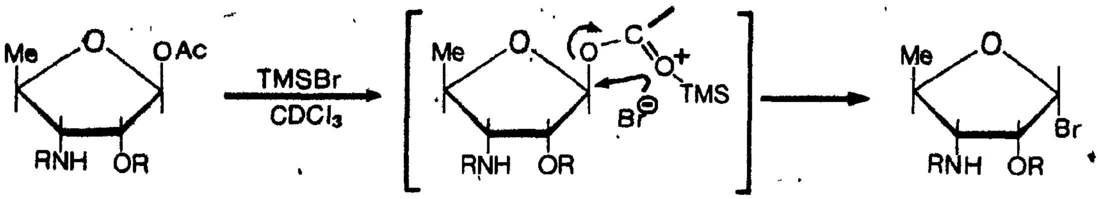
(3) The transformation of 1 to 49 cannot be effected by the protonic acid (HX). The change in site selectivity could not have been due to traces of HX, which might be present in TMSX.

(4) Although 2,5-dimethoxy THF was an equal mixture of the *cis*- and *trans*-isomers and 2,6-dimethoxy THP was a 9:1 mixture of *trans*-52 to *cis*-52, the relative stereochemistry of the two methoxy groups was lost in these chemical transformations.

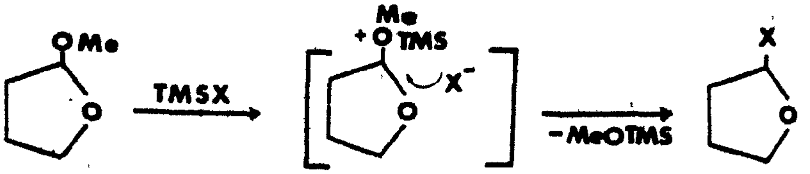
The cleavage reactions of a variety of O-heterocyclic compounds with TMSX are summarized in Table 3.

C. Mechanistic Rationale

Even though the mechanism of acetal cleavage by TMSX has not been delineated, one can assume that it has S_N2 type character in its critical step in the monomethoxy substituted system (43 → 45). This is based on the following arguments: (1) The nature of halide has a dramatic effect on the reaction. (2) There is predominant inversion of stereochemistry observed at the anomeric carbon[71] (A → B) as mentioned before. (3) The regioselection in the opening of unsymmetrical systems was observed as follows: Kricheldorf *et al.*[63] have investigated the cleavage of ethers, focusing their interest on (i) regioselectivity of the cleavage of epoxides, (ii) influence of ring size on the reactivity, and (iii) reactivity of sterically different ethers. It was observed that the reaction of propylene oxide (35) with TMSBr gave regio-



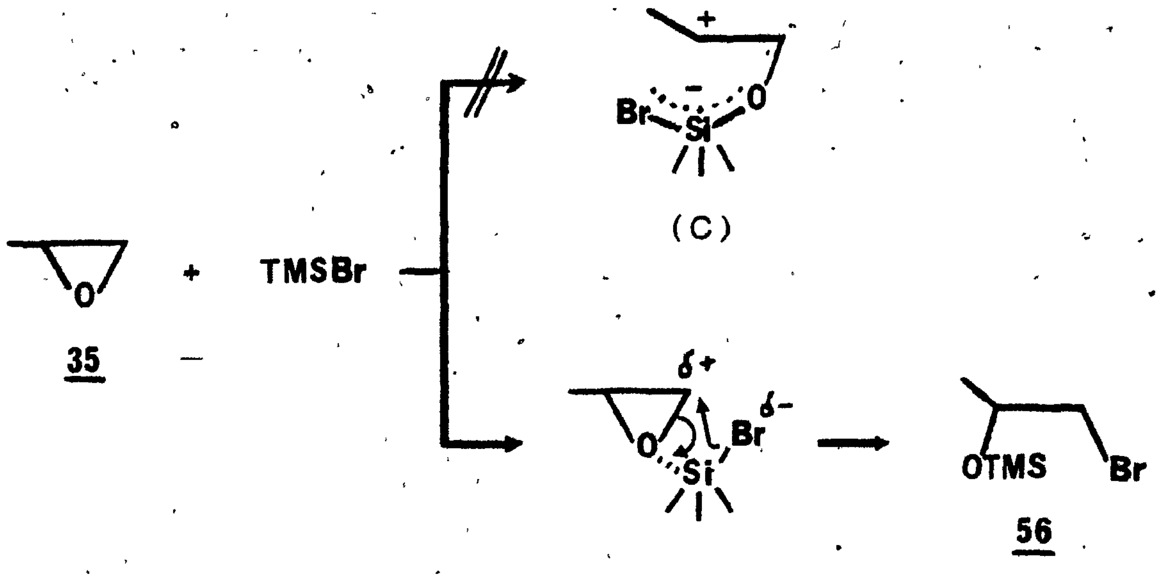
A **B**

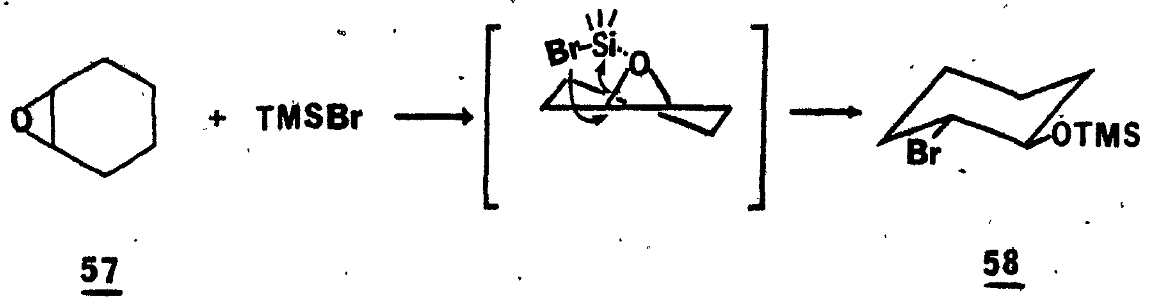


SN_2-Type

selectively primary bromide compound <u>56</u> and the reaction of cyclohexene oxide (<u>57</u>) gave the *trans* product with two equatorial substituents <u>58</u> by a *trans*-opening.

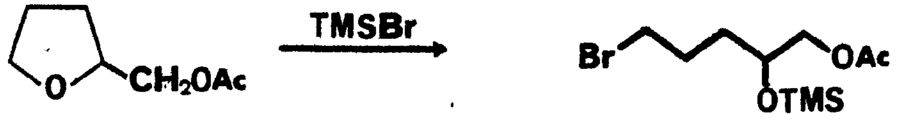
Therefore, they suggested that the carbenium ion (C) as intermediate is unlikely because of the anti-Markownikow course of the reaction and stereoselectively clean reaction of <u>57</u> to the *trans*-product <u>58</u>.





Our observations are in agreement with this. The primary bromide 60 was obtained exclusively from the reaction of 2-methyl THF (59) with TMSBr. Tetrahydrofurfuryl acetate (61) also gave[63] the primary bromide 62.

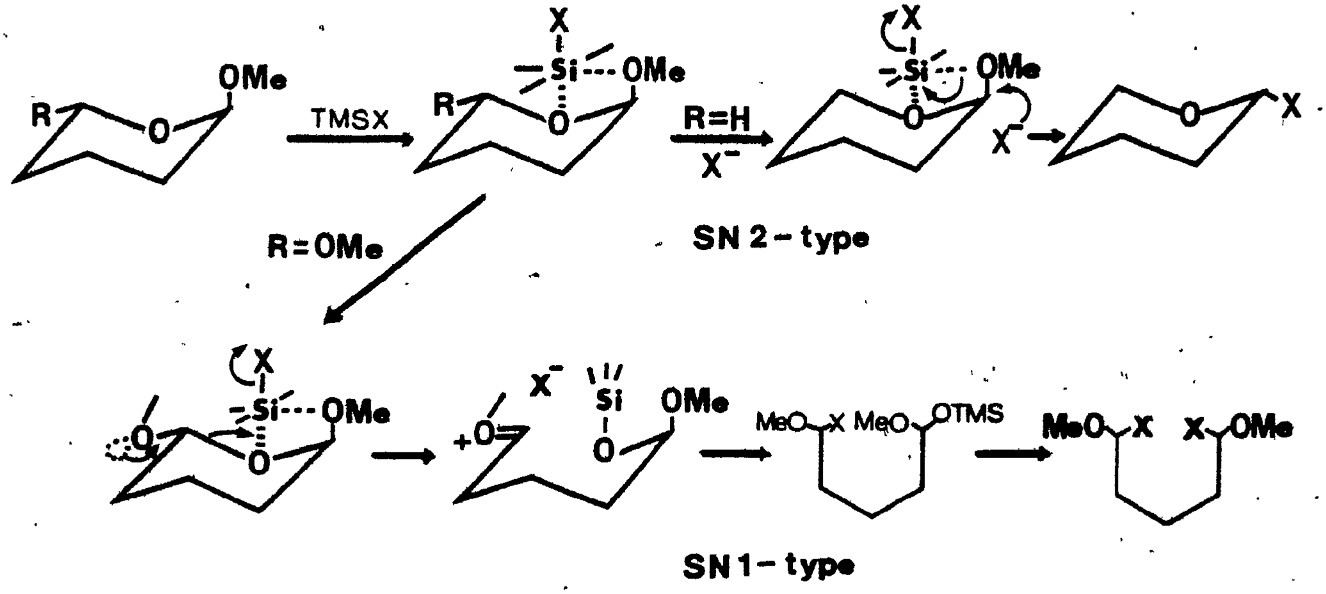
59 **60**



61 **62**

In the dimethoxy substituted systems, it seems that, from the facts outlined on p. 32-34, the reaction is more likely to have S_N1-type character in one of its critical steps.

A scheme which accounts reasonably for the site selectivity is proposed as follows (Scheme 4).



Scheme 4

Table 3: Cleavage products of O-heterocyclic compounds by TMSX

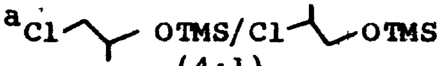
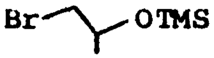
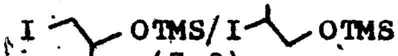
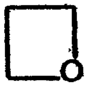
substrate	reaction condition	product	% yield (lit.)
	TMSBr/$CHCl_3$, 0°C → r.t.	$Br(CH_2)_2OTMS$	69 (63)
	TMSI/hex., -10°C	$I(CH_2)_2OTMS$	(76)
	TMSCl/$CHCl_3$, 0°C → r.t.	[a]  (4:1)	82 *
	TMSBr/$CHCl_3$, 0°C		61 (63)
	TMSI/hex., -10°C	 (7:3)	(76)
	5 eq. TMSCl/$CHCl_3$, r.t./2 days	$Cl(CH_2)_3OTMS$	92 *
	TMSBr/$CHCl_3$, 100°C/2 hrs	$Br(CH_2)_3OTMS$	73 (63)

Table 3: (cont'd)

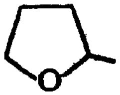
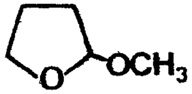
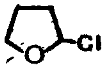
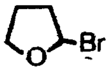
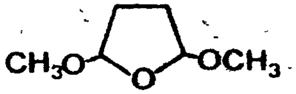
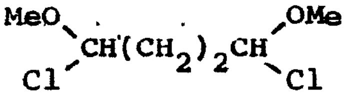
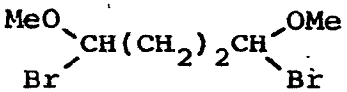
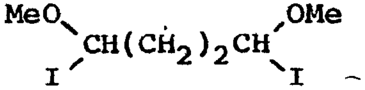
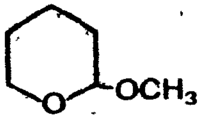
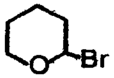
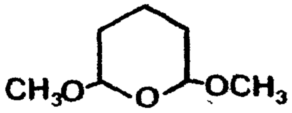
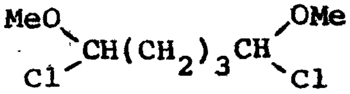
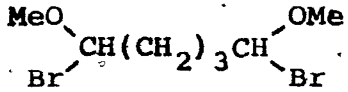
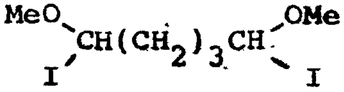
substrate	reaction condition	product	% yield (lit.)
	TMSCl/CHCl$_3$, r.t./3 days	no reaction	*
	TMSBr/CHCl$_3$, r.t./3 days	Br(CH$_2$)$_4$OTMS	85 *
	TMSBr, reflux/40 hrs		82 (63)
	TMSBr/CHCl$_3$, r.t./1 day	[b]Br(CH$_2$)$_3$CH(CH$_3$)OTMS	84 *
	5 eq. TMSCl/CHCl$_3$, r.t./3 days		25 *
	2 eq. TMSBr/CHCl$_3$, r.t./4 hrs		75 *
	10 eq. TMSCl/CHCl$_3$, r.t./2 days	 $\mathrm{MeO(Cl)CH(CH_2)_2CH(Cl)OMe}$	86 *
	2.2 eq. TMSBr/CHCl$_3$, 0°C/2 hrs	 $\mathrm{MeO(Br)CH(CH_2)_2CH(Br)OMe}$	quant. *
	2.2 eq. TMSI/CHCl$_3$, 0°C/1 hr	 $\mathrm{MeO(I)CH(CH_2)_2CH(I)OMe}$	quant. *

Table 3: (cont'd)

substrate	reaction condition	product	% yield (lit.)
	$TMSCl/CHCl_3$, r.t./3 days	no reaction	*
	$TMSBr/CHCl_3$, r.t./3 days	no reaction	*
	IBr/TMSBr reflux/2 hrs	$Br(CH_2)_5Br$	71 (66)
	5 eq. $TMSCl/CHCl_3$, r.t./3 days	no reaction	*
	2 eq. $TMSBr/CHCl_3$, r.t./4 hrs		60 *
	10 eq. $TMSCl/CHCl_3$, r.t./3 days	 $\mathrm{(MeO)(Cl)CH(CH_2)_3CH(OMe)(Cl)}$	84 *
	2.2 eq. $TMSBr/CHCl_3$, 0°C/2 hrs	 $\mathrm{(MeO)(Br)CH(CH_2)_3CH(OMe)(Br)}$	quant. *
	2.2 eq. $TMSI/CHCl_3$, 0°C/1.5 hr	 $\mathrm{(MeO)(I)CH(CH_2)_3CH(OMe)(I)}$	quant. *

* carried out in our laboratory

[a] the ratio estimated by nmr

[b] one isomer was shown in nmr

An important aspect of this mechanism is the formation of the hexacoordinated silicon intermediate involving both the ring oxygen and one of the methoxy oxygens. The formation of pentacoordinated[78] as well as hexacoordinated[79a] silicon complexes is well established. It is based on the availability of the silicon d-orbitals, thus expanding its octet to accommodate more than eight electrons by using the 3d-orbitals. Some examples are the octahedral $SiF_6^{=}$ ion[79b] and the complex $SiCl_4 \cdot 2pyr$[79a] as well as $[Si(OMe)_2(bipy)_2]Cl_2$[80].

In the monomethoxy system, cleavage of the methoxy group requires an external nucleophile X^- in an S_N2 process leading to overall inversion of configuration. In the α,α'-dimethoxy system, the other methoxy oxygen serves as the "nucleophile" leading to cleavage of the ring system in an essentially S_N1 process. Addition of the external nucleophile X^- gives then the terminal halides.

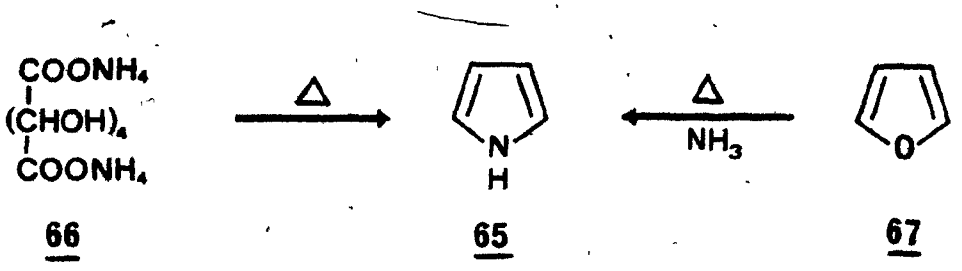
CHAPTER IV

1,4-DICHLORO-1,4-DIMETHOXYBUTANE AS A MILD REAGENT FOR THE CONVERSION OF PRIMARY AMINES TO PYRROLES

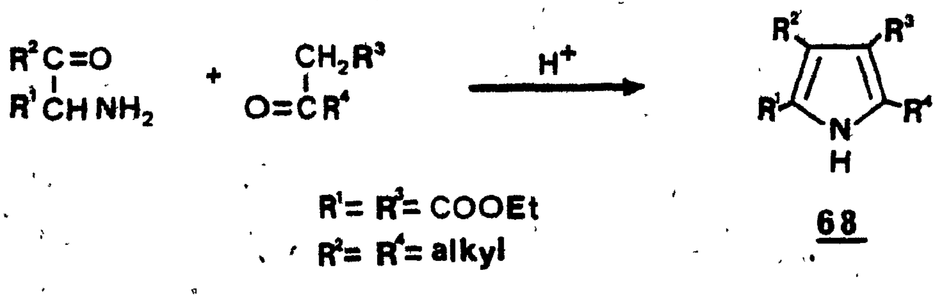
A. General Considerations; synthetic methods leading to pyrrole

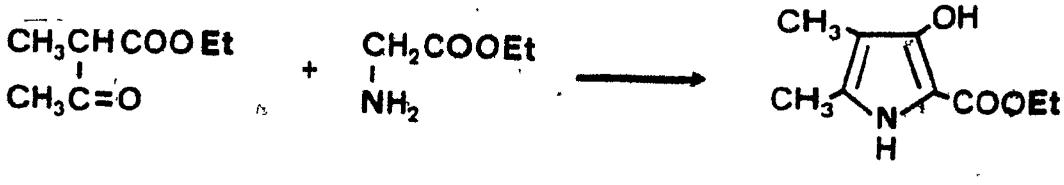
The discovery that the pyrrole ring was an integral part of haemin and of chlorophyll molecules[81,82] not only created intense interest in the chemistry of pyrrole and its derivatives, but also resulted in the majority of the investigations conducted during the latter part of the nineteenth century and the early years of the twentieth century being dominated by this relationship of pyrrole with naturally occurring compounds. Pyrrole 65 may be prepared in the laboratory by the classical method[83] of heating the ammonium salt of mucic acid 66. On an industrial scale, pyrrole is manufactured by the catalytic reaction[84] of furan 67 with ammonia over a molybdenum or vanadium oxide catalyst at 350° ∿ 400°.

In addition to these reactions, one can classify the preparative procedures for the pyrrole synthesis arbitrarily according to the number of carbon atoms furnished to the pyrrole ring by the original reactants. For example, a variety of substituted pyrroles can be prepared according to



the 2C + 2C mode by the condensation of α-aminoketones with carbonyl compounds having a highly reactive methylene group adjacent to the carbonyl group. A good example is the procedure developed by Knorr for the synthesis of diester substituted pyrroles, which are frequently referred to as Knorr pyrroles[85,86] 68. An example[87] of the 1 + 3 carbon mode is the condensation of ethyl glycinate with β-keto esters 69 to produce ethyl 3-hydroxypyrrole-2-carboxylate 70.

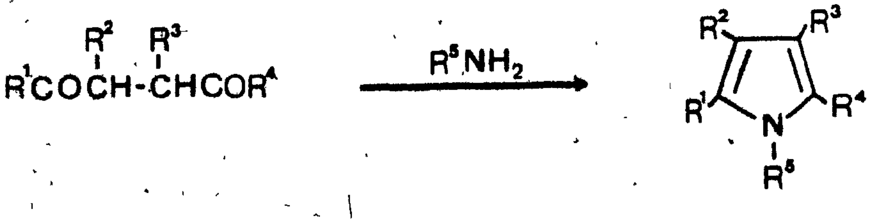




69

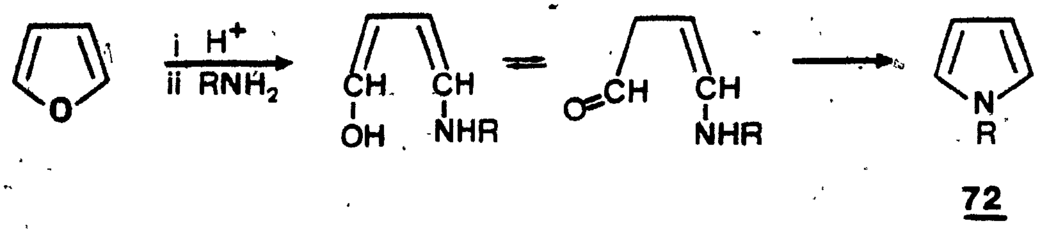
70

In particular, the Paar-Knorr condensation[88] of γ-diketones, a 4-carbon unit, with primary amines, provides a convenient synthesis of pyrroles 71.



71

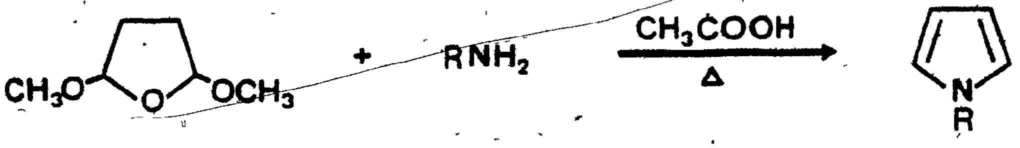
As mentioned earlier, the vapour phase reaction of furan and its derivatives with amines has been extensively studied by Yurev[89]. In this way, pyrrole, 1-methylpyrrole and 1-arylpyrrole are commercially produced[90]. The reaction probably involves an acid-catalyzed ring-opening of the furan ring followed by amination and subsequent ring-closure to the pyrrole 72. Similarly, the conversion of



72

primary amines to pyrroles has been achieved by reaction with 2,5-dimethoxytetrahydrofuran under refluxing acetic acid[15-17] as mentioned in Chapter I. This reaction is useful for the synthesis of a number of N-substituted pyrroles.

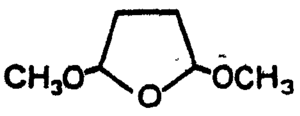
This latter reaction is obviously not applicable to compounds which are acid or heat sensitive.



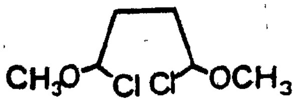
1

B. Syntheses of Pyrroles[91]

As mentioned in Chapter II, 1,4-dichloro-1,4-dimethoxybutane (49) was prepared by the reaction of 2,5-dimethoxytetrahydrofuran (1) with TMSCl *via* ring opening.

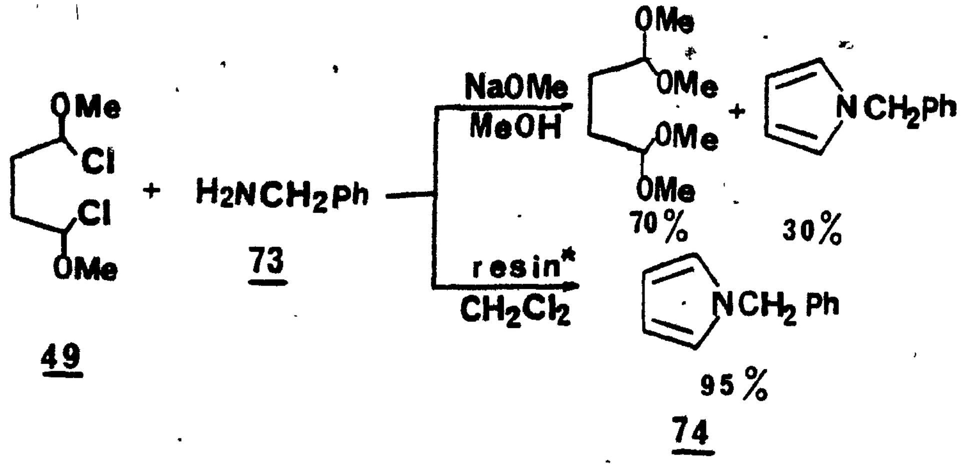


1



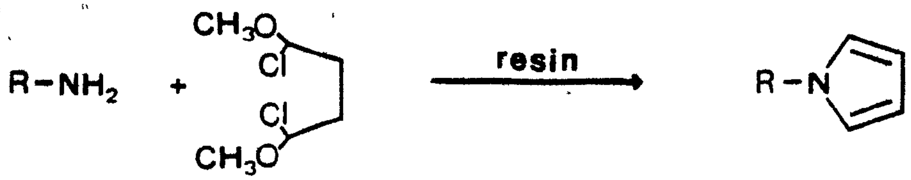
49

Compound 49 can be considered as a more reactive functional equivalent of 1 as well as a 4-carbon unit and should be capable of converting primary amines to pyrroles. It was found that when benzylamine 73 reacted with 49 in the presence of a tertiary base such as triethylamine or diisopropylethylamine, 1-benzylpyrrole 74 was indeed obtained but in poor yield (5 ∿ 30%). When sodium methoxide in methanol was used as a neutralizing agent, the predominant product was 1,1,4,4-tetramethoxybutane (75) with 1-benzylpyrrole in about 30% yield.



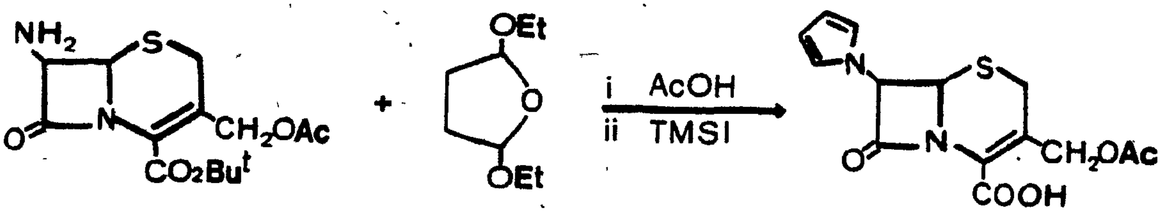
*weakly basic resin Amberlyst A-21.

We were thus pleased to find that when the weakly basic ion-exchange resin Amberlyst A-21[73] was used for neutralization, the reaction gave 1-benzylpyrrole in nearly quantitative yield. The reaction conditions were very mild and were applied to the conversion of α-aminoesters (*e.g.* 76-78) to the corresponding pyrrole compounds (*e.g.* 80-82). By using a more polar solvent, even amino acids (*e.g.* 79) were converted directly to the pyrrole derivatives (*e.g.* 83).



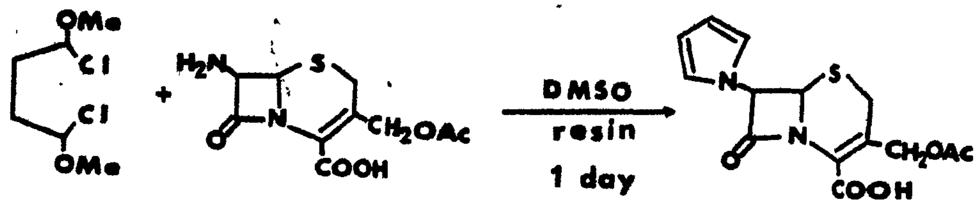
76	R = CH_2CO_2Et	**80**
77	$CH(CH_2Ph)CO_2Et$	**81**
78	$CH(CH_3)CO_2Et$	**82**
79	CH_2COOH	**83**

The utility of this reaction can be illustrated by the following example. Nudelman *et al.*[92] prepared 7-(1-pyrrolyl)-cephalosporanic acid (84) in two steps by reacting t-butyl-7-aminocephalosporanate (85) with 86 in refluxing acid, followed by hydrolysis in an overall yield of 7 ∿ 8 %. We were however able to prepare 84 directly



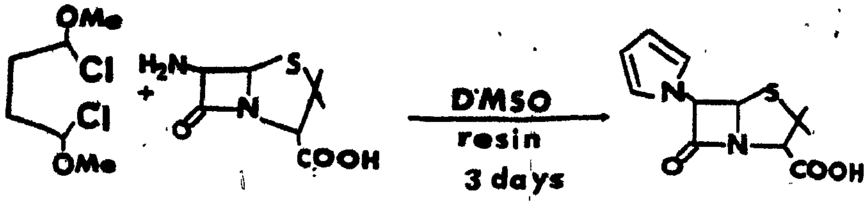
85 **86** 7 % **84**

from 7-aminocephalosporanic acid (87) and 49 in 65% isolated yield. Furthermore, using our conditions, the much more labile 6-(1-pyrrolyl)-penicillanic acid (88) was also prepared directly from 6-aminopenicillanic acid (89) in 67% isolated yield. The acids 84 and 88 showed very weak antibacterial activities with MIC of > 63 μg/mL against streptococcus aureus and E.Coli[92,93].



87

65%, 84



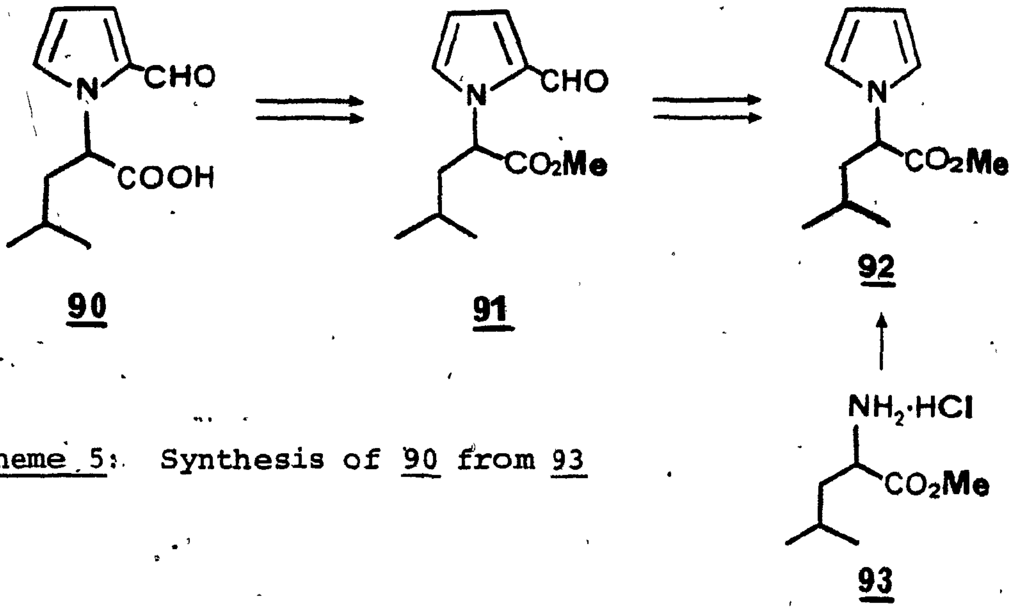
89

67 %, 88

C. Synthesis of 2-(2-Formylpyrrol-1-yl)-4-methyl pentanoic Acid (90) from Tobacco

Since primary amines are easily converted to the corresponding pyrroles by the reaction with 49 in the presence of resin, we have applied the reaction to the synthesis of the 2-formylpyrrole derivative 90, a compound which has been found in flue-cured tobacco and may have desirable flavour properties. This compound was first isolated by Lloyd *et al.*[94]. The suggestion was made that it might be formed in the tobacco leaf by the reaction of amino acid with sugar[94,95].

Accordingly, a synthesis of 2-(2-formylpyrrol-1-yl)-4-methylpentanoic acid (90) from L-leucine methyl ester (93) could be designed according to Scheme 5 and we have, in fact, realized this synthesis in the laboratory.



Scheme 5: Synthesis of 90 from 93

In the first step, the pyrrole compound 92 was obtained from leucine methyl ester hydrochloride (93) using the procedure developed in 71% isolated yield.

The regioselective formylation at the 2-position of the pyrrole 92 in lieu of the 3-position turned out to be a difficult problem.

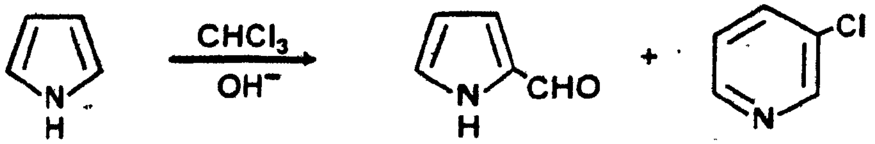
For the formylation of pyrroles, several methods are usually employed. They are:

(1) Vilsmeier-Haack reaction which takes place in dimethylformamide and phosphorus oxychloride[96-97].

(2) Reimer-Tiemann conditions with haloform in the presence of strong base, and

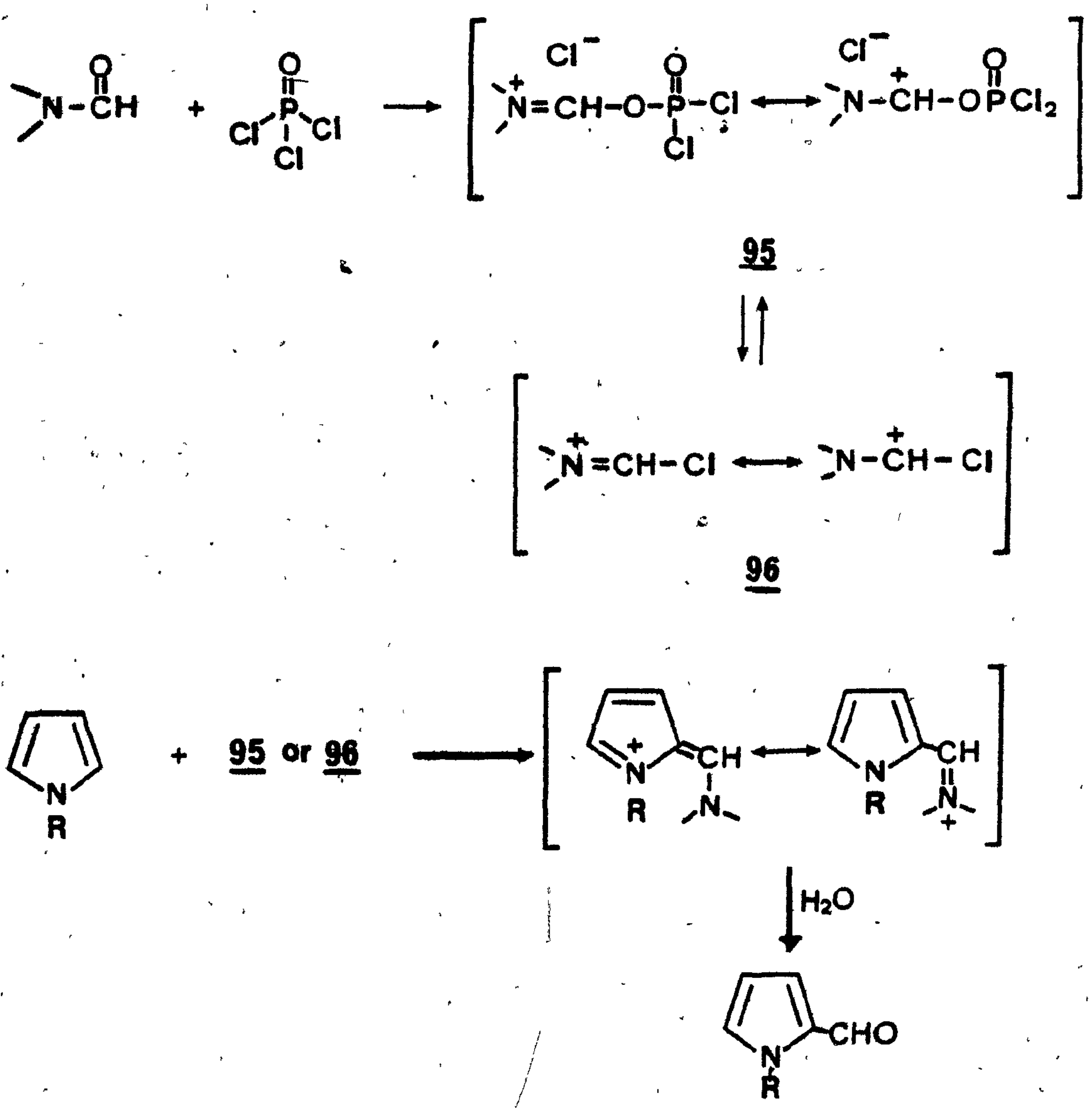
(3) Friedel-Crafts formylation[101] with dichloromethyl methyl ether in the presence of a Lewis acid catalyst (*e.g.* $AlCl_3$).

Of these, method (2), the Reimer-Tiemann conditions, is known to give not only very poor yield of formylpyrrole but also ring expansion product[102] 94.



94

The most generally applicable method for the preparation of formylpyrroles is the Vilsmeier-Haack reaction, in which the pyrrole is allowed to react with the electrophile, generally formulated as 95 or 96, formed from the reaction of dimethylformamide with phosphorus oxychloride (Scheme 6).



Scheme 6: Vilsmeier-Haack reaction with pyrrole

Formylation of pyrrole and its 1-alkyl and 1-aryl derivatives using the procedure outlined above (Scheme 6) gives good yields of the monoformylated products[104] (Table 4).

The investigation of Jones *et al.*[103] showed that, as the size of the N-substituted alkyl group increased, so did the relative proportion of the 3-formyl isomer to the 2-formyl isomer.

<u>Table 4</u>: Formylation of 1-substituted pyrroles by the Vilsmeier-Haack reaction[104]

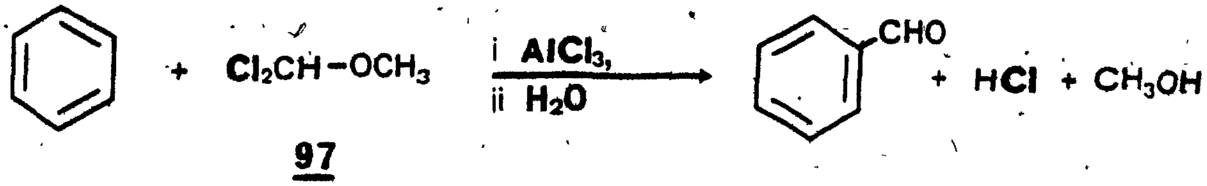
1-substituent	ratio $\frac{\text{2-isomer}}{\text{3-isomer}}$	yield (%)
H	a	89[b]
Me	a	89
Et	11.5	85
i-Pr	1.9	79
t-Bu	0.07	69
CH_2Ph	6.2	89
Ph	9.0	93
P-$MeOC_6H_4$	7.0	93
P-MeC_6H_4	11.0	92

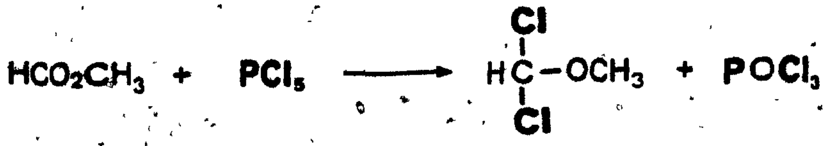
[a] Exclusive formylation at 2-position

[b] Cited from ref. 105

Since the predominance of 3-isomers in the electrophilic substitution of sterically hindered N-substituted pyrroles is a general phenomenon, it was therefore expected that the Vilsmeier-Haack reaction would not give us the desired 2-formyl pyrrole <u>91</u>.

In 1960, Rieche *et al.*[101] reported that dichloromethyl methyl ether can formylate aromatic rings with Friedel-Crafts catalysts. Since pyrroles behave in the same way as benzene in the Friedel-Crafts acylation, it would be interesting to see how they react under these conditions (method (3)). Dichloromethyl methyl ether (<u>97</u>) could be prepared[106] by stirring methyl formate and phosphorus pentachloride without solvent. Distillation gave a colorless liquid, dichloromethyl methyl ether (<u>97</u>), b.p. 87-89°C, ^{1}H nmr at δ = 7.1 (s), 3.6 (s).

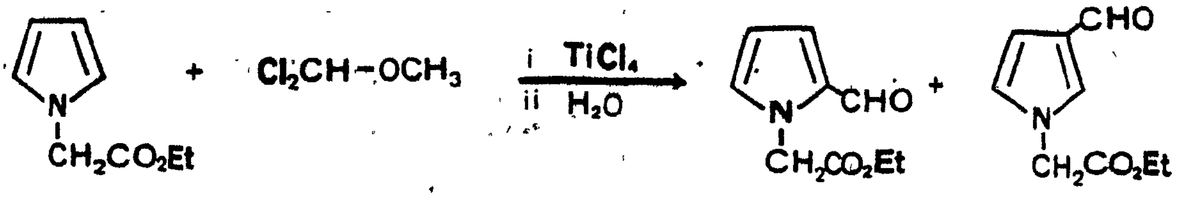




$$HCO_2CH_3 + PCl_5 \longrightarrow H\overset{Cl}{\underset{Cl}{C}}-OCH_3 + POCl_3$$

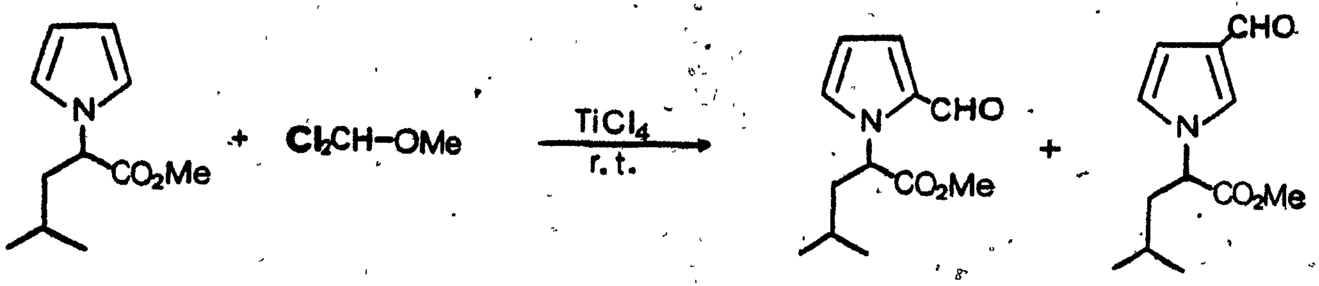
97

Indeed, the reaction of pyrrole 80 with ether 97 in the presence of $AlCl_3$ gave a mixture of 2- and 3-formyl pyrrole, 98 and 99 in less than 30% yield. By using $TiCl_4$ as the catalyst at room temperature, the formylpyrrole was obtained in 84% yield with the ratio of 2- to 3-isomer at about 5:1.



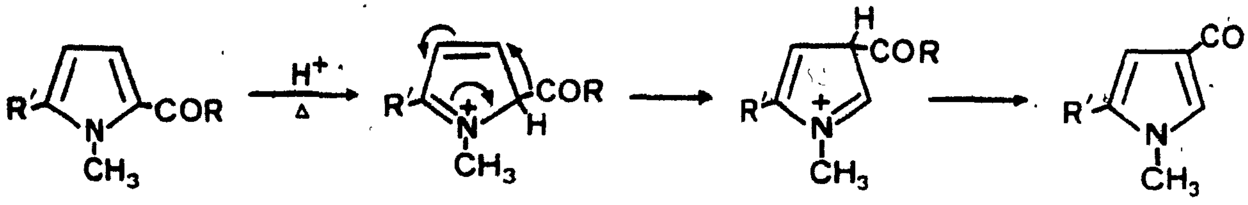
80 **97** **98** 5 : 1 **99**

However, when the formylation reaction of pyrrole 92 was carried out in the same way as above (97/$TiCl_4$), the formylpyrroles were indeed obtained but the predominant product was the 3-formyl isomer 100 (the ratio of 2- to 3-isomer was about 1:5).



92 **91** 1 : 5 **100**

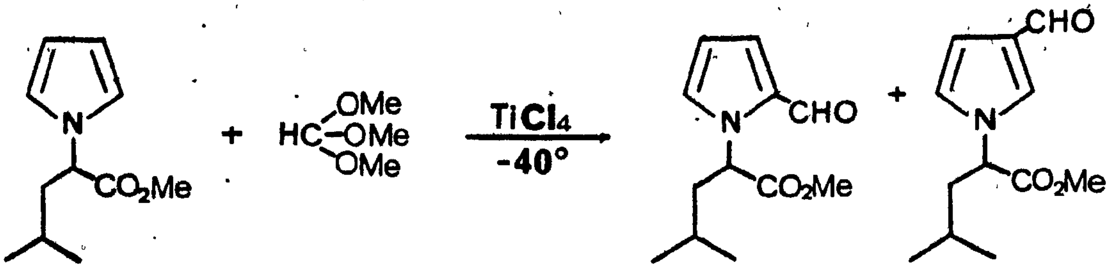
Recently, it has been reported that 2-acylpyrroles 101 were easily converted[107,108] to 3-acylpyrroles 102 by refluxing in the presence of acid (*e.g.* TFA, TsOH, MsOH or TfOH). Migration of sulfinyl[109], chloro[110], bromo[110], sulfenyl[111] and sulfonyl[111] groups has also been demonstrated in the same way. Carson *et al.*[107] proposed that the mechanism for this reaction is the 1,2-acyl shift of the C-protonated species 103.



101 **103** **102**

Accordingly, the reaction for the 2-formylation of 92 was carried out at a lower temperature to prevent the 2-formyl group from migrating to the 3-position of pyrrole. As expected, it gave exclusive 2-formylation with, however, a considerable amount of unreacted 92. Fortunately, we were able to overcome this problem effectively by using trimethyl orthoformate/titanium tetrachloride as a more reactive formylating agent.

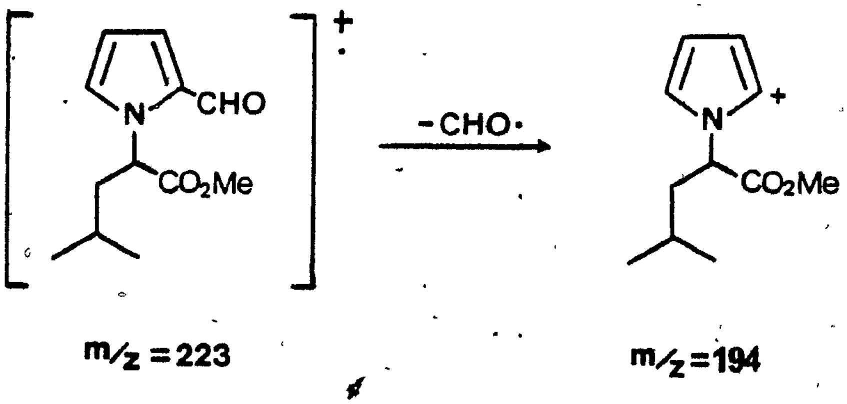
H. Gross *et al.*[112], have developed the formylation of phenol by using triethyl orthoformate/aluminum chloride or dichloromethyl methyl ether/titanium tetrachloride. Indeed, when pyrrole 92 was formylated with trimethyl orthoformate/titanium tetrachloride at -40°, the 2-isomer 91 was obtained in high yield to the near exclusion of the 3-isomer 100, which could be separated by column chromatography (the ratio of 91 to 100 was about 8:1).



92 **91** 8 : 1 **100**

The spectral data of 2-formyl 91 and 3-formyl 100 showed significant differences between the two isomers. The ^{1}H nmr peak of the methine proton at C-1' in 91 appears at 6.1 ppm (t) and that in 100 at 4.65 ppm (dd). The downfield shift of the proton peak at C-1' in 2-formyl isomer 91 can be due to the anisotropic effect of the formyl group and is consistent with the structure (Figs. 1 and 2).

Another important difference is the mass spectral fragmentation of the two isomers. The relative abundance at m/z = 194 ($M^{+\cdot}$ -CHO) in the 3-formyl 100 was nearly negligible in contrast with the 70% abundance for the same ion in the 2-formyl pyrrole 91 (Fig. 3). This is attributed to the relative ease of the following fragmentation process in the 2-formyl pyrrole 91. This is similar to most α-cleavages in the mass spectra of nitrogen containing compounds.



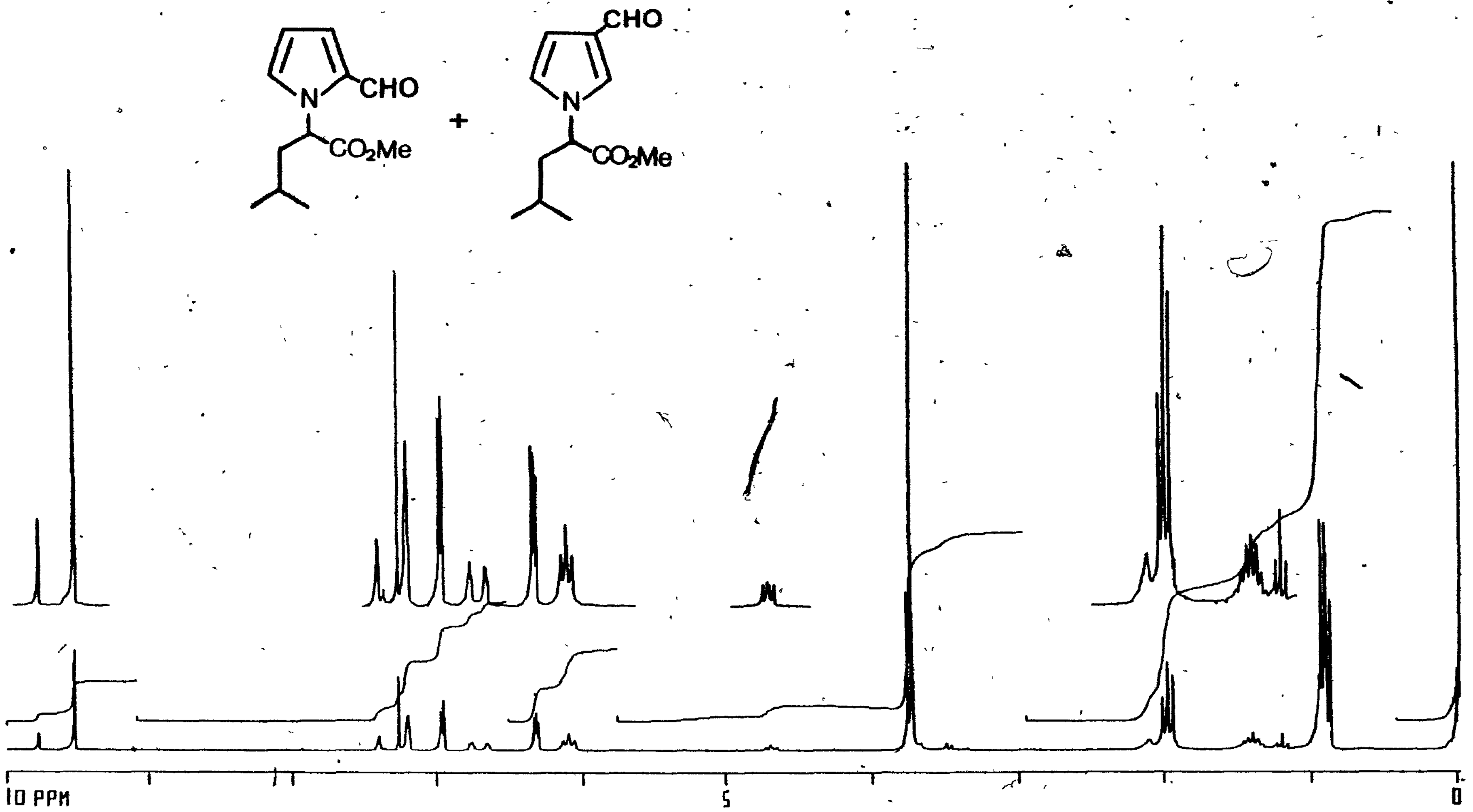


Fig. 1: 200 MHz ^{1}H nmr spectrum of unseparated mixture of <u>91</u> and <u>100</u>

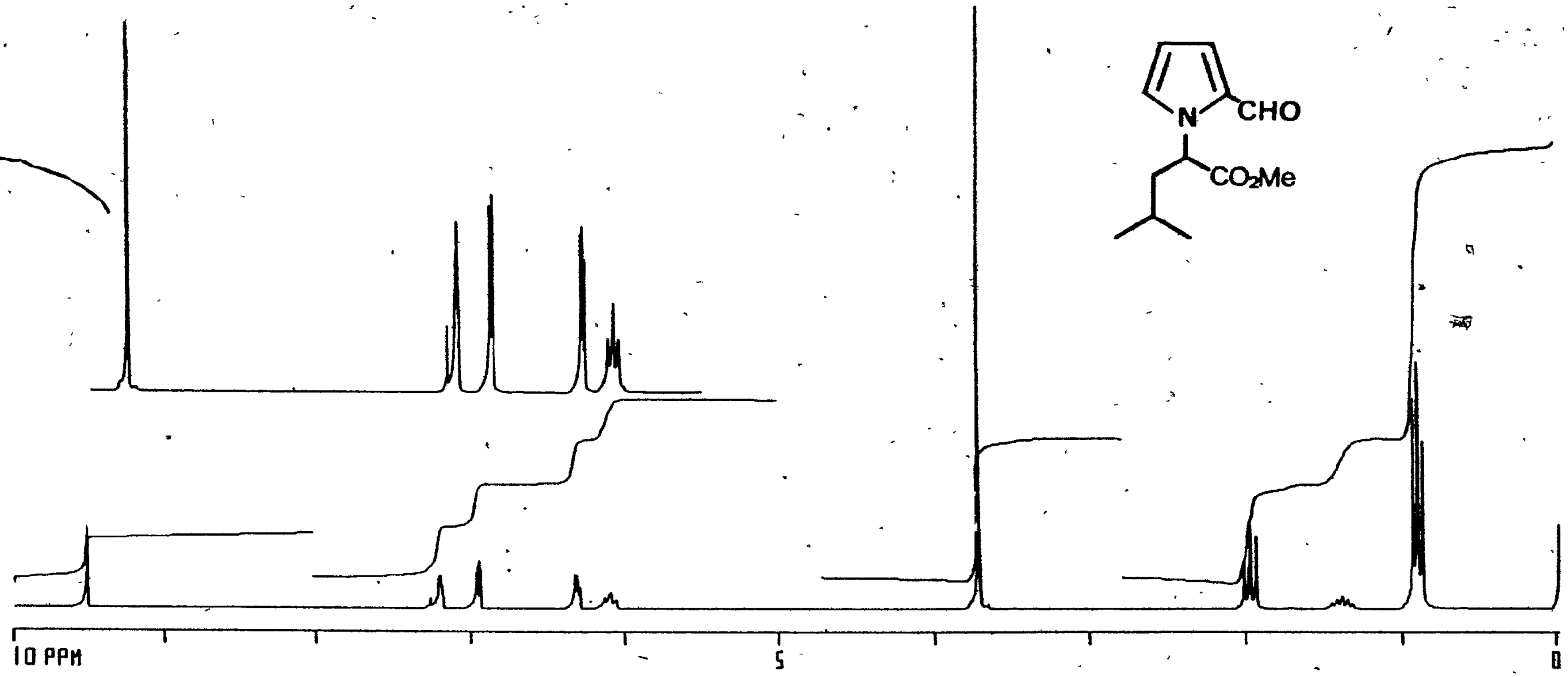


Fig. 2: 200 MHz ^{1}H nmr spectrum of 2-formylpyrrole <u>91</u>

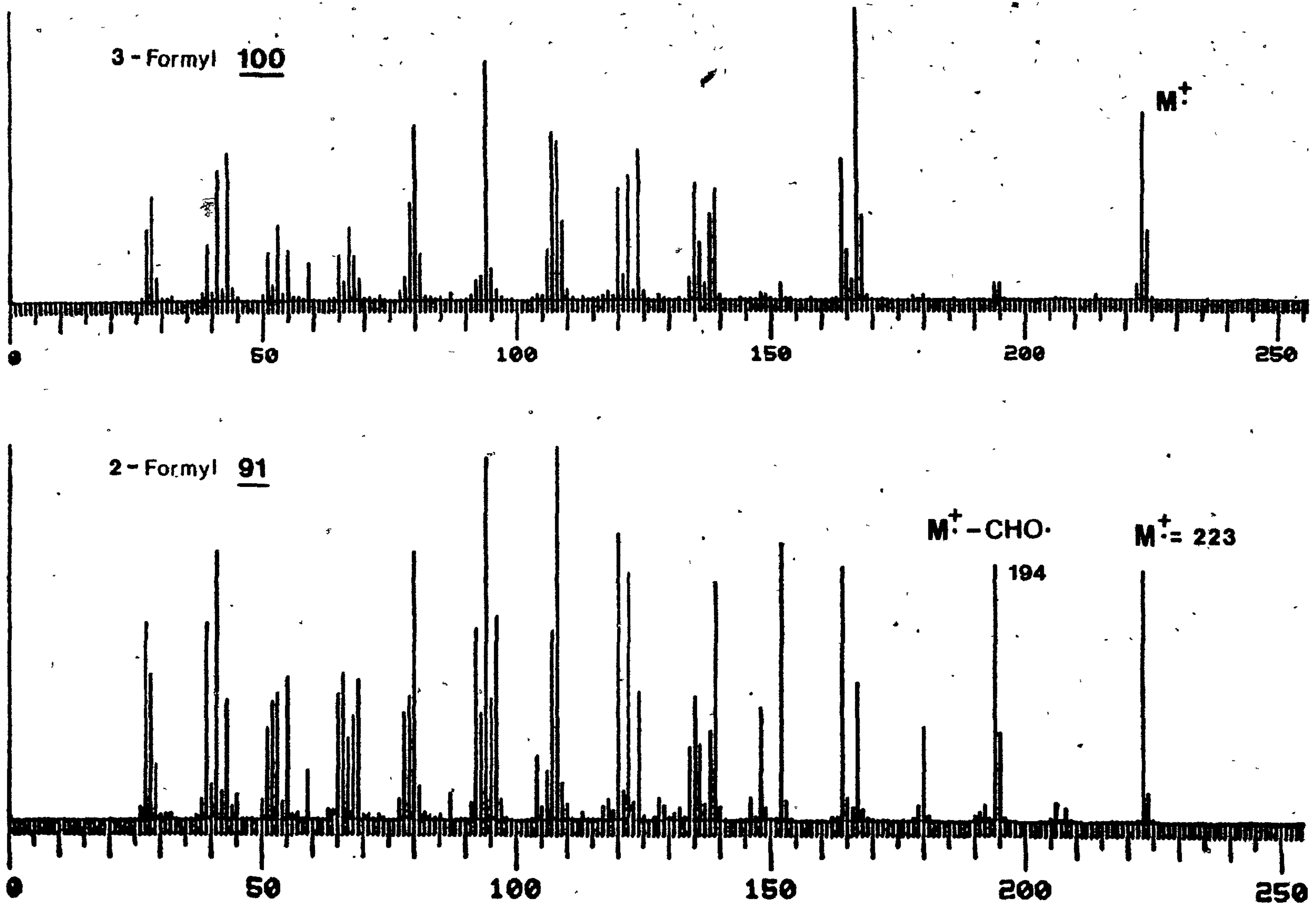
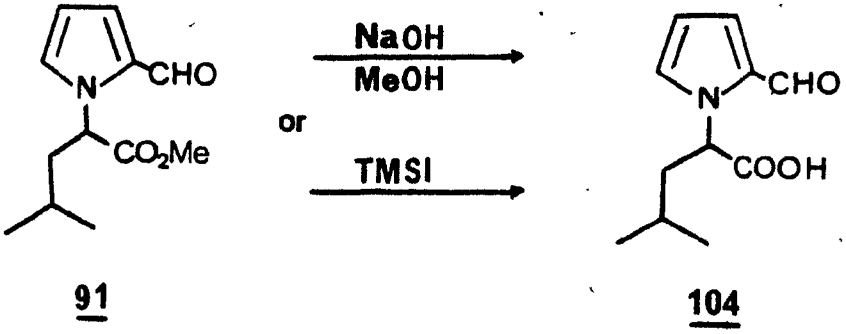


Fig. 3: Mass spectra of 91 and 100

Hydrolysis of 91 with sodium hydroxide in methanol gave acid 104. When excess hydroxide was used, the compound 91 was devoid of optical activity, indicating that racemization at the chiral center had occurred. The problem can be overcome by hydrolysis with 1 equivalent of sodium hydroxide. Alternatively, cleavage of the methyl ester



moiety with trimethyliodosilane[113] proved equally satisfactory, giving 104 with optical rotation of $[\alpha]_D = -16.4°$ ($CDCl_3$) (Fig. 4).

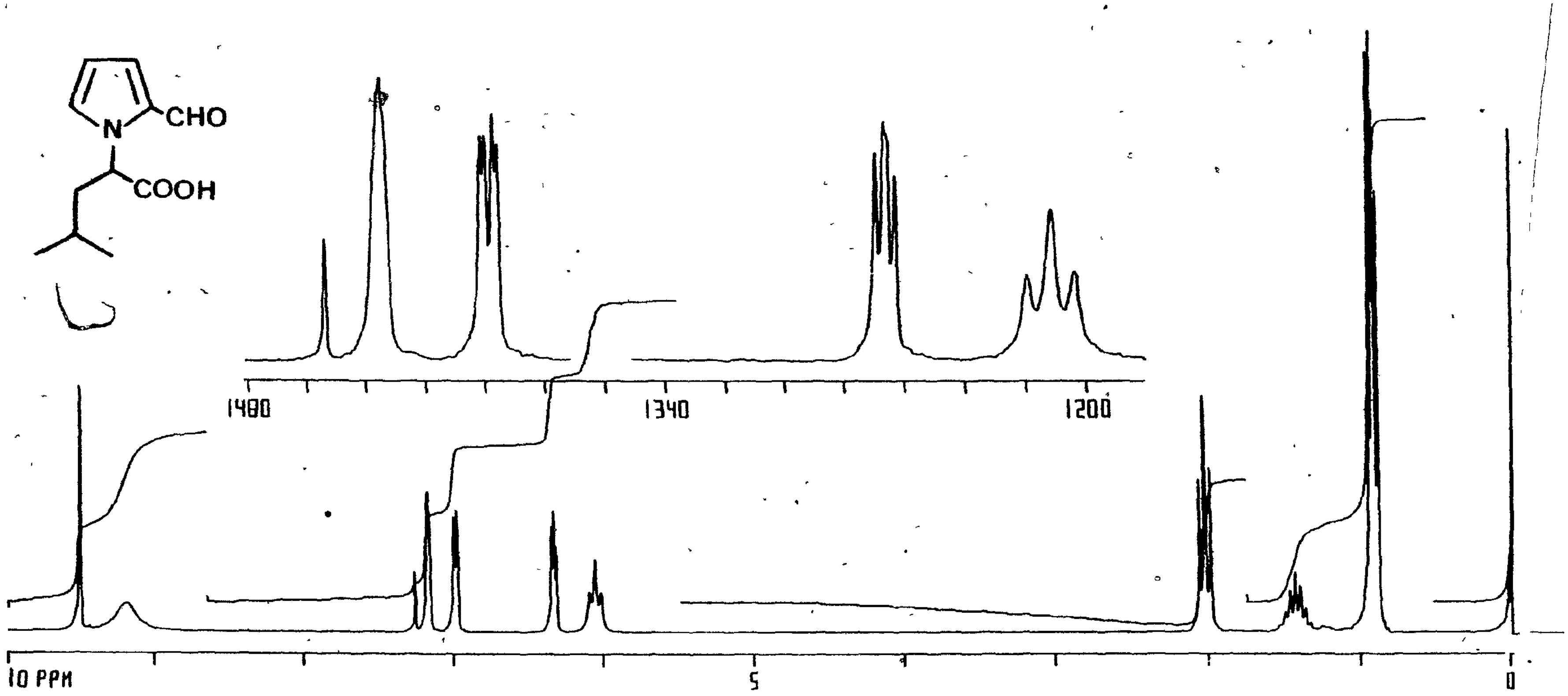


Fig. 4: 200 MHz ^1H nmr spectrum of 104

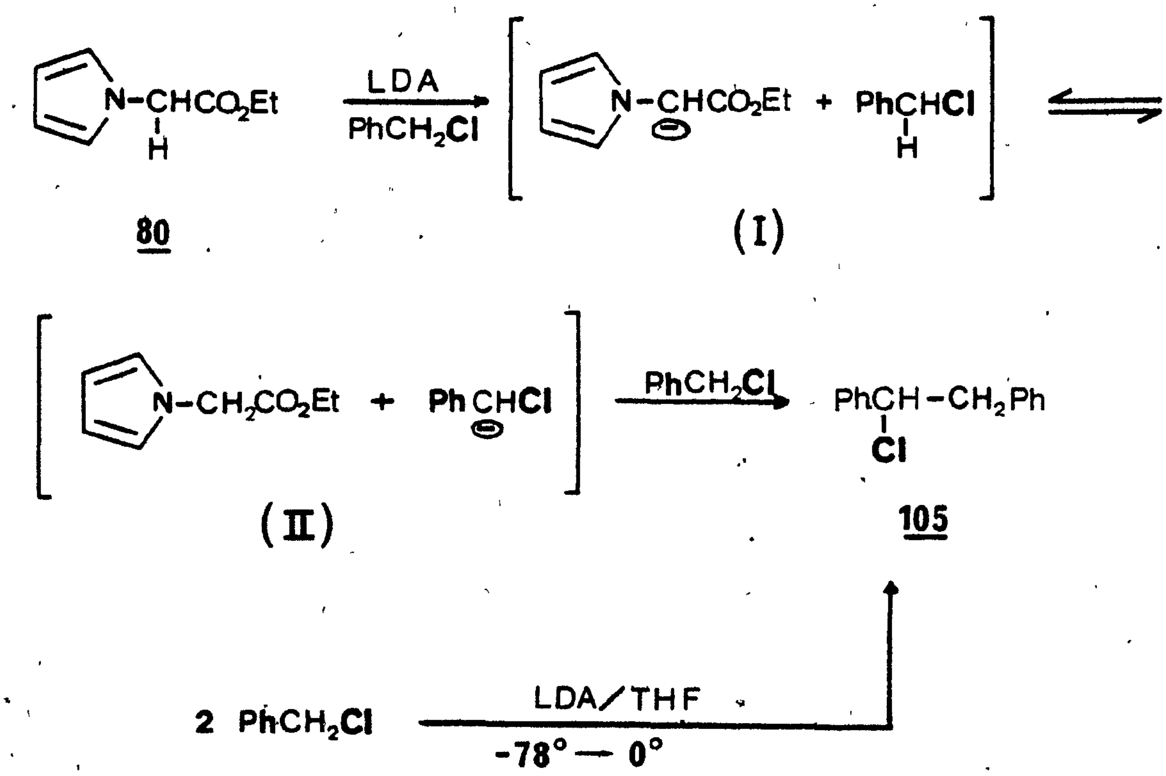
D. The Preparation of α-Substituted Pyrrole Derivatives from the Pyrroles of Amino Acid Esters

The amino group readily undergoes oxidation, alkylation, acylation and a variety of other reactions, so there is a need to protect it while other parts of the molecule are undergoing chemical changes. For example, carbamates are formed by reaction of an amine with chloroformate or with a carbonate; amides are formed from acid chloride. Carbamates[114] can be used as protective groups for amino acids to minimize racemization in peptide synthesis, while amides permit racemization during the base-catalyzed coupling reaction of an N-protected, carboxyl-activated amino acid. However, monoacylation[115] of a primary amine often affords, sufficient protection, *i.e.*, against oxidation, alkylation, *etc.*, and more complete protection is obtained by forming cyclic diacyl derivatives.

The other special derivatives[116] used to protect an -NH group belong to one of three classes: N-alkyl or N-aryl derivatives; imines from carbonyl compounds and enamines from β-dicarbonyl compounds; or N-hetero atom derivatives. These derivatives must be easily and selectively formed, stable during the synthetic sequence, and readily removed. Even though they, like carbamates and amides, have been used to protect amino acids and nucleosides, they have been used more to protect isolated primary and secondary amines.

The pyrroles of amino acid esters can be deprotonated at the α-carbon and the pyrrole ring can withstand the strong-base conditions (*e.g.* LDA or LiHMDS). Such a pyrrole may offer potential as a protecting group for nitrogen.

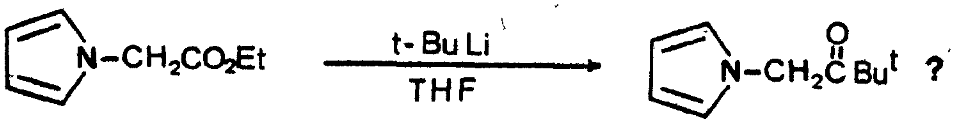
When the glycine ethyl ester pyrrole (80) was treated with lithium diisopropylamide (LDA) and followed by quenching with benzyl chloride, the product was the compound 105 without any α-substituted pyrrole derivative. An explanation for the formation of 105 is given below:



Assuming that the anion (I) was first generated at the α-position of 80, proton exchange with benzyl chloride could give the benzylic anion (II). Alternatively, the anion (I) was never formed, and LDA simply abstracted a proton directly from benzyl chloride. Subsequently, reaction with another benzyl chloride gave compound 105: ^{1}H nmr ($CDCl_3$) δ: 7.3 (m, 10H), 5.1 (t, 1H), 3.4 (d, 2H); ms, m/z (intensity), 218 (M^+ +2, 32.6), 216 (M^+, 64.3).

This latter possibility appears more likely since the same product 105 could be obtained from the reaction of benzyl chloride itself by LDA in THF as depicted.

When t-BuLi instead of LDA was used as the base with 80, α-substitution was still not observed. Instead, in the nmr spectrum of the product, a clear single peak was observed for the t-butyl group at 1.2 ppm without the ethoxy peaks of the ester. It seems that the product has the structure 106, derived from the conversion of the ester to the t-butyl ketone.



80

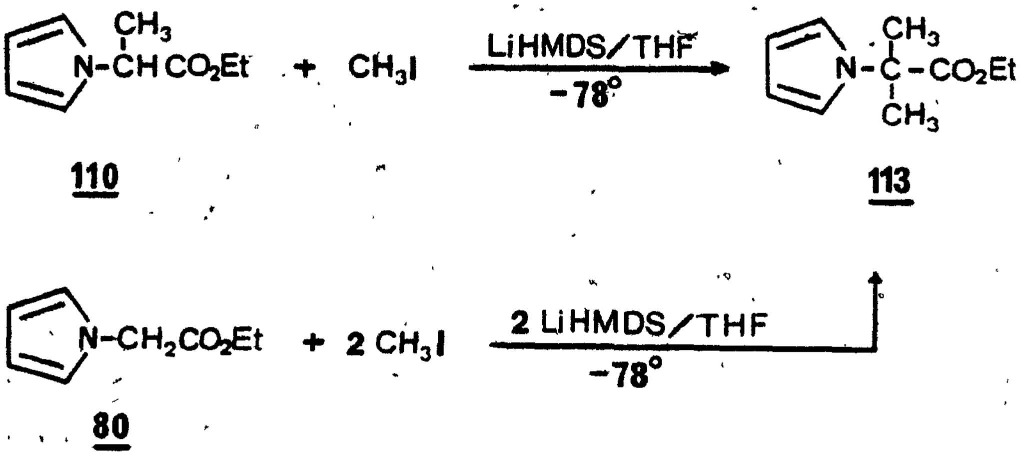
106

When lithium hexamethyldisilazide (LiHMDS) was used as a more sterically hindered strong base, reaction with 80, followed by addition of alkylbromide or iodide compounds 107-109, gave the desired α-substituted pyrrole derivatives (110-112). Compounds 110 and 111 were

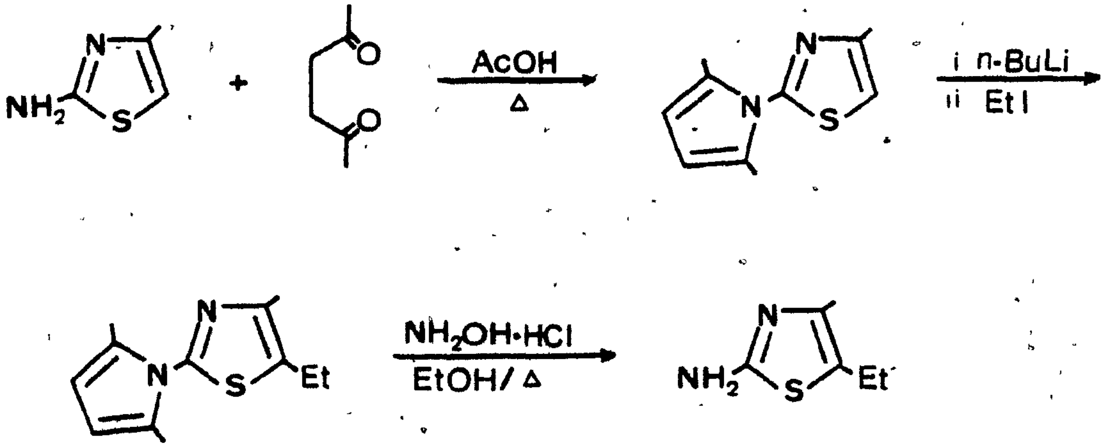
80	107	R=CH_3	X= I	110
	108	CH_2Ph	Br	111
	109	CH_2PhCH_3-o	Br	112

identical to compounds 82 and 81 obtained previously (p. 47). Furthermore, dialkylation is possible. Thus, 110 reacted with LiHMDS/CH_3I to give the dimethylated compound 113.

Compound 113 could also be obtained by the reaction of 80 with 2 equivalents of CH_3I in the presence of 2 equivalents of LiHMDS.



After completion of this work, a report[117] appeared in the literature, which employed the use of 2,5-dimethylpyrrole as the protecting group for amines. They[117] reported that N-pyrroles of a primary amine could withstand strong basic conditions (*e.g.*, n-BuLi or KOH), thus acting as a protecting group for the amine, which could subsequently be regenerated by treatment with hydroxylamine hydrochloride. A good example is depicted below:



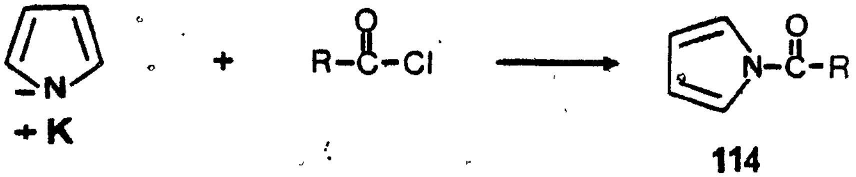
Since the idea of our work is essentially the same, we chose not to continue with this aspect of our investigation.

CHAPTER V

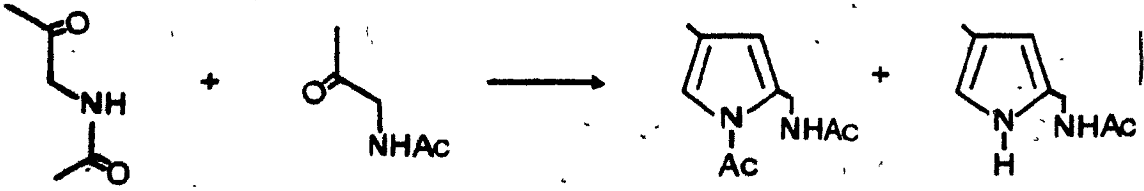
N-ACYLPYRROLE SYNTHESIS AND ITS APPLICATION IN ORGANIC SYNTHESIS

A. N-Acylpyrroles from Primary Amides

N-Acylpyrroles (114) were first obtained in 1904[118] by the reaction of acid chlorides with the potassium salt of pyrrole. Afterwards, several investigations of N-acylpyrrole synthesis were reported. As described in Chapter 4, in a 2C + 2C mode for the pyrrole synthesis, the α-amide ketone (115) undergoes a base-catalyzed self-condensation[119] to give the corresponding N-acylpyrrole 116 together with N-unsubstituted pyrrole 117. Similarly, the Paar-Knorr

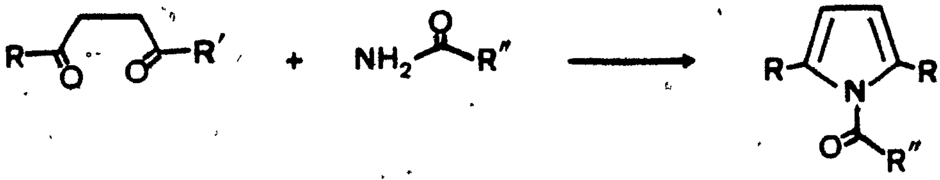


114

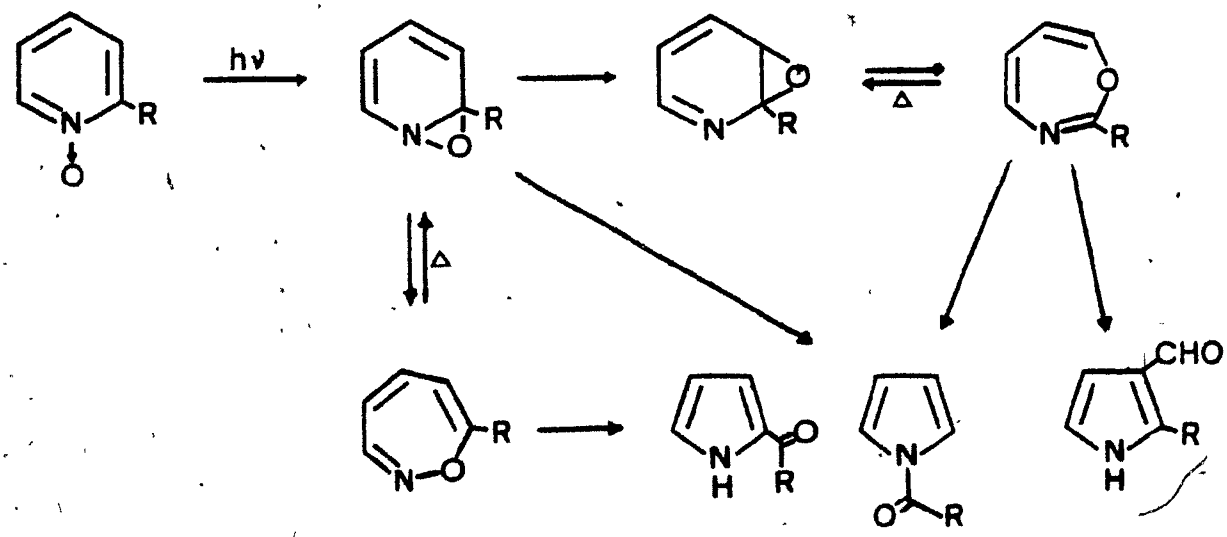


115 116 117

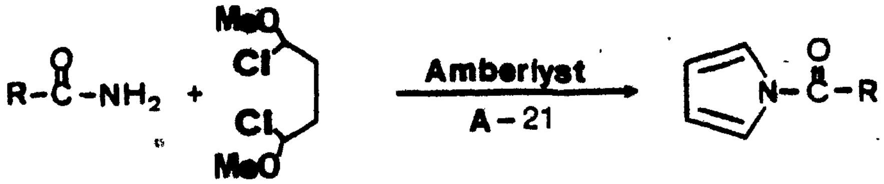
condensation of γ-diketones, a 4-carbon unit with primary amides, provides N-acylpyrroles[120].



Alternatively, it was reported[121-123] that the thermal rearrangement of oxazepines obtained from the photolysis of pyridine-N-oxides yields N-acylpyrroles. They were however obtained in poor yield together with other isomers as depicted.



Nevertheless, N-acylpyrrole synthesis from primary amides and 1,4-dichloro-1,4-dimethoxybutane is not known up to this time. We found that 1,4-dichloro-1,4-dimethoxybutane 49, a compound[72] obtained from 2,5-dimethoxytetrahydrofuran 1 and trimethylchlorosilane, reacts with primary amides (118-121) to give N-acylpyrroles (122-125).



118	R= Ph	122
119	$CH_2CH_2CH_3$	123
120	CH_3	124
121	$CH_2(CH_2)_{15}CH_3$	125

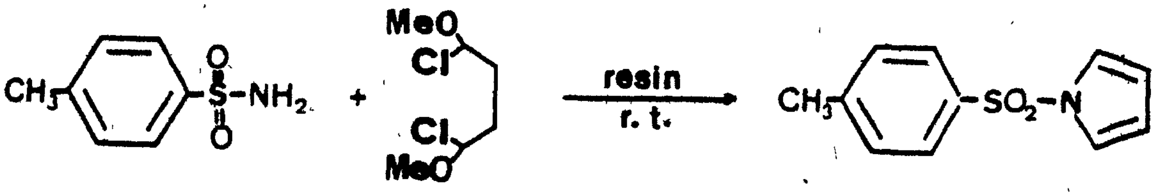
This reaction is somewhat more difficult to perform in comparison with the reaction of 49 with primary amines. The nucleophilicity of the amide nitrogen is expected to be considerably reduced due to resonance effects. Using the same procedure, the reaction of amides with 49 gave poor yields (20 ∿ 40%). In trying to overcome the problem by raising the reaction temperature to over 70°C, a black polymer was obtained. It seems that compound <u>49</u> polymerized at moderately high temperature. We found that by carrying out the reaction at the optimum temperature between 45° ∿ 65°C[124] (Table 5), using weakly basic ion-exchange resin Amberlyst A-21 for neutralization, a good yield of acylpyrrole could be obtained.

<u>Table 5</u>: Conversion of primary amides into N-acylpyrroles

primary amide	pyrrole	reaction temperature	% yield	(ref)
118	122	60° ∿ 65°C	85	(127)
119	123	50° ∿ 55°C	73	(118)
120	124	45° ∿ 50°C	55	(128)
121	125	48° ∿ 53°C	72,	mp = 62 ∿ 64°C

Even though N-acylpyrrole can be considered as a tertiary amide, the carbonyl stretching frequencies observed for N-acylpyrroles (<u>123</u>-<u>125</u>) was at 1715 ∿ 1725 cm^{-1} compared with the frequency of 1630 ∿ 1670 cm^{-1} normally observed for tertiary amides[125]. The higher carbonyl frequency in acylpyrroles is attributed to the aromatic character of the pyrrole ring and there is therefore less resonance interaction between nitrogen and the carbonyl group. The same phenomenon is observed for N-acylimidazole and similar compounds[126].

Finally, the reaction of p-toluenesulfonamide (126) with 49 under the same reaction conditions also gave 1-(p-toluenesulfonyl)pyrrole (127) in good yield.

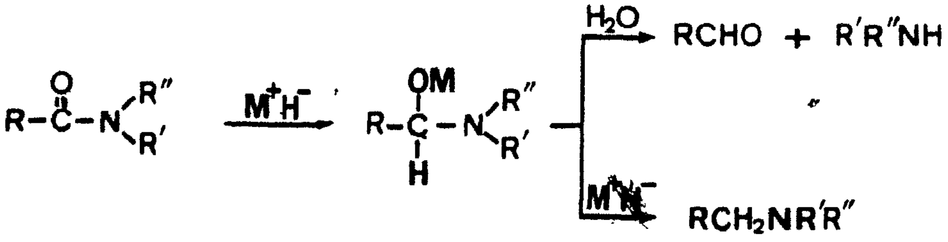


127

B. The Reduction of Primary Amides via Acylpyrroles

Nystrom and Brown[129] found that the reduction of tertiary amides by lithium aluminum hydride under ordinary conditions, *i.e.*, with an excess of the reducing agent present, usually produces the corresponding tertiary amines with the same number of carbon atoms. This work was extended by Uffer and Schlittler[130]. On the other hand, the carbonyl group in amides is resistant to reduction by sodium borohydride[131], although the reduction occurs in the presence of $CoCl_2$[132,133], $POCl_3$ or PCl_5[134], or carboxylic acids[135] such as acetic or trifluoroacetic acid. With lithium aluminum hydride[131], primary amides are normally reduced to primary amines, with the carbon-nitrogen bond intact. In some cases, reductive cleavage to an alcohol or to a secondary amine has been observed[136]. The controlled reduction of selected tertiary amides by lithium aluminum hydride, followed by hydrolysis, has been utilized for the synthesis of aldehydes[137]. For example, Brown *et al.*[141], reported the reduction of N-acylaziridines, N,N'-dialkylamides, *etc.*, to aldehydes. This supplements the reduction of acid chlorides by lithium *tri*-t-butoxyaluminohydride as a method for the synthesis of aldehydes[138,139].

It has been suggested that the reduction of tertiary amides proceeds to its various products through a common intermediate[136,140]. In this mechanism, the first step is postulated to be the nucleophilic attack of the metal hydride, M^+H^-, on the carbonyl group to form the intermediate complex I. Treatment with water transforms this complex to an aldehyde and a secondary amine. Alternatively, it can be reduced further to the amine *via* an imine intermediate.

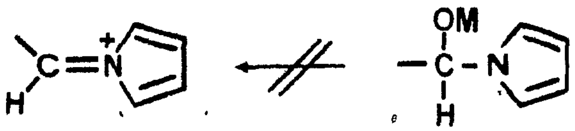


(I)

In order to maximize the yield of aldehyde, one can try to reduce the pathway leading to the imine. This was achieved by using acylaziridines[141]. Because of the ring size of aziridine, formation to the intermediate imine X is prohibited.

X

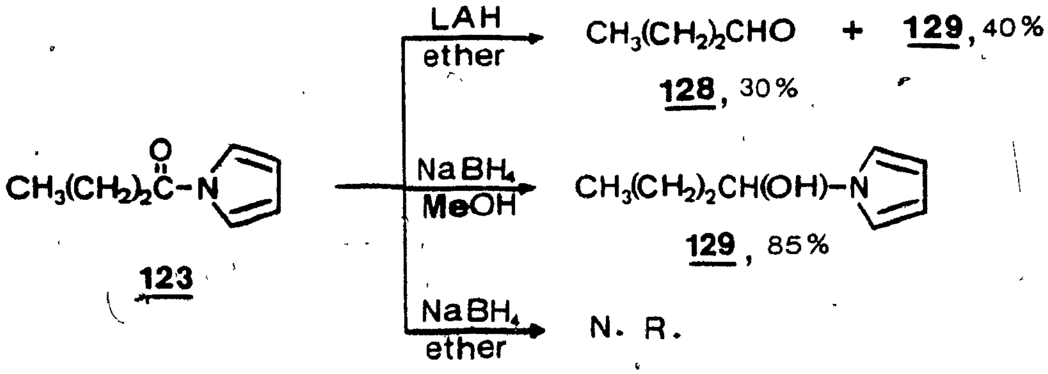
Another approach which was examined by Brown *et al.*[141], was to use acylpyrroles. Because of the aromatic character of pyrroles, the corresponding imine intermediate W should similarly be inhibited.



W

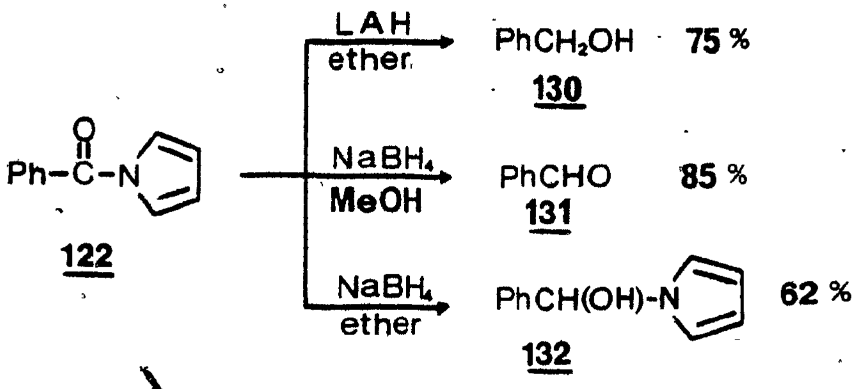
However, the reduction of N-butanoylpyrrole (123) with lithium aluminum hydride studied by Brown and his coworker[141] was found to give disappointing results in that only 30% butanal was obtained as the reduction product. In contrast, 88% butanal was obtained from N-butanoylaziridine.

With our facile synthesis of acylpyrroles, we decided to reinvestigate this reaction. We found[124] that reduction of N-butanoylpyrrole with LAH gave indeed only 30% yield of butanal (128). The major product of the reaction was the pyrrole hemiacetal compound 129 in 40% yield. Furthermore, if the reduction of 123 was carried out with sodium borohydride in methanol, the pyrrole hemiacetal 129 was obtained as the sole product in 85% yield. The use of methanol as solvent is important in this case, since reduction with $NaBH_4$ did not occur in ether.



The structure of 129 was assigned on the basis of its ^1H nmr spectrum. The hydroxyl peak (2.45 ppm) of 129 disappeared upon shaking the sample with D_2O in the nmr tube.

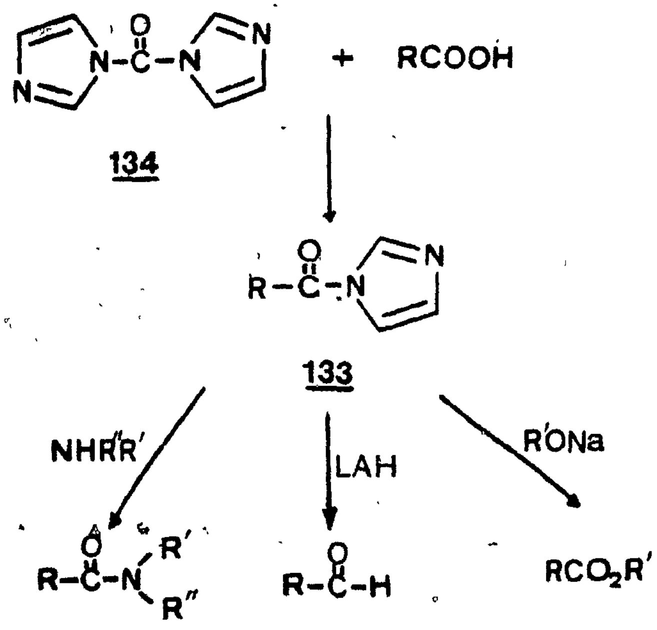
Reduction of benzoylpyrrole (122) with LAH gave benzyl alcohol (130) in 75% yield. The reaction with sodium borohydride in methanol, on the other hand, gave benzaldehyde (131) in good yield. The same reduction with sodium borohydride in ether gave the hemiacetal 132 instead. The OH peaks of 132 (2.95 ppm) also disappeared in the ^{1}H nmr spectrum when the sample was shaken with D_2O in the nmr tube.



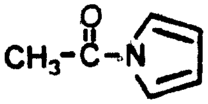
It is clear that the carbonyl group in acylpyrroles can easily be reduced by hydrides in agreement with their expected activation.

C. Substitution Reactions of N-Acylpyrroles with a Variety of Nucleophiles

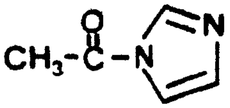
Because of resonance interaction, the carbon-nitrogen bond of amides possesses partial double bond character. Chemically, this is manifested in the difficulty[142] by which amides undergo hydrolysis, alcoholysis and aminolysis. There are reports of many investigations seeking to overcome this problem. Staab[126] had reported that the imidazolides 133, which were simply prepared[143] by the reaction of N,N'-carbonyldiimidazole (134) and carboxylic acids in equimolar proportions at room



temperature, are particularly easy to hydrolyze because of the high degree of reactivity of azolides in nucleophilic reactions. He places these compounds on the same level as acylhalides and acid anhydrides. He also compared[126] the reactivities between N-acetylpyrrole (124) and N-acetylimidazole (133) in water at pH 7. Whereas N-acetylpyrrole (124) was not hydrolyzed at a measurable rate in neutral aqueous media, the half-life of the hydrolysis of N-acetylimidazole (133) at 25°C was 41 min.



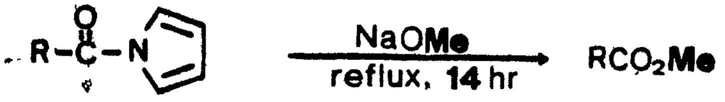
124



133

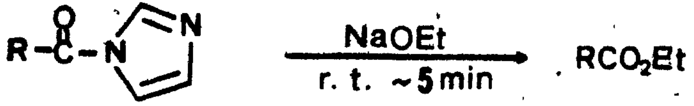
In agreement with this fact, we found that N-acylpyrroles (122, 123) reacted with NaOMe under reflux overnight in methanol to give the corresponding esters (135, 136), while N-acylimidazoles 133 reacted[144,145] with NaOEt at room temperature within a few minutes to give the esters 137.

It is clear that even though acylpyrroles are less reactive than acylimidazoles, they can nevertheless be readily transformed into esters.



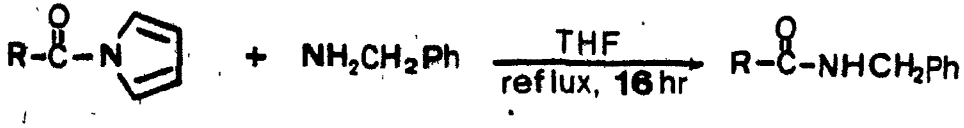
122 R= Ph 135

123 $CH_2CH_2CH_3$ 136

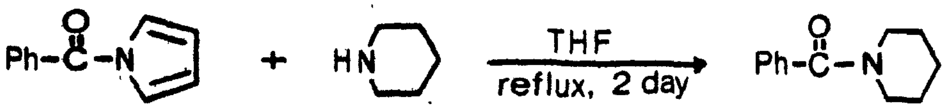


133 R=alkyl or aryl 137

Similar to the reactions of N-acylimidazoles, reaction of acylpyrroles (122, 123, 125) with primary amines (*e.g.* benzylamine) in refluxing tetrahydrofuran gave secondary amides (138-140) in good yields. On the other hand, when methylene chloride (b.p. = 40 ∿ 41°C) was used as solvent, the reaction was not complete even after prolonged (3 days) heating. Likewise, the reaction of acylpyrrole 122 with a secondary amine (piperidine) gave the corresponding tertiary amide 141.

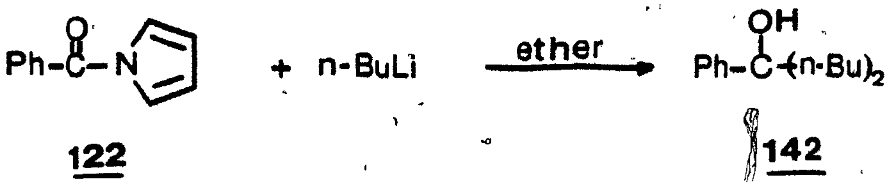


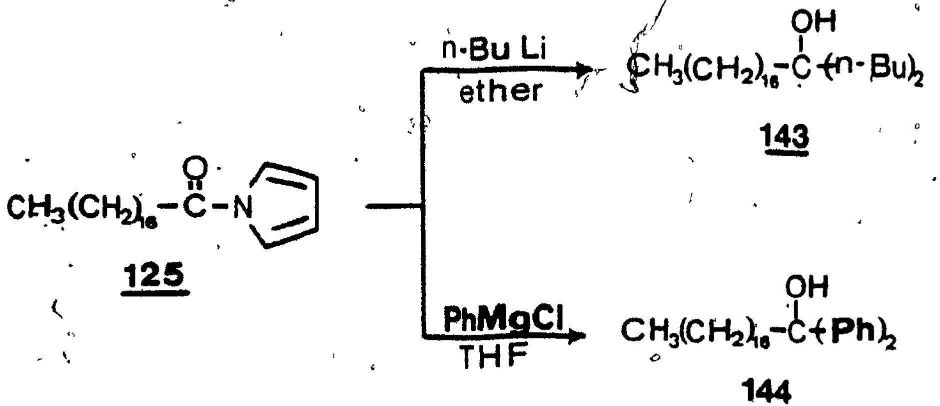
122	R = ph	138
123	= $CH_2CH_2CH_3$	139
125	= $CH_2(CH_2)_{15}CH_3$	140



122 **141**

Finally, acylpyrroles (122, 125) react with either organolithium or Grignard reagents to give the corresponding tertiary alcohols (142 ∿ 144) with cleavage of the carbon-nitrogen bond as illustrated by the following reactions.





D. Conclusion

Usually, it is difficult for primary amides to undergo hydrolysis, alcoholysis and aminolysis as well as to be transformed to the corresponding aldehydes or alcohols.

In this chapter, we have shown that 1,4-dichloro-1,4-dimethoxybutane (49) is very useful for making N-acylpyrroles from primary amides. This permits the facile transformation of primary amides into esters, secondary and tertiary amides as well as aldehydes and alcohols. These reactions are summarized in Scheme 7 and Table 6.

Table 6: Reactions of acylpyrroles with various nucleophiles

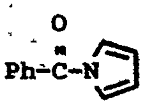
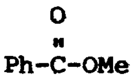
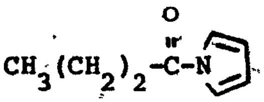
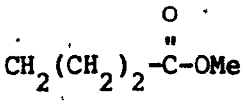
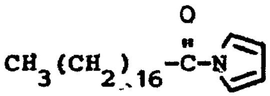
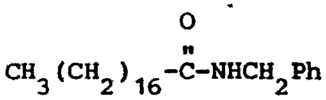
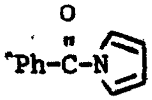
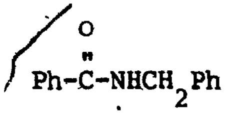
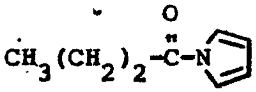
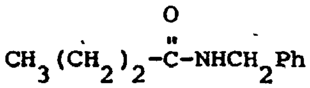
acyl pyrrole	nucleophile	reaction conditions	products	% yield (lit.)
	MeONa	MeOH/reflux, 14 hrs	 $\mathrm{Ph{-}\overset{O}{\overset{\Vert}{C}}{-}OMe}$	85%^{c}
	MeONa	MeOH/reflux, 14 hrs	 $\mathrm{CH_2(CH_2)_2{-}\overset{O}{\overset{\Vert}{C}}{-}OMe}$	89%^{c}
	$H_2N{-}CH_2Ph$	THF/reflux, 16 hrs	 $\mathrm{CH_3(CH_2)_{16}{-}\overset{O}{\overset{\Vert}{C}}{-}NHCH_2Ph}$	87%, mp = 85-88°
	$H_2N{-}CH_2Ph$	THF/reflux, 16 hrs	 $\mathrm{Ph{-}\overset{O}{\overset{\Vert}{C}}{-}NHCH_2Ph}$	85%, mp = 104-106°
	$H_2N{-}CH_2Ph$	THF/reflux, 16 hrs	 $\mathrm{CH_3(CH_2)_2{-}\overset{O}{\overset{\Vert}{C}}{-}NHCH_2Ph}$	80%

Table 6: (cont'd)

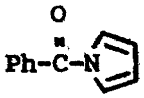
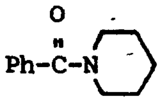
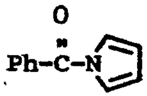
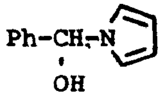
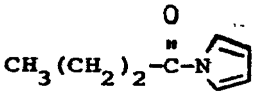
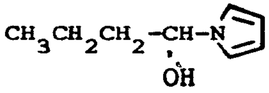
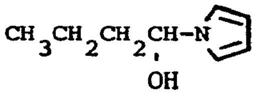
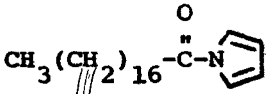
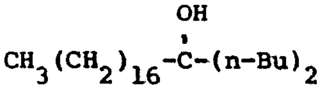
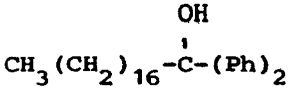
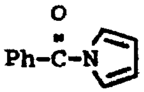
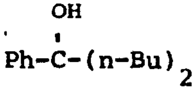
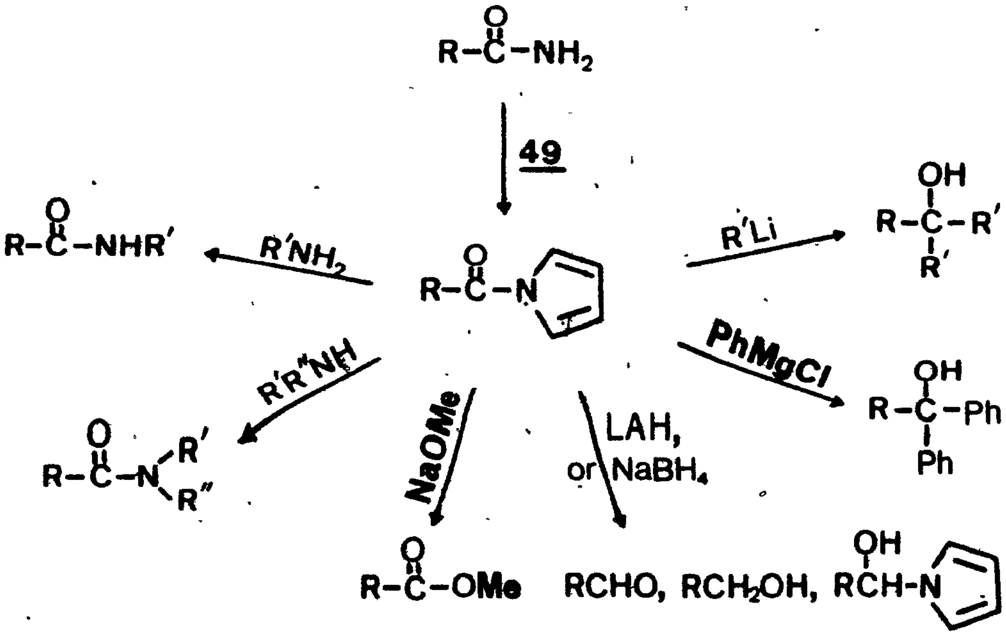
acyl pyrrole	nucleophile	reaction conditions	products	% yield (lit.)
		THF/reflux, 2 days		55%[a]
	$LiAlH_4$[b]	ether, 0°/1 hr → r.t./14 hrs	$PhCH_2OH$	75% (75)
	$NaBH_4$	MeOH, -20°/5 hrs	PhCHO	85%
	$NaBH_4$	ether, r.t./14 hrs		62%[a]
	$LiAlH_4$	ether, 0°/1 hr → r.t./14 hrs	$CH_3CH_2CH_2CHO$	30% (80)
				40%[a]
	$NaBH_4$	MeOH, -20°/5 hrs		85%[a]

Table 6: (cont'd)

acyl pyrrole	nucleophile	reaction conditions	products	% yield (lit.)
	n-BuLi[b]	ether, 0°/2 hrs	 $CH_3(CH_2)_{16}-\overset{OH}{\overset{|}{C}}-(n\text{-}Bu)_2$	65%[a]
	PhMgCl[b]	THF, r.t./4 hrs	 $CH_3(CH_2)_{16}-\overset{OH}{\overset{|}{C}}-(Ph)_2$	55%[a], mp = 40-43°
	n-BuLi[b]	ether, 0°/2 hrs	 $Ph-\overset{OH}{\overset{|}{C}}-(n\text{-}Bu)_2$	72%[a]

[a] isolated yield by column chromatography
[b] more than 2 equivalents of amount were used
[c] by distillation



Scheme 7: The reactions of N-acylpyrroles with various nucleophiles

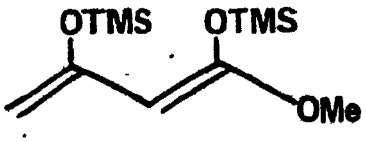
CHAPTER VI

ATTEMPTED SYNTHESIS OF NONACTIN

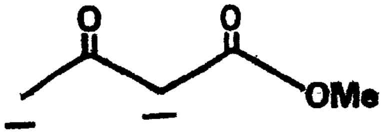
A. General Considerations

Enol silyl ethers have come to play an important part in organic synthesis[42,43]. They were first introduced[146,147] as precursors of specific enolates and subsequently have been used as such in numerous reactions with electrophiles. Their usefulness now surpasses that of all other enol derivatives[148], because of their ease of preparation, clean reactions and the mildness of desilylation processes.

It was recently found[149] in our laboratory that 1,3-*bis*(trimethylsiloxy)-1-methoxybuta-1,3-diene (19) can serve as the equivalent of the dianion of methylacetoacetate (20).



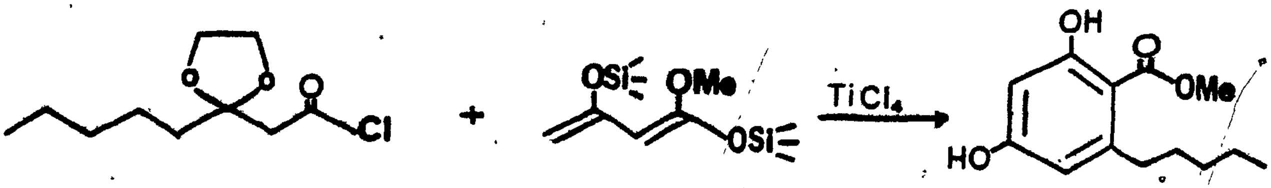
19



20

It is known[45] that the reactivity of 19 differs from that of 20 in two important respects: i) 19 reacts with electrophiles under neutral or acidic conditions whereas 20 is only formed under strongly basic conditions; ii) 20 reacts typically as a "hard" nucleophile in giving 1,2-adducts with conjugated carbonyl compounds whereas 19 reacts to give Michael adducts.

Furthermore, 19 can be considered as a three-carbon unit with two nucleophilic sites. It can therefore react with other fragments containing two electrophilic sites to give cyclic products. Thus, novel regiocontrolled cycloaromatization reactions have been developed on the basis of this concept[150,151]. A good example for this reaction was shown by the preparation of methyl olivetolate (145) as a precursor in the synthesis of $^1\Delta$-tetrahydrocannabinol[152].

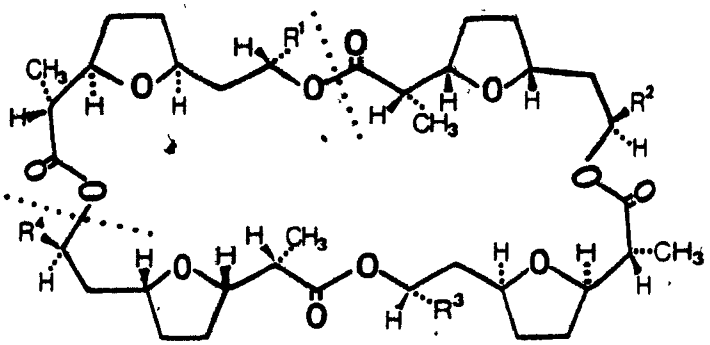


19

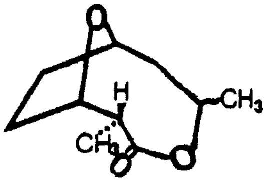
145

Similarly, 19 condenses with bicyclic acetals such as 2,5-dimethoxytetrahydrofuran and 2,6-dimethoxytetrahydropyran in the presence of titanium tetrachloride to give the bicyclic products[45] 25 and 26 respectively, as mentioned in Chapter 2. That reaction seems to have considerable potential for the synthesis of natural products.

Accordingly, as part of the attempted synthesis of the antibiotic macrotetrolide nonactin[153] (N), we have tried to prepare the bicyclic lactone 146 as an intermediate, the monomeric unit of the macrotetrolide M. The synthesis of this is discussed more fully at the end of this chapter.

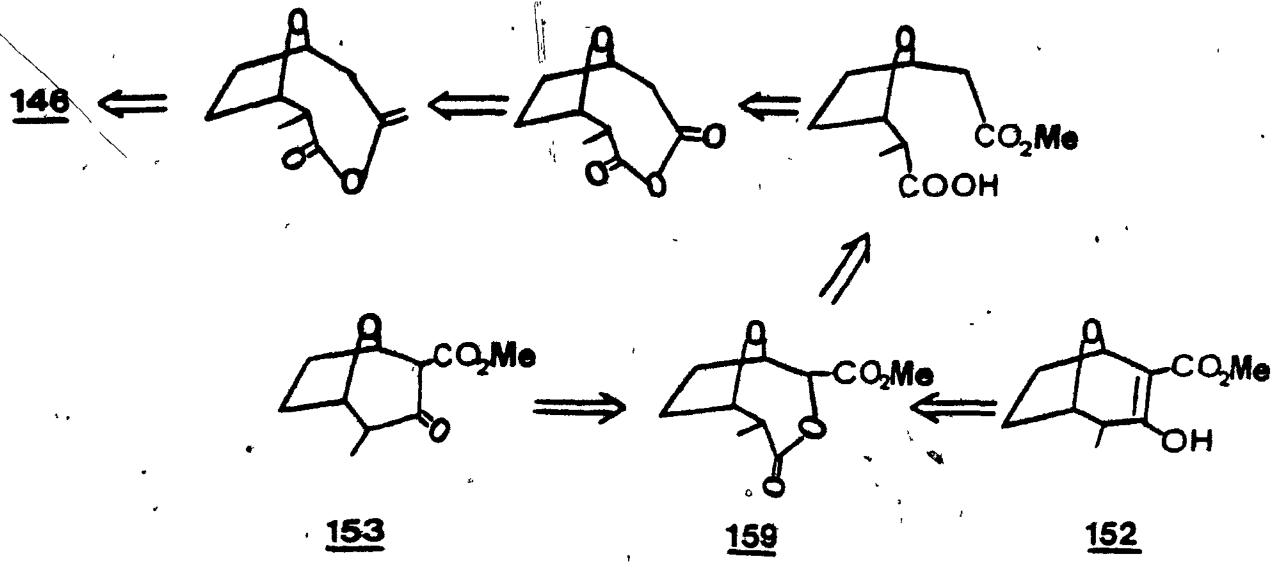


Macrotetrolide (M)



146

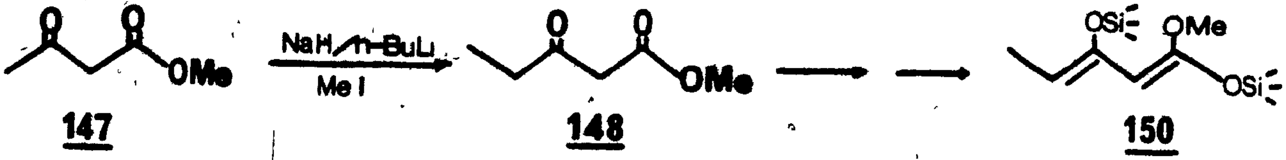
Tentative pathways to 146 could be considered as shown in Scheme 8.



Scheme 8

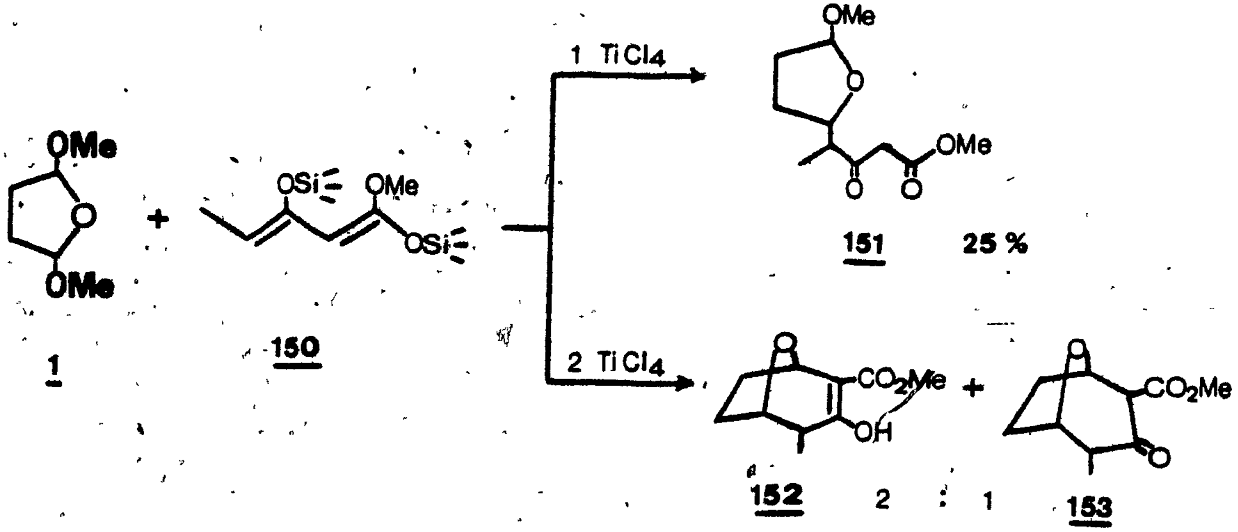
B. Determination of Configuration at C-4 in Bicyclic System (152,153) and Related Reactions

The *bis*-enol silyl ether 150 was prepared by the following scheme. First, compound 148 was prepared according to Weiler's method[153] by the alkylation of the dianion 20. Compound 148 was converted to the mono-enol silyl ether 149[154] and then to the *bis*-enol silyl ether 150[150] using LDA/Me_3SiCl.



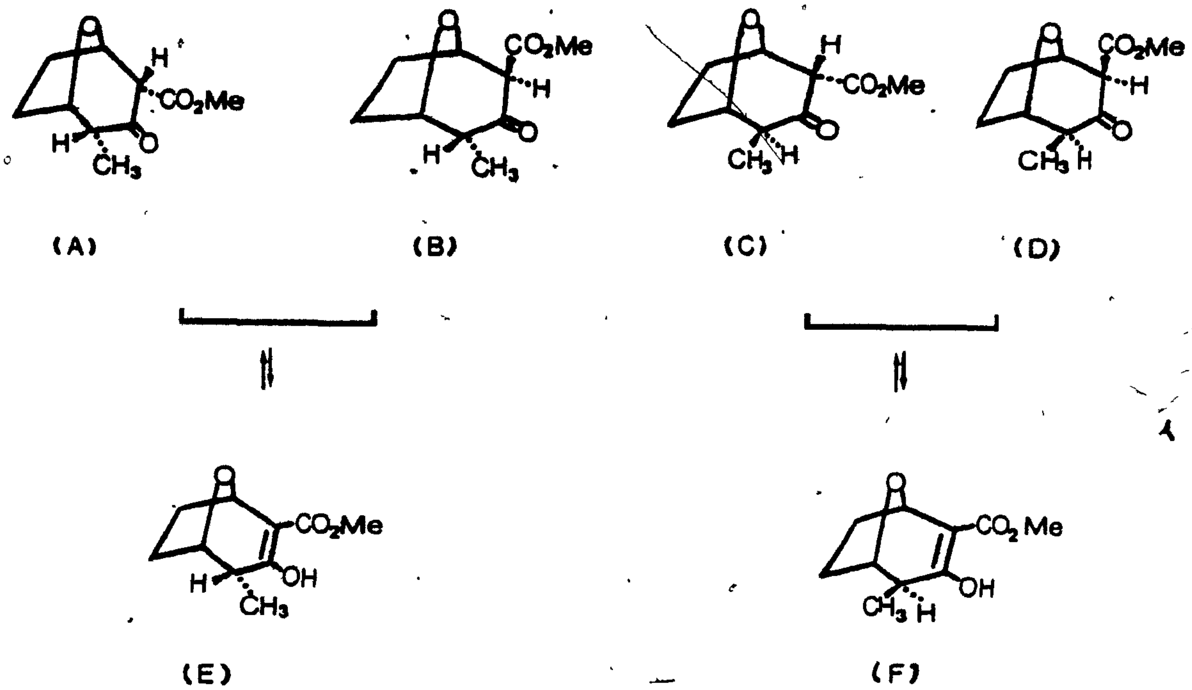
When $\underline{150}$ was condensed with $\underline{1}$ in the presence of 1 equiv. of $TiCl_4$, compound $\underline{151}$ was obtained. Spectral data of $\underline{151}$ showed peaks at 3.7 ppm (s, 3H) for the methyl ester and at 3.28 ppm (s, 3H) for OCH_3 in its ^1H nmr; 1750 cm^{-1} (CO_2Me) and 1715 cm^{-1} (C=O) in ir; m/z (rel. int.) 199 ($M^{+\cdot}-OCH_3$, 14.8) in ms.

When 2 equiv. of $TiCl_4$ were used, a mixture of $\underline{152}$ and $\underline{153}$ was obtained in the ratio of 2:1 in an overall yield of 57%.



Interestingly, 152 and 153 could be separated by TLC-Mesh Column Chromatography[155]. This indicates that 152 and 153 are not simply keto-enol tautomers but have different configurations at the C-4 positions. The distinctions between 152 and 153 were quite apparent in their spectroscopic data. The ^1H nmr peak of the enolic proton of 152 appeared at 11.68 ppm (Fig. 5); In the ir spectrum, enolic O-H, C=C and C=O (ester) stretching frequencies appeared at 3600 ∿ 3300 cm^{-1} (br), 1615 cm^{-1} and 1660 cm^{-1}, respectively. On the other hand, compound 153 seems to be two isomers (2 spots on TLC) which could not be separated in our hands (Fig. 6). Its ^1H nmr spectrum clearly showed signals at 3.76, 3.73 ppm (s, each OMe) for the methoxy groups and at 1.01, 0.98 ppm (d, each CH_3, J = 6.8 Hz) for the methyl groups, respectively; carbonyl stretching frequencies for ketone and ester appeared at 1715 and 1740 cm^{-1} in the ir spectrum.

Since a knowledge of the stereochemistry at C-4 in the bicyclic compounds 152 and 153 is very important for the eventual synthesis of the macrotetrolide (M), the configuration at C-4 should be assigned. Since the configurations at C-1 and C-5 were already fixed, four stereoisomers (A-D) in the keto-form are expected from the reaction of 150 with 1. Actually, only three products appeared on TLC, one of which was 152, which, being the enol form, must have either structure (E) or (F) resulting from the loss of chirality at C-2 (Scheme 9).



Scheme 9

^{1}H nmr Spectra of 152 and 153 (Figs. 5 and 6) were sufficiently complicated so that confirmation concerning the stereochemistry at C-4 was not readily apparent.

Their O-silylation and O-acylation, *etc.*, derivatives were examined with a view to simplifying the interpretation of the spectra. O-Silylation product 154 was obtained in quantitative yield by the reaction of 152 and TMSCl in the presence of Et_3N. Similarly, O-acylation product 155 was obtained by the reaction of 152 and acetyl chloride in the presence of pyridine. C-Methylated products 156 and 157 were obtained in good yield by the reaction of

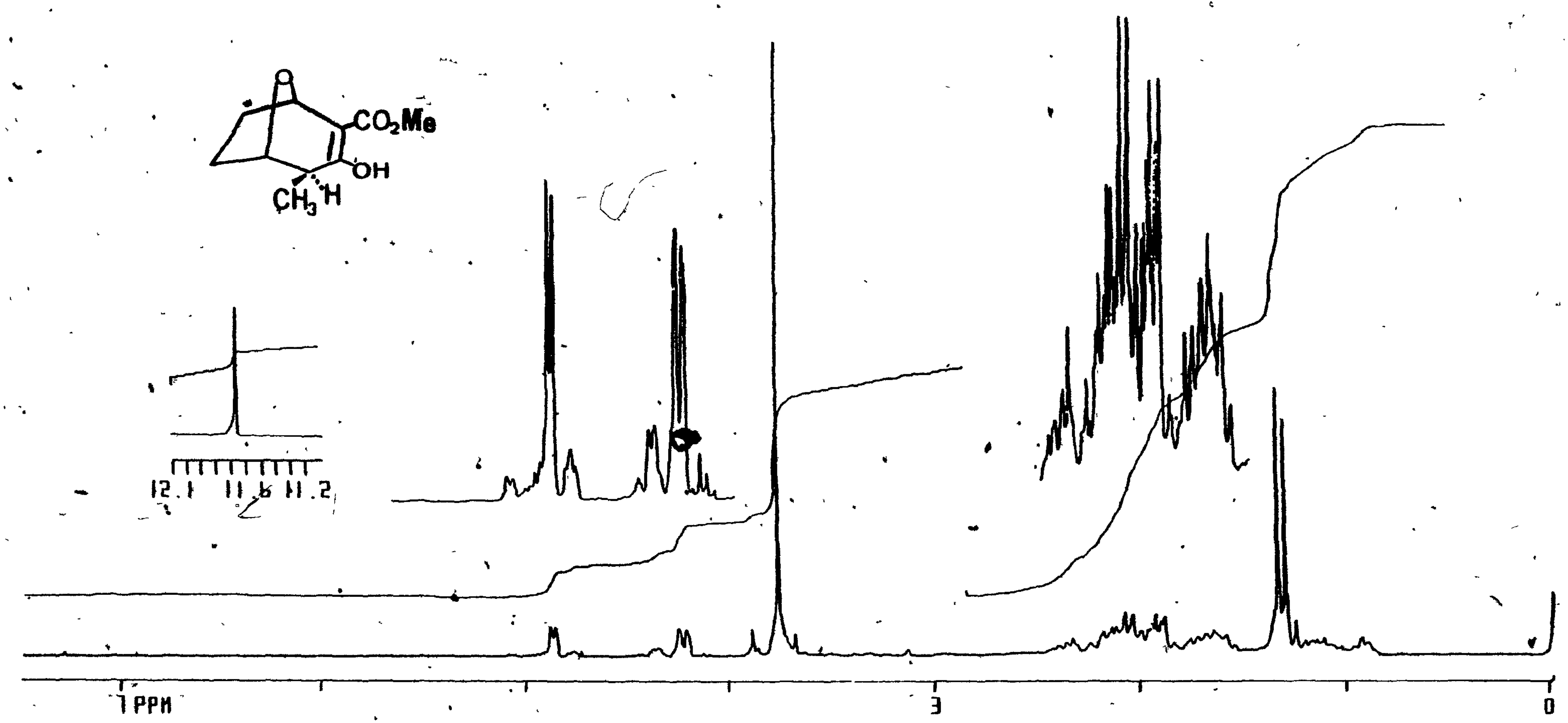


Fig. 5: 200 MHz ^1H nmr spectrum of <u>152</u> (one isomer).

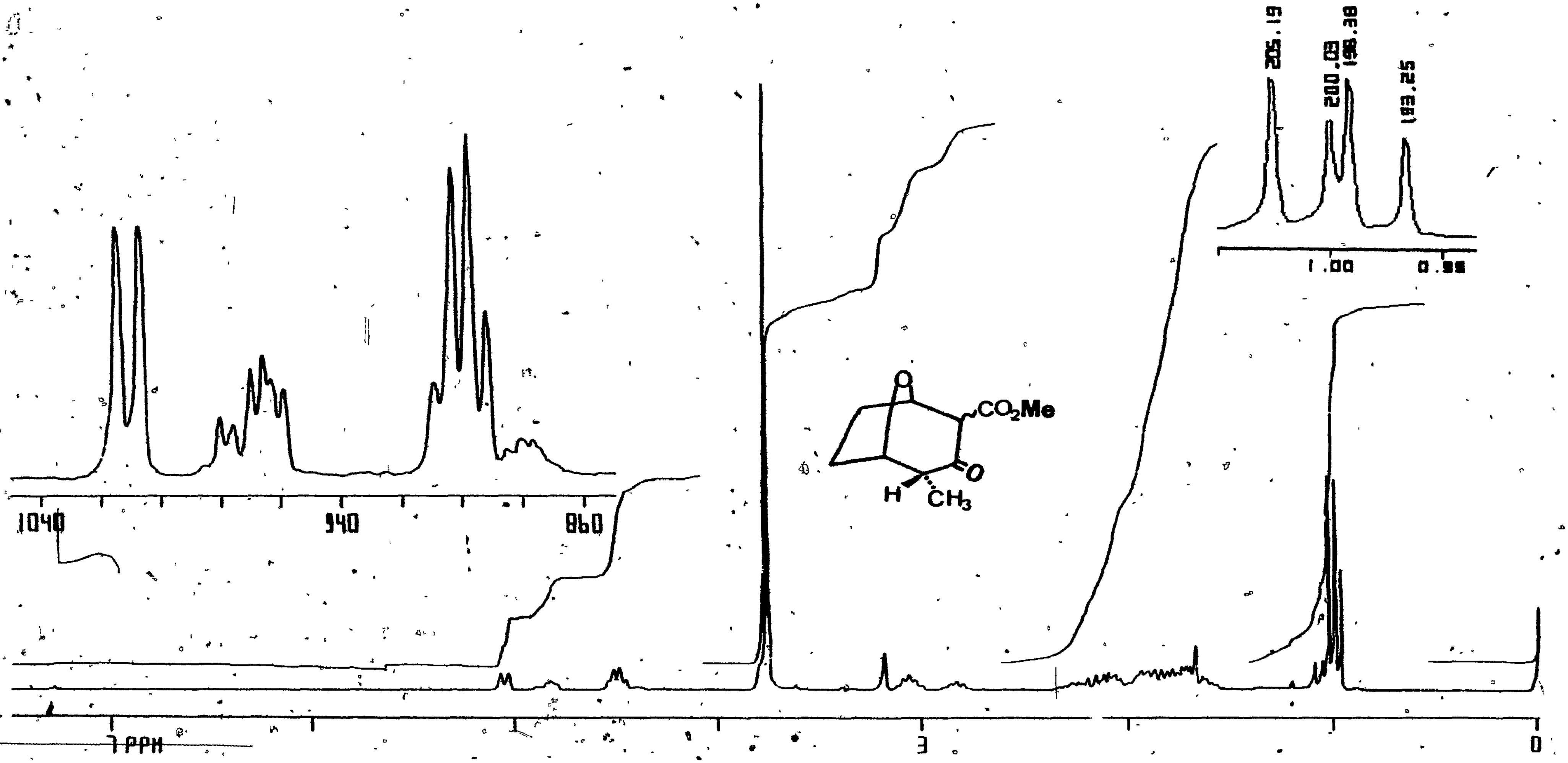
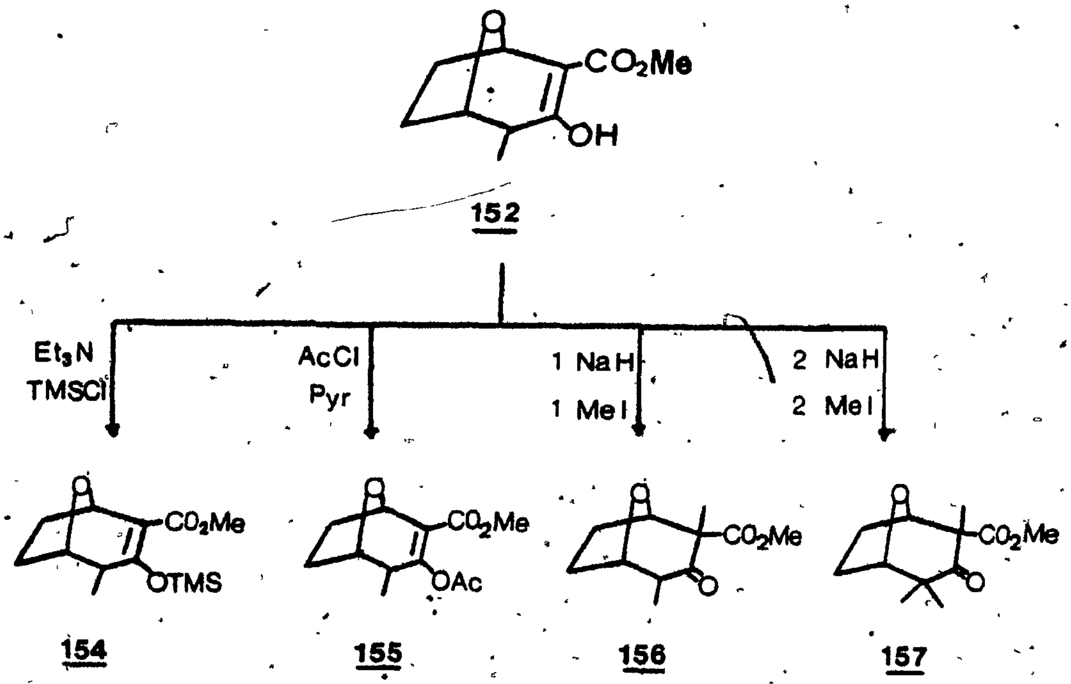


Fig. 6: 200 MHz ^{1}H nmr spectrum of 153 (two isomers)

152 and iodomethane in the presence of sodium hydride. ^{1}H nmr spectra of 154 and 155 showed clearly that the configuration at C-4 could be deduced easily. As shown in Fig. 7, one could see a clear quartet for H-4 at ∿ 1.8 ppm



Decoupling experiments with 154 and 155 (Figs. 7 and 8) show the results of irradiating the methyl doublets at 1.28 ppm and at 1.23 ppm, respectively. For 154 (Fig. 7), the quartet at 1.80 ppm collapsed to a broad singlet. This suggests that the coupling constant between H-4 and H-5 is close to zero and using the Karplus equation[156], the

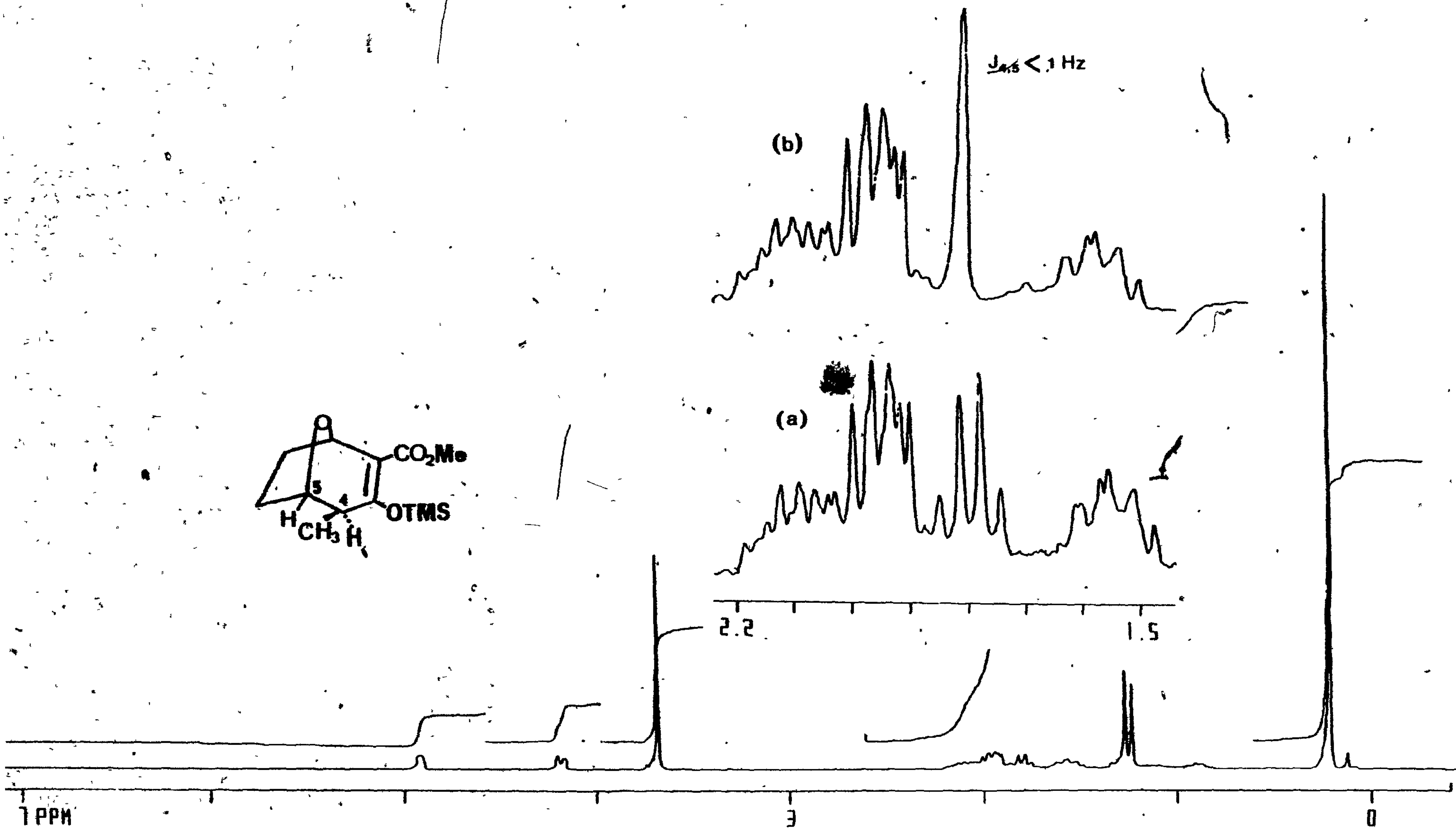
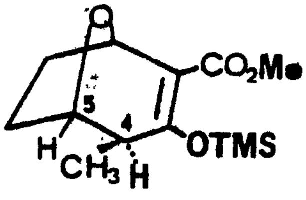


Fig. 7: 200 MHz ^{1}H nmr and related decoupled spectra of <u>154</u>

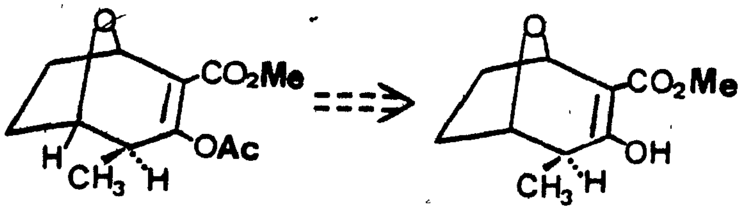
(a) expanded spectrum between 2.2 and 1.5 ppm

(b) decoupled spectrum on irradiation of methyl group at C-4 dihedral angle between H-4 and H-5 should be approximately 80°. This conclusion is consistent with that of the decoupled spectrum of 155, since irradiation of the methyl doublet at 1.23 ppm reduced the quartet at 2.06 ppm to a singlet (Fig. 8). Therefore, with the aid of a molecular model, we can conclude that the methyl group at C-4 in 154 or 155 should be directed to the exo-site.

Karplus Equation; $J = 8.5\cos^2\phi - 0.28$, ϕ = dihedral angle

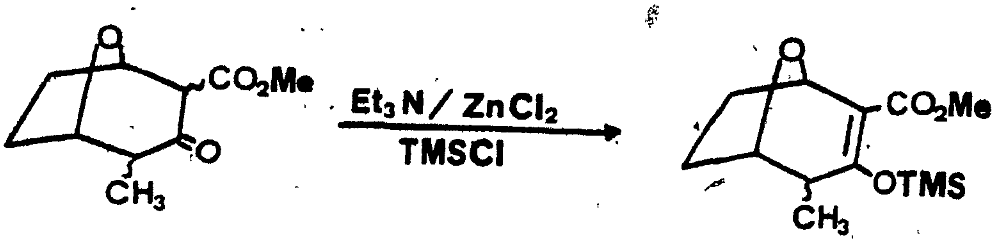


154



155 152

On the other hand, enol silyl ether 158 (Fig. 9) was obtained from 153 by Danishefsky's method[154]. Compound 158 is distinct from 154. This suggests that the two isomers of 153 are isomeric at C-2. As a matter of fact,



153 158

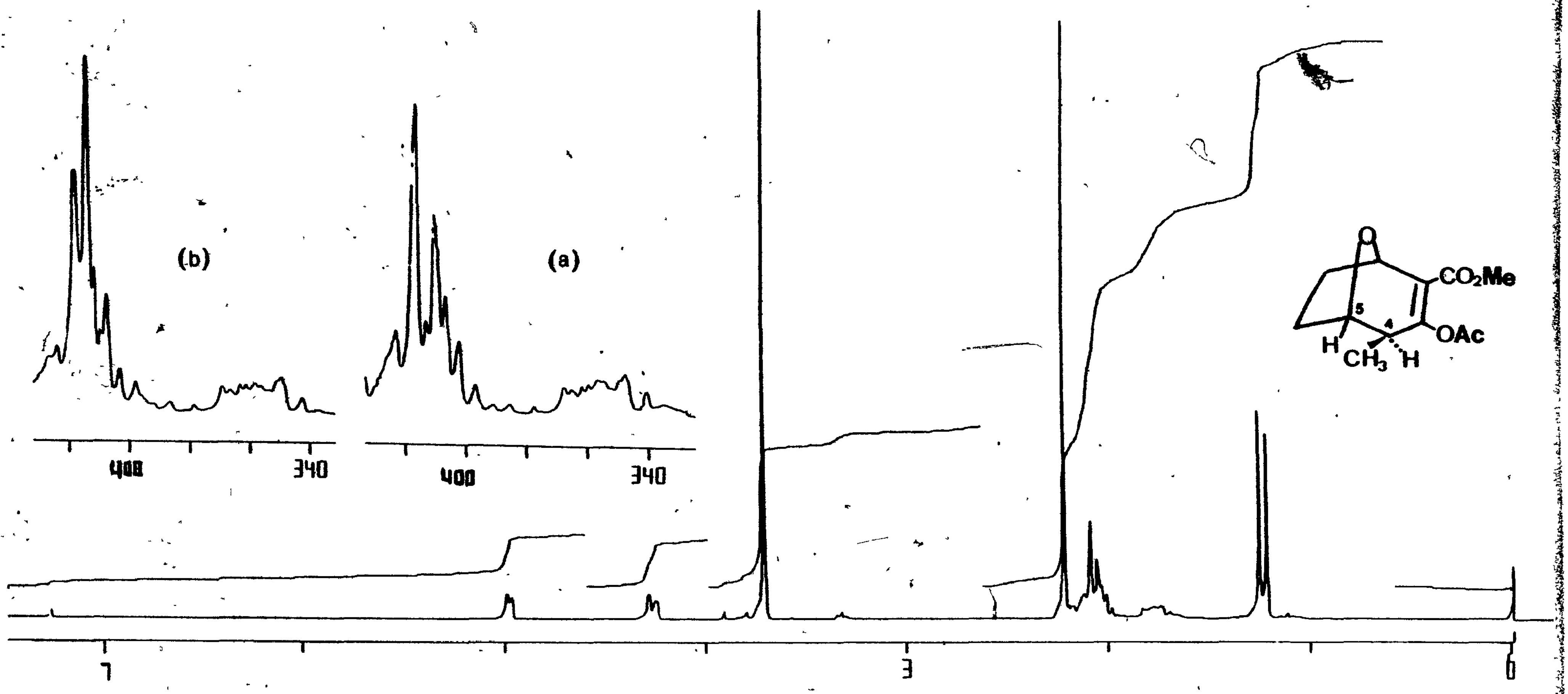


Fig. 8: 200 MHz ^{1}H nmr and related decoupled spectra of <u>155</u>

(a) expanded spectrum between 2.2 and 1.7 ppm

(b) decoupled spectrum on irradiation of methyl group at C-4 the ^{1}H nmr spectrum of <u>158</u> shows a singlet for methoxy and a doublet for the methyl group at 3.63 ppm and 0.93 ppm, respectively. Carbon-carbon double bond stretching was evident at 1615 cm^{-1} in the ir spectrum of <u>158</u>.

The decoupled spectrum (Fig. 9) for compound <u>158</u> shows the results of double irradiation. The multiplet at 2.76 ppm, assigned to C-4, was simplified to a quartet when H-5 at 4.31 ppm was irradiated. The methyl doublet at 0.93 ppm collapsed to a singlet when H-4 was irradiated. Inversely, the methine multiplet at 2.76 ppm changed to a doublet, on irradiation of the methyl group at C-4. Finally, when both methylene groups at 1.83 ppm were irradiated, the bridgehead proton (H-1) peak at 4.9 ppm collapsed to a singlet and another bridgehead proton (H-5) peak at 4.31 ppm to a doublet.

From these experiments, the coupling constant for H-4 and H-5, $J_{4,5}$ = 4.8 Hz, could be easily deduced. Again, using the Karplus equation, the dihedral angle[156] between H-4 and H-5 would be about 40°, which means that the methyl group at C-4 in <u>158</u> should be directed to the endo-site.

The fact that only <u>154</u> was obtained from <u>152</u> and only <u>158</u> was obtained from <u>153</u> suggests that in silylation reaction conditions, stereochemistry at C-4 remains intact. We can therefore conclude that <u>152</u> has the methyl at C-4 exo, whereas <u>153</u> has the methyl at C-4 endo.

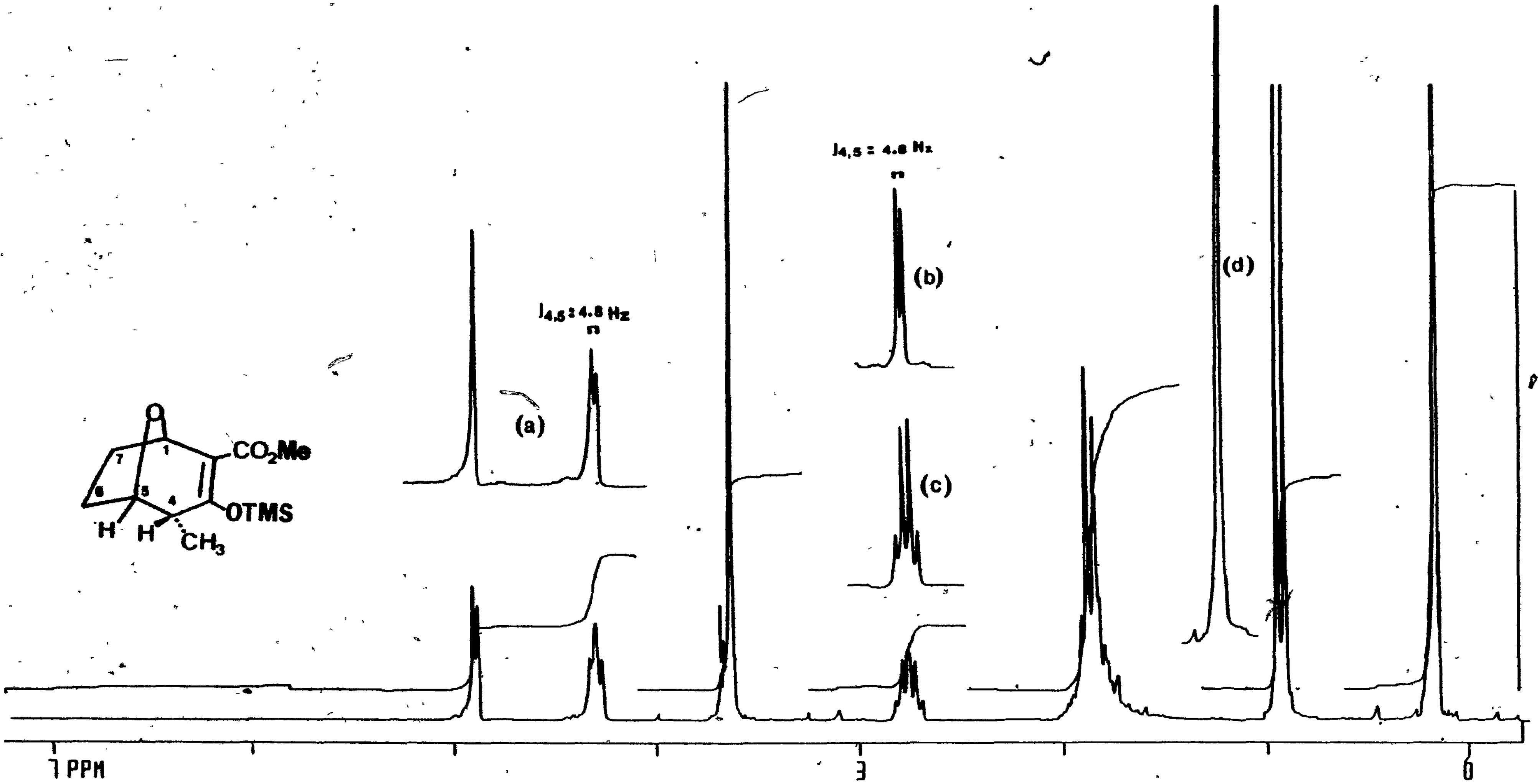


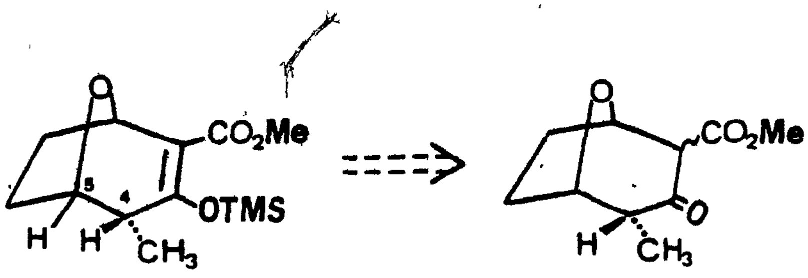
Fig. 9: 200 MHz ^{1}H nmr and related decoupled spectra of <u>158</u>

(a) on irradiation of H-6 and H-7,

(b) on irradiation of methyl group at C-4

(c) on irradiation of H-5

(d) on irradiation of H-4



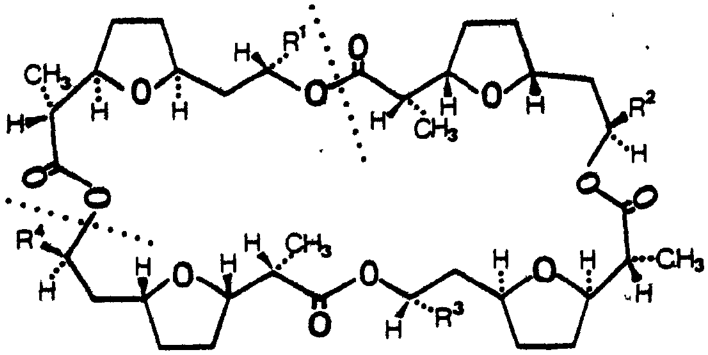
158 153

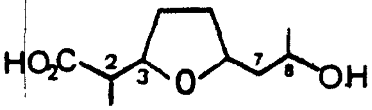
Furthermore, 156 and 157 obtained from the methylation of 152 are found to be probably the same C-2 isomer according to the ^{1}H nmr spectra and TLC (R_f = 0.33 and 0.44 in ethylacetate: hexane (3:7), respectively). The configuration at C-2 can probably be considered as the exo-methyl form due to the less hindered exo-site. Carbonyl stretching frequencies of ester and ketone in 156 and 157 appeared at 1735 cm^{-1} and 1715 ∿ 1710 cm^{-1}, respectively, while we could not find any C=C stretching frequency (1620 ∿ 1680 cm^{-1}).

The next step in our synthetic study is to attempt cleavage of the C-2 and C-3 bond.

C. Attempted Synthesis of Bicyclic Lactone, 159 from 1 and 150

The macrotetrolides (N, O, P, Q, R) are ionophore antibiotics produced by several strains of streptomyces[157]. The macrocyclic ring of nonactin (N), the parent compound, is very unusual in that it is a tetramer composed of both enantiomers of nonactic acid (160) and these are combined in a (-) (+) (-) (+) fashion with the result that nonactin is an achiral molecule possessing S_4 symmetry, and thus is optically inactive.





160

(N) Nonactin: $R^1 = R^2 = R^3 = R^4 = Me$

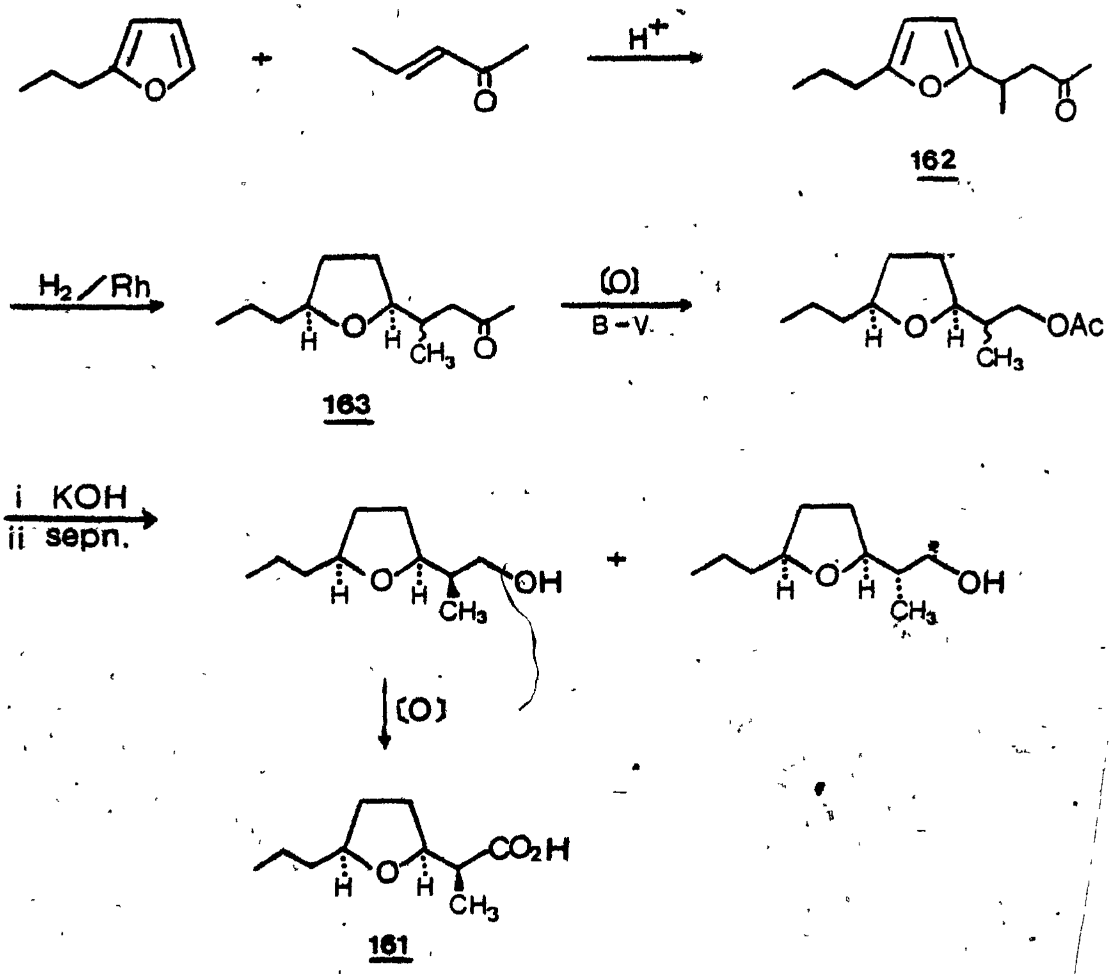
(O) Monactin: $R^1 = R^3 = R^4 = Me,\ R^2 = Et$

(P) Dinactin: $R^1 = R^3 = Me,\ R^2 = R^4 = Et$

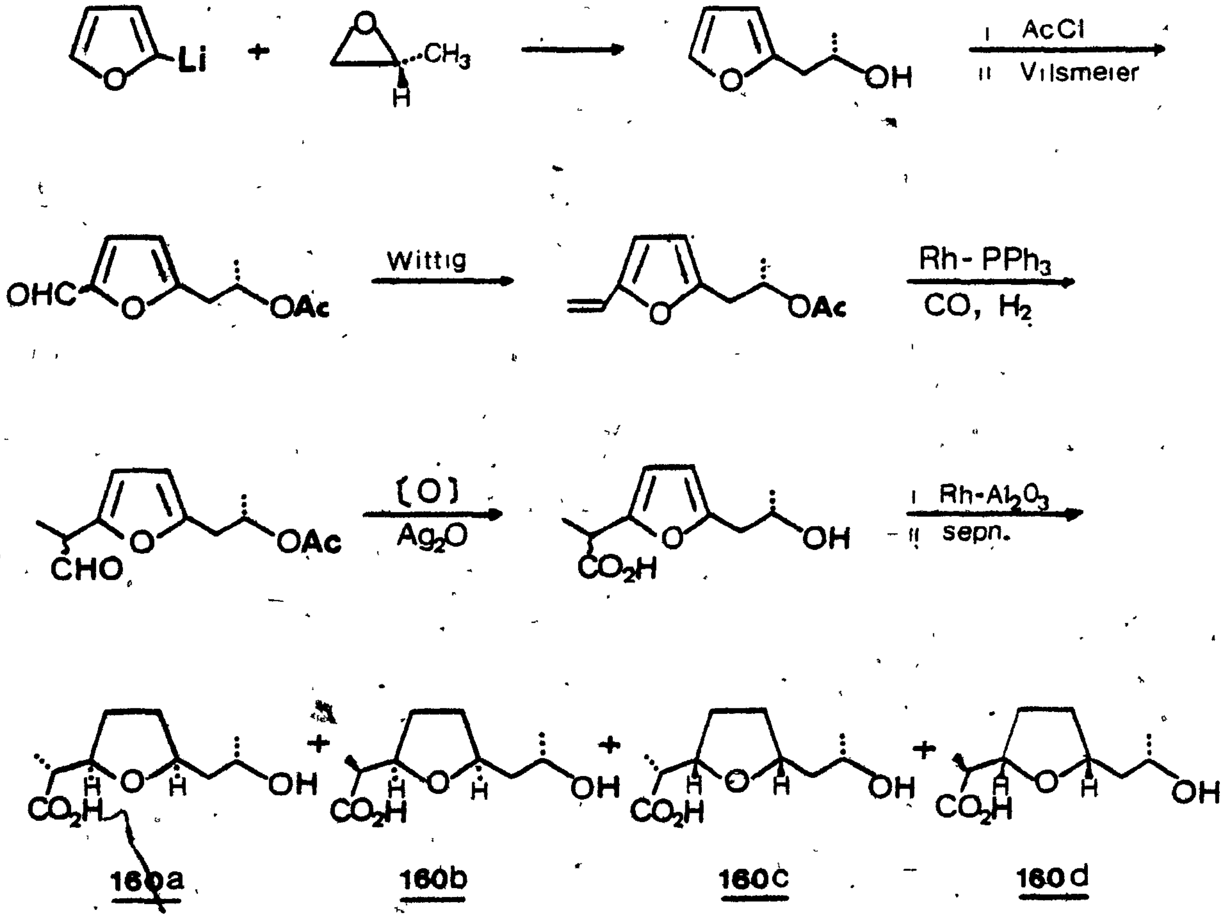
(Q) Trinactin: $R^1 = Me,\ R^2 = R^3 = R^4 = Et$

(R) Tetranactin: $R^1 = R^2 = R^3 = R^4 = Et$

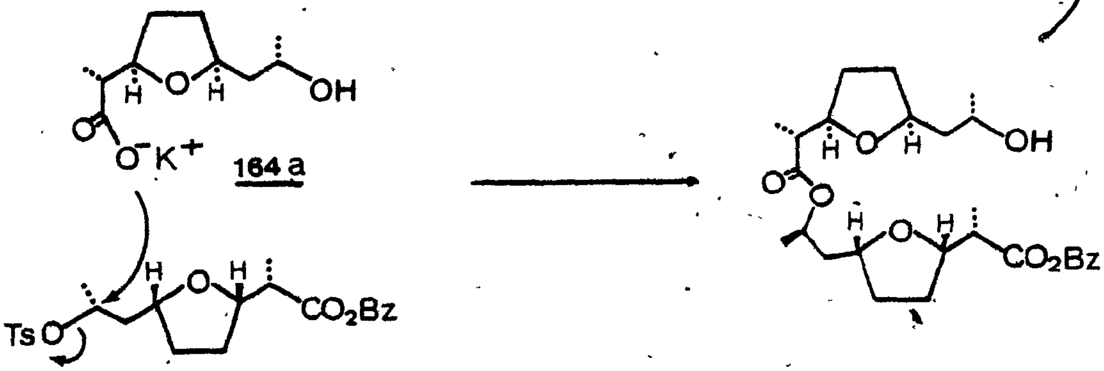
Therefore, nonactic acid 160 can be considered as the monomer of nonactin (N). H. Gerlach and E. Huber[158] reported that 8-deoxynonactic acid (161), a degradation product of the antibiotic nonactin, had been synthesized as depicted below. Rhodium catalyzed hydrogenation of furan derivative 162 gave only *cis*-tetrahydrofuran derivatives 163. This method was, in fact, quite useful for the nonactin synthesis because of its stereoselectivity.



Several years later, Schmidt *et al.*[159] reported that methyl-(-)-(2R,3R,6S,8S)-nonactate (ester of 160a) was prepared by using optically active propylene oxide and furan as depicted. The mixture of 160a and 160b was separated by chromatography and the ratio of 160a to 160b was about 4:1.



Subsequently, these epimers (160a ∿ 160d) were used[160] for the synthesis of nonactin. The intermolecular condensation between the potassium salt of (-)-nonactic acid (164a) and the 8-tosylate of 8-epi-(+)-nonactic acid benzyl ester (164c) derived from 8-epi-(+)-nonactic acid (160c) gave 8-epi-(-)-nonactinyl-(+)-nonactic benzyl ester (164) as dimer, involving the inversion at the position of tosyl group.

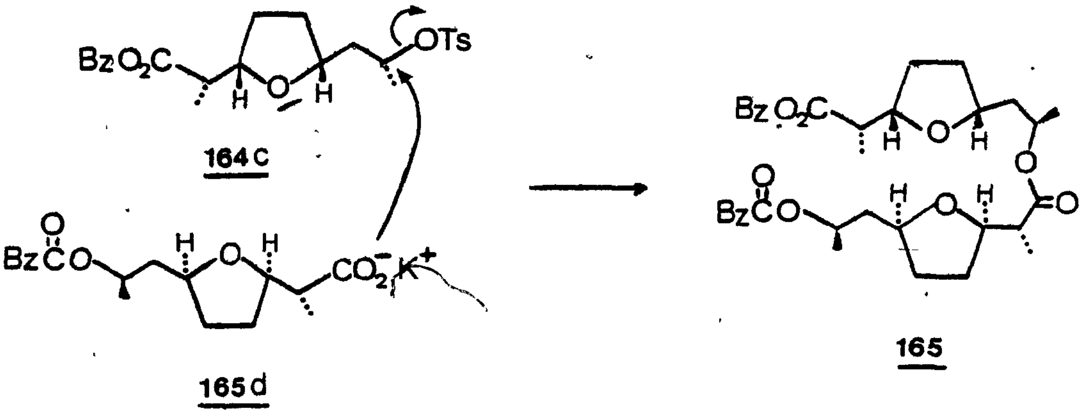


164a

164C

164

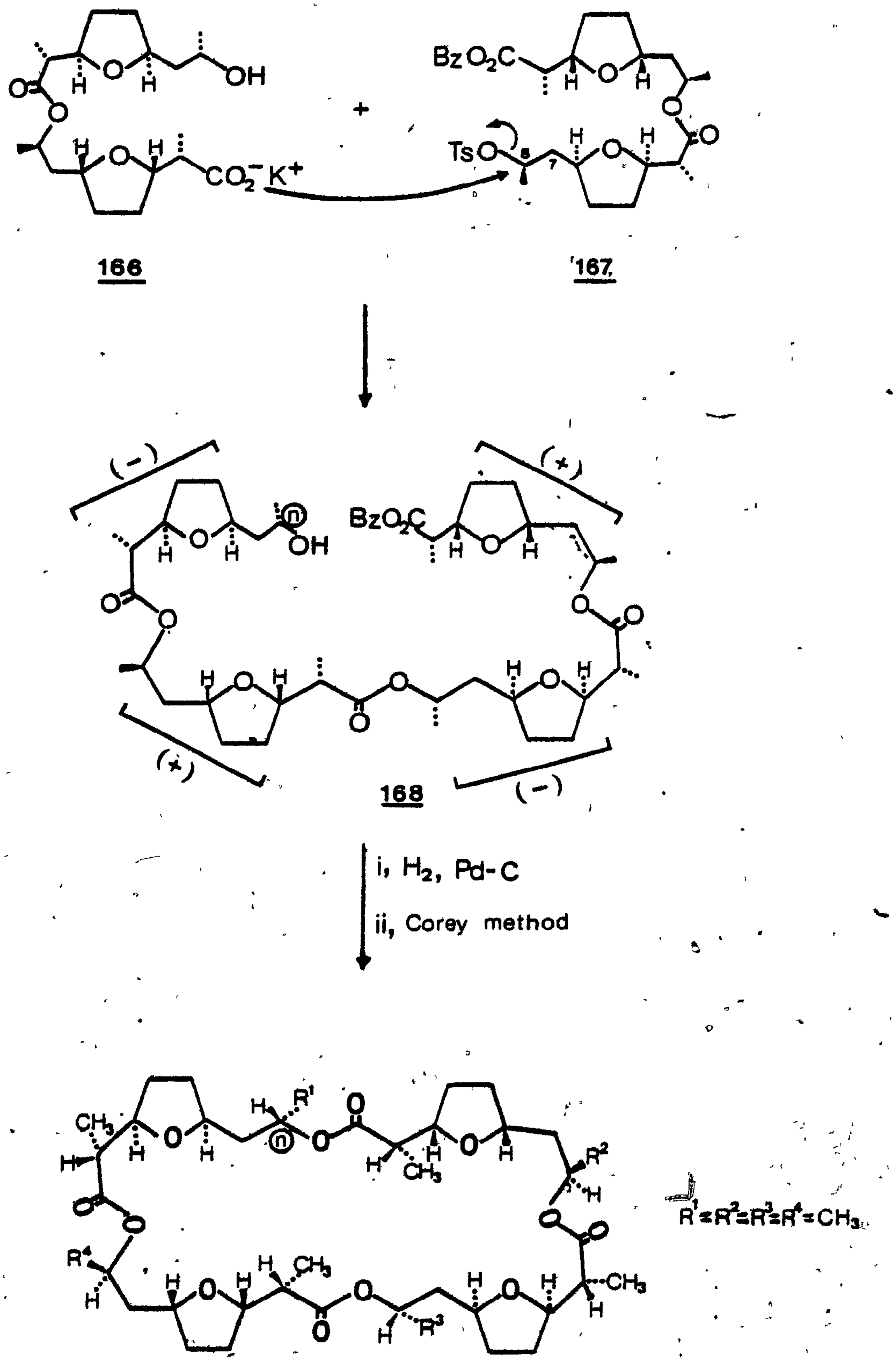
In the same way, dimerization of 164c and the benzyl ester of 8-epi-(-)-nonactic acid potassium salt (165d) derived from 8-epi-nonactic acid (another enantiomer of 160d) gave 8-epi-(-)-nonactinyl-(+)-nonactic acid benzyl ester (165).



The potassium salt (166) of hydrolysed acid obtained from 164 and the 8-tosylate (167) of 165 combined to give (-)-nonactinyl-(+)-nonactinyl-(-)-nonactinyl-(+)-nonactic acid benzyl ester (168) as depicted.

Finally, in order to retain the S-configuration at n , treatment[161] of the hydrogenolysis product of 168 with 2,2'-dipyridyl disulfide and triphenyl phosphine in benzene afforded the tetramer, nonactin (169).

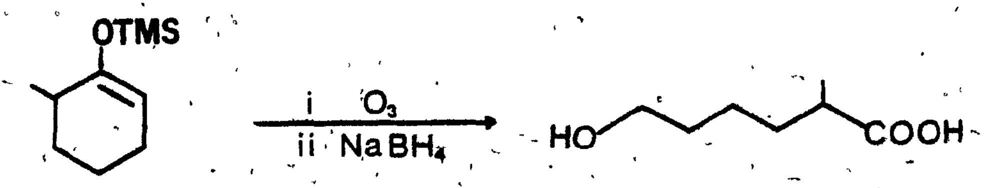
As investigated above, whatever the configuration at C-2 in nonactic acid 160 is, it can alternately be applied to the nonactin synthesis. We have already obtained the exo-methylated enolic compound 152 and the endo-methylated keto compound 153. The methyl groups α to the ester groups in nonactin are alternately arranged and configuration at C-8 in nonactic acid can be readjusted with reaction conditions.



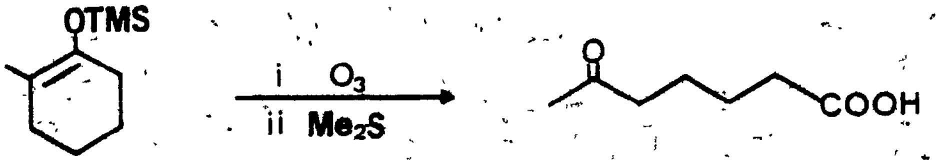
Nonactin (**169**)

Accordingly, we decided to carry out the ozonolysis of 152 and the Baeyer-Villiger reaction of 153 to see if the lactone 159 can be obtained as shown in Scheme 8.

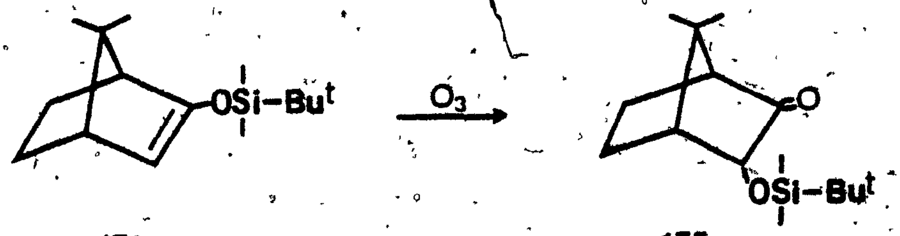
Heathcock *et al.*[162] have found that siloxyalkenes 170 and 171 were ozonized to give hydroxyacid 172 and ketoacid 173 and when the enol silyl ether 174 of camphor was ozonized, it however yielded the silylated α-hydroxyketone 175 rather than a cleavage product.



170 **172**

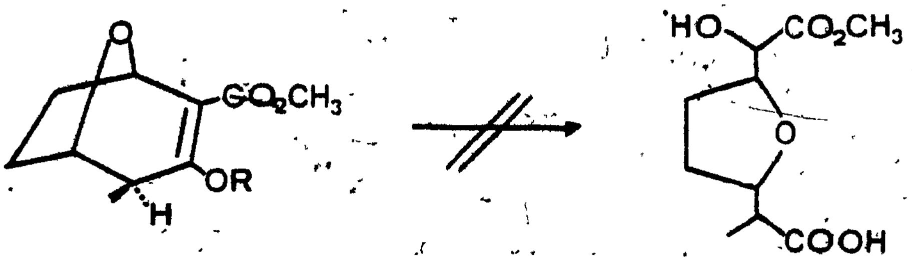


171 **173**



174 **175**

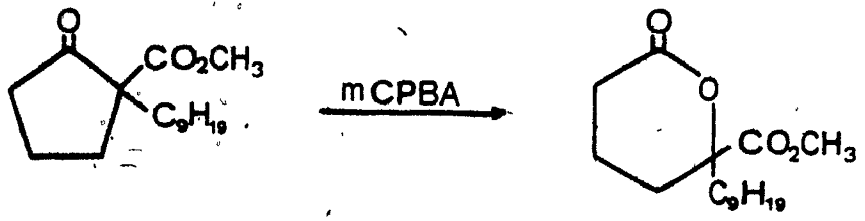
In the same way, ozonolysis of 154 or 155 was carried out in CH_2Cl_2-MeOH solution at -40°C and then worked up with $NaBH_4$ or Me_2S to give a complicated mixture of products. Unfortunately, we could not purify and identify any structure. Moreover, this reaction was carried out under a variety of conditions such as room temperature, 0°C or -78°C and also in several solvents such as methylene chloride, methanol or THF. The reactions were still unsuccessful.



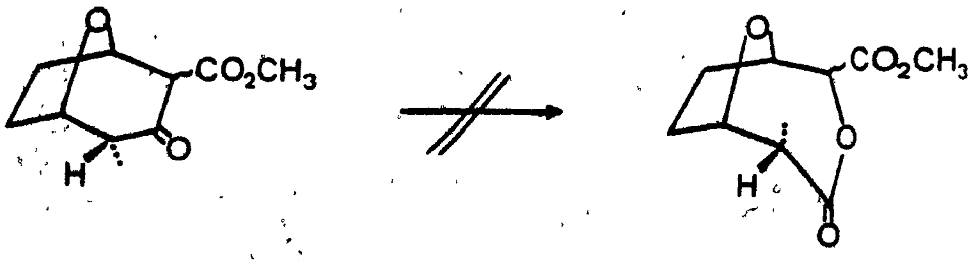
154 R = TMS
155 Ac

176

Alternatively, since it was recently reported[163] that the oxidation product 177 of 176 was obtained in good yield, the Baeyer-Villiger oxidation of 153 was also attempted. It didn't however give any of the lactone 178.

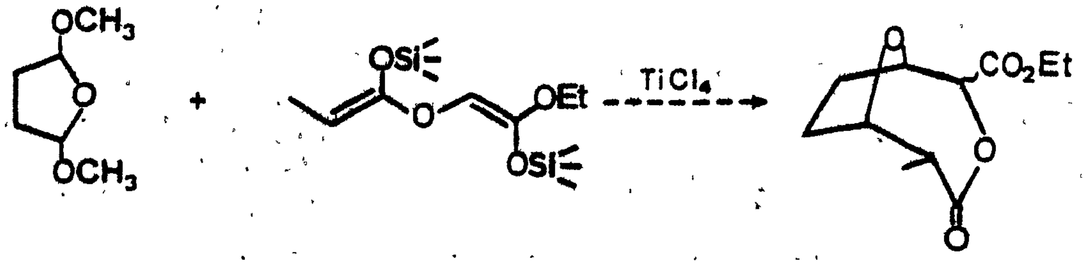


176 **177**



153 **178**

This led us to consider a different, and perhaps shorter approach for the construction of the bicyclic lactone 180 according to the following scheme; similar to the reaction of enol silyl ether 150 with 1, *viz*, the reaction of 179 with 1.



1 **179** **180**

CHAPTER VII

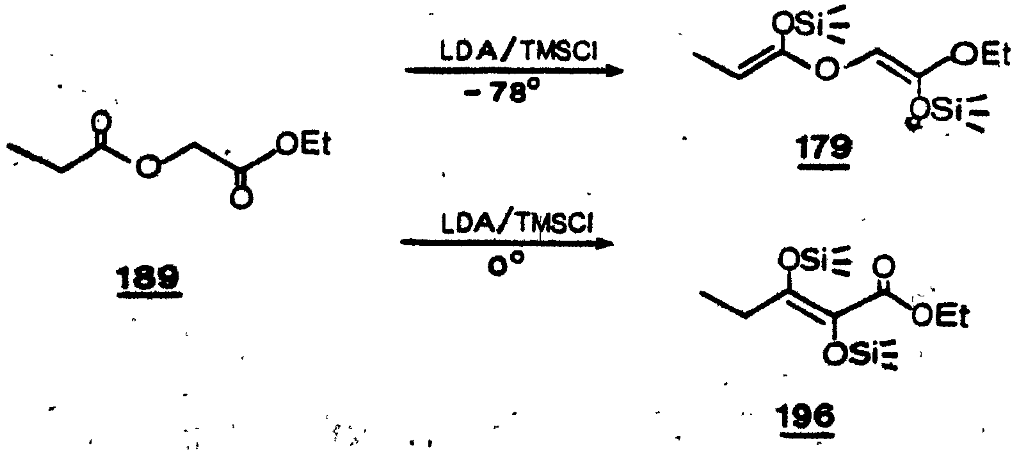
A NEW REARRANGEMENT OF α-ACYLOXY ACETATE INTO 2-HYDROXY-3-KETO ESTER

In order to test the above approach (p. 111), a number of α-acyloxy esters have been prepared. Those compounds (189-195) were prepared by the treatment of carboxylic acids (182-188) with ethyl bromoacetate 181 and anhydrous potassium carbonate in refluxing acetone[164,165].

182	R = Et	189
183	= Me	190
184	= $CH_2(CH_2)_3CH_3$	191
185	= $(CH_2)_6$	192
186	= Ph	193
187	= CH_2Ph	194
188	= $CH(CH_3)CH_2CH_2CH_3$	195

When ester 189 was treated with 2 equiv. of LDA and then quenched with TMSCl at -78°C, the *bis*-enol silyl ether 179 was obtained. Its ^{1}H nmr spectrum showed a single isomer about C 4-5, and a roughly 3:1 (E/Z) mixture of isomers about C 1-2; δ ($CDCl_3$), 5.67$^{\underline{Z}}$ and 5.33$^{\underline{E}}$ (1H, each s, -O-$\underline{CH}$=), 4.23 (m, 1H, $CH_3\underline{CH}$=), 3.76 (m, $O\underline{CH_2}CH_3$), 1.56 (m, $\underline{CH_3}CH$=), 1.3 (m, $-OCH_2\underline{CH_3}$), 0.18 (s, $-OSiMe_3$). The ir spectrum showed olefinic absorption at 1685 cm^{-1} without carbonyl stretching frequencies.

In contrast with this, when the reaction was performed at 0°C, unexpectedly, the disiloxy vinyl ester 196 was obtained in 87% yield. Spectral data of 196 are as follows: in ^{1}H nmr, δ ($CDCl_3$), 4.22 (q, $O-\underline{CH_2}-CH_3$), 2.63 (q, $\underline{CH_2}-CH_3$), 1.31 (t, $O-CH_2-\underline{CH_3}$), 1.1 (t, $-CH_2-\underline{CH_3}$), 0.23 (s, $-OSiMe_3$), 0.17 (s, $-OSiMe_3$); in ir (neat), 1710 cm^{-1} for C=O stretching, and 1620 cm^{-1} for olefinic stretching frequency; in ms, m/z = 304 (M^+) and 259 (M^+-OEt). It is

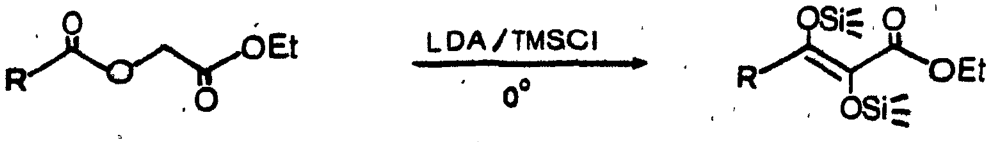


clear from the ^{1}H nmr spectrum that both the ethyl and the ethoxy groups are intact as triplets and quartets without adjacent vinylic proton peaks.

As mentioned in the previous chapter, *bis*-enol silyl ether 179 was deemed suitable for the formation of the bicyclic compound 180.

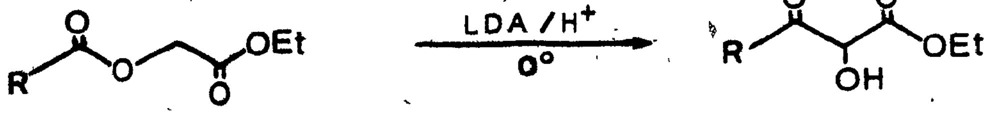
Based on this idea, the reaction of 179 with 1 was attempted in the presence of 2 equiv. of titanium tetrachloride at -78°C. No desired product 180 was obtained. Variation of reaction conditions, *e.g.* when 1 equiv. of $TiCl_4$ was used, did not lead to any meaningful or identifiable products.

Accordingly, the reaction was suspended at this stage and further investigations into the α-acyloxy ester rearrangement process were performed. First, we had to establish the generality of the rearrangement process. Indeed, several disiloxy vinyl esters (197-199) were obtained in the same way.



191	R = $CH_2(CH_2)_3CH_3$	197
192	R = $(CH_2)_6$	198
195	R = $CH(CH_3)CH_2CH_2CH_3$	199

When the reaction was quenched with 0.1 N HCl instead of TMSCl, the corresponding 2-hydroxy-1,3-diketo esters (200-203) were obtained. 2-Hydroxy-1,3-diketo ester 200 was also identical to the desilylated product of disiloxy vinyl ester 196 by treatment with dilute HCl solution in THF.

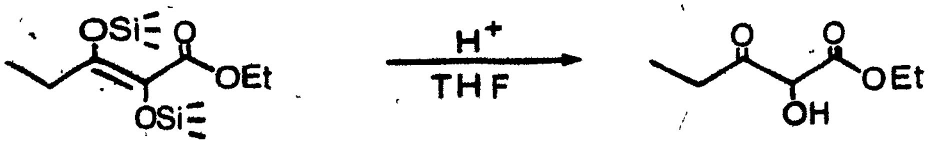


R = Et 200

= $CH_2(CH_2)_3CH_3$ 201

= $(CH_2)_6$ 202

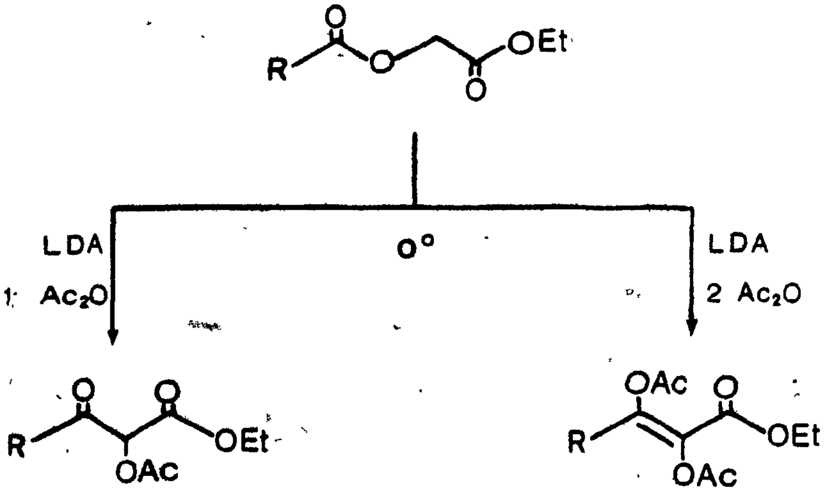
= $CH(CH_3)CH_2CH_2CH_3$ 203



196

200

When quenched with acetic anhydride, the corresponding 2-acetoxy-1,3-diketo esters, (204-207) or diacetoxy vinyl esters (208,209) were obtained, depending on the amount of acetic anhydride used.



R = Et	204	R = $(CH_2)_6$	208
= $CH_2(CH_2)_3CH_3$	205	= $CH(CH_3)CH_2CH_2CH_3$	209
= $(CH_2)_6$	206		
= $CH(CH_3)CH_2CH_2CH_3$	207		

In the examples of 203 and 207, the 200 MHz ^1H nmr spectra indicated that they are mixtures of the diastereomers due to the presence of two chiral centers in the molecule as depicted. For example, in compound 203 (Fig. 10), two singlet

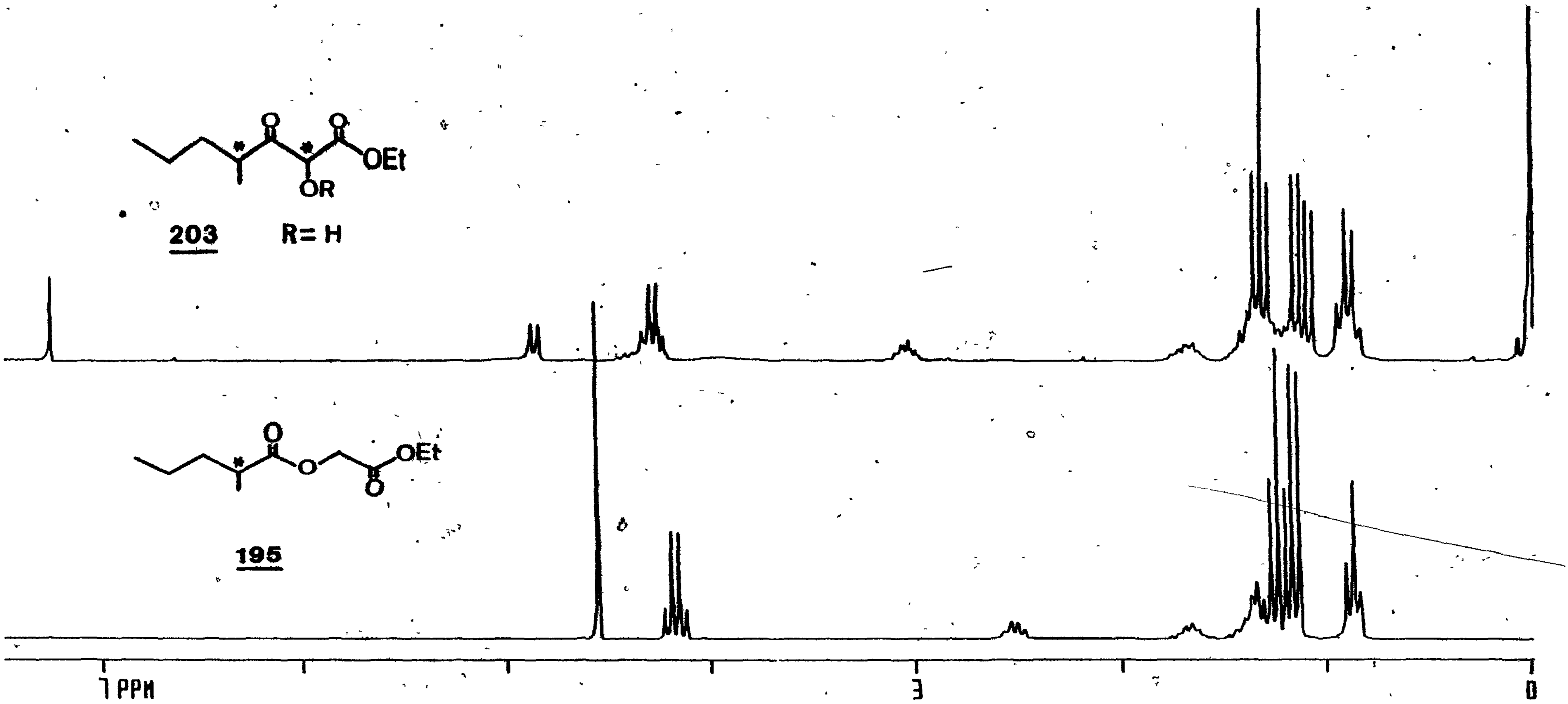
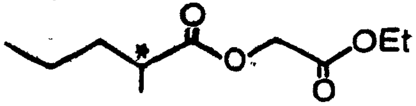
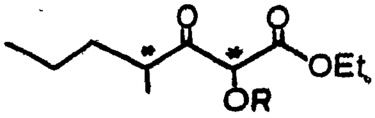


Fig. 10: 200 MHz ^{1}H nmr spectra of 195 and 203



195

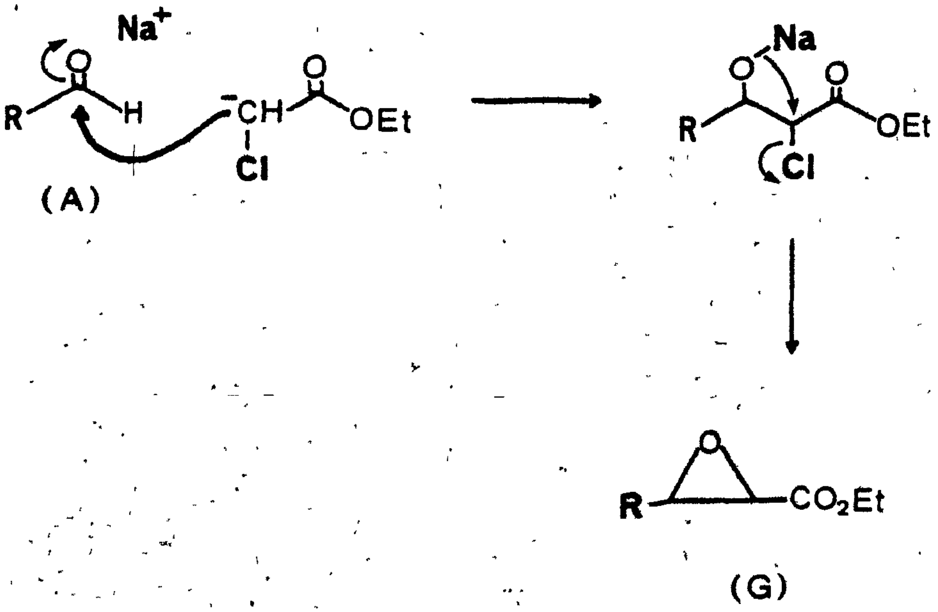


203 R= H

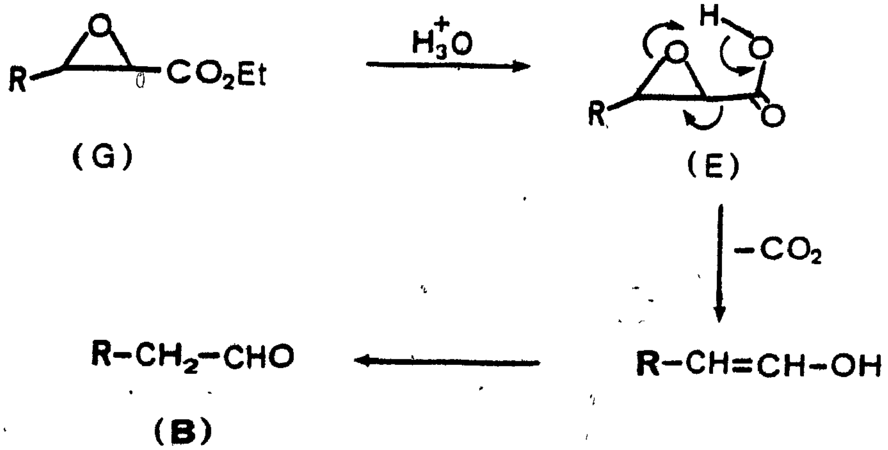
207 Ac

peaks are observed for the methine protons at C-2 and two doublets for the methyl peaks at C-4.

From the above investigations, the reaction seems to be similar to the Darzens[166,167] glycidic ester condensation. The Darzens reaction is an intermolecular condensation of an α-halo ester with an aldehyde (or ketone) in the presence of sodium alkoxide or sodium amide to give glycidic ester G as depicted. The glycidic esters are of

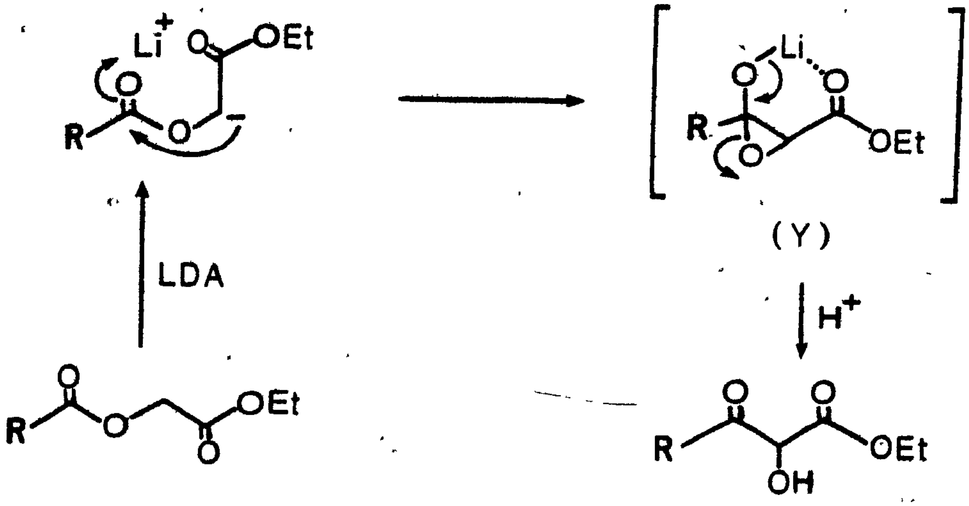


interest primarily because they can be further converted into aldehydes and ketones (B) having a higher content than the original aldehydes or ketones (A). This



transformation occurs after hydrolysis to the epoxy acids (E), followed by decarboxylation.

In comparison with this, the present rearrangement seems to be an intramolecular aldol-type reaction *via* the α,β-epoxy ester intermediate (Y). One might postulate that the mechanism of the rearrangement process is as follows:



This new rearrangement reaction of α-acyloxyacetates seems to be quite interesting because it offers a new approach to the synthesis of 2-functionalized 1,3-diketo esters.

CHAPTER VIII

CONTRIBUTIONS TO KNOWLEDGE

1. Unexpected site selectivity in the reactions of 2,5-dimethoxy THF and 2,6-dimethoxy THP with halotrimethylsilanes was observed, thereby producing 1,4-dihalo-1,4-dimethoxybutane and 1,5-dihalo-1,5-dimethoxypentane. The reactions of related cyclic ethers were also examined.

2. It was shown that 1,4-dichloro-1,4-dimethoxybutane was a mild reagent for the conversion of primary amines to pyrroles.

3. The synthesis of 2-(2-formylpyrrol-1-yl)-4-methyl pentanoic acid, a compound isolated from flue-cured tobacco, was described. A selective formylation reaction at the 2-position of pyrrole was also developed.

4. The preparation of α-substituted derivatives from the pyrroles of amino acid esters was achieved by using LiHMDS as base.

5. Synthesis of N-acylpyrroles from primary amides was developed. The use of acylpyrroles as active acylating agents was investigated.

6. The configurations at C-4 in bicyclic enol form <u>152</u> and keto form <u>153</u> were determined with the aid of 200 MHz ^{1}H nmr decoupled spectra. The potential of this approach to the synthesis of nonactin was investigated.

7. A new rearrangement of α-acyloxy esters into 2-hydroxy-3-keto esters was found.

CHAPTER IX

EXPERIMENTAL

Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Likewise, boiling points obtained were uncorrected.

Mass spectra (ms) were obtained on a DuPont 21-492B mass spectrometer, by the direct insertion probe or the batch inlet.

Gas chromatograms were performed on a Hewlett-Packard 5730 A Gas Chromatograph: 10' x 1/8" stainless steel column was used; 6% OV-101, chromosorb W 80/100 mesh.

Proton magnetic resonance (^1H nmr) spectra were recorded on Varian T-60, T-60A, and XL-200 spectrometers, using tetramethylsilane (TMS) or chloroform as an internal standard. Chemical shifts were given in the δ scale in parts per million (ppm). Doublet (d), triplet (t), quartet (q) and multiplet (m) were recorded at the center of the peaks; other abbreviations used are singlet (s) and broad (b). ^{13}C nmr spectra were recorded on XL-200 or Bruker WH-90 spectrometers.

Infrared spectra (ir) were obtained on a Perkin Elmer 297 Spectrophotometer. Spectra were calibrated with the 1601 cm^{-1} or 1028 cm^{-1} band of polystyrene film.

Ultraviolet-visible (uv-vis) spectra were recorded on a Unicam SP. 800 Ultraviolet Spectrophotometer.

Analytical thin layer chromatography (tlc) was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in C-H_2SO_4/H_2O (10 mL/90 mL) and heating on a hot plate. Merck Silica (Kieselgel 60, 40-63 μ) was used for flash column chromatography[50] and Kieselgel 60 HF_{254} for TLC-mesh[155] chromatography.

Solvents were reagent grade unless otherwise specified. THF was dried over Na and benzophenone, benzene over Na, CH_3CN, diisopropylamine and triethylamine over CaH_2, CH_2Cl_2, $CHCl_3$ and hexane over P_2O_5, methanol over Mg, DMSO over NaOH, and distilled prior to use. All evaporations were carried out under reduced pressure (water aspirator) with a bath temperature of 25° ∼ 40°C.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Elemental analyses were performed by Guelph Chemical Lab. Ltd., Guelph, Ontario, Canada.

2,5-*Bis*(trimethylsiloxy)furan derivatives[44] 24 and 31

Dry triethylamine (0.16 mol, 16 g) and zinc chloride (0.5 g) were stirred vigorously under N_2 atmosphere for 1 hr, giving a fine suspension. Succinic anhydride (50 mmol) in dry acetonitrile (40 mL) was added, followed after 5 mins by excess chlorotrimethylsilane (18 mL). After the mixture was stirred overnight, 200 mL of dry ether was added. The mixture was filtered and concentrated. The residue was diluted with dry hexane (300 mL) and cooled to precipitate any remaining solid. It was filtered and the filtrate was concentrated to give a product, as a slightly yellowish oil.

Compound 24: Yield 95%; ^1H nmr ($CDCl_3$), δ: 1.8 (s, 6H), 0.26 (s, 18H, $SiMe_3$).

Compound 31: Yield 97%; ^1H nmr ($CDCl_3$), δ: 0.23 (s, 18H), 1.73 (s, 3H), 4.80 (s, 1H).

The reaction of 3-methyl-2,5-*bis*(trimethylsiloxy)furan (31) with 2,5-dimethoxytetrahydrofuran (1) to give 32.

To a solution of the acetal (5 mmol, 0.66 g) in dry methylene chloride (15 mL) at -78°C under N_2 atmosphere was added titanium tetrachloride (5 mmol, 0.55 mL). A solution of enol silyl ether (5 mmol, 1.29 g) in CH_2Cl_2 (25 mL) was added dropwise over 20 mins and stirring at -78°C continued for 3 hrs. The reaction mixture was quenched with 2 mL of saturated sodium bicarbonate solution and stirred for 15 mins. The solution was extracted with ether, dried over anhydrous magnesium sulfate, evaporated under reduced pressure and the residue was separated by flash column chromatography using ethylacetate-petroleum ether (1:4) as eluent to give the products as four diastereomers (denoted as I, II, III, and IV).

Isomers I and II: (R_f = 0.5 ∿ 0.51, yield 31.2%); ^{1}H nmr ($CDCl_3$), δ: 5.77 (m, vinylic Hs), 4.92 and 5.08 (bd, J = 4.6 Hz, anomeric Hs), 4.20 and 4.0 (dd, J = 4.8 Hz, quart. Hs), 3.25 and 3.3 (s, OCH_3 each), 2.04 and 2.12 (d, J = 1.8 and 1.4 Hz, vinylic CH_3 each), 2.05 (m, 4H each), 0.12 and 0.11 (s, $OSiMe_3$ each); ^{13}C nmr ($CDCl_3$), δ: 170.45 and 167.38, 118.18 and 117.80, 108.31, 106.42, 81.87, 78.42, 55.01 and 54.79, 31.92 and 31.33, 24.80 and 23.77, 14.06 and 12.82, 1.17; ms, m/z (rel. intensity), 255 (M^+-OMe, 3.7), 186 (35.8), 183 (5.3), 101 (100), 69 (68.3), 59 (19.9), 41 (21.0); ir (film), ν_{max}: 3040 ∿ 2800, 1780 (lactone), 1650 (olefin), 845 cm^{-1} ($OSiMe_3$); uv, λ_{max}: 220 ∿ 222 nm (95% EtOH, ε = 10200); glc (10 ft, 5% OV-101 column (o.d. 1/8"), column temp. 100-250°C), ret. time 8.28 mins and 8.49 mins.

Isomer III: (R$_f$ = 0.43, yield 11.2%); ^{1}H nmr (CDCl$_3$), δ: 5.77 (q, J = 1.6 Hz, 1H), 4.95 (bd, 1H), 4.0 (dd, J = 6 Hz, 1H), 3.26 (s, OCH$_3$), 2.17 (d, J = 1.5 Hz, vinylic CH$_3$), 1.95 (m, 4H), 0.13 (s, OSiMe$_3$); ^{13}C nmr (CDCl$_3$), δ: 169.98, 118.09, 105.41, 87.87, 83.78, 78.38, 54.32, 32.64, 25.54, 13.97, 1.08; ms, m/z (rel. intensity), 183 (7.2), 101 (100), 69 (75.2), 59 (16.4), 41 (21.4); ir (film), ν_{max}: 3000 ∿ 2800, 1775 (lactone), 1648 (olefin), 845 (OSiMe$_3$); uv, λ_{max}: 216 nm (95% EtOH); glc (10 ft, 5% OV-101 column (o.d. 1/8"), column temp. 100-250°C) ret. time, 8.79 mins.

Isomer IV: (R$_f$ = 0.35, yield 10.6%); ^{1}H nmr (CDCl$_3$), δ: 5.79 (q, J = 1.7 Hz, 1H), 4.9 (bd, 1H), 4.17 (dd, J = 6 Hz, 1H), 3.16 (s, OCH$_3$), 2.05 (d, J = 1.7 Hz, vinylic CH$_3$), 2.01 (m, 4H), 0.11 (s, OSiMe$_3$); ^{13}C nmr (CDCl$_3$), δ: 167.77, 117.82, 107.46, 106.0, 87.88, 80.54, 54.97, 32.58, 24.11, 12.62, 1.08; ms, m/z (rel. intensity), 186 (3.1), 183 (7.9), 101 (100), 69 (59.3), 59 (12.3), 41 (11.3); ir (film), ν_{max}: 3020 ∿ 2800, 1780 (lactone), 1659 (olefin), 850 (OSiMe$_3$); uv, λ_{max}: 214 nm (95% EtOH); glc (10 ft, 5% OV-101 column (o.d. 1/8"), temp. 100-250°C), ret. time, 8.30 mins.

The reaction of 24 with 1 was not successful. The resultant compound was, however, maleic anhydride (30), air oxidation product of 24.

Compound 30: ^1H nmr ($CDCl_3$), δ: 2.1 ppm (s, CH_3); ms, m/z (rel. intensity), 126 (M^+, 80.9), 82 (M^+-CO_2, 100); mp = 91 ∿ 93°C (lit.[49] 93 ∿ 96°C).

The reaction of propylene oxide with TMSCl to give 1-(2-chloro)propyl and 2-(1-chloro)propyl trimethylsilyl ethers (36a and 36b)

To a solution of propylene oxide (10 mmol, 0.58 g) in dry chloroform (10 mL) was added TMSCl (15 mmol, 1.9 mL) dropwise at 0°C under N_2 atmosphere. After the reaction mixture was stirred at room temperature for 30 hrs, the solution was concentrated *in vacuo* to give a colorless liquid as product in 82% yield. The ratio of 36a to 36b was about 1:4 according to ^1H nmr spectrum and the mixture was not separated. ^1H nmr ($CDCl_3$), δ: 3.9 (m, 1H), 3.35 (d, 2H), 1.25 and 1.45 (d, 3H), 0.8 (s, 9H); ms, m/z (rel. intensity), 153 (28.9), 151 (M^+-CH_3, 66.4), 130 (M^+-HCl, 27.6), 95 (52.9), 93 (M^+-TMS, 100).

The reaction of oxetane with TMSCl to give 3-chloropropyl trimethylsilyl ether (38)

The same procedure as above except that 5 equiv. of TMSCl was used and the reaction time was 2 days. Yield 92%; ^{1}H nmr ($CDCl_3$), δ: 3.72 (t, 2H), 3.61 (t, 2H), 1.95 (m, 2H), 0.13 (s, 9H).

Preparation[45] of 2-methoxytetrahydropyran (44) and 2,6-dimethoxytetrahydropyran (52)

To a solution of dihydropyran (0.1 mol) in 50 mL of CH_2Cl_2 was added a catalytic amount of p-toluenesulfonic acid[45] and 0.11 mol (3.5 g) of absolute methanol. After refluxing for 4 hrs, 0.5 g of K_2CO_3 was added. The mixture was allowed to cool to room temperature and the solution was then concentrated. The residue was diluted with ether, washed with water, dried over anhydrous potassium carbonate and then evaporated *in vacuo* to give a product.

Compound 44: Yield 95%; ^{1}H nmr ($CDCl_3$), δ: 4.46 (m, 1H), 3.73 (m, 2H), 3.37 (s, 3H), 1.63 (m, 6H); ms, m/z (rel. intensity), 116 (M^+, 1.3), 85 (27.9).

Compound 52: Yield 87%; bp = 81 ∿ 83°C/12 mm. The ratio of *cis* to *trans* was about 1:9 by ^{1}H nmr spectrum. ^{1}H nmr ($CDCl_3$), δ: (for *cis* and *trans*) 4.46 and 4.76 (m, 2H), 3.51 and 3.45 (s, 6H), 1.72 (m, 4H), 1.52 (m, 2H); ^{13}C nmr ($CDCl_3$), δ: (for *cis* and *trans*) 100.52 and 98.09, 55.26 and 54.72, 29.85 and 29.63, 17.77 and 16.96; ms, m/z (rel. intensity), 115 (M^+-OCH_3, 4.1), 71 (41.3), 58 (100).

Preparation of 2-halotetrahydrofurans (45, 63) and 2-bromotetrahydropyran (46)

To a solution of 2-methoxytetrahydrofuran or pyran (10 mmol) in dry chloroform (10 mL) under N_2 atmosphere at 0°C was added 20 mmol (2.6 mL) of bromotrimethylsilane. The reaction mixture was allowed to warm to room temperature. After 4 hrs, the solution container was directly connected to a water-aspirator to concentrate the solution and finally *in vacuo* (0.5 mm) to give a pale yellowish liquid as product.

Compound 46: Yield 60%; ^{1}H nmr ($CDCl_3$), δ: 6.8 (b, 1H), 3.9 (m, 2H), 2.0 (m, 6H); ^{13}C nmr ($CDCl_3$), δ: 95.22, 63.87, 35.98, 24.76, 18.02.

Compound 45: Yield 75%; ^{1}H nmr ($CDCl_3$), δ: 6.75 (m, 1H), 4.15 (m, 2H), 2.20 (m, 4H); ^{13}C nmr ($CDCl_3$), δ: 95.59, 70.13, 40.08, 21.63.

Compound 63: The same procedure except that the reaction time was 3 days and 5 equiv. of chlorotrimethylsilane was used. Yield 25%; ^{1}H nmr ($CDCl_3$), δ: 6.30 (b, 1H), 3.80 (m, 2H), 2.30 (m, 4H).

The reaction of <u>44</u> with TMSCL did not take place.

Preparation of 1,4-dihalo-1,4-dimethoxybutanes (47-49) and 1,5-dihalo-1,5-dimethoxypentanes (53-55)

The solution of 2,5-dimethoxy THF (or 2,6-dimethoxy THP) (10 mmol) in dry chloroform (20 mL) was cooled to -78°C. To the solution was added TMSX (22 mmol) dropwise under N_2 atmosphere. The reaction mixture was stirred at 0°C for 2 hrs. The solvent was removed *in vauco* to give a pale yellowish oil as product in quantitative yield.

<u>1,4-dibromo-1,4-dimethoxybutane (47)</u>: ^{1}H nmr ($CDCl_3$), δ: 5.92 (m, 2H), 3.45 (s, 6H), 2.40 (m, 4H); ^{13}C nmr ($CDCl_3$), δ: 97.88, 59.38, 36.81.

<u>1,4-diiodo-1,4-dimethoxybutane (48)</u>: ^{1}H nmr ($CDCl_3$), δ: 6.22 (m, 2H), 3.43 (s, 6H), 2.38 (m, 4H).

<u>1,4-dichloro-1,4-dimethoxybutane (49)</u>: The same procedure except that the reaction time was 2 days and 10 equiv. of TMSCl was used. Yield 86%; bp = 71 ∿ 74°C/0.8 mm; ^{1}H nmr ($CDCl_3$), δ: 5.50 (m, 2H), 3.45 (s, 6H), 2.25 (m, 4H); ^{13}C nmr ($CDCl_3$), δ: 99.87, 57.47, 34.54.

1,5-dibromo-1,5-dimethoxypentane (53): ^1H nmr ($CDCl_3$), δ: 5.85 (t, 2H), 3.40 (s, 6H), 2.10 (m, 4H), 1.70 (m, 2H); ^{13}C nmr ($CDCl_3$), δ: 99.10, 59.39, 39.97, 22.44.

1,5-diido-1,5-dimethoxypentane (54): ^1H nmr ($CDCl_3$), δ: 6.10 (t, 2H), 3.25 (s, 6H), 2.10 (m, 4H), 1.80 (m, 2H).

1,5-dichloro-1,5-dimethoxypentane (55): The same procedure except that the reaction time was 3 days and 10 equiv. of TMSCl was used. Yield 84%; bp = 81 ∿ 83°C/0.8 mm; ^1H nmr ($CDCl_3$), δ: 5.48 (t, 2H), 3.43 (s, 6H), 1.97 (m, 6H); ^{13}C nmr $CDCl_3$), δ: 100.57, 57.63, 38.75, 20.46.

Preparation of 1,1,5,5-tetramethoxypentane (50b) from 3,4-dihydro-2-methoxy-2H-pyran

To a solution of 3,4-dihydro-2-methoxy-2H-pyran in 30 mL of absolute methanol was added a catalytic amount of p-toluenesulfonic acid. After refluxing overnight, 0.5 g of potassium carbonate was added and allowed to cool to room temperature. The solution was concentrated, diluted with ether, washed with water, dried over anhydrous potassium carbonate, and then evaporated *in vacuo* to give product in 86% yield; bp = 101 ∿ 102°C/12 mm; ^1H nmr ($CDCl_3$), δ:

4.3 (t, 2H), 3.26 (s, 12H), 1.54 (m, 4H), 1.35 (m, 2H); ^{13}C nmr ($CDCl_3$), δ: 104.22, 52.44, 32.10, 19.65; ms, m/z (rel. intensity), 128 (M^+-2MeOH, 79), 127 (41.5), 97 (83)[45].

Preparation of α,α,ω,ω-tetramethoxyalkanes 50a and 50b from the corresponding dichloro-dimethoxy compounds 49 and 55

A solution of dichloro-dimethoxy compound 49 or 55 (10 mmol) in 30 mL of dry methanol was stirred at 0°C for 1 hr under N_2 atmosphere. After the reaction mixture was refluxed overnight, the solvent was removed under reduced pressure. The residue was partitioned between ether and water. The organic layer was dried over anhydrous potassium carbonate, filtered and then concentrated *in vacuo* to give the corresponding tetramethoxy compound as product in quantitative yield.

1,1,4,4-tetramethoxybutane (50a): ^1H nmr ($CDCl_3$), δ: 4.3 (m, 2H), 3.23 (s, 12H), 1.57 (m, 4H); ^{13}C nmr ($CDCl_3$), δ: 104.1, 52.5, 27.4.

1,1,5,5-tetramethoxypentane (50b): The spectroscopic data for this compound were identical with those obtained by diacetalization of 3,4-dihydro-2-methoxy-2H-pyran (p. 132).

The reaction of 2-methyl THF with TMSBr to give 2-(5-bromo)-pentyl trimethylsilyl ether (60)

The same procedure as that in the case of propylene oxide (p. 128). Yield 84%; ^{1}H nmr ($CDCl_3$), δ: 3.75 (m, 1H), 3.35 (t, 2H), 1.7 (m, 4H), 1.14 (d, 3H), 0.15 (s, 9H).

A typical procedure for the conversion of primary amines to N-substituted pyrroles (74, 80-82)

To a solution of primary amine (5 mmol) in dry methylenechloride (30 mL) was added the dichloro compound 49 (6 mmol, 1.13 g) dropwise at 0°C under N_2 atmosphere. To the mixture, 3 g of Amberlyst A-21 resin[73] was added. The reaction mixture was allowed to warm to room temperature. After stirring overnight, the mixture was filtered on a fine-sintered glass filter and the filtrate evaporated *in vacuo*. The product was purified by flash column chromatography using hexane-ethylacetate as eluent.

N-benzyl pyrrole (74)[168]: Yield 90%; ^{1}H nmr ($CDCl_3$), δ: 7.5 (m, 5H), 6.9 (t, 2H), 6.3 (t, 2H), 5.3 (s, 2H); ms, m/z (rel. intensity), 157 (M^+, 50.8), 91 (100).

ethyl 2-(1-pyrrolyl)acetate (80)[170]: Yield 92%; ^{1}H nmr ($CDCl_3$), δ: 6.65 (t, 2H), 6.2 (t, 2H), 4.6 (s, 2H), 4.2 (q, 2H), 1.25 (t, 3H); ms, m/z (rel. intensity), 153

(M^+, 88.5), 80 (100). Anal. calcd: C 62.8, H 7.2, N 9.2; found: C 62.8, H 7.3, N 9.2.

ethyl 2-(1-pyrrolyl)-2-benzylacetate (81): Yield 94%; ^{1}H nmr ($CDCl_3$), δ: 7.4 (m, 5H), 6.95 (t, 2H), 6.3 (t, 2H), 4.82 (dd, 1H), 4.22 (m, 2H), 3.4 (m, 2H), 1.2 (t, 3H); ms, m/z (rel. intensity), 243 (M^+, 93.2), 170 (100), 152 (99.3), 91 (70). Anal. calcd: C 74.1, H 7.0, N 5.8; found: C 74.0, H 7.1, N 5.7.

ethyl 2-(1-pyrrolyl)propanoate (82): Yield 91%; ^{1}H nmr ($CDCl_3$), δ: 6.7 (t, 2H), 6.1 (t, 2H), 4.6 (q, 1H), 4.0 (q, 2H), 1.5 (d, 3H), 1.0 (t, 3H); ms, m/z (rel. intensity), 167 (M^+, 60.5), 94 (100). Anal. calcd: C 64.67, H 7.78, N 8.38; found: C 64.69, H 7.76, N 8.48.

When primary amine hydrochloride salt as a starting material was used, another 1.5 g of weakly basic Amberlyst A-21 ion-exchange resin was added.

Preparation of 2-(1-pyrrolyl)acetic acid (83)

Glycine (1 mmol, 75 mg) and 0.5 g of resin were stirred in dimethylsulfoxide (10 mL) for 1 day. Under N_2 atmosphere, the dichloro compound 49 (1.2 mmol, 0.236 g) was added dropwise and followed by another 0.5 g of resin. The reaction mixture was stirred overnight and then filtered and concentrated under reduced pressure (0.5 mm) to remove DMSO. The residue was purified by flash column chromatography using methanol-ethylacetate (3:2) as eluent to give 83 in 60% yield. ^1H nmr (DMSO + $CDCl_3$), δ: 6.65 (t, 2H), 6.1 (t, 2H), 4.55 (s, 2H), 8.9 (b, 1H). The same compound was obtained by hydrolysis of 80 in the presence of aqueous NaOH in refluxing ethanol.

Preparation of 7-(1-pyrrolyl)-cephalosporanic acid (84)[92]

A quantity of 0.27 g (1 mmol) of 7-aminocephalosporanic acid (85) was stirred in 10 mL of DMSO for 20 mins and then 1 g of resin was added. After 1 day, the dichloro compound 49 (0.236 g, 1.2 mmol) was added dropwise. The reaction mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure (0.5 mm) to remove DMSO. The residue was purified by flash column chromatography using methanol-ethylacetate (1:1) as eluent to give the product 84 in 65% yield. ^1H nmr (DMSO), δ: 6.72 (t, 2H), 6.23 (d, 1H), 6.07 (t, 2H), 5.2 (d, 1H), 4.9 (q, 2H), 3.5 (q, 2H), 2.0 (s, 3H); ir (KBr)[92]: 1760 cm^{-1} (β-lactam).

Preparation of 6-(1-pyrrolyl)-penicillanic acid (88)

A quantity of 0.216 g (1 mmol) of 6-aminopenicillanic acid (89) was stirred overnight in 10 mL of DMSO and then 0.5 g of resin was added. After 1 day, the dichloro compound 49 (0.236 g, 1.2 mmol) was added dropwise and followed by another 0.5 g of resin. The reaction mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure (0.5 mm) to remove DMSO. The residue was purified by flash column chromatography using methanol-ethylacetate (2:3) as eluent to give the product 88 in 67% yield. ^{1}H nmr (CD_3OD), δ: 6.78 (t, 2H), 6.03 (t, 2H), 5.21 (d, 1H), 4.69 (d, 1H), 3.44 (s, 1H), 1.58 (s, 3H), 1.23 (s, 3H); ir (KBr): 1735 cm^{-1} (β-lactam).

Preparation of pyrrole of L-leucine methyl ester, 92

L-Leucine methyl ester hydrochloride (93) (1.82 g, 10 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 10 mins. Amberlyst A-21 resin (2.5 g) was introduced and then the dichloro compound 49 (2.26 g, 12 mmol) was added dropwise at 0°C under N_2. After 30 mins, to the mixture was added 5 g of the resin again. The reaction mixture was allowed to warm to room temperature. After stirring overnight, the mixture was filtered on fine-sintered glass filter and the filtrate evaporated *in vacuo*. The crude product was purified by TLC-mesh chromatography using hexane-ethylacetate (7:3) as eluent; $R_f = 0.48$; $[\alpha]_D = -3.8°$ ($c = 0.0034$, $CDCl_3$); yield 71%; ^1H nmr ($CDCl_3$), δ: 6.75 (t, 2H), 6.17 (t, 2H), 4.65 (t, 1H), 3.70 (s, 3H), 1.95 (m, 2H), 1.40 (m, 1H), 0.95 (d, 3H), 0.83 (d, 3H); ms, m/z (rel. intensity), 195 (M^+, 50.9), 139 (100). Anal. calcd: C 67.7, H 8.7, N 7.2; found: C 67.7, H 8.7, N 7.3.

Preparation of dichloromethyl methyl ether (97) from methyl formate

This compound was obtained by the method of Rieche and Gross[106].

To 20.8 g (0.1 mol) of PCl_5 was added 6.2 mL (0.1 mol) of methyl formate slowly without solvent under N_2 atmosphere. After the reaction mixture was stirred at room temperature for 1 hr, distillation gave a colorless liquid as product in 85% yield. Bp = 87 ∿ 89°C (lit.[101,106] 85 ∿ 87°C); ^1H nmr ($CDCl_3$), δ: 7.1 (s, 1H), 3.6 (s, 3H).

2-Formyl pyrrole 98 and 3-formyl pyrrole 99 from pyrrole 80

To a solution of dichloromethyl methyl ether (0.125 g, 1.1 mmol) in dry methylene chloride (5 mL) was added $TiCl_4$ (0.21 g, 1.1 mmol) dropwise at -20°C under N_2 atmosphere and then followed by pyrrole 80 (0.153 g, 1 mmol). The reaction mixture was stirred for 4 hrs at -20°C and quenched with saturated aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with 10% aqueous sodium bicarbonate and finally with water. After drying over anhydrous magnesium sulfate, the solution was concentrated. The residue was separated by flash chromatography using ethylacetate-hexane (2:3) as eluent to give 2-formyl pyrrole 98 in 70% yield and 3-formyl pyrrole 99 in 14% yield.

2-formyl pyrrole 98: ^1H nmr ($CDCl_3$), δ: 9.6 (s, 1H), 6.93 (m, 2H), 6.3 (m, 1H), 5.05 (s, 2H), 4.23 (q, 2H), 1.27 (t, 3H); ms, m/z (rel. intensity), 181 (M^+, 69.5), 153 (M^+-CO, 39.8), 108 (100).

3-formyl pyrrole 99: ^1H nmr ($CDCl_3$), δ: 9.8 (s, 1H), 7.25 (m, 1H), 6.65 (m, 2H), 4.65 (s, 2H), 4.25 (q, 2H), 1.3 (t, 3H); ms, m/z (rel. intensity), 181 (M^+, 83.8), 153 (M^+-CO, 22.0), 152 (29.5), 108 (100).

When aluminum chloride was used as Lewis acid, the products were obtained in poor yield (<30%).

Formylation of pyrrole 92 to give 2-formyl pyrrole 91 and 3-formyl pyrrole 100

(a) Using dichloromethyl methyl ether

To a solution of dichloromethyl methyl ether (0.125 g, 1.1 mmol) in dry methylene chloride (5 mL) was added titanium tetrachloride (0.21 g, 1.1 mmol) dropwise at -20°C under N_2 atmosphere. After 10 mins, pyrrole 92 (0.195 g, 1 mmol) in dry methylene chloride (2 mL) was added dropwise over 5 mins. The reaction mixture was stirred for 5 hrs at -20°C and allowed to warm to room temperature. After overnight, the mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with 10% aqueous sodium bicarbonate solution and then with water. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure. The residue was separated by TLC-mesh column chromatography using hexane-ethylacetate (7:3) as eluent to give 2-formyl pyrrole 91 in 10% yield and 3-formyl pyrrole 100 in 50% yield.

When the reaction was carried out for 6 hrs at -40°C, it gave 2-formyl pyrrole 91 in 10% yield together with the unreacted starting material 92.

(b) Using trimethyl orthoformate

To a solution of trimethyl orthoformate (0.127 g, 1.2 mmol) in dry methylene chloride (5 mL) was added titanium tetrachloride (0.21 g, 1.2 mmol) dropwise at -40°C under N_2 atmosphere. Pyrrole 92 (0.195 g, 1 mmol) in dry methylene chloride (2 mL) was then added dropwise over 5 mins. After the reaction mixture was stirred at -40°C for 1.5 hr, the mixture was allowed to warm to room temperature. The solution was quenched with 1 mL of water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The crude product was separated by TLC-mesh column chromatography using hexane-ethylacetate (7:3) as eluent to give 2-formyl pyrrole 91 in 81% yield and 3-formyl pyrrole 100 in 10% yield.

2-formyl pyrrole 91: ^{1}H nmr ($CDCl_3$), δ: 9.53 (s, 1H), 7.2 (b, 1H), 6.97 (dd, 1H), 6.33 (dd, 1H), 6.1 (t, 1H), 3.72 (s, 3H), 1.98 (m, 2H), 1.4 (m, 1H), 0.92 (d, 3H), 0.89 (d, 3H); ms, m/z (rel. intensity), 223 (M^+, 68.5), 194 (69.9), 164 (69), 152 (75.6), 122 (67.6), 108 (100), 94 (97.2), 80 (72.7); ir ($CDCl_3$), ν_{max}: 1745, 1668 cm^{-1}; $[\alpha]_D$ = -6.5° (c = 0.005, $CDCl_3$). Anal. calcd: C 64.5, H 7.7; found: C 64.6, H 7.7.

3-formyl pyrrole 100: ^{1}H nmr ($CDCl_3$), δ: 9.8 (s, 1H), 7.37 (t, 1H), 6.73 (t, 1H), 6.56 (m, 1H), 4.65 (dd, 1H), 3.7 (s, 3H), 1.92 (m, 2H), 1.4 (m, 1H), 0.91 (d, 3H), 0.89 (d, 3H); ms, m/z (rel. intensity), 223 (M^+, 63.4), 167 (100), 164 (49.3), 122 (44.2), 108 (55), 94 (82), 80 (60.9).

Hydrolysis of methyl 2-(2-formylpyrrol-1-yl)-4-methylpentanoate (91) to give 2-(2-formylpyrrol-1-yl)-4-methylpentanoic acid (104)

(a) Using sodium hydroxide

To a solution of 2-formyl pyrrole 91 (0.112 g, 0.5 mmol) in methanol (5 mL) was added aqueous sodium hydroxide solution (1.2 equiv.; 24 mg of NaOH in 1 mL of water). After the reaction mixture was refluxed overnight, the mixture was cooled to room temperature and then poured into 10 mL of water. This solution was washed with ether and the aqueous layer was then acidified with dilute hydrochloric acid to pH 3, and extracted with ether. The combined ethereal layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to give quantitatively a pale yellowish solid. Mp = 74 ∿ 77°C; $[\alpha]_D$ = 16.4° (c = 0.0075, $CDCl_3$); ^1H nmr ($CDCl_3$), δ: 11.0 (b, 1H), 9.48 (s, 1H), 7.17 (b, 1H), 6.98 (dd, 1H), 6.32 (dd, 1H), 6.05 (t, 1H), 2.0 (m, 2H), 1.4 (m, 1H), 0.91 (d, 3H), 0.88 (d, 3H);

ms, m/z (rel. intensity), 209 (M^+, 52.7), 180 (75.4), 138 (63.6), 122 (66), 108 (71.3), 94 (78.1), 80 (62.2), 41 (100); ir (KBr), ν_{max}: 3250 ∿ 2400, 1740, 1610 cm^{-1}. Anal. calcd: C 63.1, H 7.2; found: C 63.2, H 7.3.

When an excess of aqueous sodium hydroxide solution was used, acid compound 104 showed no optical activity.

(b) Using trimethyliodosilane

This reaction was carried out according to Jung's method[113].

To a solution of 2-formyl pyrrole 91 (0.112 g, 0.5 mmol) in dry chloroform (5 mL) was added trimethyliodosilane (0.143 mL, 1 mmol). The solution was stirred overnight at room temperature while protected from light. The mixture was then poured into 5% aqueous sodium bicarbonate. The aqueous layer was washed with ether, acidified with dilute hydrochloric acid to pH 3, and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give a yellowish solid 104 in 55% yield. The physical data was identical with that obtained from method (a).

Reaction of benzylchloride with LDA to give 1-chloro-1,2-diphenylethane (105)

To a solution of diisopropylamine (1.1 mmol, 0.16 mL) in THF (8 mL) was added n-BuLi (1.1 mmol, 0.69 mL of 1.6 M in hexane) dropwise at 0°C under N_2 atmosphere. After 5 mins, the solution was cooled to −78°C and then to it was added benzylchloride (2 mmol, 0.25 g) solution in THF (2 mL). After stirring for 3 hrs at room temperature, the reaction mixture was concentrated, diluted with ether, washed with water, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The crude product was purified by flash column chromatography using ethylacetate-hexane (3:7) as eluent to give 105 in 61% yield. ^{1}H nmr ($CDCl_3$), δ: 7.3 (m, 10H), 5.1 (t, 1H), 3.4 (d, 2H); ^{13}C nmr ($CDCl_3$), δ: 140.87, 137.27, 129.47 ∿ 126.88 (aromatic peaks), 64.09, 46.59; ms, m/z (rel. intensity), 218 (M^+ +2, 32.6), 216 (M^+, 64.3).

Preparation of α-substituted compounds (110-113) from pyrroles of glycine ethyl ester and alanine ethyl ester

Typical Procedure:

Under N_2 at 0°C, to a solution of 1.2 mmol of hexamethyldisilazane (HMDS) in THF (10 mL) was added 1.2 mmol of n-BuLi (0.69 mL of 1.6 M in hexane). After 10 mins, to the mixture was added 1 mmol of pyrrole of glycine ethyl ester 80. After 30 mins, the reaction mixture was cooled to -78°C and then the alkyl halide (1 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 3 hrs, the solution was evaporated, diluted with anhydrous ether (20 mL), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane-ethylacetate (4:1) as eluent.

Products 110 (85% yield) and 111 (80% yield): Were identical to those (82, 81) obtained by the reactions of the corresponding amino-acid esters and dichloro-compound 49.

ethyl 2-(1-pyrrolyl)-1-(0'-methylphenyl)propanoate (112): Yield 75%; ^1H nmr ($CDCl_3$), δ: 7.10 (m, 4H), 6.7 (t, 2H), 6.1 (t, 2H), 4.75 (dd, 1H), 4.15 (q, 2H), 3.4 (m, 2H), 2.3 (s, 3H), 1.2 (t, 3H); ms, m/z (rel. intentisy), 257 (M^+, 93.8), 184 (85.7), 152 (100), 105 (98.9), 80 (93.3).

ethyl 2-(1-pyrrolyl)-2-methyl propanoate (113): Yield 81%; ^1H nmr ($CDCl_3$), δ: 6.8 (t, 2H), 6.2 (t, 2H), 4.05 (q, 2H), 1.6 (s, 6H), 1.0 (t, 3H); ms, m/z (rel. intensity), 181 (M^+, 33.3), 108 (85.2), 94 (100). This compound 113 was obtained by the reaction of the pyrrole of alanine ethyl ester (110) with LiHMDS and methyl iodide. It could also be prepared by the reaction of the pyrrole of glycine ethyl ester 80 with 2 equiv. of methyl iodide in the presence of 2 equiv. of LiHMDS.

Conversion of primary amides (118-121 and 126) into N-acylpyrroles (122-125 and 127)

Typical Procedure:

To a solution of amide (1 mmol) in dry acetonitrile at 0°C under N_2 atmosphere was added 1.3 mmol of dichloro-compound 49 dropwise. After 10 mins, 1 g of resin was added and the reaction mixture was then allowed to warm to room temperature. After further stirring at 45° ∿ 65°C for 14 hrs, the mixture was filtered, evaporated and purified by flash or TLC-mesh column chromatography to give the product.

N-benzoylpyrrole (122)[127,169]: Yield 85%; ^1H nmr ($CDCl_3$), δ: 7.55 (m, 5H), 7.2 (t, 2H), 6.25 (t, 2H); ms, m/z (rel. intensity), 171 (M^+, 42.1), 105 (M^+-66, 100); ir (neat): 1700 cm^{-1} (C=O).

N-butanoylpyrrole (123)[118,141]: Yield 73%; ^1H nmr ($CDCl_3$), δ: 7.22 (t, 2H), 6.17 (t, 2H), 2.65 (t, 2H), 1.7 (m, 2H), 0.95 (t, 3H)~~;~~ ms, m/z (rel. intensity), 137 (M^+, 6.3); ir (neat): 1725 cm^{-1} (lit.[141] 1755 cm^{-1}).

N-acetylpyrrole (124)[128]: Yield 55%; ^1H nmr ($CDCl_3$), δ: 7.35 (t, 2H), 6.36 (t, 2H), 2.6 (s, 3H); ir (neat): 1725 cm^{-1} (C=O).

N-stearoylpyrrole (125): Yield 72%. This reaction was carried out in chloroform. Mp = 62 ∿ 64°C; ^1H nmr ($CDCl_3$), δ: 7.2 (t, 2H), 6.1 (t, 2H), 2.63 (t, 2H), 1.1 (b, 33H); ir ($CHCl_3$): 1715 cm^{-1} (C=O).

N-(p-toluenesulfonyl)pyrrole (127)[169]: The same procedure as above except that the reaction was carried out at room temperature for 3 hrs. Yield 71%; mp = 101 ∿ 103°C (lit.[169] 100 ∿ 101°C); ^1H nmr ($CDCl_3$), δ: 7.8 (d, 2H), 7.3 (d, 2H), 7.22 (t, 2H), 6.3 (t, 2H), 2.42 (s, 3H); ms, m/z (rel. intensity), 221 (M^+, 56.9), 155 (40.4), 91 (100).

The reactions of acylpyrroles with LAH

Typical Procedure:

To a solution of N-acylpyrrole (1 mmol) in anhydrous ether (5 mL) was added lithium aluminum hydride (0.75 mmol) at 0°C under N_2 atmosphere. After further stirring for 1 hr at 0°C, the reaction was continued overnight at room temperature. The reaction mixture was quenched with a few drops of methanol and then 20 mL of water was added dropwise. The solution was extracted with ether, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the product.

benzyl alcohol (130): Yield 75%; ^1H nmr ($CDCl_3$), δ: 7.2 (s, 5H), 4.53 (s, 2H), 2.05 (b, 1H); ms, m/z (rel. intensity), 108 (M^+, 100).

butanal (128) and 1-(1-pyrrolyl)-1-butanol (129): The analysis for 128 in ethereal solution was carried out[171] by refluxing with 2,4-dinitrophenylhydrazine solution in EtOH, giving the hydrazone solid. Mp = 119 ∿ 120°C (lit.[141] 122°C); yield 30%. After this reaction, the remaining solution was concentrated under reduced pressure and then the residue was purified by TLC-mesh column chromatography using hexane-ethylacetate (7:3) as eluent to give 129 in 40% yield; ^1H nmr ($CDCl_3$), δ: 6.75 (t, 2H), 6.13 (t, 2H), 5.3 (t, 1H), 2.45 (b, 1H), 1.4 (m, 7H); ms, m/z (rel. intensity), 139 (M^+, 42.5), 67 (100).

The reactions of acylpyrroles with $NaBH_4$

(a) Using methanol as a solvent

To a solution of acylpyrrole (1 mmol) in dry methanol (5 mL) was added sodium borohydride (1.3 mmol, 0.052 g) at -20°C under N_2 atmosphere. After further stirring for 5 hrs at -20°C, the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure, diluted with ether, washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give product.

benzaldehyde (131): Yield 85% (not purified); ^1H nmr ($CDCl_3$), δ: 10.0 (s, 1H), 7.76 (m, 2H), 7.4 (m, 3H).

1-(1-pyrrolyl)-1-butanol (129): This compound was purified by TLC-mesh column chromatography using hexane-ethylacetate (7:3) as eluent. Yield 85%. Spectroscopic data for this was identical with that obtained from the reaction of 123 with LAH (p. 148).

(b) Using ether as a solvent

To a solution of acylpyrrole (1 mmol) in anhydrous ether (7 mL) was added sodium borohydride (1.5 mmol, 0.06 g) at 0°C under N_2 atmosphere. After further stirring for 2 hrs at 0°C, the reaction mixture was allowed to warm to room temperature and the stirring was continued overnight. The solution was washed with water (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by TLC-mesh column chromatography using ethylacetate-hexane (2:3) as eluent.

(1-pyrrolyl)-benzyl alcohol (132): R_f = 0.43; yield 62%; ^1H nmr ($CDCl_3$), δ: 7.3 (s, 5H), 6.7 (t, 2H), 6.5 (d, 1H), 6.1 (t, 2H), 2.95 (d, 1H); ms, m/z (rel. intensity), 173 (M^+, 14.9), 107 (18.4), 106 (70.7), 105 (62.9), 67 (100).

N-Butyrylpyrrole did not react with $NaBH_4$ in ether.

The reactions of acylpyrroles with NaOMe

Typical Procedure:

To a solution of acylpyrrole (0.1 mol) in dry methanol (30 mL) was added sodium methoxide (0.15 mol, 8.1 g) under N_2 atmosphere. The reaction mixture was refluxed for 14 hrs and then cooled to room temperature. The solution was concentrated under reduced pressure, diluted with ether, washed with water, dried over anhydrous magnesium sulfate, filtered, and then distilled to give product.

methyl butanoate (136): Yield 85%; bp = 101 ∿ 104°C (lit.[49] 102°C); ^1H nmr ($CDCl_3$), δ: 3.65 (s, 3H), 2.25 (t, 2H), 1.7 (m, 2H), 0.95 (t, 3H).

methyl benzoate (135): Yield 89%; bp = 196 ∿ 198°C (lit.[49] 198-9°C); ^{1}H nmr ($CDCl_3$), δ: 8.0 (m, 2H), 7.4 (m, 3H), 3.8 (s, 3H).

Pyrrole (127) of p-toluenesulfonylamide did not react with NaOMe in refluxing methanol.

The reactions of acylpyrroles with benzylamine to give amides (138-140)

Typical Procedure:

To a solution of the acylpyrrole (1 mmol) in dry THF (7 mL) was added benzylamine (1.2 mmol, 0.13 g). After refluxing for 16 hrs, evaporation of the reaction mixture under reduced pressure gave solid residue which was washed with cold ether (3 x 15 mL) to give fine crystals.

N-benzyl benzamide (138): Yield 85%; mp = 104 ∿ 106°C; ^{1}H nmr (acetone-d_6), δ: 7.65 (m, 2H), 7.3 (m, 3H), 7.25 (s, 5H), 6.4 (b, 1H), 4.6 (d, 2H); ir (KBr), ν_{max}; 3300 (N-H), 3060 (aryl C-H), 1630 and 1540 cm^{-1} (amide), 1600 (aromatic); ms, m/z (rel. intensity), 211 (M^+, 77.6), 210 (M^+-1, 40.4), 105 (100), 77 (62.6).

N-benzyl butyramide (139): which was not purified. ^{1}H nmr ($CDCl_3$), δ: 7.25 (s, 5H), 4.36 (d, 2H), 2.15 (t, 2H), 1.65 (m, 2H), 0.9 (t, 3H).

N-benzyl stearamide (140): Yield 87%; mp = 85 ∿ 88°C; ^{1}H nmr ($CDCl_3$), δ: 7.25 (s, 5H), 4.4 (d, 2H), 2.2 (t, 2H), 1.25 (s, 33H); ir (KBr), ν_{max}: 3300 (N–H), 3080 (aryl C–H), 2980 ∿ 2800, 1625 and 1540 cm^{-1} (amide); ms, m/z (rel. intensity), 373 (M^+, 37.5).

The reaction of N-benzoylpyrrole with piperidine to give N-benzoylpiperidine (141)

To a solution of N-benzoylpyrrole (1 mmol) in dry THF (5 mL) was added piperidine (1.5 mmol, 0.13 g). After refluxing for 2 days, the reaction mixture was concentrated under reduced pressure, which was purified by TLC-mesh column chromatography using ethylacetate-hexane (3:7) as eluent to give product in 55% yield. R_f = 0.14; ^{1}H nmr ($CDCl_3$), δ: 7.3 (s, 5H), 3.5 (b, 4H), 1.64 (b, 6H); ir ($CHCl_3$), 2980 ∿ 2850, 1630 cm^{-1} (t-amide); ms, m/z (rel. intensity), 189 (M^+, 52.6), 188 (M^+-1, 89.3), 105 (100), 84 (48.4), 77 (63.9).

The reaction of acylpyrrole with n-BuLi to give 142 and 143

To a solution of acylpyrrole (1 mmol) in dry THF (5 mL) was added n-BuLi (1.56 mL of 1.6 M in hexane, 2.5 mmol) at 0°C under N_2 atmosphere. After 2 hrs at 0°C, the solution was concentrated under reduced pressure. The residue was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, filtered, and then evaporated *in vacuo*. It was purified by TLC-mesh column chromatography on silica gel to give a colorless oil.

5-phenylnonan-5-ol (142): Yield 72%; ^{1}H nmr ($CDCl_3$), δ: 7.3 (m, 5H), 1.25 (m, 18H); ir ($CHCl_3$), ν_{max}: 3610 (OH), 3050 (aryl C-H), 2990 ∿ 2820 cm^{-1}; ms, m/z (rel. intensity), 220 (M^+, 0.3), 202 (M^+-OH, 14.6), 163 (M^+-Bu, 100).

5-n-butyldocosan-5-ol (143): Yield 65%; ^{1}H nmr ($CDCl_3$), δ: 1.9 (m, 6H), 1.2 (m, 47 H); ir (neat), ν_{max}: 3600 (OH), 2980 ∿ 2800 cm^{-1}; ms, m/z (rel. intensity), 364 (M^+-OH, 8.1), 325 (M^+-Bu, 43.9), 143 (78.4).

The Grignard reaction of stearoylpyrrole (125) to give 1,1-diphenylsteraryl alcohol (144)

To a solution of stearoylpyrrole (1 mmol, 0.33 g) in dry THF (5 mL) was added PhMgCl (2.5 mmol, 1.25 mL of 2 M in THF) dropwise at 0°C under N_2 atmosphere. The reaction mixture was allowed to warm to room temperature. After 4 hrs, the mixture was quenched with a few drops of water, extracted with 20 mL of ether, dried over anhydrous magnesium sulfate, filtered and then evaporated *in vacuo* to give crude product which was purified by TLC-mesh column chromatography using hexane-ethylacetate (4:1) as eluent. R_f = 0.42; yield 55%; mp = 40 ∿ 43°C; ^1H nmr ($CDCl_3$), δ: 7.3 (m, 10H), 1.2 (s, 35H); ir (KBr): 3550 (OH), 3050 (aryl C-H), 2980 ∿ 2820 cm^{-1}; ms, m/z (rel. intensity), 404 (M^+-OH, 2.8), 344 (M^+-benzene, 8.2), 105 (68.3).

Methyl 3-oxopentanoate (148) from methyl acetoacetate (147)

This reaction was carried out according to Weiler's method[153].

Under N_2 atmosphere at 0°C, to a solution of sodium hydride (5.4 g 50% dispersion in mineral oil) in 200 mL of THF was added methyl acetoacetate (0.1 mol, 11.6 g) dropwise. The green solution was stirred for 10 mins and n-BuLi (70 mL of

1.5 M in hexane, 0.11 mol) was then added to give the orange dianion. After 10 mins, 0.11 mol (7 mL) of methyl iodide in THF (14 mL) was added and the reaction mixture was then stirred at room temperature for 15 mins. The mixture was quenched with dilute hydrochloric solution (20 mL of C-HCl in 70 mL of H_2O) and diluted with 150 mL of ether. The organic phase was washed with water until the aqueous extracts were neutral pH. The organic solution was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was distilled to yield 9.5 g (73%) of methyl 3-oxovalerate (148). Bp = 85 ∿ 87°C/20 mm, (lit.[153] 70 ∿ 71°/14 mm); ^{1}H nmr ($CDCl_3$), δ: 3.75 (s, 3H), 3.45 (s, 2H), 2.6 (q, 2H), 1.1 (t, 3H).

Preparation of methyl 5-trimethylsiloxy-2-pentenoate (149)

This reaction was performed by Danishefsky's method[154].

Dry triethylamine (0.11 mol, 15.5 g) and zinc chloride (0.5 g) were stirred vigorously under N_2 atmosphere for 1 hr, giving a fine suspension. Methylvalerate (0.05 mol, 6.5 g) in dry benzene (50 mL) was added, followed after 5 mins by TMSCl (0.1 mmol, 12.7 mL). The mixture was stirred overnight, 200 mL of dry ether added, filtered, and concentrated. The residue was diluted with dry hexane (300 mL), cooled to precipitate any remaining solids, filtered, and concentrated, giving the mono-enol silyl ether product 149 in 94% yield. ^{1}H nmr ($CDCl_3$) (a 4:1 mixture $^{\underline{E}}$ and $^{\underline{Z}}$ of isomers), δ: 5.09$^{\underline{Z}}$ and 5.02 $^{\underline{E}}$ (1H, each s), 3.65 (s, 3H), 2.75$^{\underline{E}}$ and 2.17$^{\underline{Z}}$ (2H, each q), 1.1 (t, 3H), 0.27 (s, 9H).

1,3-*Bis*(trimethylsiloxy)-1-methoxypenta-1,3-diene (150)

This compound was prepared by Chan's method[150] without TMEDA.

Under N_2 atmosphere at 0°C, to a solution of diisopropylamine (24 mmol, 3.4 mL) in THF (30 mL) was added *n*-BuLi (15 mL of 1.6 M in hexane, 24 mmol). After 5 mins, the mixture was cooled to -78°C and enol silyl ether 149 (20 mmol, 4.04 g) was then added dropwise. After 10 mins, the reaction mixture was quenched with TMSCl (4 mL). The mixture was allowed to warm to 0°C and concentrated on the rotary evaporator. The residue was triturated with dry hexane (200 mL) with cooling to precipitate salts and filtered. The filtrate was concentrated (finally under high vacuum) to give product as a pale yellowish oil in 95% yield. ^{1}H nmr ($CDCl_3$), δ: 4.97 (q, 1H), 4.0 (s, 1H), 3.6 (s, 3H), 1.65 (d, 3H), 0.3 (s, 9H), 0.27 (s, 9H).

From the ^{1}H nmr spectrum, it appears to be exclusively one isomer which is tentatively assigned to be the E-isomer.

The reactions of *bis*(enol silyl ether) 150 with 2,5-dimethoxy THF to give 151-153

To a solution of 2,5-dimethoxy THF (1) (5 mmol, 0,66 g) in dry methylene chloride (15 mL) at -78°C under N_2 atmosphere was added titanium tetrachloride (10 mmol, 1.9 g) dropwise. A solution of *bis*(enol silyl ether) 150 (5 mmol, 1.37 g) in dry CH_2Cl_2 (25 mL) was added over 20 mins. The mixture was stirred at -78°C for 3 hrs and then allowed to warm to 0°C. To the dark red solution was then added excess 5% aqueous sodium bicarbonate solution (2 mL). The mixture was extracted with ether, dried over anhydrous magnesium sulfate, and evaporated. The residue was separated by flash column chromatography on silica gel using hexane-ethylacetate (7:3) as eluent to give the bicyclic enol compound 152 (38%) and keto compounds 153 (20%) as a mixture of two isomers.

2-carbomethoxy-3-hydroxy-4-methyl-8-oxabicyclo[3,2,1]-2-octene (152): (one isomer exo-methylated at C-4);

R_f = 0.51; ^{1}H nmr ($CDCl_3$), δ: 11.68 (s, 1H), 4.88 (m, 1H), 4.28 (m, 1H), 3.76 (s, 3H), 1.95 (m, 5H), 1.32 (d, 3H); ms, m/z (rel. intensity), 198 (M^+, 19.6); ir (neat): $3600 \sim 3300$ (b, OH), $3040 \sim 2800$, 1660, 1615 cm^{-1}.

2-carbomethoxy-3-oxo-4-methyl-8-oxabicyclo-[3,2,1]-octane (153): (mixture of two isomers, both with endo-methyl group at C-4); R_f = 0.4 and 0.31 (without separation); ^{1}H nmr ($CDCl_3$), δ: 5.05 and 4.84 (m, each H-1, 1H), 4.49 (m, 1H, H-5), 3.76 and 3.73 (s, each OMe, 3H), 3.0 (m, each H-2 and H-4, 1H), 1.8 (m, 4H), 1.01 and 0.98 (d, J = 6.8 Hz, each CH_3 at C-4, 3H); ir (neat): 3040 ∿ 2820, 1740, 1715 cm^{-1}; ms, m/z (rel. intensity), 198 (M^+, 2.4).

When 1 equiv. of titanium tetrachloride was used as a Lewis acid, monosubstituted THF derivative 151 was obtained in 25% yield with traces of bicyclic products (152 and 153).

methyl 3-oxo-4-[5-(2'-methoxytetrahydrofuranyl)]-pentanoate (151): ^{1}H nmr ($CDCl_3$), δ: 4.95 (m, 1H), 4.08 (m, 1H), 3.7 (s, $-CO_2Me$), 3.59 (s, 2H), 3.28 (s, OMe), 2.7 (m, 1H), 1.85 (m, 4H), 1.0 (d, 3H); ir (neat): 3020 ∿ 2800, 1750, 1715 cm^{-1}; ms, m/z (rel. intensity), 199 (M^+-OCH_3, 14.8), 198 (M^+-CH_3OH, 15.4), 167 (16.3), 130 (28.4), 125 (17.6), 101 (100).

O-Silylation of bicyclic enol 152 to give 2-carbomethoxy-3-trimethylsiloxy-4-methyl-8-oxabicyclo[3,2,1]-2-octene (154)

To a solution of bicyclic enol 152 (4.3 mmol, 0.85 g) in dry ether (30 mL) was added by triethylamine (6 mmol, 0.84 mL) dropwise and followed by TMSCl (8 mmol, 1 mL) under N_2 atmosphere. After 1 hr, the mixture was filtered and the filtrate was evaporated *in vacuo* to give the enol silyl ether product 154 quantitatively. ^1H nmr ($CDCl_3$), δ: 4.95 (m, 1H), 4.21 (m, 1H), 3.7 (s, CO_2Me), 1.93 (m, 4H), 1.80 (q, 1H), 1.28 (d, 3H), 0.22 (s, 9H); ir (neat): 3020 $\sim$ 2860, 1720 and 1680 (CO_2Me), 1620 (olefin), 880 and 850 cm^{-1} ($OSiMe_3$); ms, m/z (rel. intensity), 270 (M^+, 7.9).

O-Acylation of bicyclic enol 152 to give 2-carbomethoxy-3-acetoxy-4-methyl-8-oxabicyclo[3,2,1]-2-octene (155)

To the mixture of bicyclic enol 152 (2 mmol, 0.4 g) and acetyl chloride (2.2 mmol, 0.17 mL) was slowly added 2 mL of pyridine at 0°C. The reaction mixture was allowed to warm to room temperature. After 5 hrs, ice-hydrochloric acid solution was added dropwise to the mixture until pH 5. The mixture was extracted with ether (3 x 15 mL) and the ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography using ethylacetate-hexane (3:7) as eluent to give 155; $R_f = 0.38$, in 81% yield. ^1H nmr ($CDCl_3$), δ: 4.97 (m, 1H), 4.27 (m, 1H), 3.72 (s, 3H), 2.21 (s, 3H), 2.10 ∿ 1.70 (m, 5H), 1.23 (d, 3H); ir (neat): 3040 ∿ 2820, 1765 ($C{=}C{-}O\overset{O}{\underline{C}}CH_3$), 1650 cm^{-1} (olefin); ms, m/z (rel. intensity), 240 (M^+, 1.6).

Preparation of 3-oxo-8-oxabicyclo[3,2,1]-2-octane derivatives 156 and 157

Under N_2 atmosphere at 0°C, to NaH (0.05 g, 50% dispersion in mineral oil) in dry THF (7 mL) was added bicyclic enol 152 (1 mmol, 0.2 g) in THF (2 mL) dropwise. After 10 mins, methyl iodide (1.1 mmol, 0.07 mL) in THF (1 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with dilute hydrochloric acid solution, diluted with 30 mL of ether. The organic phase was washed with saturated $Na_2S_2O_3$ solution until the aqueous layer was neutral pH, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography using ethylacetate-hexane (3:7) as eluent to give product 156 in 52% yield. $R_f = 0.33$; ^1H nmr ($CDCl_3$), δ: 4.35 (bt, H-1 and H-5, 2H), 3.73 (s, CO_2Me), 2.34 (q, 1H), 2.07 (m, 4H), 1.61 (s, 3H), 1.33 (d, 3H); ir (neat): 3040 ∿ 2820, 1735, 1715 cm^{-1}; ms, m/z (rel. intensity), 212 (M^+, 13.2).

When more than 2 equiv. each of NaH and MeI were used, dimethylated product 157 was obtained in 65% yield. R_f = 0.44; ^{1}H nmr ($CDCl_3$), δ: 4.36 (m, 1H), 4.15 (m, 1H), 3.75 (s, 3H), 2.0 (m, 4H), 1.66 (s, 3H), 1.36 (s, 3H), 1.1 (s, 3H); ir (neat): 3040 ∿ 2820, 1735, 1710 cm^{-1}; ms, m/z (rel. intensity), 226 (M^+, 46.8).

The ozonolysis reactions of 154 or 155, carried out according to Heathcock's[162] method, gave a complicated mixture of products; we could not purify and identify any structure.

Preparation of 3-trimethylsiloxy-8-oxabicyclo[3,2,1]-2-octene derivative 158

Dry triethylamine (11 mmol, 1.55 g) and zinc chloride (50 mg) were stirred vigorously under N_2 atmosphere for 1 hr, giving a fine suspension. A solution of 153 (5 mmol, 1 g) in dry benzene (10 mL) was added, followed by TMSCl (10 mmol, 1.3 mL). The mixture was stirred overnight, 25 mL of anhydrous ether added, filtered and concentrated. The residue was diluted with dry hexane (30 mL), cooled to precipitate any remaining solids, filtered and concentrated, giving the enol silyl ether product 158 in 92% yield. ^{1}H nmr ($CDCl_3$), δ: 4.9 (bd, 1H), 4.31 (m, 1H), 3.63 (s, CO_2Me), 2.76 (m, 1H), 1.83 (m, 4H), 0.93 (d, 3H), 0.16

(s, 9H); ir (neat): 3020 ∿ 2820, 1720 and 1690 (CO_2Me), 1615 cm^{-1} (olefin), 880 and 845 (OTMS); ms, m/z (rel. intensity), 270 (M^+, 9.7).

Esterification from carboxylic acid and α-bromoester to give α-acyloxy esters (189-195)

Typical Procedure:[164,165]

To a solution of acid (0.15 mol) in 120 mL of acetone was added anhydrous potassium carbonate (0.23 mol, 31.5 g) followed by α-bromo ester (0.1 mol) under N_2 atmosphere. After the reaction mixture was refluxed overnight, it was cooled to room temperature and evaporated *in vacuo*. The residue was partitioned between ether and 10% aqueous potassium carbonate solution. The organic layer was washed with water until neutral pH and finally with brine solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the ester product in quantitative yield.

ethyl α-propanoyloxyacetate (189): Yield 91%; 46° ∿ 48°C/0.1 mm; ^1H nmr ($CDCl_3$), δ: 4.6 (s, 2H), 4.2 (q, J = 7.2 Hz, 2H), 2.43 (q, J = 7.2 Hz, 2H), 1.3 (t, J = 7.2 Hz, 3H), 1.2 (t, J = 7.2 Hz, 3H); ir (neat): 3020 ∿ 2860, 1770 and 1750 cm^{-1}; ms, m/z (rel. intensity), 160 (M^+, 11.6), 115 (24.3), 57 (93.8).

ethyl α-acetoxyacetate (190): Yield 92%; ^{1}H nmr ($CDCl_3$), δ: 4.6 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.17 (s, 3H), 1.3 (t, J = 7.2 Hz, 3H); ms, m/z (rel. intensity), 1.46 (M^+, 1.3), 101 (38.2).

ethyl α-hexanoyloxyacetate (191): Yield 94%; ^{1}H nmr ($CDCl_3$), δ: 4.53 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.36 (t, 2H), 1.4 (m, 6H), 1.2 (t, J = 7.2 Hz, 3H), 0.85 (m, 3H); ir (neat): 3020 ∿ 2840, 1770 and 1750 cm^{-1}; ms, m/z (rel. intensity), 157 (M^+-45, 26.2), 99 (100).

ethyl α-cyclohexanecarbonyloxyacetate (192): Yield 92%; ^{1}H nmr ($CDCl_3$), δ: 4.5 (s, 2H), 4.1 (q, J = 7.2 Hz, 2H), 1.6 (m, 11 H), 1.15 (t, J = 7.2 Hz, 3H); ir (neat): 3020 ∿ 2830, 1765 and 1745 cm^{-1}; ms, m/z (rel. intensity), 214 (M^+, 0.8), 169 (25.3), 111 (93.4), 83 (100).

ethyl α-benzoyloxyacetate (193): Yield 95%; ^{1}H nmr ($CDCl_3$), δ: 8.1 (m, 2H), 7.53 (m, 3H), 4.86 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.3 (t, J = 7.2 Hz, 3H); ms, m/z (rel. intensity), 208 (M^+, 29.1), 163 (15.9), 105 (100).

ethyl α-phenylacetoxyacetate (194): Yield 98%; ^{1}H nmr ($CDCl_3$), δ: 7.26 (s, 5H), 4.58 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.7 (s, 2H), 1.2 (t, J = 7.2 Hz, 3H); ms, m/z (rel. intensity), 222 (M^+, 2.5), 177 (14.6), 119 (26.4), 118 (84.8), 91 (100).

ethyl α-2-methylpentanoyloxyacetate (195): Yield 93%; ^{1}H nmr (CDCl$_3$), δ: 4.55 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.55 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.2 (d, 3H), 1.1 (m, 7H); ir (neat): 3020 ∿ 2840, 1750 cm^{-1}; ms, m/z (rel. intensity), 160 (M^{+}-42, 40.6), 157 (M^{+}-45, 36.9), 99 (73.7), 71 (100); ^{13}C nmr (CDCl$_3$), δ: 171.61, 167.52, 60.82, 60.11, 38.59, 35.46, 19.87, 16.53, 13.67, 13.50.

4,7-Dioxa-3,6-*bis*(trimethylsiloxy)non-2,5-diene (179) from ethyl α-propanoyloxy acetate (189)

Under N$_2$ atmosphere at 0°C, to a solution of diisopropylamine (24 mmol, 3.4 mL) in dry THF (30 mL) was added n-BuLi (15 mL of 1.6 M in hexane, 24 mmol). After 5 mins, the mixture was cooled to -78°C and ester 189 (10 mmol) was then added dropwise. After 10 mins, the reaction mixture was quenched with TMSCl (4 mL). The mixture was allowed to warm to 0°C and concentrated on the rotary evaporator. The residue was triturated with dry hexane (200 mL) with cooling to precipitate salts and filtered. The filtrate was concentrated to give product as a pale yellowish oil in 55%. Bp = 75 ∿ 78°C/0.1 mm; ^{1}H nmr (CDCl$_3$), δ (single isomer about C 4-5 and a *ca.* 3:1 (E/Z) mixture isomers about C 1-2) 5.67$^{\underline{Z}}$ and 5.33$^{\underline{E}}$ (1H, each s, -O$\underline{\text{CH}}$=), 4.23

(m, 1H, $CH_3\underline{CH}$=), 3.76 (m, 2H, $O\underline{CH_2}CH_3$), 1.56 (m, $\underline{CH_3}$CH=, 3H), 1.3 (m, $-OCH_2\underline{CH_3}$, 3H), 0.18 (s, OTMS); ir (neat): 1685 cm^{-1} (olefin), 845 cm^{-1} (OTMS); ms, m/z (rel. intensity), 304 (M^+, 24.8). 187 (39.2).

The cyclisation of <u>179</u> with <u>1</u> in the presence of 2 equiv. of $TiCl_4$ was not successful.

<u>Ethyl 2,3-*bis*(trimethylsiloxy)-2-alkenoates (196-199)</u>

Under N_2 atmosphere at 0°C, to a solution of diisopropylamine (6.8 mL, 48 mmol) in dry THF (100 mL) was added n-BuLi (30 mL of 1.6 M in hexane, 48 mmol) and followed by the acyloxy ester (20 mmol) in THF (20 mL). After 30 mins, the reaction mixture was cooled to -78°C and quenched with TMSCl (8 mL). The mixture was allowed to warm to room temperature and evaporated *in vacuo*. The residue was diluted with cold dry hexane (200 mL) to precipitate salts, filtered and concentrated *in vacuo* to give a product.

<u>ethyl 2,3-*bis*(trimethylsiloxy)-2-pentenoate (196)</u>: Yield 87%; 82 ∿ 84°C/0.2 mm; ^1H nmr ($CDCl_3$), δ: 4.22 (q, J = 7.2 Hz, 2H), 2.63 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.1 (t, J = 7.6 Hz, 3H), 0.23 (s, 9H), 0.17 (s, 9H); ir (neat): 1710, 1620, 885, 850 cm^{-1}; ms, m/z (rel. intensity), 304 (M^+, 27.2), 289 (M^+-CH_3, 63.7), 259 (15.0), 245 (51.4), 231 (28.5).

ethyl 2,3-*bis*(trimethylsiloxy)-2-octenoate (197): Yield 65%; 105° ∿ 108°C/0.25 mm; ^{1}H nmr (CDCl$_3$), δ: 4.16 (q, 2H), 2.57 (t, 2H), 1.1 (m, 11H), 0.22 (s, 9H), 0.16 (s, 9H); ir (neat): 1710, 1620, 840 cm^{-1}; ms, m/z (rel. intensity), 346 (M$^+$, 0.6), 331 (M$^+$-CH$_3$, 3.2).

ethyl 2,3-*bis*(trimethylsiloxy)-3-cyclohexyl-2-propenoate (198): Yield 50%; 118° ∿ 121°C/0.2 mm; ^{1}H nmr (CDCl$_3$), δ: 4.22 (q, 2H), 1.46 (m, 11H), 1.33 (t, 3H), 0.26 (s, 9H), 0.18 (s, 9H); ir (neat); 1710, 1605, 850 cm^{-1}; ms, m/z (rel. intensity), 358 (M$^+$, 1.9), 343 (M$^+$-CH$_3$, 8.2).

ethyl 2,3-*bis*(trimethylsiloxy)-5-methyl-2-heptenoate (199): Yield 62%; 83 ∿ 86°C/0.05 mm; ^{1}H nmr (CDCl$_3$), δ: 4.2 (q, 2H), 1.95 (m, 1H), 1.33 (t, 3H), 1.2 (m, 7H), 1.03 (d, 3H), 0.28 (s, 9H), 0.2 (s, 9H); ir (neat): 1710, 1605, 840 cm^{-1}; ms, m/z (rel. intensity), 346 (M$^+$, 44.9), 331 (M$^+$-CH$_3$, 58.8).

2-Hydroxy-1,3-dioxo ester derivatives (200-203)

The reaction procedure was the same as in the case of compounds (196-199) except that the reaction mixture was quenched with 0.1 N hydrochloric acid instead of TMSCl and diluted with ether instead of hexane. The product was purified by flash column chromatography using ethylacetate-hexane as eluent.

ethyl 3-oxo-2-hydroxypentanoate (200): Yield 57%; ^1H nmr ($CDCl_3$), δ: 4.7 (s, 1H), 4.2 (q, 2H), 3.87 (b, 1H), 3.63 (q, 2H), 1.3 (t, J = 7.2 Hz, 3H), 1.1 (t, J = 7.6 Hz, 3H); ir ($CHCl_3$): 3620 ∿ 3250, 3060 ∿ 2860, 1735 cm^{-1}; ms, m/z (rel. intensity), 160 (M^+, 3.9), 104 (22.6). The same compound was obtained by acidic hydrolysis of 196 as follows: To a solution of 196 (0.5 mmol) in THF (2 mL) was added 2 drops of dilute hydrochloric acid. Stirring was continued overnight at room temperature. The reaction mixture was concentrated and then extracted with ether. The ether solution was concentrated to give 200. It was purified by flash column chromatography.

ethyl 3-oxo-2-hydroxyoctanoate (201): Yield 52%; ^1H nmr ($CDCl_3$), δ: 4.76 (s, 1H), 4.3 (q, J = 7.2 Hz, 2H), 4.1 (b, 1H), 3.67 (t, 2H), 1.4 (m, 6H), 1.33 (t, J = 7.2 Hz, 3H), 0.92 (t, 3H); ir (neat): 3600 ∿ 3250, 3020 ∿ 2820, 1750, 1725 cm^{-1}. When D_2O was added to the nmr tube, the broad peak at 4.1 ppm disappeared.

ethyl 3-oxo-2-hydroxy-3-cyclohexylpropanoate (202): Yield 65%; mp = 127 ∿ 130°C; ^1H nmr ($CDCl_3$), δ: 4.8 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.2 (b, 1H), 2.8 (m, 1H), 1.4 (m, 10H), 1.27 (t, J = 7.2 Hz, 3H); ir (KBr):

3600 ∿ 3260, 3020 ∿ 2820, 1740, 1690 cm^{-1}; ms, m/z (rel. intensity), 214 (M^+, 0.9), 111 (41.6), 104 (19.4), 83 (100).

ethyl 3-oxo-2-hydroxy-4-methylheptanoate (203): Yield 65%; ^1H nmr ($CDCl_3$) (mixture of two diastereomers), δ: 4.89 and 4.85 (1H, each s), 4.32 (b, 1H), 4.28 (q, 2H), 3.0 (m, 1H), 1.32 (m, 4H), 1.29 (t, 3H), 1.12 and 1.06 (3H, each d), 0.89 (m, 3H); ir (neat): 3600 ∿ 3300, 3020 ∿ 2840, 1755, 1725 cm^{-1}; ms, m/z (rel. intensity), 202 (M^+, 0.4), 104 (6.6), 99 (51.9).

2-Acetoxy-1,3-diketo ester derivatives (204-207) and 2,3-diacetoxy-α,β-unsaturated esters (208-209)

(a) In order to obtain compounds (204-207), the same reaction procedure as above was used except that the reaction mixture was treated with 1 equiv. each of acetic anhydride and LDA.

ethyl 3-oxo-2-acetoxypentanoate (204): Yield 35%; ^1H nmr ($CDCl_3$), δ: 5.5 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 2.2 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.6 Hz, 3H); ir ($CHCl_3$): 3020 ∿ 2850, 1755, 1735 cm^{-1}; ms, m/z (rel. intensity), 202 (M^+, 1.9), 160 (35.7), 157 (18.6), 146 (43.4), 104 (83.9).

ethyl 3-oxo-2-acetoxyoctanoate (205): Yield 45%; ^1H nmr ($CDCl_3$), δ: 5.48 (s, 1H), 4.27 (q, 2H), 2.65 (t, 2H), 2.22 (s, 3H), 1.36 (m, 6H), 1.30 (t, 3H), 0.9 (t, 3H); ir (neat): 3020 ∿ 2840, 1765, 1755, 1735 cm^{-1}; ms, m/z (rel. intensity), 244 (M^+, 0.5), 202 (5.8), 199 (2.9), 146 (21.3), 104 (32.4).

ethyl 3-oxo-2-acetoxy-3-cyclohexylpropanoate (206): Yield 67%; ^1H nmr ($CDCl_3$), δ: 5.6 (s, 1H), 4.26 (q, 2H), 2.2 (s, 3H), 1.65 (m, 11H), 1.3 (t, 3H); ir (neat): 3020 ∿ 2840, 1755, 1730 cm^{-1}; ms, m/z (rel. intensity), 256 (M^+, 0.9), 214 (4.1), 211 (15.3), 168 (32.0), 146 (3.9), 104 (42.6).

ethyl 3-oxo-2-acetoxy-4-methylheptanoate (207): Yield 65%; ^1H nmr ($CDCl_3$), δ (mixture of two isomers): 5.64 (s, 1H), 4.28 (q, 2H), 2.98 (m, 1H), 2.23 (s, 3H), 1.7 (m, 2H), 1.31 (t, 3H), 1.28 (m, 2H), 1.15 and 1.09 (3H, each d), 0.9 (m, 3H); ir (neat): 3020 ∿ 2840, 1755, 1735 cm^{-1}; ms, m/z (rel. intensity), 244 (M^+, 1.4), 202 (18.5), 146 (6.3), 104 (32.8), 99 (61.4), 71 (100).

(b) For compounds 208 and 209, 2.5 equiv. each of LDA and acetic anhydride were used.

ethyl 2,3-diacetoxy-3-cyclohexyl-2-propenoate (208): Yield 59%; ^1H nmr ($CDCl_3$), δ: 4.26 (q, 2H), 2.4 (s, 3H), 2.26 (s, 2H), 1.6 (m, 11H), 1.25 (t, 3H); ir (neat): 1750, 1720, 1630 cm^{-1}; ms, m/z (rel. intensity), 298 (M$^+$, 2.5), 256 (13.5), 214 (55.4).

ethyl 2,3-diacetoxy-4-methyl-2-heptenoate (209): Yield 62%; ^{1}H nmr (CDCl$_3$), δ: 4.25 (q, 2H), 2.41 (s, 3H), 2.3 (s, 3H), 1.3 (t, 3H), 1.05 (m, 11H); ms, m/z (rel. intensity), 286 (M$^+$, 0.3), 244 (4.9), 202 (42.4); ir (neat): 1760, 1725, 1635 cm^{-1}.

BIBLIOGRAPHY

1. (a) N. Clauson-Kaas, F. Limborg, and J. Fakstorp, Acta Chem. Scand., 2, 109 (1950).

   (b) J. Fakstorp, D. Raleigh, and L.E. Schniepp, J. Am. Chem. Soc., 72, 869 (1950).

2. N. Elming, in R.A. Raphael, E.C. Taylor, and H. Wynberg, "Advances in Organic Chemistry", Vol. 2, Interscience Publishers, New York (1960) pp. 67-115.

3. J.T. Nielson, N. Elming, and N. Clauson-Kaas, Acta Chem. Scand., 12, 63 (1958).

4. N. Clauson-Kaas, F. Limborg, and K. Glens, Acta Chem. Scand., 6, 531 (1952).

5. K.E. Kolb and W.A. Black, Chem. Comm., 1119 (1969).

6. M.P. Jain, R.S. Thakur, and P.R. Rao, Res. Ind., 20, (1), 3 (1975).

7. A. Kankaanpera and K. Miiki, Acta Chem. Scand., 23, 1471 (1969).

8. F. Riddell, Quart. Rev., 21, 372 (1967); E.M. Arnett, in "Progress in Physical Organic Chemistry", Eds. S.G. Cohen, A. Streitweiser, and R.W. Toft, Wiley, New York (1963) Vol. 1, p. 289.

9. R.L. Letsinger and R. Lasco, J. Org. Chem., 21, 764 (1956).

10. R. Robinson, J. Chem. Soc., 762 (1917).

11. C. Schöpf and G. Lehmann, Ann., 518, 1 (1935).

12. A. Stoll, E. Jucker, and A. Lindenmann, Helv. Chim. Acta, 37, 495, 649 (1954).

13. J.C. Sheehan and B.M. Bloom, J. Am. Chem. Soc., 74 3825 (1952).

14. K. Zeile and A. Heusner, Chem. Ber., 90, 2809 (1957).

15. N. Clauson-Kaas and Z. Tyle, Acta Chem. Scand., 6, 667 (1952).

16. N. Elming and N. Clauson-Kaas, *ibid*., 6, 867 (1952).

17. P. Nedenskov, N. Elming, J.T. Nielsen, and N. Clauson-Kaas, *ibid*., 9, 17 (1955).

18. N. Clauson-Kaas and P. Nedenskov, Acta Chem. Scand., 9, 14 (1955).

19. J.T. Nielsen, N. Elming, and N. Clauson-Kaas, *ibid*., 9, 9, 30 (1950).

20. H. Takahasi, K. Hirayama, and T. Kuroda, Toxic. Appl. Pharmac., 18, 988 (1971).

21. F.L. Garvan, in "Chelating Agents and Metal Chelates", Eds. F.P. Dwyer and D.P. Mellor, Academic Press, London, (1964), p. 283.

22. M.M. Jones, J. Inorg. Nucl. Chem., 36, 194 (1974).

23. R.L. Coates and M.M. Jones, *ibid*., 37, 443 (1975).

24. M. Robiquet, Ann. Chim., [I] 76, 302 (1810).

25. (a) T.H. Waddell, H. Jones, and A.L. Keith, J. Chem. Educ., 57, 341 (1980).

(b) "Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals", Medical Economics Inc., (1970), p. 1727).

26. J. Gadamer, Arch. Pharm., 252, 609 (1914).

27. F. von Bruchhausen and H.W. Bersch, Arch. Pharm., 266, 697 (1928).

28. O. Diels and K. Alder, Ber., 62, 554 (1929).

29. R.B. Woodward and H. Baer, J. Am. Chem. Soc., 70, 1161 (1948).

30. K. Ziegler, G. Schenck, E.W. Krockow, A. Siebert, A. Wenz, and H. Weber, Ann., 551, 1 (1942).

31. O. Diels and S. Olsen, J. Prakt. Chem., [2] 156, 285 (1940).

32. K. Ziegler, W. Flaig, and G. Velling, Ann., 567, 204 (1950).

33. K. Alder and G. Stein, Angew. Chem., 50, 510 (1937).

34. G. Stork, E.E. van Tamelen, L.J. Friedman and A.W. Burgstahler, J. Am. Chem. Soc., 73, 4501 (1951); *ibid.*, 75, 384 (1953).

35. W.G. Dauben and H.O. Krabbenhoft, J. Am. Chem. Soc., 98, 1992 (1976).

36. A. Albert, "Heterocyclic Chemistry", 2nd ed., Oxford University Press, New York, N.Y., (1968) p. 257.

37. N.L. Allinger, J.A. Hirsch, M.A. Miller, I.J. Timinski, and F.A. Van-Catledge, J. Am. Chem. Soc., 90, 1199 (1968).

38. J.A. Gladysz, CHEMTECH, 372 (1979).

39. W.G. Dauben, C.R. Kessel, and K.H. Takemura, J. Am. Chem. Soc., 102, 6893 (1980).

40. (a) A.D. Petrov and S.J. Sadykh-Zade, Dokl. Akad. Nauk SSSR, 121, 119 (1958).

(b) G. Stork and P.F. Hudrlik, J. Am. Chem. Soc., 90, 4462 (1968).

41. E. Colvin, "Silicon in Organic Synthesis"' Chapt. 17, Butterworths, (1981).

42. J.K. Rasmussen, Synthesis, 91 (1977).

43. P. Brownbridge, Synthesis, 1, 85 (1983).

44. P. Brownbridge and T.H. Chan, Tet. Lett., 3423 (1980).

45. P. Brownbridge and T.H. Chan, Tet. Lett., 4437 (1979).

46. P. Brownbridge and T.H. Chan, Tet. Lett., 3427 (1980).

47. T. Mukaiyama, Angew. Chem., Internat. Ed. Engl., 16, 817 (1977).

48. A.I. Vogel, "A Textbook of Practical Organic Chemistry" 3rd Ed., John Wiley and Sons, New York (1962) p. 375.

49. "Aldrich Catalogue of Fine Chemicals", Aldrich Chem. Co., (1983).

50. W.C. Still, M. Khan, and A. Mitra, J. Org. Chem., 43, 2923 (1978).

51. E. Yoshii, T. Koizumi, E. Kitatsuji, T. Kawazol, and T. Taneko, Heterocycles, 4, 1663 (1976).

52. P. Brownbridge and T.H. Chan, Tet. Lett., 3431 (1980).

53. H. Gross, Angew Chem., 72 268 (1960).

54. H. Gross, Chem. Ber., 95, 83 (1962).

55. M.E. Jung and M.A. Lyster, J. Am. Chem. Soc., 99, 968 (1977).

56. T.L. Ho and G.A. Olah, Angew. Chem., 88, 847 (1976).

57. (a) C.B. Reese, in "Protective Groups in Organic Chemistry", J.F.W. McOmie, Ed., Plenum Press, London, (1973) pp. 95-143.

(b) E. Halsam, *ibid.*, pp. 145-182.

(c) R.L. Burwell, Chem. Rev., 54, 615 (1954).

58. I.T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Vol. 1, Wiley-Interscience, New York, N.Y., (1971), p. 127.

59. M.E. Jung and T.A. Blumenkopf, Tet. Lett., 3657 (1978).

60. G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra, J. Org. Chem., 44, 1247 (1979), and Synthesis, 61 (1979).

61. G.A. Olah, A. Husain, B.G.B. Gupta, and S.C. Narang, Angew. Chem. Intern. Ed. Engl., 20, 690 (1981).

62. I.N. Denis, R. Magnane, M. van Eenos, and A. Krief, Nouv. J. Chim., 3, 705 (1979).

63. H.R. Kricheldorf, G. Mörber, and W. Regel, Synthesis, 383 (1981).

64. (a) U. Krüerke, Chem. Ber., 95, 174 (1962).

    (b) M. Kumada and H. Hattari, J. Chem. Soc. Jpn. Ind. Chem. Sect., 56, 269 (1953).

    (c) M.W. Jung and G.C. Hatfield, Tet. Lett., 4483 (1978)

65. T.H. Chan and S.D. Lee, unpublished results.

66. E.C. Friedrich and G. DeLucca, J. Org. Chem., 48, 1678 (1983).

67. T. Ibaraki and K. Ito, Bull. Chem. Soc. Jpn., 54, 3235 (1981).

68. M.E. Jung and M.A. Lyster, J. Org. Chem., 42, 3761 (1977); M.E. Jung, W.A. Andrews, and P.L. Ornstein, Tet. Lett., 4175 (1977).

69. A.H. Schmidt, Aldrichima Acta, 14, 31 (1981).

70. T. Aida, D.N. Harpp, and T.H. Chan, Tet. Lett., 3247 (1980).

71. J.W. Gillard and M. Israel, Tet. Lett., 513 (1981).

72. T.H. Chan and S.D. Lee, Tet. Lett., 1225 (1983).

73. Available from Aldrich Chemical Co.,

74. Y. Arto, T. Matsuo, and C. Aso, Bull. Chem. Soc. Jpn., 40, 130 (1967).

75. H.R. Greenberg and A.S. Perlin, Carbohydrate Research, 35, 195 (1974).

76. M.G. Voronkov, V.G. Komarov, A.I. Albanov, and E.I. Dubinskaya, Izv. Akad. Nauk SSSR, Ser. Khim., 2623 (1978).

77. S. Wolfe, Acc. Chem. Res., 5, 102 (1972).

78. K. Bohrends and G. Kiel, Naturwissenchaften, 54, 537 (1967).

79. (a) R. Hulme, G.J. Leigh, and I.R. Beattie, J. Chem. Soc., 366 (1960).

    (b) J.A.A. Keteelar, Z. Kristallog., 22, 155 (1935).

80. D. Kummer and H. Köster, Z. Anorg. Allg. Chem., 398, 279 (1973).

81. F.A. Hoppe-Seyler, Med. Chem. Untersuchunger, 3, 379 (1868); 4, 540 (1871); 4, 542 (1871).

82. F.A. Hoppe-Seyler, Z. Physiol. Chem., 3, 339 (1879).

83. H. Gilman, "Org. Syn.", Col. Vol. 1, 473 (1941).

84. U.S. Patent 2478456; Chem. Abstr., 44, 665 (1950).

85. L. Knorr, Ber., 17, 1635 (1884); Ann., 236, 290 (1886).

86. H. Fischer, "Org. Syn.", Col. Vol. 2, 202 (1943).

87. R. Chong and P. Clezy, Austral. J. Chem., 20, 935 (1967).

88. C. Paal, Ber., 18, 367 (1885); L. Knorr, *ibid.*, 18, 229, 1568 (1885).

89. Y.K. Yurev, Ber., 69, 440, 1944; 2492 (1936).

90. L. Meszares and M. Bantok, Chem. Abstr., 53, 15040 (1959); U.S. Patent 2600289; Chem. Abstr., 47, 4373 (1953); U.S. Patent 2951081; Chem. Abstr., 55, 4532 (1961).

91. T.H. Chan and S.D. Lee, J. Org. Chem., 48, 3059 (1983).

92. A. Nudelman, F. Braun, and E. Karoly, J. Org. Chem., 43 3788 (1978).

93. These tests were performed by Dr. T.A. Pursiano, Bristol Lab., Candiac, Canada.

94. R.A. Lloyd, C.W. Miller, D.L. Roberts, J.A. Giles, J.P. Dickerson, N.H. Nelson, C.E. Rix, and P.H. Ayers, Tob. Science, 20, 40 (1976).

95. H. Shigematsu, S. Shibata, T. Kurata, H. Kato, and M. Fiujimaki, J. Agri. Food Chem. 23, 233 (1975).

96. A. Vilsmeier and A. Haack, Ber., 60, 119 (1927).

97. G. Martin and S. Povignant, J. Chem. Soc. Perkin II, 1964 (1972).

98. K. Reimer, Ber., 9, 423 (1876); K. Reimer, and F. Tiemann, Ber., 9, 824 (1876).

99. E. Bamberger and G. Djierdjian, Ber., 33, 536 (1900).

100. H. Fischer, H. Beller, and A. Stern, Ber., 61, 1078 (1928).

101. A. Rieche, H. Gross, and E. Höft, Chem. Ber., 93, 88 (1960).

102. J. March, "Advanced Organic Chemistry", 2nd Ed., McGraw-Hill, (1977) p. 496.

103. R.A. Jones, C.F. Candy, and P.H. Wright, J. Chem. Soc., (C), 2563 (1970).

104. Cited from "Organic Chemistry (The Chemistry of Pyrroles)", Vol. 34, Academic Press, (1977), p. 153.

105. R.M. Silverstein, E.E. Ryskiewicz, C. Williams, and R.C. Koehler, J. Org. Chem., 20, 668 (1955).

106. A. Rieche and H. Gross, Chem. Technol., 10, 515 (1958).

107. J.K. Carson and N.M. Davis, J. Org. Chem., 46, 839 (1981).

108. M.H. Palmer, D.S. Leitch, and C.W. Greenhalgh, Tetrahedron, 34, 1015 (1978).

109. O. Carmora, R. Greenhouse, R. Landeros, and J.M. Muchowski, J. Org. Chem., 45, 5336 (1980).

110. H.M. Gilow and D.E. Burton, *ibid.*, 46, 2221 (1981).

111. J. DeSales, R. Greenhouse, and J.M. Muchowski, *ibid.*, 47, 3668 (1982).

112. H. Gross, A. Rieche, and G. Matthey, Chem. Ber., 96, 308 (1963).

113. M.E. Jung and M.A. Lyster, J. Am. Chem. Soc., 99, 968 (1977).

114. T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, (1981), Chapt. 7.

115. J.W. Barton, in "Protective Groups in Organic Chemistry", J.F.W. McOmie, Ed., Plenum, New York and London, (1973), pp. 46-56.

116. J.W. Barton, *ibid.*, pp. 61-83.

117. S.P. Breukelman, G.D. Meakins, and M.D. Tirel, J. Chem. Soc., Chem. Comm., 800 (1982).

118. A. Pictet, Ber., 37, 2796 (1904).

119. S.I. Zavyalov, N.I. Ardnova, and I.E. Mustafaeva, Chem. Abstr., 77, 164361 (1972).

120. S. Fattuta, Gazzetta, 90, 1645 (1960).

121. A. Alkaitis and M. Calvin, Chem. Comm., 292 (1968).

122. H. Sukawa, O. Seshimoto, T. Tezuka, and T. Mukai, Chem. Comm., 696 (1974).

123. T. Tezuka, O. Seshimoto, and T. Mukai, Tet. Lett., 1067 (1975).

124. T.H. Chan, M.A. Brook, and S.D. Lee, Tet. Lett., 1569 (1983).

125. D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 2nd Ed., McGraw-Hill, London, (1973), p. 58.

126. H.A. Stabb, Angew. Chem. Internat. Ed. Engl., 1, 351 (1962).

127. J.L. Rainey and H. Adkins, J. Am. Chem. Soc., 61, 1104 (1939).

128. A.A. Berlin, Chem. Abstr., 4606 (1945).

129. R.F. Nystrom and W.G. Brown, J. Am. Chem. Soc., 70, 3738 (1948).

130. A. Uffer and E. Schlittler, Helv. Chim. Acta, 31, 1397 (1948).

131. B.C. Challis and J.A. Challis, "The Chemistry of Amides", Interscience Publishers, New York (1970), pp. 795-801.

132. T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, Tet. Lett., 4555 (1969).

133. Y. Maki, K. Kikuchi, H. Sugiyama, and S. Seto, Chem. Ind., (London) 322 (1976).

134. A. Rahman, A. Basha, N. Waheed, and S. Ahmed, Tet. Lett., 219 (1976).

135. N. Umino, T. Iwakuma, and N. Itoh, *ibid.*, 763 (1976).

136. V.M. Mićović and M.L. Mihailović, J. Org. Chem., 18, 1190 (1953).

137. E. Mosettig, "Organic Reactions", Vol. VIII, John Wiley and Sons, Inc., New York, N.Y. (1948), pp. 218-257.

138. H.C. Brown and R.F. McFarlin, J. Am. Chem. Soc., 80, 5372 (1958).

139. H.C. Brown and B.C. Subbarao, *ibid.*, 80, 5377 (1958).

140. W. Weigant, E. Eberhardt, H. Linden, F. Schofer, and H. Linden, Angew. Chem., 65, 525 (1953).

141. H.C. Brown and A. Tsukamoto, J. Am. Chem. Soc., 83, 4549 (1961).

142. B.C. Challis and J.A. Challis, " The Chemistry of Amides", Interscience Publishers, New York, (1970), pp. 733-734.

143. H.A. Staab, M. Lüking, and F.H. Dürr, Chem. Ber., 95, 1275 (1962).

144. H.A. Staab, W. Rohr, and A. Mannschreck, Angew. Chem., 73, 143 (1961).

145. H.A. Staab and A. Mannschreck, Chem. Ber., 95, 1284 (1962).

146. G. Stork and P.F. Hudrlik, J. Am. Chem. Soc., 90, 4462, 4464 (1968).

147. H.O. House, L.J. Czube, M. Gall, and H.D. Olmstead, J. Org. Chem., 34, 2324 (1969).

148. I. Fleming, Chimia, 265 (1980).

149. T.H. Chan and P. Brownbridge, J. Chem. Soc., Chem. Comm., 578 (1979).

150. T.H. Chan and P. Brownbridge, J. Am. Chem. Soc., 102, 3534 (1980); Tetrahedron, 37, 387 (1981).

151. P. Brownbridge, T.H. Chan, M.A. Brook, and G.J. Kang, Can. J. Chem., 61, 688 (1983).

152. T.H. Chan and T. Chaly, Tet. Lett., 2935 (1982).

153. L. Weiler, J. Am. Chem. Soc., 92, 6702 (1970).

154. S. Danishefsky and T. Kitahara, *ibid.*, 96, 7807 (1974).

155. D.F. Taber, J. Org. Chem., 47, 1351 (1982).

156. From Karplus equation in D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 2nd Ed., McGraw-Hill, (1973), p. 101.

157. W. Keller-Schierlein and H. Gerlach, Fortschr. Chem. Org. Naturst., 26, 161 (1968).

158. H. Gerlach and E. Huber, Helv. Chim. Acta, 50, 2087 (1967).

159. J. Gombos, E. Haslinger, H. Zak, and U. Schmidt, Monatsch. Chem., 106, 219 (1975).

160. J. Gombos, E. Haslinger, H. Zak, and U. Schmidt, Tet. Lett., 3391 (1975).

161. E.J. Corey, K.C. Nicolaou, and L.S. Melvin, Jr., J. Am. Chem. Soc., 97, 653 (1975).

162. R.D. Clark and C.H. Heathcock, Tet. Lett., 2027 (1974).

163. S. Kim, C.Y. Hong, and Y.C. Moon, J. Org. Chem., 47, 4350 (1982).

164. R.E. Ireland, D.A. Evans, D. Glover, G.M. Rubottom, and H. Young, J. Org. Chem., 34, 3717 (1969).

165. S.C. Welch and R.Y. Wong, Tet. Lett., 1853 (1972).

166. G. Darzens, Compt. Rend., 139, 1214 (1904).

167. M.S. Newman and B.J. Magerlein, "Organic Reactions", Vol. 5, John Wiley and Sons, New York, N.Y. (1949), p. 413.

168. J.G. Grasselli and W.M. Ritchey, "Atlas of Spectral Data and Physical Constants for Organic Compounds", Vol. IV, 2nd Ed., CRC Press (1975); M.F. Fegley, N.M. Bortnick, and C.H. McKeever, J. Am. Chem. Soc., 79, 4144 (1959).

169. J.W.F. Wasley and K. Chan, Syn. Comm., 3(4), 303 (1973).

170. R.A. Jones, Aust. J. Chem., 19, 289 (1966); I. Gloede, K. Poduska, H. Gross, and J. Rudinger, Collect. Czech. Chem. Comm., 33, 1307 (1968).

171. R.L. Shriner and R.C. Fuson, "The Systematic Identification of Organic Compounds", John Wiley and Sons, New York, N.Y. (1948), pp. 229-230.