1989

The [1,4] C-->O silyl migrations of various 2-(trialkylsilyl)-3-(hydroxymethyl) furans and thiophenes toward the synthesis of furanoplagiochilal.

Patrick Gianpietro. Spinazze
University of Windsor

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THE [1,4] C→O SILYL MIGRATIONS OF VARIOUS 2-(TRIALKYLSILYL)-3-(HYDROXYMETHYL)FURANS AND THIOPHENES : TOWARD THE SYNTHESIS OF FURANOPLAGIOCHILAL

by

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A Thesis
submitted to the
Faculty of Graduate Studies and Research
through the Department of
Chemistry and Biochemistry in Partial Fulfillment
of the requirements for the Degree
of Master of Science at
the University of Windsor

Windsor, Ontario, Canada

1989

ISBN 0-315-50535-4

ACB 5/25

ABSTRACT

Part 1: **THE [1,4] C→O SILYL MIGRATIONS OF VARIOUS 2-(TRIALKYLSILYL)-3-(HYDROXYMETHYL)FURANS AND THIOPHENES**

Many 2-trialkylsilyl-3-hydroxymethyl-furans and -thiophenes undergo a [1,4] C→O silyl migration when treated with bases containing either potassium or sodium counterions to produce 3-[(trialkylsilyl)oxymethyl]-furans and -thiophenes in excellent yields. The reaction proceeds efficiently in DMF, THF and DME; however the reaction would not proceed in ether. The reactivity of the bases in various solvents was directly related to their hard/hard interactions with the oxygen atom and counterion solvation capabilites. The reaction proceeds along a catalytic route when sodium hydride is employed as the base, and the rearrangement proceeds through an intramolecular migration of the silyl group. The proton transferred to the α-furan carbon originates from the hydroxyl group of unrearranged starting material and not the solvent.

Part 2: **TOWARD THE SYNTHESIS OF FURANOPLAGIOCHILAL**

Synthesis of the natural product furanoplagiochilal 94 was attempted. While progress has been made, difficulties have been encountered in the 7-membered ring closing steps including the intramolecular cyclopropanation and Aldol reactions. Further problems have been observed with the attempted β-keto ester formation in the last sequence.

To My Family

ACKNOWLEDGEMENTS

The author is grateful to his supervisor Dr. Brian A. Keay for his encouragement and guidance during the course of this work.

Thanks are also directed to members of the faculty and staff of the Department of Chemistry and Biochemistry, as well as my fellow graduate students, in particular, C. Rogers-Goulin, Jean-Louis Bontront and Edward Bures for their useful discussions, interesting company, and patience.

The author would also like to thank D. Jones and M. Fuerth for their expertise in providing numerous spectral data.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

bp	boiling point
Bu	butyl
$Cu(acac)_2$	cupric acetylacetonate
d	doublet
DEPT	Distortionless Enhancement by Polarization Transfer
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
eq	equivalents
Et	ethyl
Et_2O	diethyl ether
g	gram
h	hour
HMPA	hexamethylphosphoramide
IR	infrared
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
min	minute
mmol	millimole
mp	melting point
MEM	methoxymethyl
NMR	nuclear magnetic resonance
OAc	acetate
Ph	phenyl
Pr	propyl
q	quartet
s	singlet
t	triplet
THF	tetrahydrofuran
THP	tetrahydropyran
tlc	thin layer chromatography

Ts	p-toluenesulfonyl

1.0.0 *The [1,4] C→O Silyl Migrations of Various 2-(Trialkylsilyl)-3-(Hydroxymethyl)Furans and -Thiophenes*

1.1.0 *INTRODUCTION*

1.1.1 Existing [1,4] C→O Silyl Migrations

Silyl migrations are quite common in the chemical literature. These migrations are of the form [1,n] X→Y where n is usually limited from 2 through 5[1,2]; however, rearrangements across greater numbers of atoms have been reported.[3] The elements X and Y to date have been limited to carbon and/or oxygen. Thus the types of silyl migrations reported have included [1,2-5] C→O,[4,5] [1,2-5] O→C,[6,7,8] [1,2] C→C[9] and [1,4] C→C.[9,10] Although the literature is replete with [1,2] C→O silyl migrations[1,2] only a handful of [1,4] C→O have been cited. This section will review the existing [1,4] C→O silyl migrations while the following section will outline the mechanism of silyl migrations. As [1,4] C→O silyl migrations are believed to follow a similar mechanism to [1,2] C→O silyl migrations the following section will emphasize the [1,2] C→O silyl migration mechanism.

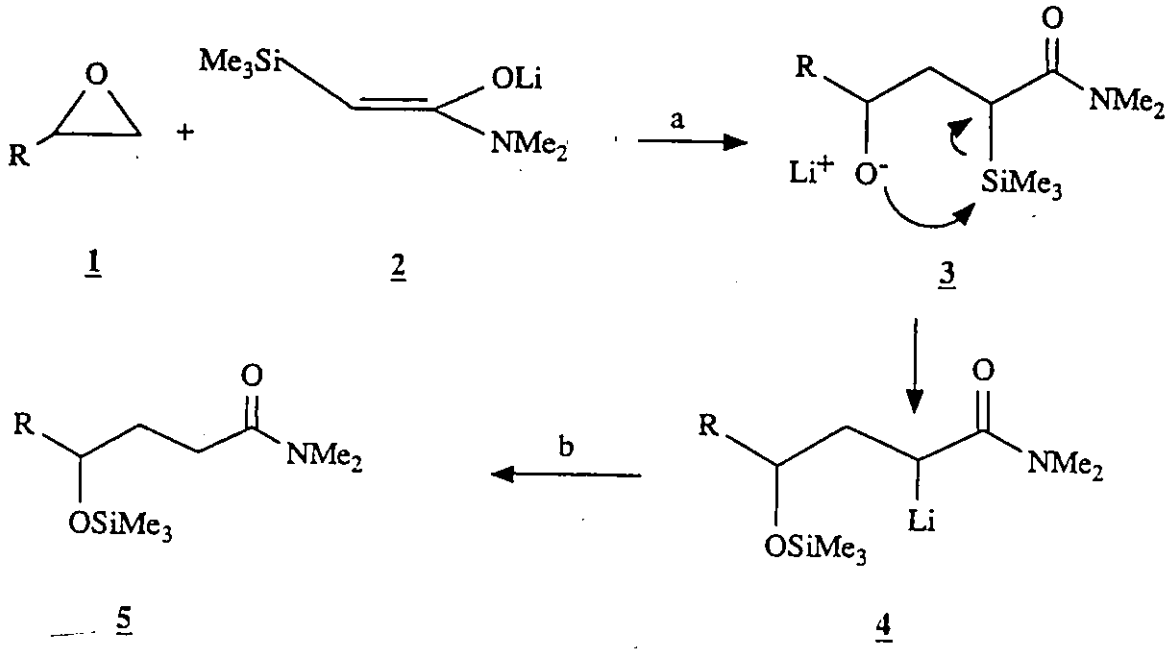
In 1978,[11] Woodbury and Rathke reported the first [1,4] C→O silyl migration. They treated epoxide 1 with the lithium enolate 2, which resulted exclusively in the formation of silyl ether 5. This was rationalized by attack of the nucleophile on the least hindered carbon of the epoxide to give 3. Compound 3 then underwent a [1,4] C→O trimethylsilyl migration to provide 4, which on workup gave 5 (Scheme 1).

Matsuda[12,13] showed that epoxide 6 (Scheme 2) in the presence of anion 7, at -75°C would produce the alkoxide 8. Compound 8 then underwent a [1,4] C→O silyl migration providing anion 9 which upon protonation gave silyl ether 10.

Isobe[14] observed that alcohol 12 (Scheme 3), when treated with a catalytic quantity of base (either NaH or KF) in THF, led to the siloxy compound 15 upon workup; however, when 1 equivalent of n-BuLi was employed as the base, the resulting carbanion 13 could be trapped with allyl bromide, providing 14 exclusively. This indicated that the migration was complete before the addition of the electrophile as no O-alkylation was observed.

Isobe[1] also showed that alcohol 16, when treated with methyllithium, provided 17 in 40% yield through a [1,4] C→O silyl migration (Scheme 4). Compound 18; however did not undergo a direct [1,4] C→O silyl migration. Apparently a 1,4 addition of MeLi to 18 provided a carbanion at C-1 which allowed rotation of the C_1-C_2 bond. A [1,4] C→O silyl migration then occurred providing a dianion 19b which on workup gave 19a. The existence of the a dianion was proven by the addition of D_2O providing 19c

Scheme 1



5a) R= Me 5b) R= Ph

a) THF, 2 hr, 25° b) H_2O

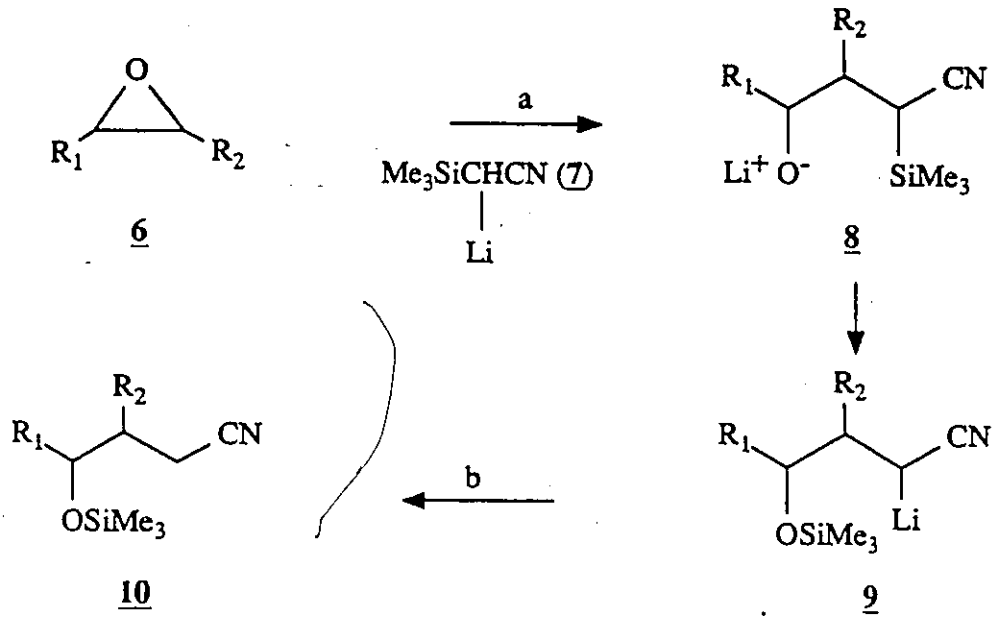
exclusively.

The examples cited above have employed an electron withdrawing group which stabilized the carbanion formed after the silyl migration. The groups employed have included amides, nitriles and sulfones. In 1981, Fleming[16] reported that a trimethylsilyl moiety would perform the same task. Alcohol 20, when treated with NaH in THF gave the rearranged compound 23 (Scheme 5); however, the migration did not proceed in ether, DME or benzene. Furthermore, the reaction did not occur when lithium or magnesium bases were used but was successful with potassium t-butoxide.

A similar [1,4] C→O silyl migration was reported[16] when styrene oxide was treated with compound 24, providing the alkoxide 25. A [1,4] C→O silyl migration then produced the carbanion 26. Cyclopropane 27 was provided by intramolecular displacement of the siloxy group. Diol 28, on the other hand, was observed when 26 reacted with excess styrene oxide in the mixture (Scheme 6).

Takeda showed[17] that he could from cyclobutanes by the reaction of 29 with (chloromethyl)oxiranes 30. The carbanion reacted to form the lithium alkoxide 31 which

Scheme 2



10a) R_1= Me R_2= H

10b) R_1= Et R_2 =H

10c) R_1= Ph R_2= H

10d) R_1+ R_2= -$(CH_2)_4$-

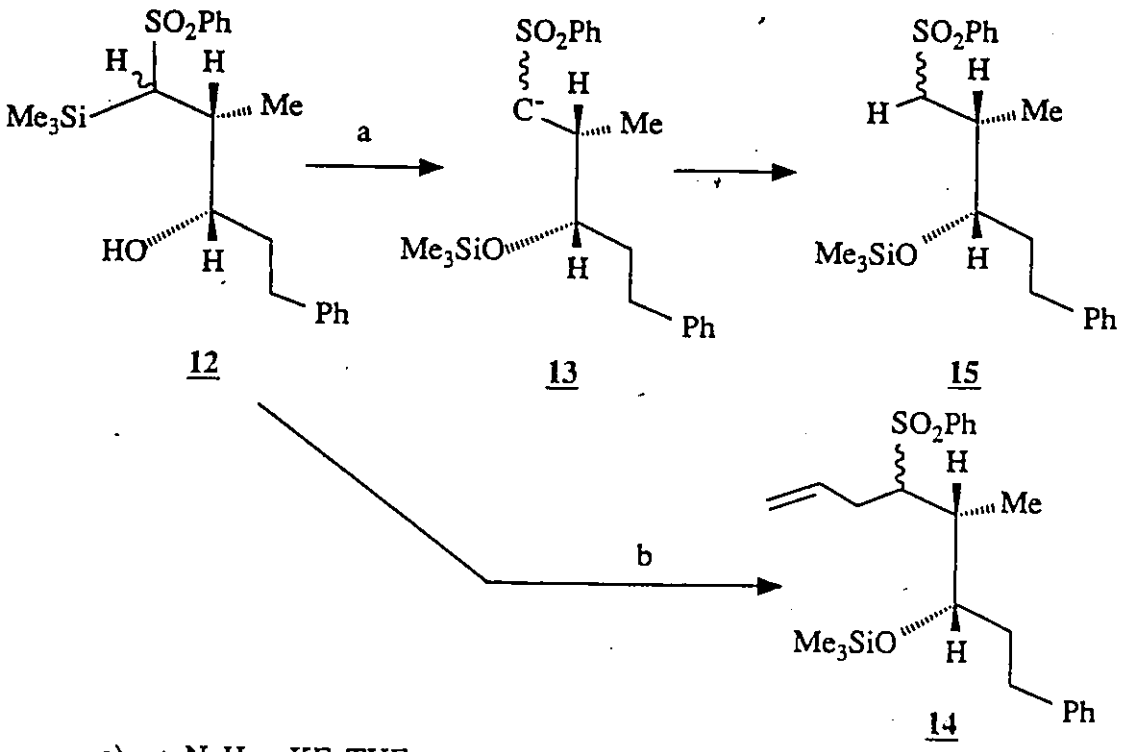
a) DMF, -75 to -35°C, 6 hr

b) NH_4Cl

then underwent a [1,4] C→O migration which gave 32. Neither intermediate was isolated but their existence was postulated by the isolation of product 33, formed by displacement of the chlorine atom by the silyl stabilized carbanion (Scheme 7).

While attempting to rationalize a previous [1,4] C→O silyl rearrangement (Scheme 5),[16] Fleming postulated that the solvent THF was the proton source for quenching the carbanion of the migrated product. In 1984, Brook[18] proved that THF was not the protonating agent. The deutero-carbinol (34) was treated with Na/K to give after migration the deuterated silyl ether 35 exclusively, thus indicating that the protonating agent is not the solvent but the proton of the hydroxy group in the starting material 34 (Scheme 8).

Scheme 3



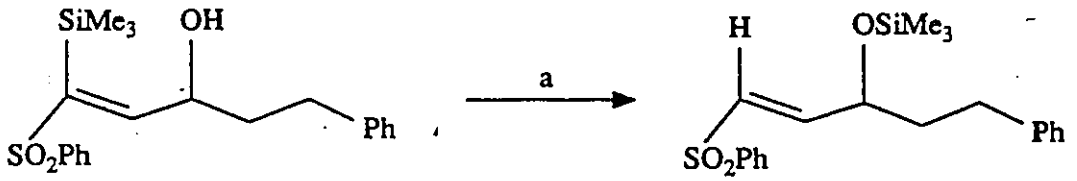
a) cat. NaH or KF, THF

b)i) 1 eq. n-BuLi ii) allyl bromide

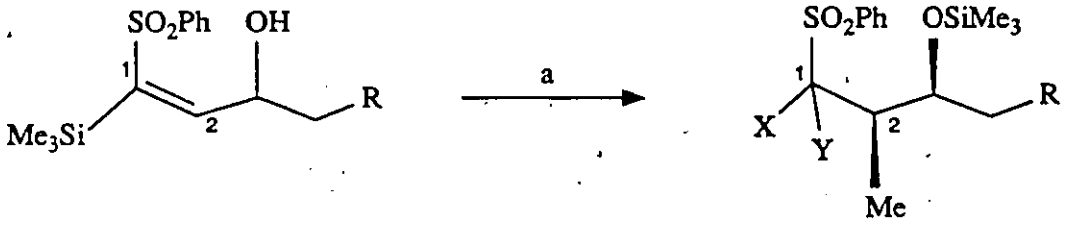
In 1985, Kuwajima[19] reported [1,4] C→O silyl migrations where the intermediate carbanion could be trapped with electrophiles. System 36, when treated with a catalytic quantity of potassium hydride provided the rearranged product 37 (89% yield); however, when the same system was treated with 1 equivalent of n-butyllithium the resulting carbanion was easily alkylated with iodohexane to give 38. Similarly, alcohol 39 provided 40 and 41 after a quench with H_2O and iodomethane respectively (Scheme 9).

This section has reviewed the previous [1,4] C→O silyl migrations in the literature. The following section will examine the mechanism of [1,4] C→O silyl migrations with emphasis on the mechanism of [1,2] C→O silyl migrations, as it has been postulated that [1,4] C→O silyl migrations proceed through an analogous mechanism.

Scheme 4



16 **17**



18 **19**

R= C≡CCH$_2$OTHP

R= C≡CCH$_2$OH

R= (CH$_2$)$_3$OCH$_2$OCH$_3$

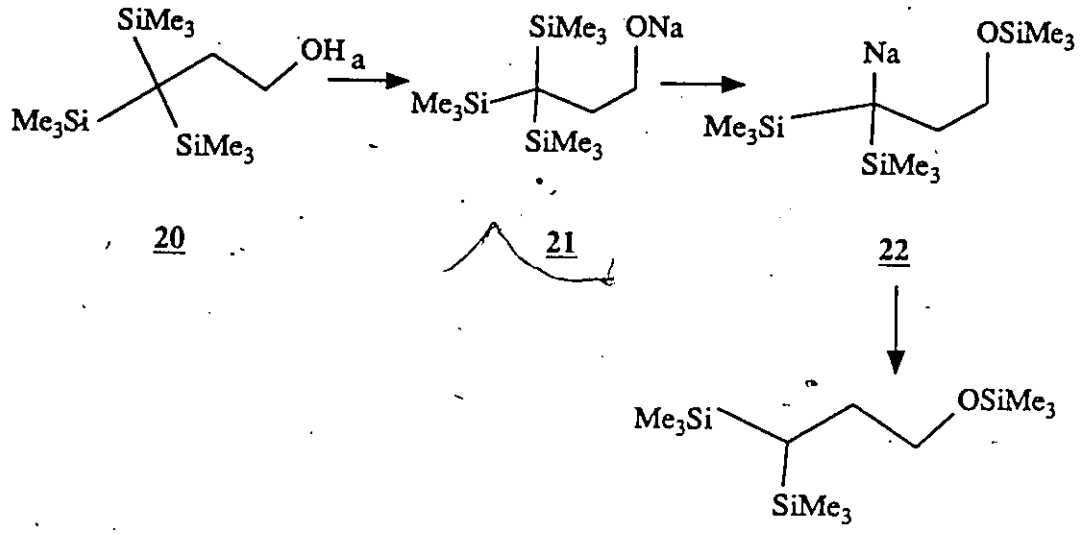
a) 2 eq. MeLi, THF, -78°C

19c) CH_2Ph X=Y=H

19b) CH_2Ph X=Y=Li

19c) CH_2Ph X=Y=D

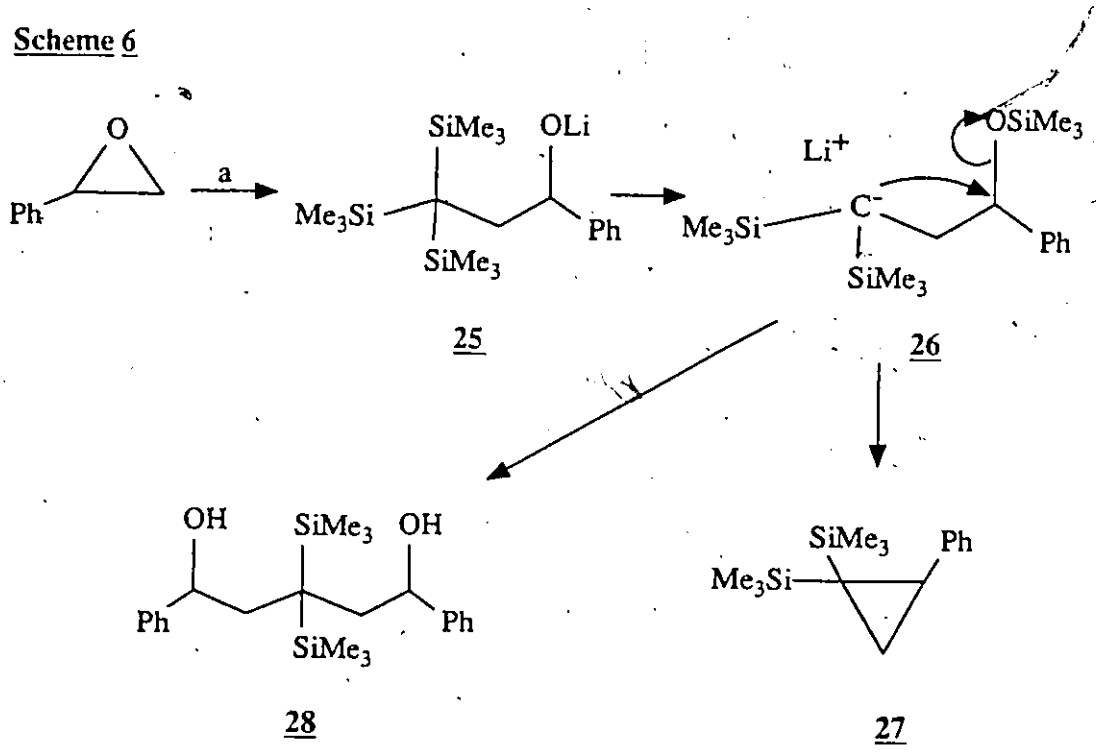
Scheme 5



20 21 22 23

a) NaH, THF

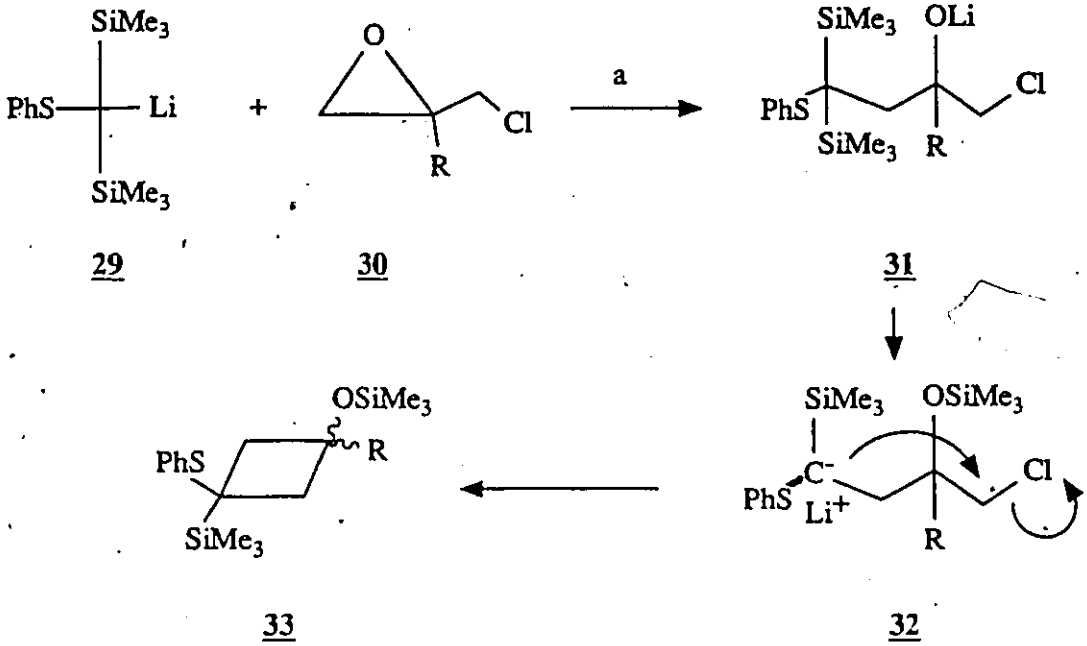
Scheme 6



25 26 28 27

a) $(Me_3Si)_3CLi$ (24), THF

Scheme 7

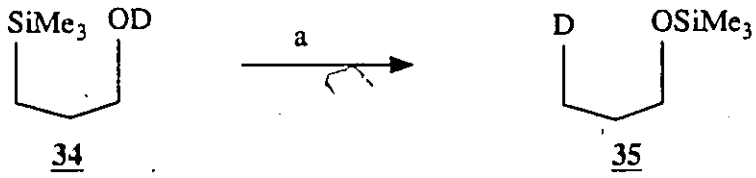


29 30 31 32 33

33a) R= H
33b) R= Me
33c) R= Et
33d) R= n-Bu
33e) R= $(CH_2)_2Ph$
33f) R= Ph

a) THF, 0°C

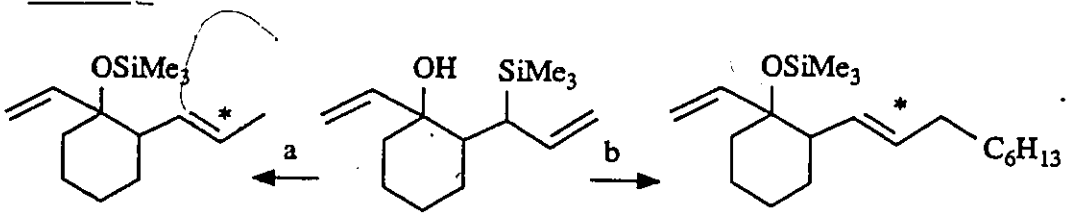
Scheme 8



34 35

a) cat. Na/K, THF

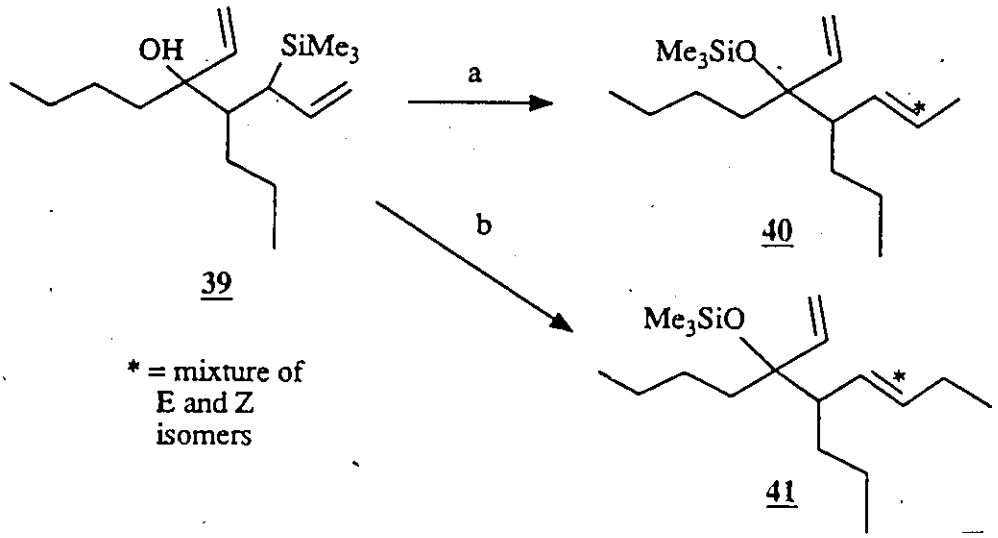
Scheme 9



36 37 38

a) cat. KH, THF

b) n-BuLi, $C_6H_{13}I$



39 40 41

* = mixture of E and Z isomers

a) 0.1 eq. KH, THF

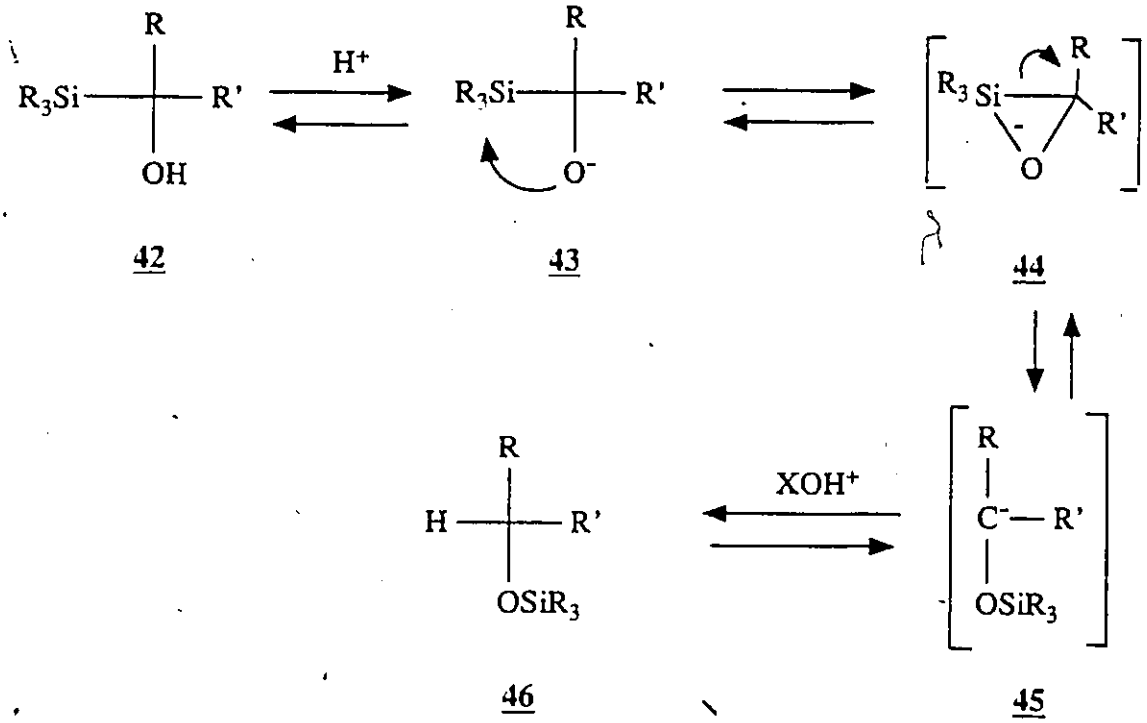
b) n-BuLi, THF; MeI

1.1.2 The Mechanism and Reaction Conditions of [1,4] C→O Silyl Migrations

The mechanism of [1,4] C→O silyl migrations is believed to be similar to that of [1,2] C→O silyl migrations. Very little work has been done on the mechanism of [1,4] C→O silyl migrations directly. Therefore this section will review the literature on the mechanism of [1,2] C→O silyl migrations to infer the characteristics of [1,4] C→O silyl migrations.

Brook reported[20] that the mechanism of [1,2] C→O silyl migration involved initial base deprotonation of the alcohol in compound 42 (Scheme 10), followed by alkoxide attack on the silicon atom in compound 43 providing a pentavalent silicon type intermediate 44.[20,21] This process is postulated due to the availability of vacant silicon d orbitals. The Si-C bond is then cleaved to compound 46 presumably through carbanion 45; however, the lack of reactivity of carbanion 45 towards electrophiles may suggest the equilibrium lies towards the pentavalent silicon intermediate 44 until a proton source is added.

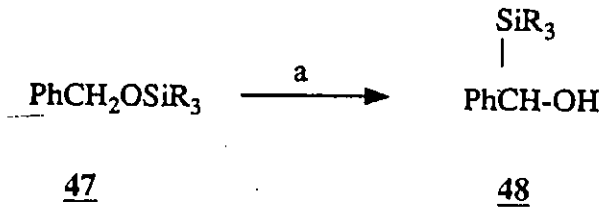
Scheme 10



The reversibility indicated in Scheme 10 is postulated since [1,2] O→C silyl migration (Wittig rearrangement) are common.[1] An example of the Wittig rearrangement is given in Scheme 11. When silyl ether 47 was treated with 1 equivalent of a strong base, a [1,2] O→C silyl rearrangement occurred providing alcohol 48 in good yield (Scheme

11).[1]

Scheme 11



47 48

a) 1 eq. RLi; NH_4Cl R = Me, Et

The reversibility of silyl migrations was rationalized qualitatively by bond energy descriptions.[1] When a catalytic quantity of base was involved ([1,2] C→O silyl migration), the driving force of the reaction was the formation of the stronger Si-O bond in silyl ether 46 at the expense of the C-Si bond in alcohol 42.[1] The equilibrium therefore shifted toward compound 46. In the situation where one equivalent of strong base was used ([1,2] O→C silyl migration) the stabilities of the anions were compared. The stability of the alkoxide in compound 43 was greater than the stability of the carbanion in 45. The energy gained in proceeding from compound 45 to 43 was greater than the energy gained by the formation of a Si-O bond thereby resulting in [1,2] O→C silyl migration.

Bases which proved efficient in the catalytic [1,2] C→O silyl migration of alcohol 42 to compound 46 included Na/K alloy, Na, NaH, MeLi, t-BuLi, Et_2NH and other amine bases.[21b]

The ([1,2] C→O silyl) rearrangements are most often performed in THF[2]; however they have also been performed in solvents such as DMSO,[20] $CHCl_3$[20] and diethyl ether.[22]

The first [1,4] silyl migration was performed in DME[9](see Scheme 1), however most rearrangements have been carried out in THF. Migrations ([1,4] C→O) using benzene, ether and dioxan as solvents were ineffective (see Scheme 5).[16]

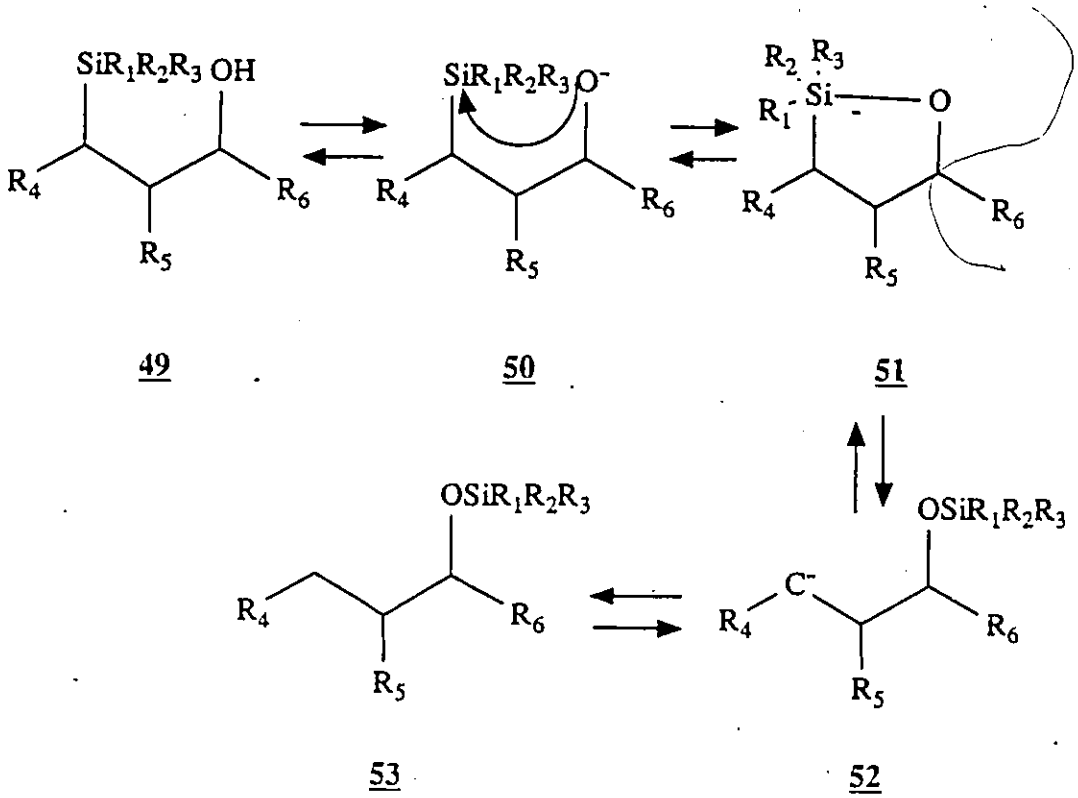
Bases used in previous [1,4] C→O silyl migrations included MeLi,[15] n-BuLi,[19] NaH,[14,16] KH,[19] KF[14] and a variety of complex lithium bases.[11-13,17]

It has been postulated that protonation of the carbanion resulting from migration was performed by the solvent (THF).[16] Further study using deutero carbinols[18] proved this theory incorrect. The alcoholic moiety was deuterated and the compound was subjected to migration conditions. The only product obtained was the 1-silyl ether-4-deuterio compound 35 (Scheme 8) proving that starting material was the

protonating agent (vide supra).

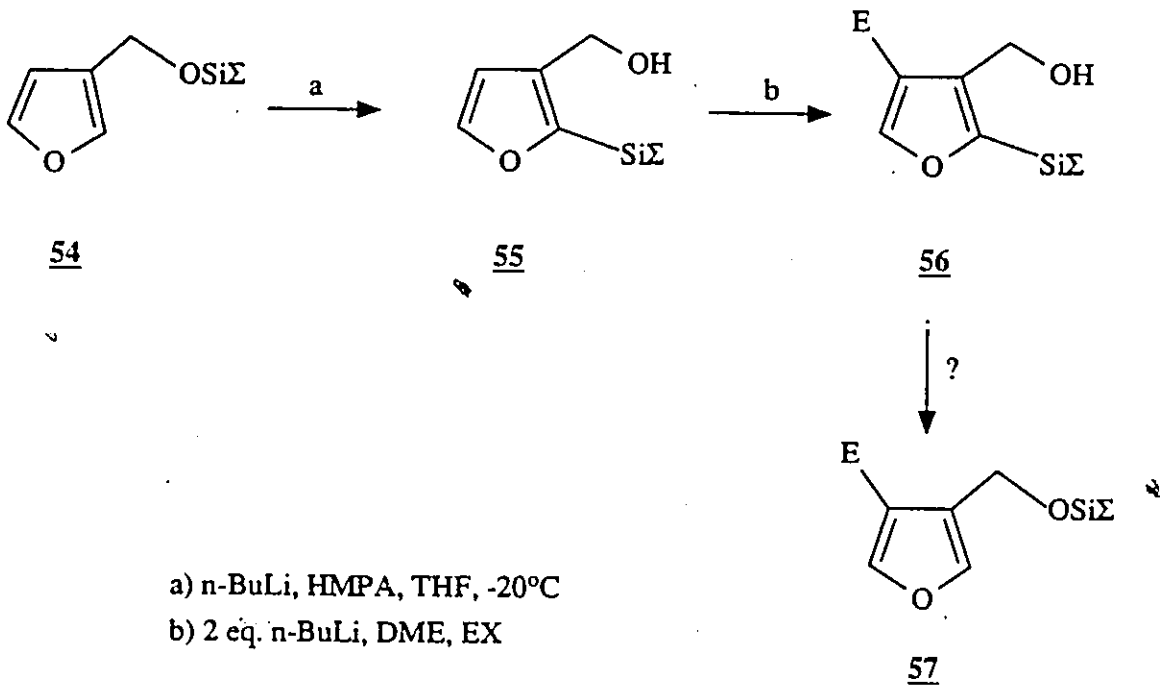
It has been postulated that [1,4] C→O silyl migrations proceed along the same mechanistic pathway as [1,2] C→O silyl migrations.[14,15] The mechanism illustrated in Scheme 12 is consistent with the data presented to this date[11-19] and as [1,4] O→C silyl migrations are known the steps shown are reversible.[8]

Scheme 12



Among the few [1,4] C→O silyl migrations reported none have been used synthetically. These rearrangements have the potential of being extremely useful in synthesis especially with furans and thiophenes since they provide a dual purpose. In systems such as 56 a silyl rearrangement would not only remove the silyl group from the ring but also concomitantly protect the alcohol moiety thus providing 3,4-disubstituted furans; a difficult system to prepare.[23] Since 3,4-disubstituted furans and thiophenes are commonly found in natural products it became of interest to determine not only if these migrations would occur, but also to explore the scope and limitations of the reaction. The methodology presented in Scheme 13 would thus provide a convenient direct route to 3,4-disubstituted furans.

Scheme 13



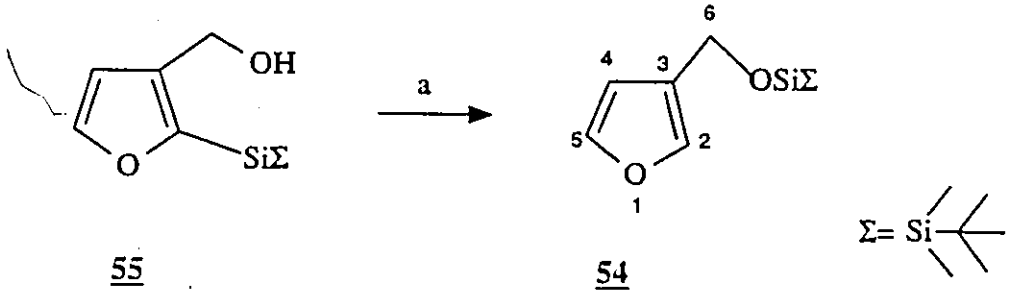
54 55 56 57

a) n-BuLi, HMPA, THF, -20°C
b) 2 eq. n-BuLi, DME, EX

1.2.0 *RESULTS AND DISCUSSION*

Treatment of furan 55 with excess sodium hydride (5 eq.) in DMF provided the silyl ether 54 (Scheme 14). The ^{1}H NMR spectrum of 54 exhibited two α-furan proton signals (H-2 and H-5) at δ 7.51 and one β-furan proton (δ 6.42) indicating that the silyl moiety was no longer attached to the furan ring. The upfield shift of the methyl groups attached to the silane from δ 0.26 (in compound 55) to δ -0.04 (in compound 54) also confirmed this observation; a silyl shift from C-2 to oxygen minimizes the anistropic effect thus shifting the methyl absorbances upfield (Figure 1). A shift in the methylene protons H-6 from δ 4.57 in alcohol 55 to δ 4.54 in silyl ether 54 was observed. The IR spectrum also indicated a lack of an O-H absorbtion (3319 cm^{-1} in 55).

Scheme 14



55 54

a) NaH (5 eq.); NaCl

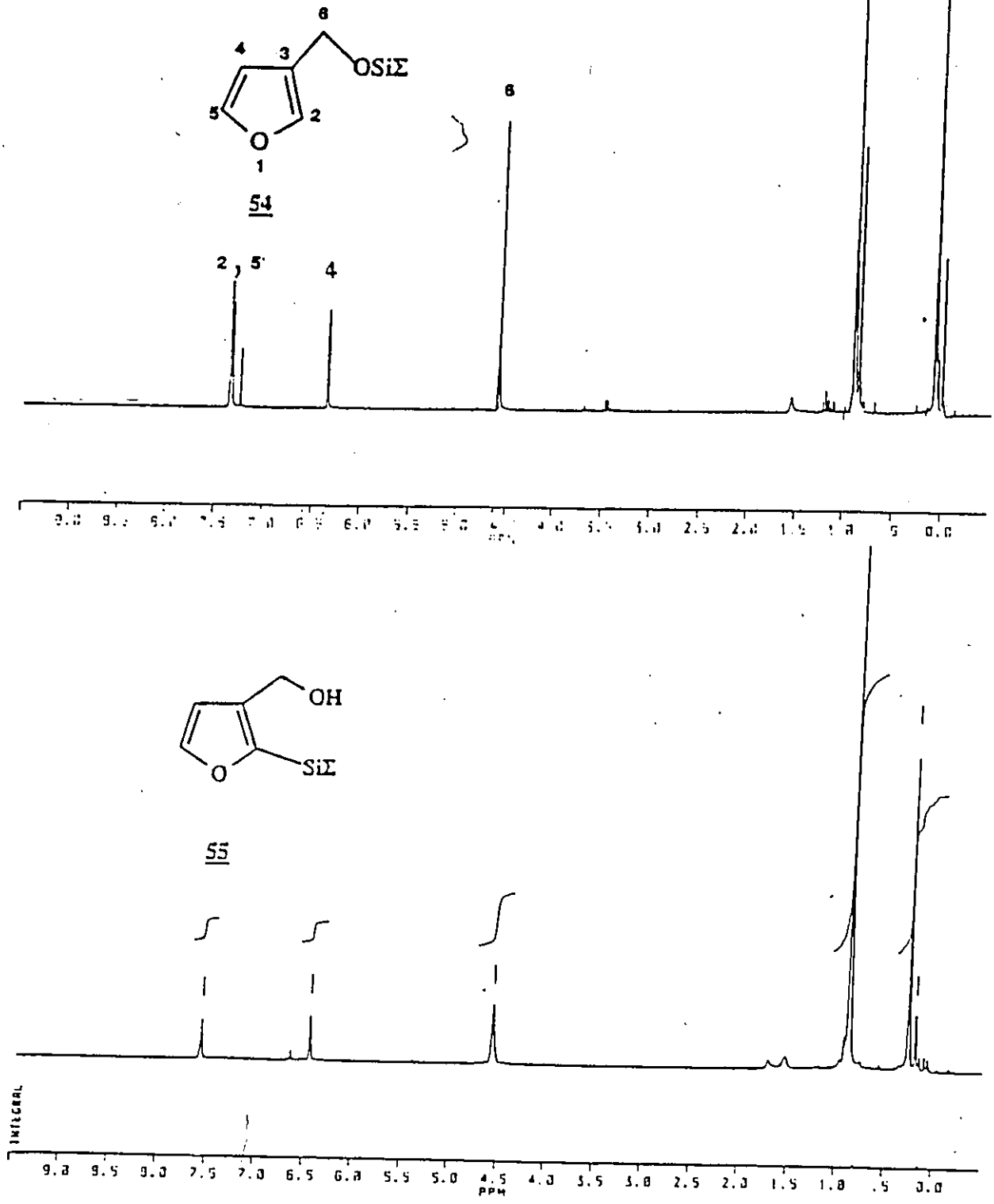
Finally the structure of 54 was confirmed by comparing the spectral data of 54 with the compound prepared by an independent synthesis. The synthesis involved the reduction of 3-furoic acid 58 with lithium aluminum hydride[24] followed by the silylation[25] of the resulting alcohol 59 (Scheme 15). The spectral data of synthetic silyl ether 54 were identical with those obtained when alcohol 55 was treated with sodium hydride (Scheme 14).

The migration was attempted with a variety of alcohols. These alcohols varied in the nature of the silyl group at the C-2 position of the ring as well as the type of hetero aromatic ring (furan or thiophene). The synthetic utility of this procedure was also of interest. Therefore, C-4 group substitution as well as the nature of the hydroxy group (primary or secondary) was varied prior to migration and the effect on the migration was studied.

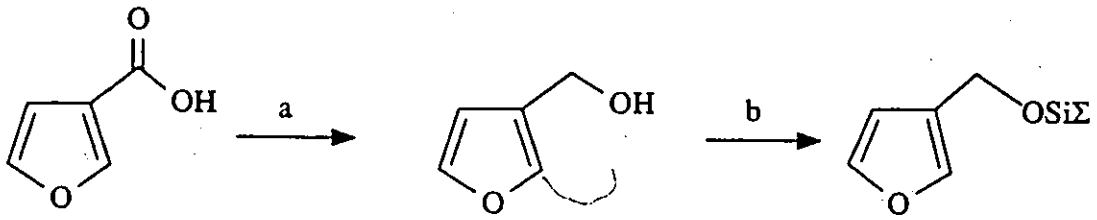
The alcohols employed in this study are shown in Table 1 and were all prepared from an appropriately O-silylated 3-hydroxymethyl furan or thiophene (ie. compound 54, Scheme 13). Compounds 60-66 and 69-71 were prepared by a [1,4] O→C silyl migration

Figure 1

^{1}H NMR spectra of 54 and 55



Scheme 15

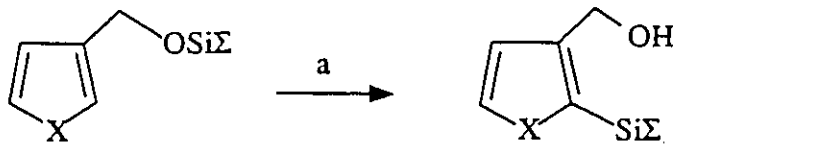


58 59 54

a) $LiAlH_4$, Et_2O

b) (t-Bu)Me_2SiCl, imidazole, DMF

Scheme 16



X = O or S

54 55

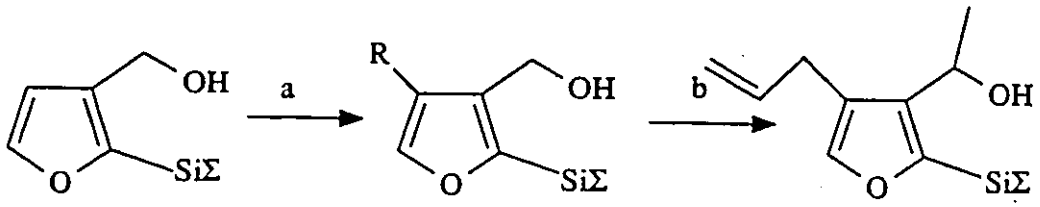
a) n-BuLi, HMPA, THF, -20°C, 1h

by treating the starting silyl ether with n-butyllithium/HMPA at -20°C (Scheme 16).[8]

Compounds 67 and 68 were prepared by the lithiation[26] of 55 with two equivalents of n-BuLi followed by a quench with N,N-dimethyl formamide and allyl bromide respectively (Scheme 16). Compound 72 was prepared by a Swern oxidation of 68 to an aldehyde followed by treatment with methyl lithium (Scheme 17).

The results of the various [1,4] C→O silyl migrations are shown in Table 1. The reaction was limited neither to the t-butyldimethylsilyl group nor to furans as evident by the many examples in Table 1 (entries 1-10 and 14). Generally the yields are high for furans and thiophenes in both DMF and THF. Various groups in the C-4 position of the furan ring were tolerated (entries 9, 10, and 14) and the migration was not limited to primary alcohols (entry 14). Several of the silyl ethers formed by the reaction were labile under the conditions of NaH/DMF (entries 11, 12 and 13). For the cases in which no silyl ether was produced, 3-hydroxymethyl furan was isolated in excellent yield. Therefore a

Scheme 17



55 67 R= CHO 72

68 R= $CH_2CH=CH_2$

a) n-BuLi; RX

b) $(COCl)_2$, DMSO; MeLi, THF

reductive cleavage of the silyl ether by NaH must be occurring.[27] To illustrate this point the O-silylated compounds of 69-71 were prepared (Scheme 16) and treated with NaH/DMF; desilylation occurred within 1 hour.

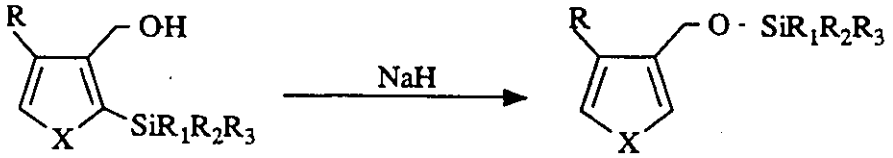
That desilylation occurred after the migration was proved by the following reactions on furan 66. Furan 66 was treated under the normal migration conditions (5 eq. NaH, 0.05M starting material in DMF) for 5 minutes in the first experiment and for 1 hour in the second experiment (Scheme 18). In the first experiment the silyl ether 79 was obtained in 81% yield; however, in the second experiment only 3-hydroxymethyl furan 59 was produced. Thus desilylation occurred after [1,4] C→O silyl migration, since if desilylation had occurred before migration, then none of the silyl ether 79 would have been observed.

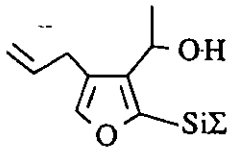
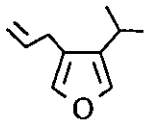
Various solvents and bases were employed in the silyl migrations to expand the scope and limitations of the reaction. These are illustrated in Table 2.

Reaction times for the different base/solvent systems varied widely. In DMF the migration was complete in 5 minutes (entry 1) while in THF and DME longer times (16h and 56h respectively) were required (entries 2, 3); no reaction occurred in diethyl ether (entry 4). This result was not unexpected since other [1,4] C→O silyl migrations using sodium hydride in ether have proved ineffective.[16] The ease of migration in DMF may be due to the high sodium solvating capabilities of this solvent.[28]

Surprisingly, the migration, when performed in DMF with alcohol 55, only provided silyl ether 54. The fact that the aldehyde was not produced indicated that a formal C-2 carbanion did not exist during the reaction (Scheme 19). It is well known that a quench of the α-furan carbanion 86 with DMF will provide the corresponding formyl furan 87.[29]

TABLE 1 1,4 C→O Silyl Migration Conditions and Yields

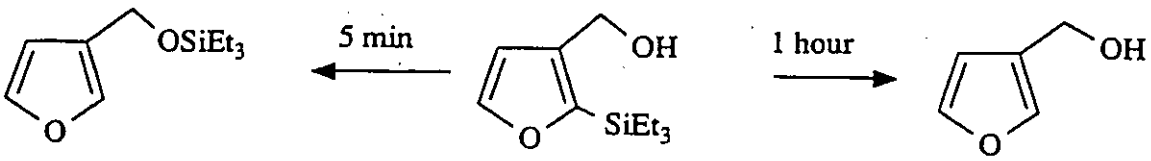


Entry	Compound		Product	Conditions[a] Time (Yield) DMF	THF
1	60	X=S, R_1=R_2=Ph, R_3=t-Bu, R_4=H	73	1h(88)	16h(93)
2	61	X=O, R_1=R_2=Ph, R_3=t-Bu, R_4=H	74	1h(89)	16h(91)
3	62	X=O, R_1=R_2=R_3=i-propyl, R_4=H	75	1h(89)	16h(15)[b]
4	63	X=S, R_1=R_2=R_3=i-propyl, R_4=H	76	1h(86)	16h(90)
5	64	X=O, R_1=R_2=R_3=n-Bu, R_4=H	77	1h(75)	16h(81)
6	55	X=O, R_1=R_2=Me, R_3=t-Bu, R_4=H	54	1h(88)	16h(86)
7	65	X=S, R_1=R_2=Me, R_3=t-Bu, R_4=H	78	1h(76)	16h(89)
8	66	X=O, R_1=R_2=R_3=Et, R_4=H	79	5 min(81)	------
9	67	X=O, R_1=R_2=Me, R_3=t-Bu, R_4=CHO	80	½h(88)	------
10	68	X=O, R_1=R_2=Me, R_3=t-Bu, R_4=$CH_2CH=CH_2$	81	-----	16h(83)
11	69	X=S, R_1=R_2=Ph, R_3=Me, R_4=H	82	1h(0)[c]	16h(0)[c]
12	70	X=O, R_1=R_2=R_3=Me, R_4=H	83	1h(0)[c]	16h(0)[c]
13	71	X=O, R_1=R_2=Me, R_3=i-propyl, R_4=H	84	1h(0)[c]	16h(0)[c]
14	 72		 85	1h(95)	------

a) All reactions were performed using 5 equivalents of NaH at a 0.05M starting material concentration.
b) 70% of 3-hydroxymethylfuran was also recovered.
c) Only 3-hydroxymethylfuran was recovered in excellent yield

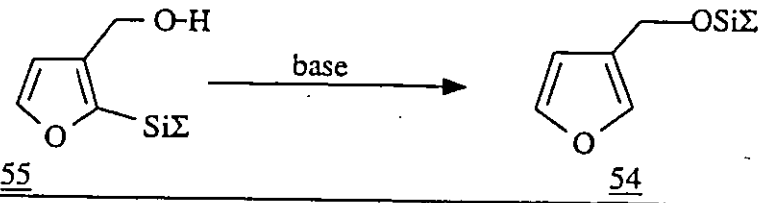
The use of various counterions (Na, K, Mg, Li) were also examined. With

Scheme 18



79 66 59

TABLE 2 The Effect of Various Bases on the 1,4 C→O Silyl Migration



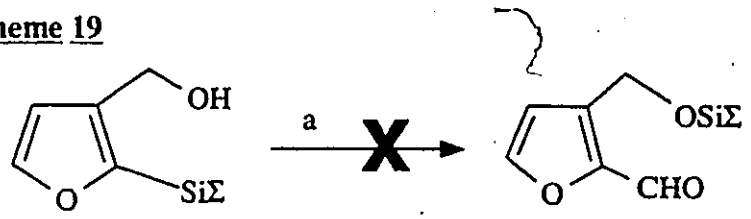
55 54

Entry	Compound	Base	Solvent	Time	Product(Yield)
1	55	5 eq. NaH	DMF	5 min	54 (88)
2	55	5 eq. NaH	THF	16 h	54 (86)
3	55	5 eq. NaH	DME	56 h	54 (96)
4	55	5 eq. NaH	Et_2O	7 d	S.M.
5	55	1 mol % NaH	DMF	15 min	54 (92)
6	55	5 eq. KH	THF	2 d	54 (61)
7	55	5 eq. NaOH	DMF	1 h	54 (64)[a]
8	55	1 eq. CH_2=CHMgBr	THF	1 d	S.M.
9	55	1 eq. MeLi	THF	1 d	S.M.
10	55	1 eq. n-BuLi	THF	1 d	S.M.

a) 3-Hydroxymethylfuran (23%) was also isolated.

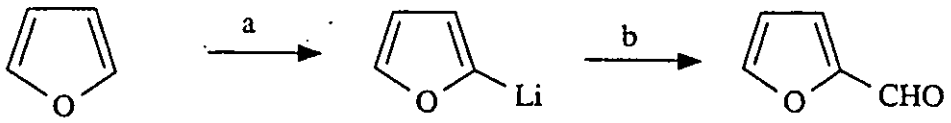
potassium hydride in THF migration occurred which provided 54 in 61% yield (entry 6). Potassium hydride was not used with DMF as it is known to reduce DMF to dimethylamine after hydrolysis[30]; however, the use of THF as solvent required extremely long reaction times (2 days). When the procedure was performed with sodium hydroxide in DMF, migration occurred (with some desilylation) which provided the expected product in 64% yield (entry 7). Vinyl magnesium bromide, MeLi, or n-BuLi only provided starting material 55 (entries 8, 9, 10).

Scheme 19



55

a) NaH, DMF



86 87

a) n-BuLi b) DMF

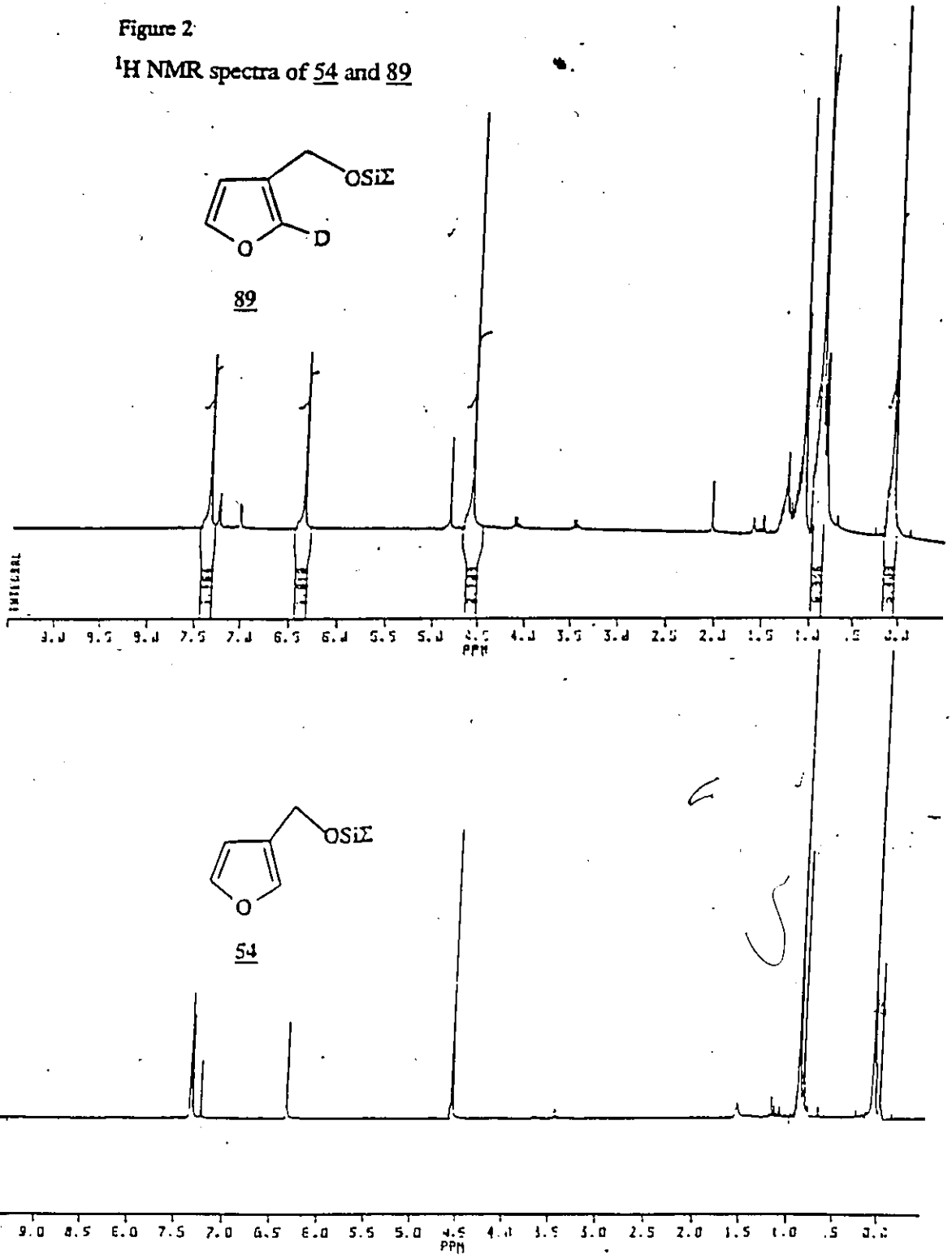
Catalytic quantities of NaH in DMF induced the silyl migration (entry 5). The rearrangement was complete in 15 minutes.

A question arose as to the source of the proton which was being transferred to the α-furan carbon. To prove that the proton source was indeed the hydroxyl hydrogen of unrearranged starting material the following experiment was conducted. Compound 88 was prepared by treating alcohol 55 with excess D_2O in DME. The solution of D_2O, compound 88 and DME was passed through a plug of sodium sulfate directly into a solution of NaH in DMF. Workup after 5 minutes gave exclusively the deuterated silyl ether 89 (Scheme 20).

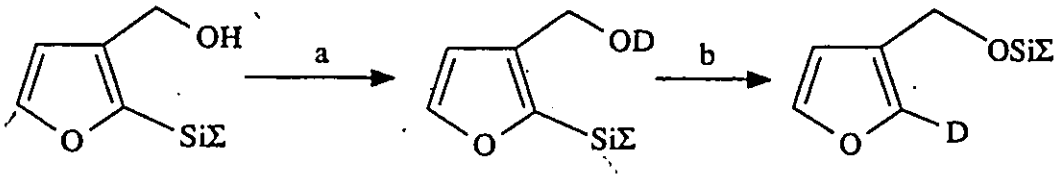
The ^1H NMR spectrum of compound 89 included signals at δ 7.35 and 6.35 (Figure 2). These were assigned to an α and β-proton respectively. The absence of a third furan proton signal indicated that a group other than H was present at the other α-furan position. The absence of the alcohol stretch in the IR spectrum as well as the characteristic shifts in the methylene protons (H-6) and the methyl protons of the silyl group indicated that the system had indeed rearranged to form an O-silylated compound (vide supra). That a deuterium atom was present in compound 89 was confirmed by the mass spectrum of compound 89, which contained a peak at 213 ($M^{\cdot+}$) and 156 ($M^{\cdot+}$-t-Bu) and no peak at 212 or 155. The mass spectrum of silyl ether 54 exhibited signals at 212

Figure 2

^{1}H NMR spectra of 54 and 89



Scheme 20

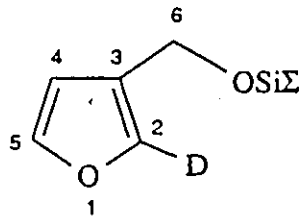


55 88 89

a) 5 eq. D_2O, DME, 15 min

b) 5 eq. NaH, DMF, 5 min

and 155. The peak at 212 corresponded to the molecular ion and the peak at 155 resulted from the loss of a t-Bu group from the molecular ion (t-Bu groups on these silyl ethers are reported to be extremely labile).[23] That the deuterium atom in 89 was at C-2 was confirmed by ^{13}C NMR.[23a] The carbon absorption for C-2 of compound 89 was noticeably missing, when compared to the ^{13}C NMR spectrum of the corresponding protic compound 54.[31]



89

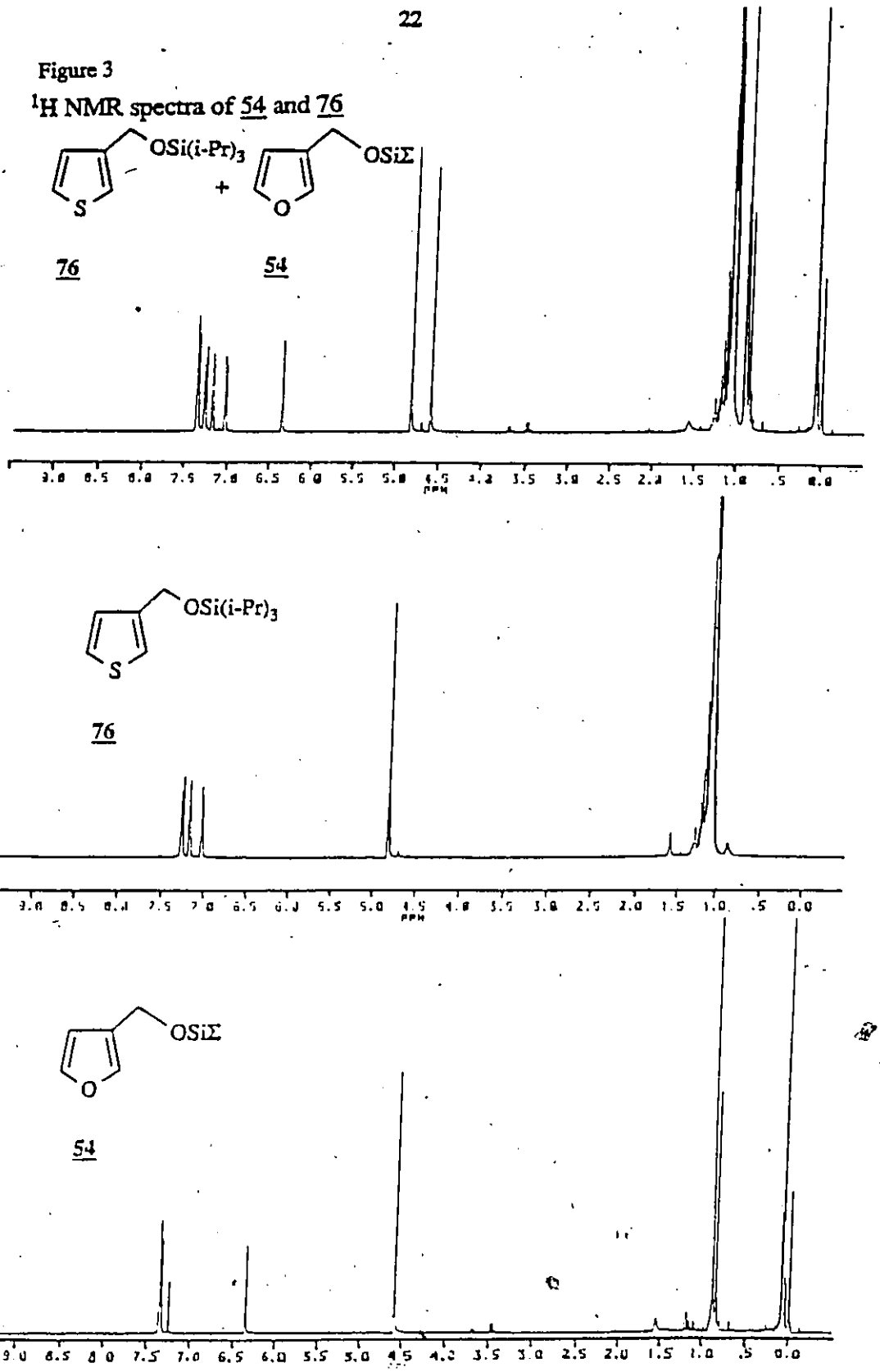
Since deuterium was incorporated at C-2 of the furan ring we may conclude that the rate of silyl migration must be greater than the rate of alkoxide formation, and the solvent is not the proton source in these reactions. If either of these conditions were not met then the product would have been silyl ether 54 after aqueous workup.

Crossover experiments indicated that the silyl rearrangement was an intramolecular process. Treatment of an equimolar mixture of 63 and 55 with NaH in DMF provided only 76 and 54 respectively (Scheme 21)(Figure 3). None of the crossover silyl ethers 78 and/or 75 were observed.

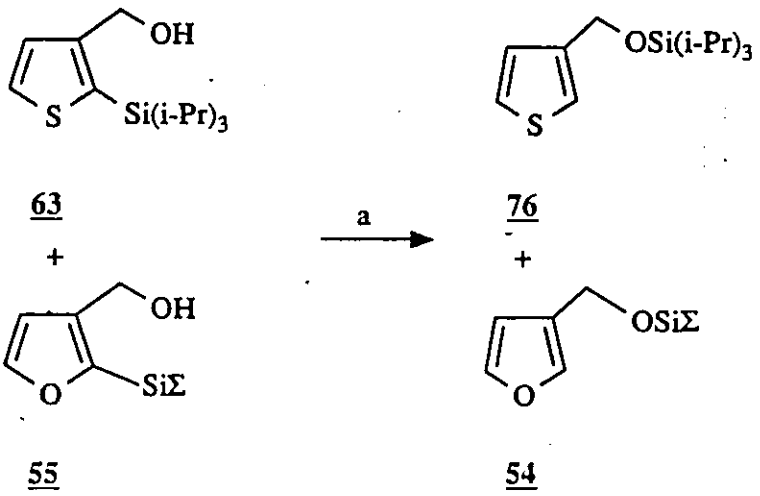
The ^1H NMR spectrum for the crossover reaction is shown in Figure 3 along with the ^1H NMR spectra of compounds 54 and 76. That no cross products were obtained was obvious because the spectrum of the reaction products contained no extraneous peaks. The ^{13}C NMR and mass spectra were also consistent with that of a mixture of 76 and 54.

Figure 3

^{1}H NMR spectra of 54 and 76



Scheme 21



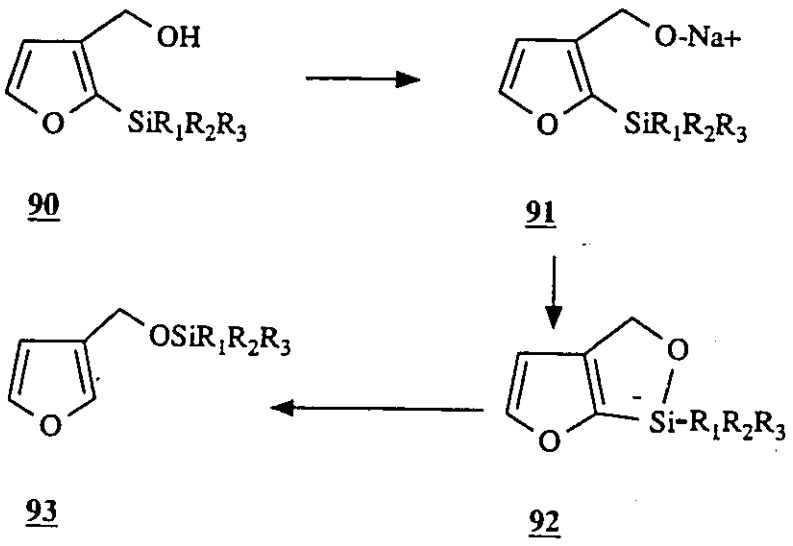
a) 5 eq. NaH, DMF

^{13}C NMR and mass spectra were also consistent with that of a mixture of 76 and 54.

Furan 55 underwent [1,4] C→O silyl migration with sodium and potassium bases; however when lithium and magnesium bases were employed the migration did not occur ([1,4] C→O silyl migration has been observed in a variety of systems with lithium bases[12,13,15,17,19]). The migration capabilties observed with the various bases may be explained using hard acid / soft base theory.[32] Lithium (and Mg) is a harder atom than sodium (or potassium) and therefore has a stronger interaction (than the sodium atom) with the oxygen atom (oxygen is a hard atom). In the case of the sodium catalysed migration, the solvent DMF strongly solvates the sodium atoms, thus weakening the hard/hard interaction and releasing the oxygen atom to attack the silicon to form the pentavalent silicon intermediate 92. The intermediate then collapses to form the silyl ether 93 upon the addition of a proton source. In the pentavalent silicon intermediate 92, the O-Si interaction is stronger than the C-Si interaction therefore the Si-C bond is lengthened and weakened. The carbon atom at C-2 will therefore have a higher negative charge character. The lack of a formal furan C-2 anion as well as the steric bulk of the pentavalent silicon atom in 92 results in the non-reactivity toward bulky electrophiles. Thus a proton source protonates at C-2 of furan ring forming 93. The driving force of the overall reaction is the formation of the extremely strong O-Si bond at the expense of the much weaker C-Si bond. When lithium (or magnesium) bases are used the hard/hard interaction between the oxygen atom and the lithium atom is not effected by solvent and

dissociation of lithium would not occur. Therefore compound 92 does not form and the addition of a proton source results in the formation of alcohol 90.

Scheme 22



90 91 92 93

In summary 2-trialkylsilyl-3-hydroxymethyl-furans and -thiophenes undergo a [1,4] C→O silyl migration when treated with bases containing either potassium or sodium counterions to produce 3-[(trialkylsilyl)oxymethyl]-furans and -thiophenes in excellent yields. The reaction proceeds efficiently in DMF, THF and DME; however the reaction would not proceed in ether. The reactivity of the bases in various solvents was directly related to their hard/hard interactions and counterion solvation capabilites. The reaction is catalytic when sodium hydride is employed as the base, and the rearrangement proceeds through an intramolecular migration of the silyl group. The proton transferred to the α-furan carbon originates from the hydroxyl group of unrearranged starting material and not the solvent.

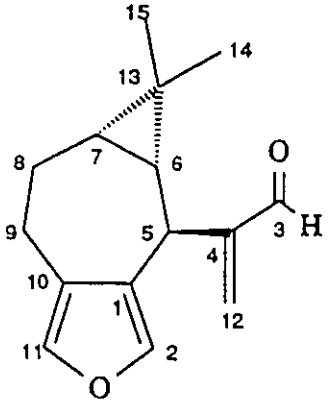
Now that we can prepare 3,4-disubstituted furans and thiophenes using the methodology of Scheme 13, we shall attempt to use this procedure to synthesize compound 94. Since we shall present a variety of routes toward the natural product, the synthetic usefulness of this method will become readily apparent.

2.0.0 *Toward The Synthesis of Furanoplagiochilal*

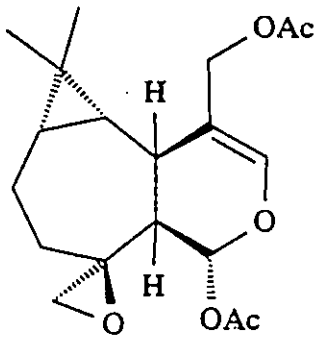
2.1.0 *INTRODUCTION*

2.1.1 The Isolation and Characterization of Furanoplagiochilal

In 1980, Asakawa and coworkers[33] isolated a new sesquiterpene hydrocarbon, named furanoplagiochilal 94, extracted from liverworts. The extreme pungency of liverworts is due to the ent-secoaromadendrane-type sesquiterpene plagiochiline Á 95, and is responsible for the strong antifeedant activity toward the African army worm.



94



95

Furanoplagiochilal is postulated to participate in the biogenetic pathway toward plagiochiline A 95. The isolated compound 94 was found to have an empirical formula of $C_{15}H_{18}O_2$.

From the infrared, ^1H and ^{13}C NMR spectra of furanoplagiochilal 94 a number of structural features were immediately apparent. Bands in the infrared (2720, 1695 cm^{-1}) spectrum, as well as the resonances of the two vinylic protons in the ^1H NMR (δ 6.21, 6.55), the aldehyde proton (δ 9.61), and the carbonyl moiety in the ^{13}C NMR (δ 193.5), indicated the presence of an α,β-unsaturated aldehyde. Both infrared (1535 cm^{-1}) and ^1H NMR (δ 6.53, 7.06) spectra supported the presence of a furan ring. Based on the ^1H NMR spectrum (δ 0.90), furanoplagiochilal also contained a cyclopropane ring. The structure of furanoplagiochilal was established by spin-decoupling experiments of the ^1H NMR spectrum and by the ^{13}C NMR spectrum.

The synthesis of compound 94 provides a variety of difficult challenges. The synthesis of a sufficiently versatile pair of groups in the C-1 and C-10 positions on the furan is vital. Introduction of the C-10 group can be performed by the method of Keay.[26] The preparation of the seven membered ring is the second challenge. The final problem will be the attachment of the cyclopropane and the α,β-unsaturated aldehyde with the correct stereochemistry. The cyclopropane must be anti to the unsaturated aldehyde.

Cyclopropanes are most often created by the use of carbene reactions on olefins; however, in this case the carbene may react with the furan ring.[34]

Furanoplagiochilal 94 has not been synthesized to date. The next section illustrates our attempts toward this goal.

2.2.0 *RESULTS AND DISCUSSION*

In principle, any complex organic molecule (target molecule) may be broken down by a series of (bond-breaking) disconnections and/or functional group interconversions (FGI) to generate successively simpler intermediates until an easily accessible starting material is obtained.[35] Using this "retrosynthetic analysis", one can envisage furanoplagiochilal (94) being derived from the tricyclic tosylate 96 via a possible first disconnection which corresponds to an S_N2 displacement of the tosylate group by the dianion of compound 97. Functional group interconversion of the tosylate to the ketone 98 would be put into place by a reduction followed by the tosylate formation step (Scheme 23). The cyclopropane bridge indicated as the site of the next disconnection could be accomplished by intramolecular carbene addition to the olefinic group on the C-4 side chain in 99. The carbene can be generated by decomposition of diazoketone 99. The interconversion of the diazo ketone group to the silyl ether 100 could be performed in the following manner. Compound 100 could be desilylated followed by the oxidation of the alcohol to the acid. This acid could be converted to the acid chloride and treated with diazomethane to yield the diazoketone 99.

Problems in the synthesis could occur in the cyclopropanation step because of possible intermolecular cyclopropanation between the carbene of one molecule and the C-4 chain of another. Cyclopropanation of the carbene with the furan ring may result as furans are susceptible to carbene addition.[34] Further difficulties may result from the reduction of the ketone 98. We predict from steric considerations that a hindered reducing agent should deliver hydride from the face which is anti to the cyclopropane moiety.

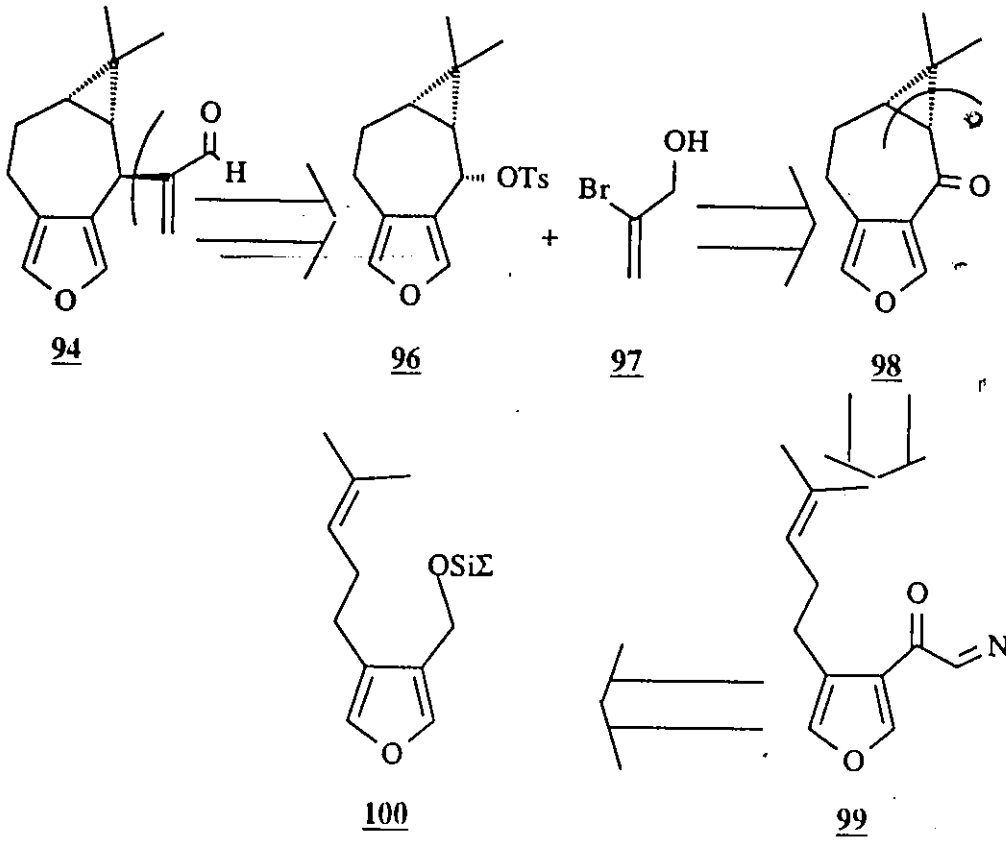
The synthesis of the silyl ether 100 was not a trivial matter. The most direct approach toward the synthesis of compound 100 involved the use of the methodology indicated in Scheme 24. Using the methodology developed by Keay[26] the dianion of alcohol 55 should have alkylated to give alcohol 101 when treated with 5-bromo-2-methyl-2-pentene. Unfortunately, no alkylation occurred and only starting material was obtained. Presumably the furan anion is acting as a base and eliminating the bromide in 5-bromo-2-methyl-2-pentene.

The synthesis of the cyclopropanation precursor 100 was attempted via many alternative methods. The first of these is shown in Scheme 25.

Alkylation of the dianion of alcohol 55 with DMF[26] proceeded smoothly which on workup provided the aldehyde 67 in 91% yield (Scheme 26).

A cursory examination of the IR spectrum of this material showed the presence of an aldehyde carbonyl group (1678 cm^{-1}) and the alcohol moiety (3415 cm^{-1}).

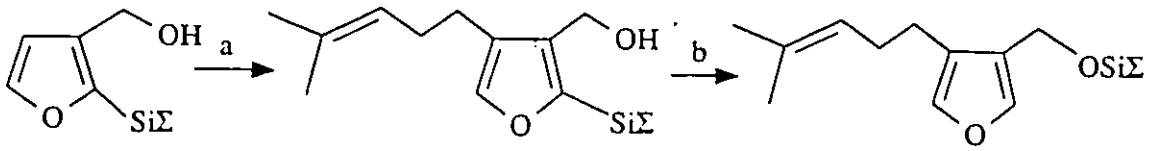
Scheme 23



94 96 97 98

100 99

Scheme 24



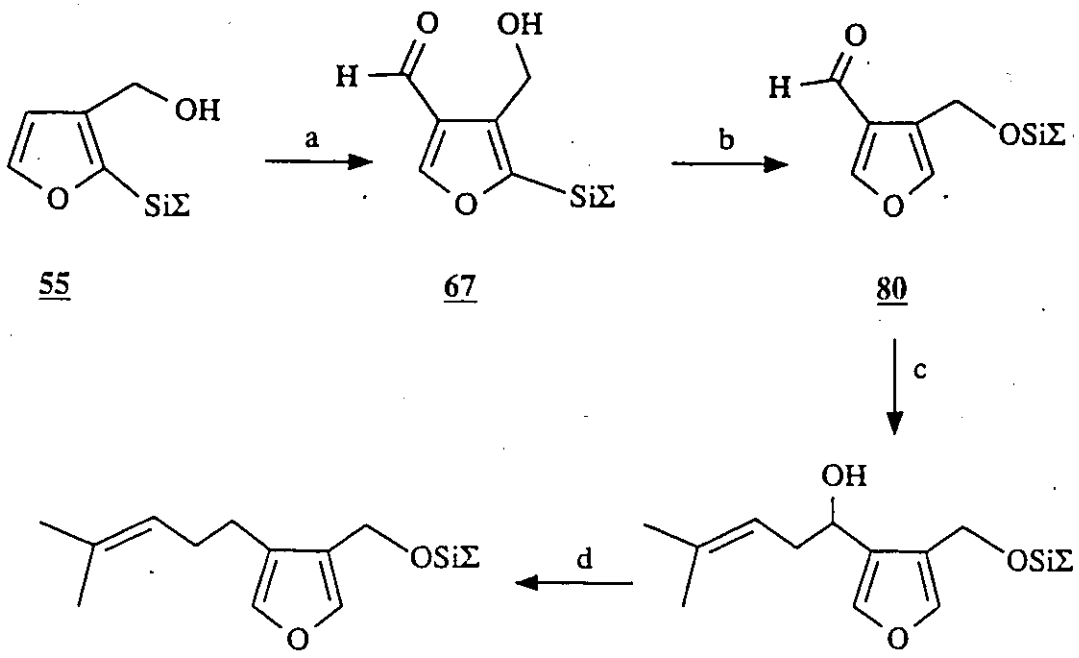
55 101 100

a) 2 eq. n-BuLi, 5-bromo-2-methyl-2-pentene

b) NaH, DMF

The aldehyde proton and furan proton (H-5) were readily apparent in the ^1H NMR as singlets at δ 9.9 and 8.26 respectively. The signal at δ 4.08 was a broad singlet and was attributed to the hydroxy group. The other diagnostic protons were the silane protons at δ 0.86 and 0.27 as well as the signal at δ 4.57 (H-6). The ^{13}C NMR exhibited a signal at δ 186.63 indicative of the aldehyde. Four furan signals were apparent (δ 125.65,

Scheme 25



55 67 80 100 102

a) 2 eq. n-BuLi, DMF
b) NaH, DMF
c) 4-bromo-2-methyl-2-butene, Mg
d) TsCl pyr.; $LiAlH_4$

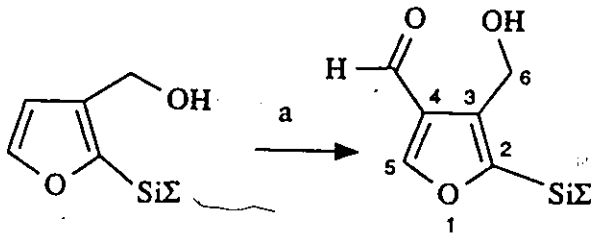
126.36, 142.02, 152.73) as well as the C-6 signal (δ 57.28). The characteristic silane group carbon signals were exhibited at δ -5.49, 18.27, 25.83.

Migration of the silyl group ([1,4] C→O) was performed with 5 equivalents of NaH in DMF. After 1 hour the silyl ether 80 was obtained in 90% yield (Scheme 27).

Immediately apparent in the IR spectrum was the disappearance of the alcohol signal as well as the existence of the aldehyde peak at 1692 cm^{-1}. In the ^1H NMR the aldehyde peak was readily apparent at δ 9.91. A shift of the silyl group methyl protons from δ 0.27 in compound 67 to δ 0.08 (in compound 80) was observed (vide supra). The ^{13}C NMR exhibited 9 distinct signals. These included the aldehyde peak at δ 185.08.

To a solution of the aldehyde 80 was added the Grignard reagent of 4-bromo-2-methyl-2-butene.[36] The experiment was performed under a variety of conditions which modified the temperature and quantity of the Grignard added. None of the desired alcohol 102 was observed. While a variety of products were observed (by tlc)

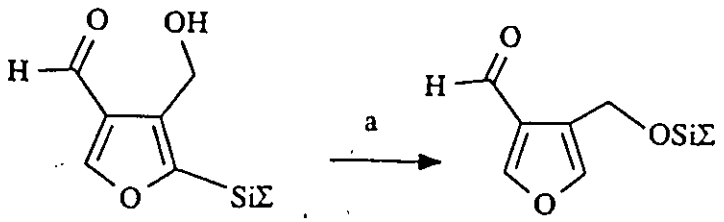
Scheme 26



55 67

a) 2 eq. n-BuLi, DMF

Scheme 27



67 80

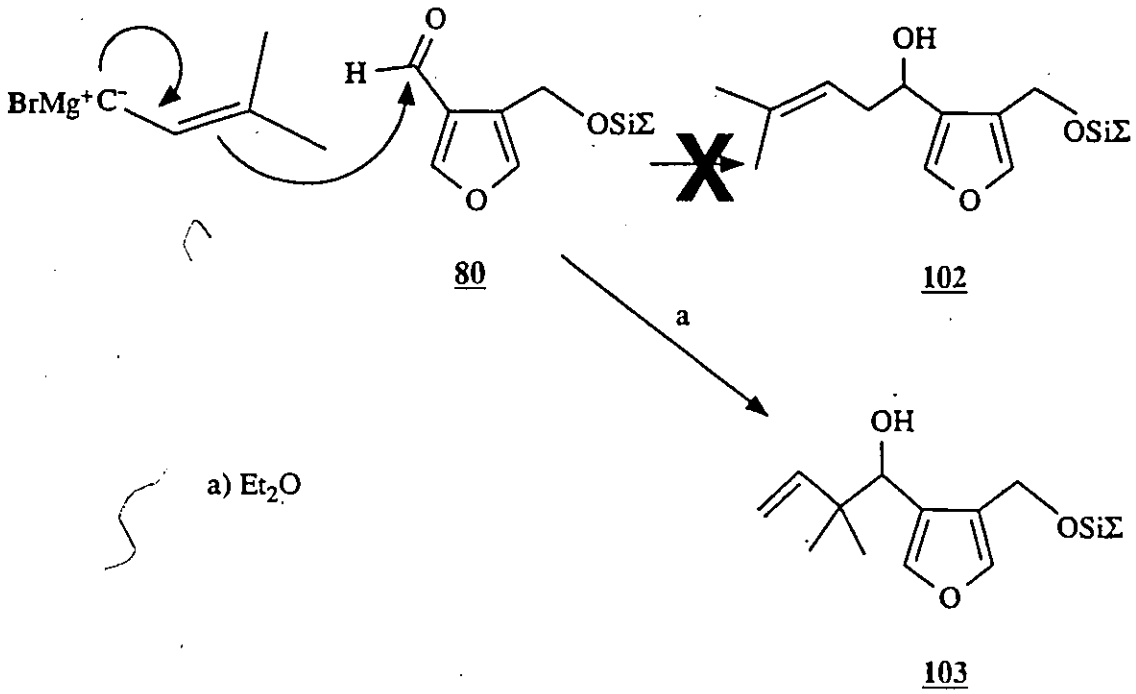
a) 5 eq. NaH, DMF

only one was identifiable (103) (Scheme 28). The observed product resulted from addition of the most hindered carbon of the grignard to the carbonyl. It is well known that substituted allylic organometallic compounds (similar to compound 104) react via the procedure shown in Scheme 29.[37] When compound 80 was treated with acrolein only alcohol 104 was obtained.[38]

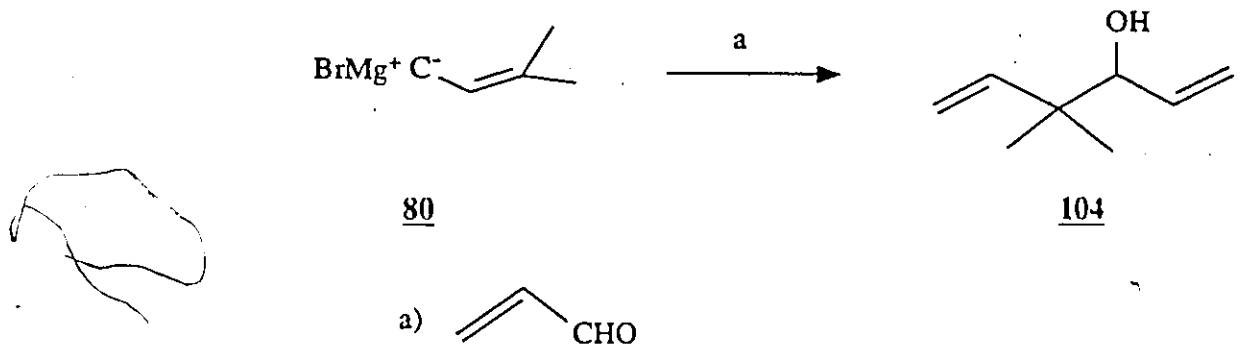
The next attempt to form the silyl ether 100 involved palladium catalyzed couplings.[39] A model study involved the coupling of 4-bromo-2-butene with compound 105 (Scheme 30).

Alkylation of the alcohol 55 under normal conditions[26] using iodine as the electrophile provided the iodide 105 in 92% yield. The alcohol was then desilylated with $(n\text{-}Bu)_4N^+F^-$ in THF which provided compound 106 in excellent yield (Scheme 31). All

Scheme 28



Scheme 29

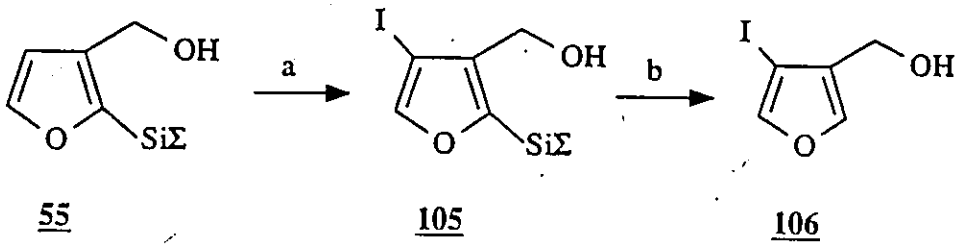


spectra for compounds 105 and 106 were entirely consistent with that previously published.[23]

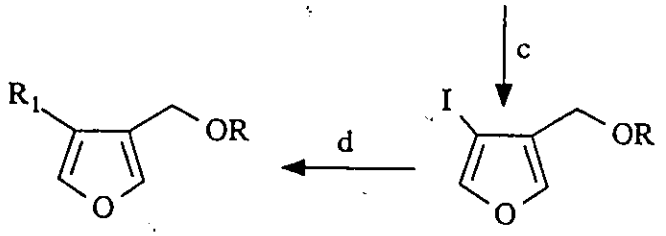
The protection of alcohol 106 was performed with NaH and DMF followed by addition of the electrophile (Scheme 32).[40] For compound 107a the electrophile was methyl iodide. In the case of compound 107b benzyl bromide was used and for compound 107c the electrophile was chloromethyl methyl ether.

The IR spectrum of these compounds indicated that the hydroxyl group was

Scheme 30

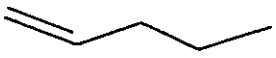


55 105 106

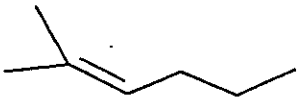


107

R = Me, CH_2Ph, MEM



$= R_1$ 108

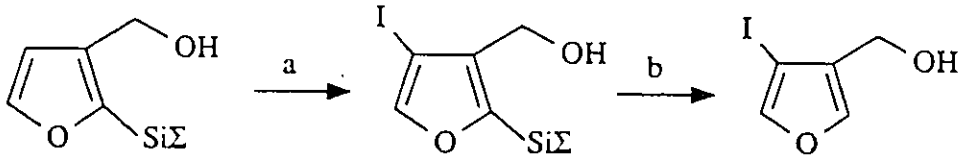


$= R_1$ 100

a) 2 eq. BuLi, DME; I_2 b) $(n\text{-}Bu)_4N^+F^-$, THF

c) NaH, RX d) $PdCl_2(PPH_3)_2$, R_1ZnBr

Scheme 31



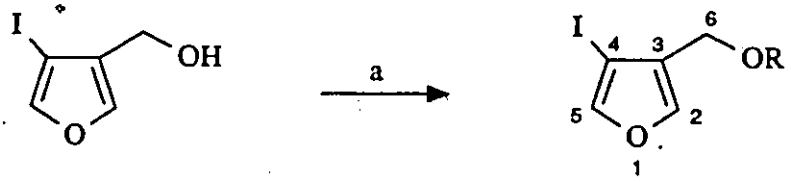
55 105 106

a) 2 eq. BuLi, DME; I_2

b) $(n\text{-}Bu)_4N^+F^-$, THF

absent. The ^1H NMR spectra of the ethers were very important in the structural determinations. In the case of compound 107a there were distinct signals corresponding to the methoxy group at δ 3.35 and the methylene group (H-6) at δ 4.21. For the benzyl protected compound 107b distinct peaks were observed for the methylene groups at δ 4.33

Scheme 32



106

107

107a) R = Me

107b) R = CH_2Ph

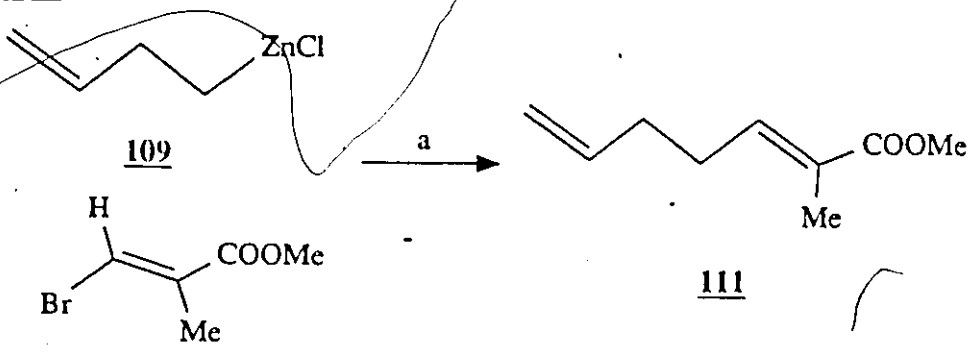
107c) R = MEM

a) NaH, DMF; RX

and 4.56. The MEM protected compound 107c contained signals at δ 3.40, 4.36 and 4.67 which resulted from the methoxy group, and, the two methylenes respectively. In the case of compound 107b the furan proton signals were obscured by the phenyl ring proton signals.

In 1980 Negishi[39] reported the coupling reaction shown in Scheme 33. The zinc compound 109 was treated with the alkenyl halide 110 in the presence of $Pd(PPh_3)_4$. After workup compound 111 was obtained in 82% yield.

Scheme 33



109

111

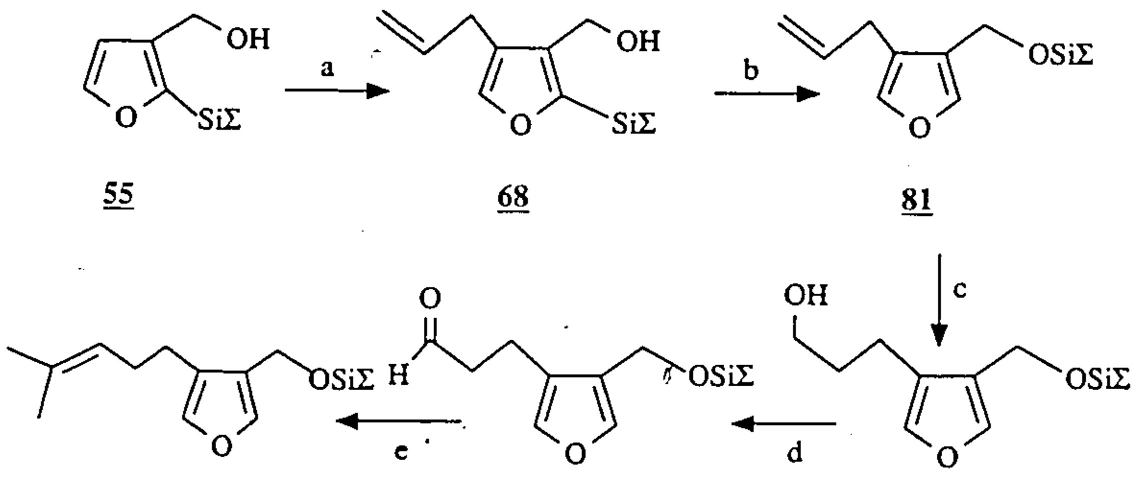
110

a) $Pd(PPh_3)_4$, THF

Analogous attempts at the coupling of 4-bromo-2-butene with furan 107 proved futile. In all cases starting material was consumed and a variety of indecipherable products were obtained, thus an alternative method towards compound 100 was explored.

The synthesis of the cyclopropanation precursor 100 was finally realized via the procedure shown in Scheme 34.

Scheme 34



a) 2 eq. n-BuLi; allyl bromide b) NaH, DMF

c) $BH_3 \cdot DMS$, Et_2O; H_2O_2, NaOH, EtOH

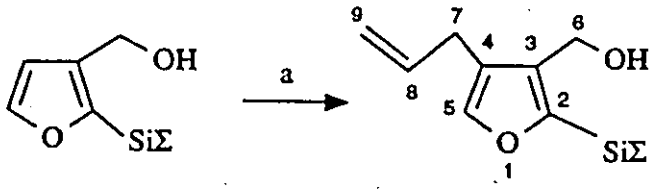
d) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

e) Et_2O, $\succ$= PPh_3

Alcohol 55 was treated with 2 equivalents of n-BuLi in DME and the anion was quenched with allyl bromide.[26] After workup with NH_4Cl the alcohol 68 was obtained in 83% yield (Scheme 35).

The presence of the hydroxyl group was evident in the IR spectrum of 68 and was located at 3324 cm^{-1}. The ^1H NMR of the compound was consistent with the proposed structure. The furan ring was apparently trisubstituted because only one furan proton was exhibited at δ 7.37 (H-5). The newly formed chain (C-7, C-8, C-9) produced three distinct patterns. The pattern which resulted from H-8 (δ 6.00) was an unresolved doublet of doublet of doublets which resulted from coupling to the two H-7 protons and nonequivalent coupling to the two H-9 protons. The protons at H-9 (δ 5.08) were nonequivalent and resulted in a doublet of doublets for each proton, which were

Scheme 35



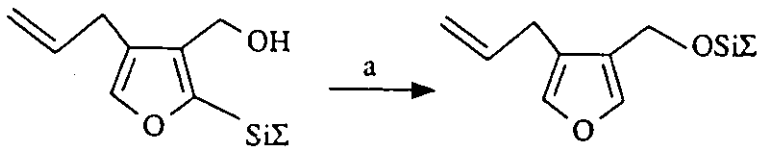
55 68

a) 2 eq. n-BuLi, DME; allyl bromide

overlapped. Further complication of this pattern occurred due to allylic coupling to the protons at H-7. The H-7 (δ 3.24) protons exhibited the pattern of a doublet of doublets. The two protons were obviously overlapped and the chemical shift difference was unresolved. The ^{13}C NMR spectrum contained 11 distinct peaks. Distortionless Enhancement by Polarization Transfer (DEPT)[31] experiment indicated that the signals at δ 27.70 and 55.32 were CH_2's. The peak at δ 55.32 was at the correct chemical shift for C-6. Therefore the signal at δ 27.70 was C-7. The peak at δ 115.74 was a CH_2 (DEPT experiment) and therefore it was C-9. The remainder of the spectrum was the furan protons and C-8. The peaks at δ 137.03 and 144.08 were assigned to furan carbon C-5 and carbon C-8.

The [1,4] C→O silyl migration performed on the alcohol 68 with 5 equivalents of NaH in THF provided silyl ether 81 in 83% yield (Scheme 36).

Scheme 36



68 81

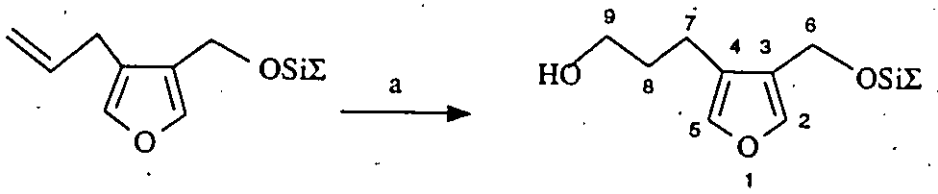
a) 5 eq. NaH, THF

The lack of a hydroxyl peak in the IR spectrum suggested that the migration had been successful. A slight shift of the silyl group methyl protons was observed in the ^1H NMR spectrum from δ 0.28 to 0.076 (vide supra). The appearance of a second α-furan

proton signal (δ 7.15 and 7.30) was observed due to the removal of the silyl group from the furan ring.

Hydroboration-oxidation of the silyl ether was accomplished efficiently when compound 81 was treated with borane-dimethyl sulfide complex in diethyl ether.[41] After 4 hours the solution was treated with a mixture of ethanol, sodium hydroxide and hydrogen peroxide. After NH_4Cl workup the alcohol 112 was obtained in 91% yield (Scheme 37).

Scheme 37



81 112

a) BH_3·DMS, Et_2O; EtOH, H_2O_2, NaOH

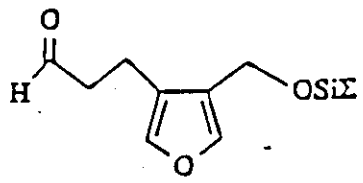
The most obvious signal in the IR spectrum of alcohol 112 was the hydroxy peak at 3379 cm^{-1}. A broad singlet at δ 1.81 in the ^1H NMR spectrum corresponded to the hydroxyl proton which was overlapped with a multiplet (dtt) assigned to H-8. A pair of triplets were observed at δ 2.50 and 3.64. These signals are assigned to protons at H-7 and H-9. The ^{13}C NMR of the alcohol contained 11 distinct signals. Three signals which corresponded to C-7, C-8 and C-9 were observed at δ 25.88, 32.41 and 61.89.

Swern oxidation of alcohol 112 to the aldehyde was performed under the following conditions.[42] The alcohol was treated with a complex of oxalyl chloride and DMSO in methylene chloride at -60°C followed by triethylamine which provided the aldehyde 113 in 91% yield (Scheme 38).

The IR spectrum of compound 113 was devoid of any signal which corresponded to an alcohol group. The existence of a carbonyl group was apparent due to the signal at 1726 cm^{-1}. The ^1H NMR spectrum of this compound contained an aldehyde peak which appeared at δ 9.78 (Figure 4). The broad singlet observed at δ 2.74 was attributed to the

Figure 4

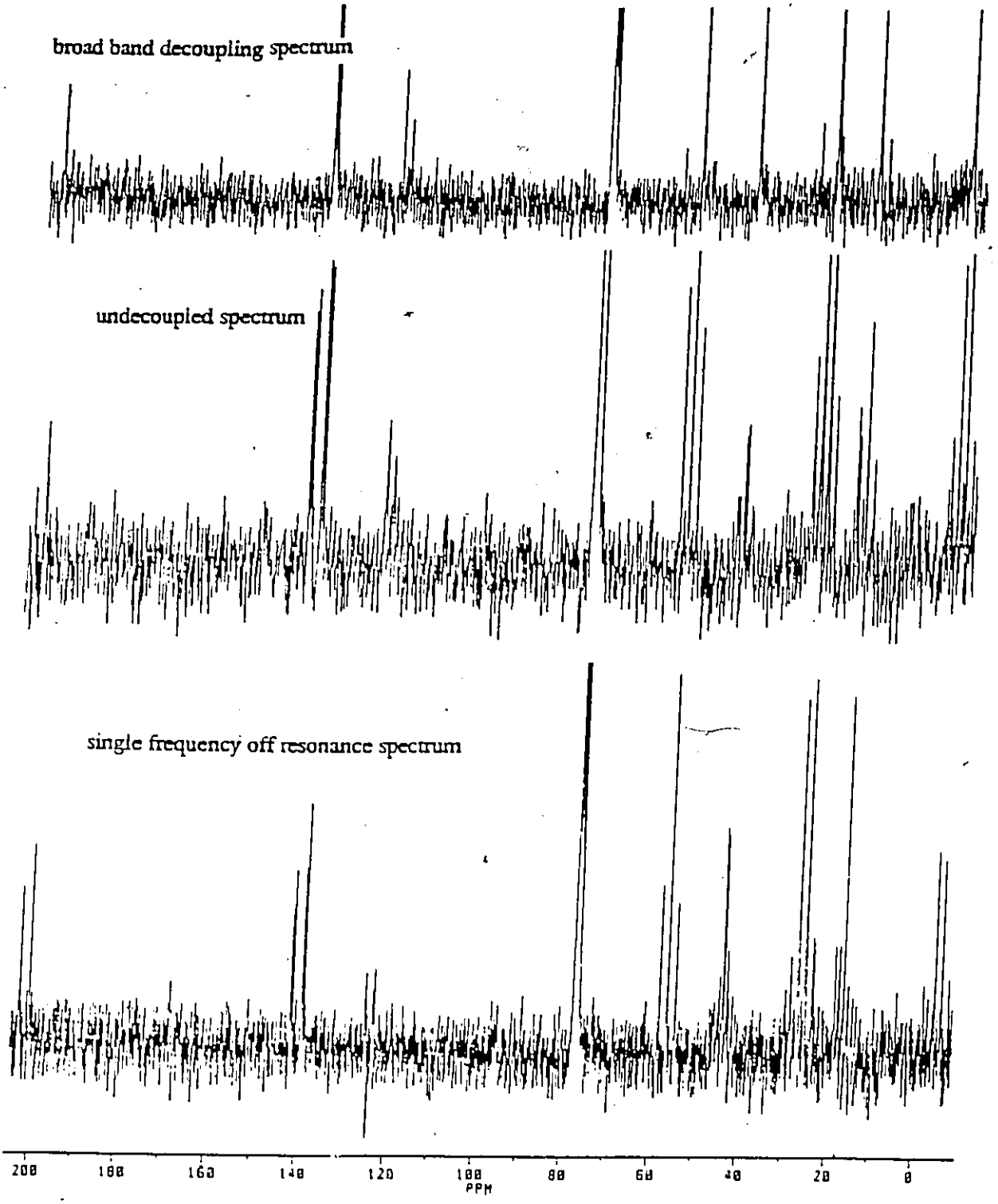
^{1}H NMR spectrum of 113



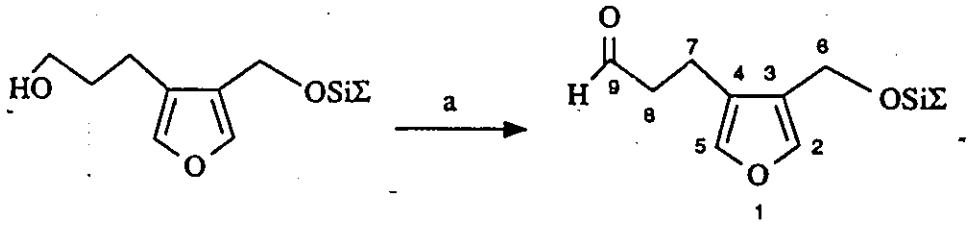
113

Figure 5

^{13}C NMR spectra of 113



Scheme 38



112 **113**

a) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

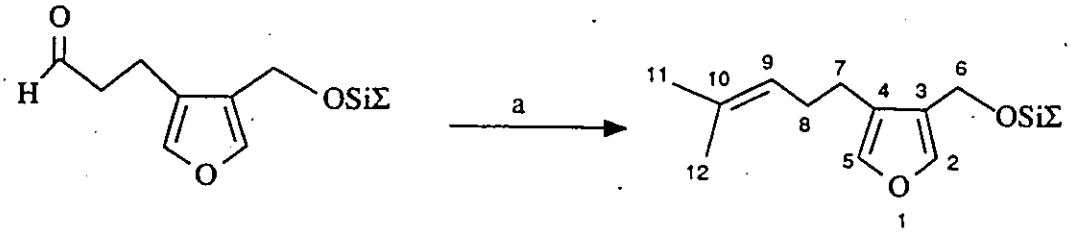
protons H-7 and H-8. One would expect these protons to exhibit a pair of doublet of triplets; however their chemical shifts were essentially identical (at 300 MHz) resulting in a broad singlet. This assignment was confirmed by a single frequency off resonance decoupling experiment. The ^{13}C carbon spectra of compound 113 is shown in Figure 5 with no decoupling (middle), broad band decoupling (top) and single frequency off resonance decoupling (irradiated at δ 2.74)(bottom). In the undecoupled spectrum (middle) the two peaks at δ 16.12 and 43.39 appeared as a triplet and a doublet of triplets respectively. In the single frequency off resonance spectrum these peaks collapsed to a singlet and a doublet (δ 16.12 and 43.39 respectively). The peak at δ 16.12 exhibited coupling to two hydrogens while the peak at δ 43.39 exhibited coupling to two hydrogens as well as coupling to a CH moiety. This proved that the signal at δ 2.74 in the ^1H NMR spectrum indeed corresponded to two separate carbons and that they were each methylene carbons.

All peaks in the ^{13}C NMR spectrum were indicative of the aldehyde 113.

A Wittig reaction was performed on aldehyde 113 with the anion of isopropyltriphenylphosphonium iodide.[43] After 1 hour at 0°C and NH_4Cl workup the silyl ether 100 was produced in 74% yield (Scheme 39).

The IR spectrum of compound 100 indicated the loss of the aldehyde group in compound 113; however, no other extremely obvious peaks were observed. The ^1H NMR spectrum of compound 100 contained a variety of well defined signals. The two methyl signals (H-11 and H-12) were observed at δ 1.60 and 1.70. The two H-7 protons resonated at δ 2.24 as a broadened triplet. This suggested that the H-8 protons were nonequivalent. The multiplet at δ 2.42 was attributed to the H-8 protons. These were an overlapped pair of doublet of doublet of triplets. The multiplet at δ 5.17 was assigned to the H-9 proton. This appeared to be an overlapped pair of doublets with slight allylic coupling to H-11 and

Scheme 39



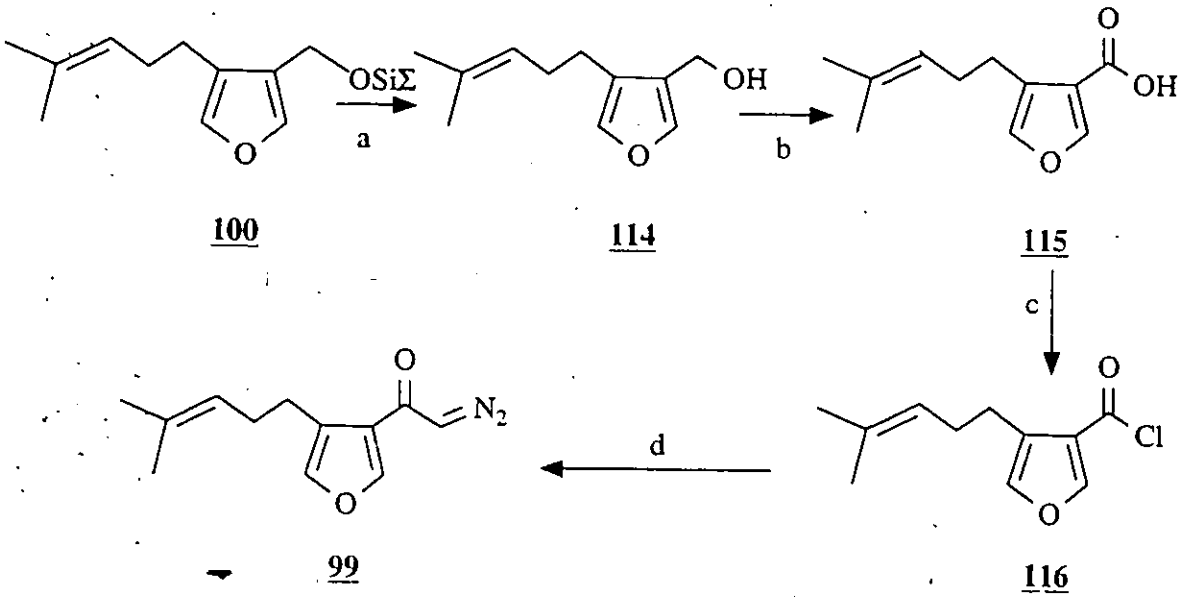
113 **100**

a) Et_2O, } PPh_3

H-12. In the ^{13}C NMR spectrum there were 14 distinct signals. The two methyl signals (C-11 and C-12) were seen at δ 25.68 and 25.89. The C-7 and C-8 carbon signals were observed at δ 23.82 and 27.90. DEPT experiment determined that the number of quaternary carbons and CH carbons which remained was 3 each. This was consistent with the furan carbons and the C-9 and C-10 carbons.

With compound 100 in hand we turned our attention toward the steps which would lead to cyclopropanation precursor 99. The procedure which was used is outlined in Scheme 40.

Scheme 40



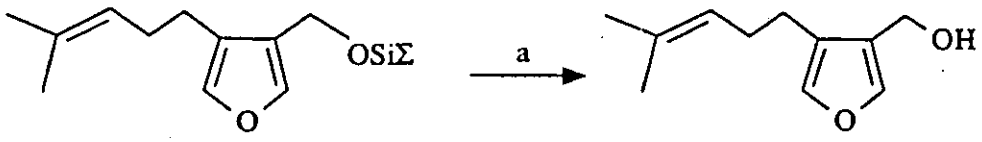
100 **114** **115** **116** **99**

a) $(n\text{-}Bu)_4N^+F^-$, THF b) $AgNO_3$, NaOH, H_2O

c) $(COCl)_2$, hexane d) CH_2N_2, Et_2O

The first reaction involved desilylation of the silyl ether with $(n\text{-}Bu)_4N^+F^-$ which provided the alcohol 114 in 85% yield (Scheme 41).[25]

Scheme 41



100 **114**

a) $(n\text{-}Bu)_4N^+F^-$, THF

The IR spectrum of alcohol 114 exhibited a strong absorption at 3365 cm^{-1} which resulted from the alcohol group. The ^1H NMR spectrum exhibited a broad singlet which corresponded to the alcohol proton at δ 1.88. The silyl group protons were absent and all other proton peaks were intact. The ^{13}C NMR spectrum contained 11 signals, however the signals which corresponded to the silyl group were absent.

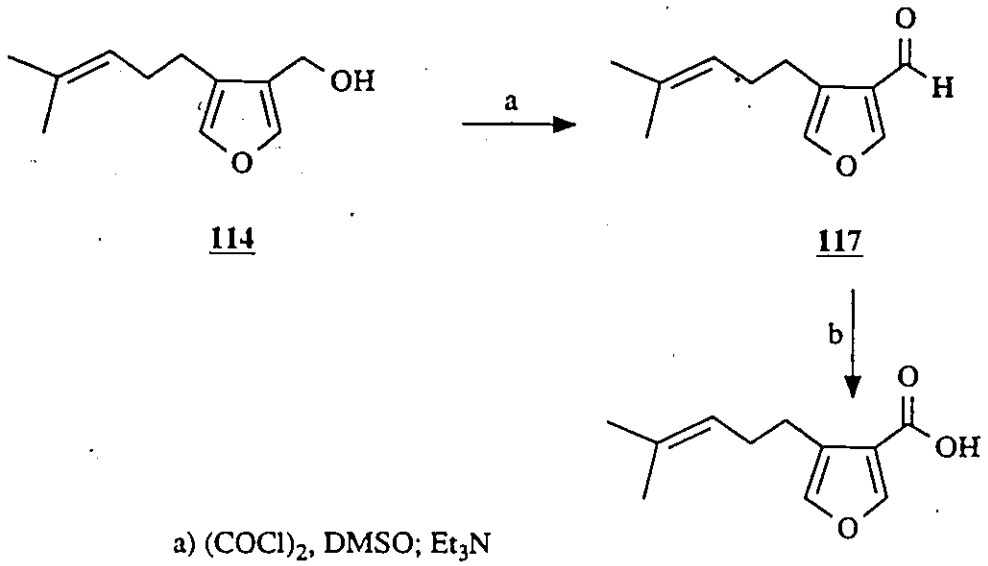
Many attempts to oxidize alcohol 114 directly to the acid using various silver and chromium reagents were futile; the yields of compound 115 were always low (>20%). A two step oxidation of the alcohol 114 through the aldehyde 117 to the acid 115 was then explored (Scheme 42).

The oxidation of alcohol 114 was performed using Swern conditions with oxalyl chloride and DMSO which provided after workup the aldehyde 117 in 95% yield (Scheme 43).[42]

The IR spectrum of compound 117 contained a strong absorption (1691 cm^{-1}) attributed to the carbonyl moiety. The ^1H NMR spectrum of the aldehyde exhibited a signal at δ 9.94 which corresponded to the aldehyde proton. All other signals maintained the pattern indicated in the silyl ether. The signals which corresponded to the furan protons were observed at δ 7.22 and 7.96. The peak at δ 7.96 was assigned to H-2 since H-2 would feel an anisotropic effect from the carbonyl of the aldehyde, while H-3 would not. A similar downfield shift of an α-proton adjacent to a β-aldehyde was observed in compound 67 (δ 8.26)(Scheme 26). The aldehyde carbon signal was observed at δ 185.12 in the ^{13}C NMR spectrum.

The aldehyde 117 was further oxidized with a mixture of silver nitrate in sodium hydroxide which provided after acidic workup the acid 115 in 77% yield (Scheme 44).[44]

Scheme 42

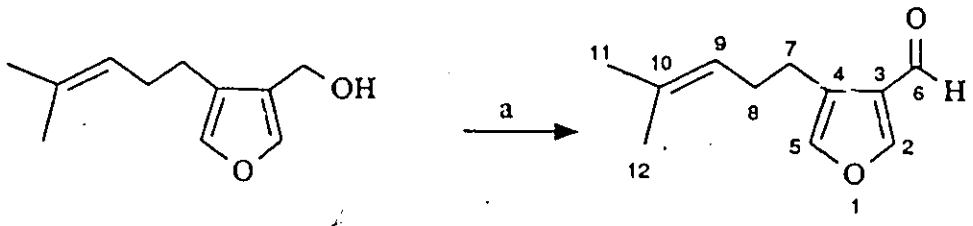


114 117 115

a) $(COCl)_2$, DMSO; Et_3N

b) $AgNO_3$, NaOH, H_2O

Scheme 43



114 117

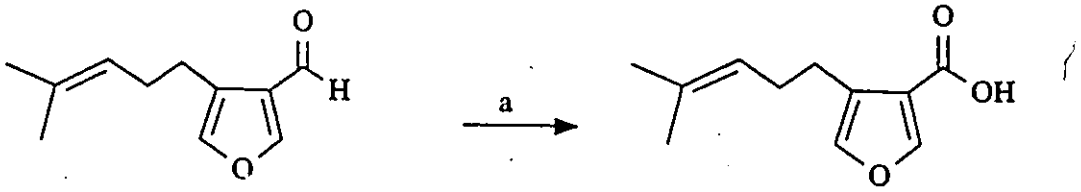
a) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

The IR spectrum of compound 115 exhibited a strong absorption at 1696 cm^{-1} which was assigned to a carbonyl moiety. The presence of an extremely broad signal centered at 2918 cm^{-1} indicated a carboxylic acid was present. The ^1H NMR spectrum of acid 115 exhibited a broad singlet at δ 7.91 which was assigned to the acid OH. The acid carbonyl signal was observed at δ 169.23 in the ^{13}C NMR spectrum .

Acid 115 was refluxed with oxalyl chloride, in hexane for two hours which provided the acid chloride which was immediately treated with diazomethane in ether for 6 hours. Workup provided the diazoketone 99 in 76% yield (Scheme 45).[45]

The ^1H NMR spectrum of the diazoketone 100 exhibited a singlet at δ 5.56

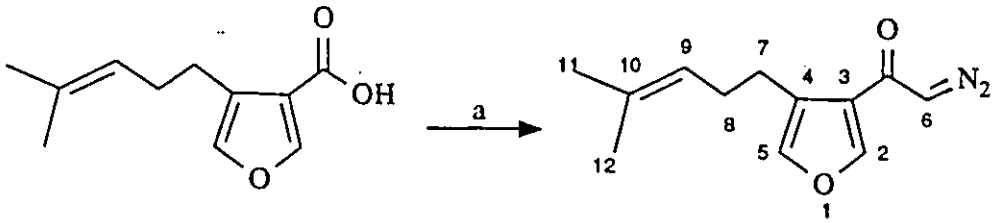
Scheme 44



117 **115**

a) $AgNO_3$, NaOH, H_2O

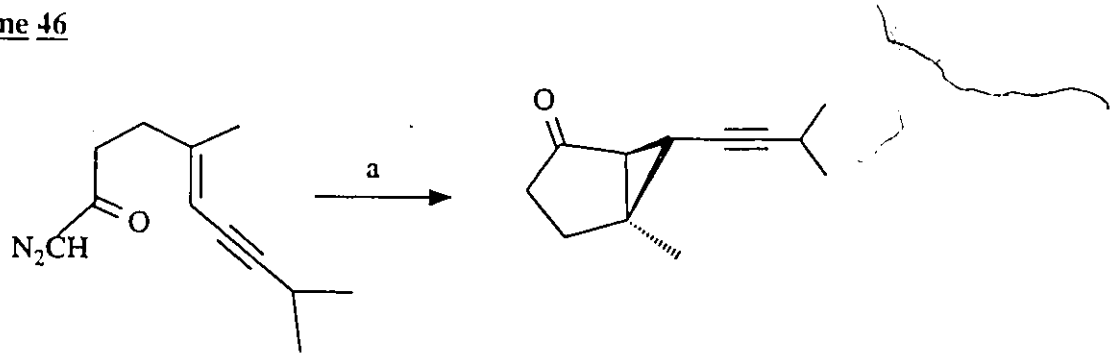
Scheme 45



115 **99**

a) $(COCl)_2$, hexane; CH_2N_2, Et_2O

Scheme 46



118 **119**

a) $Cu(acac)_2$, benzene, Δ

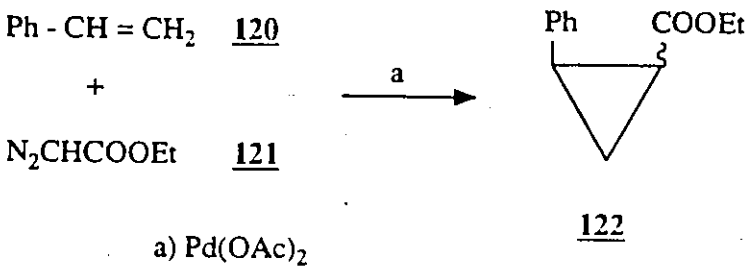
which was assigned to the proton H-6. All other peaks were consistent with the structure.

Jung[45] reported that the carbene closure of diazoketone 118 using cupric acetylacetonate provided the bicyclic ketone 119 (Scheme 46).

Analogous attempts at ring closure with diazoketone 99 proved futile. A large number of products were obtained (tlc) and attempted isolation of the desired product using silica gel chromatography proved futile.

Paulissen et. al[46] have shown that similar cyclopropanations can be performed on otherwise unreactive olefins with palladium acetate. The olefin 120 was treated with compound 121 in the presence of $Pd(OAc)_2$ which provided the cyclopropane 122 (Scheme 46). The enhanced reactivity of the olefin is due to a proposed carbene-metal-olefin complex.[47]

Scheme 47



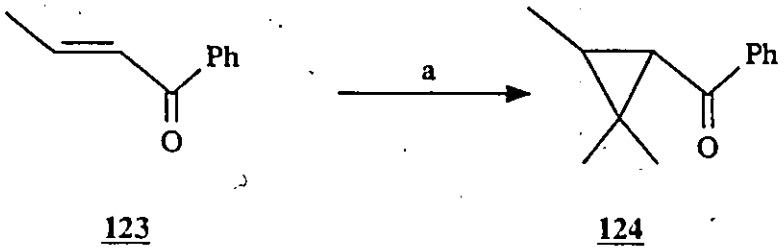
The palladium procedure was performed using two different palladium catalysts ($Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$) with dismal results. A large number of products were obtained and isolation of the desired product was futile, thus an alternative method towards the bicyclic ketone 98 was attempted.

Ono[48] has shown that the anion of 2-nitropropane can add to α,β-unsaturated ketones to provide the corresponding cyclopropane. Ketone 123 was treated with the anion of 2-nitropropane which provided the cyclopropane 124 (Scheme 48).The mechanism of the addition is shown in Scheme 49.

The ketone 98 could presumably be formed by addition of the anion of 2-nitropropane to compound 125 as indicated (Scheme 50). The α,β-unsaturated ketone 125 can be disconnected to an aldehyde ketone 126 which would be created by an Aldol condensation followed by elimination of the resulting hydroxyl group. Functional group interconversion of 126 would lead to the diol 127. Transformation of compound 127 by functional group interconversion provides system 128 (Scheme 50).

The synthesis of compound 126 corresponding to the above retrosynthesis is

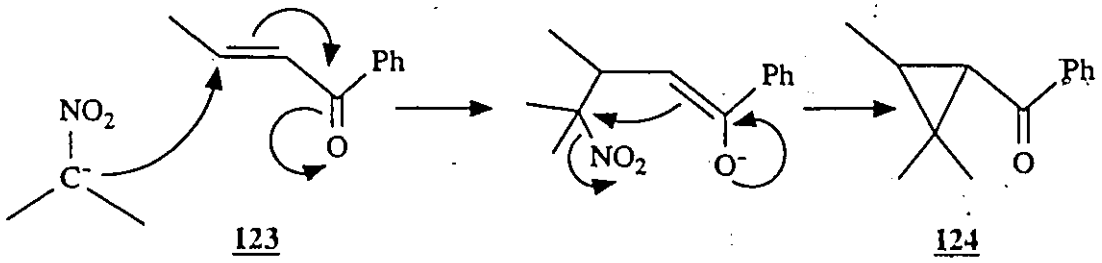
Scheme 48



123 124

a) 2-nitropropane, KOH, DMSO

Scheme 49



123 124

shown in Scheme 51.

Alcohol 68 was oxidized under Swem conditions[42] which provided aldehyde 129 in 83% yield (Scheme 52).

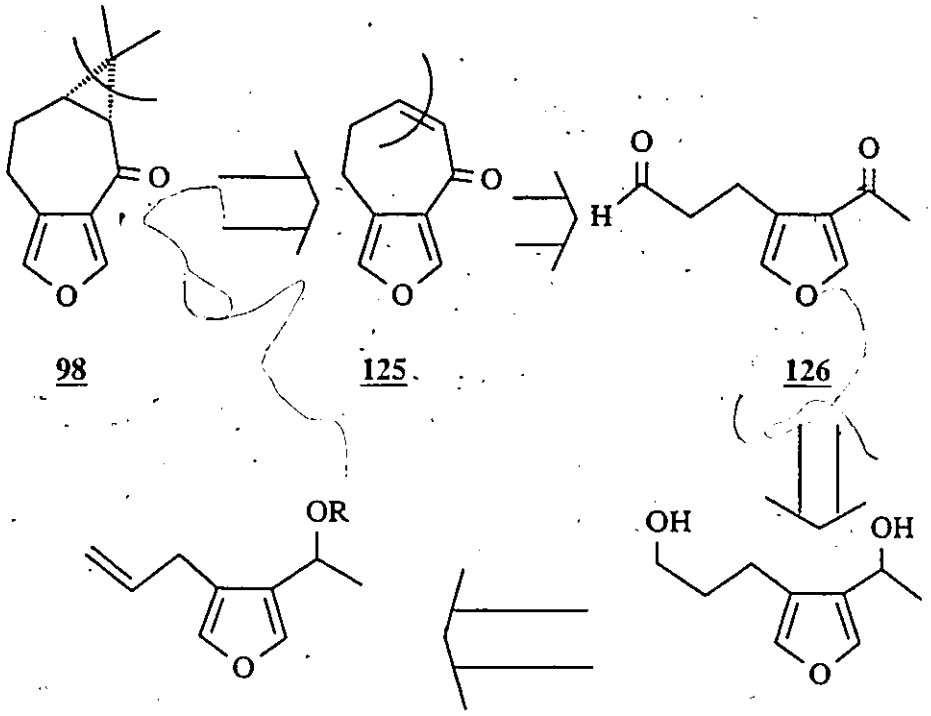
The IR spectrum of the aldehyde exhibited a very strong absorption (1684.7 cm^{-1}) which corresponded to the carbonyl.

The ^1H NMR spectrum of this compound exhibited a signal at δ 10.09 indicative of the aldehyde proton. The characteristic peaks of the silyl group, furan and olefinic chain were all present. The ^{13}C NMR contained a signal at δ 187.20 which resulted from the carbonyl carbon. Eleven other peaks were observed, all of which confirmed the proposed structure.

Aldehyde 129 was treated with methyllithium in THF which upon workup provided the alcohol 130 in 94% yield (Scheme 53).[36]

The IR spectrum of compound 130 contained a strong broad absorption at 3324 cm^{-1} which corresponded to the alcohol moiety. This was further substantiated by the singlet observed at δ 2.08 in the ^1H NMR spectrum. The doublet at δ 1.46 was assigned to the H-7 protons and the multiplet at δ 5.03 was the quartet which resulted from H-6

Scheme 50



98 125 126

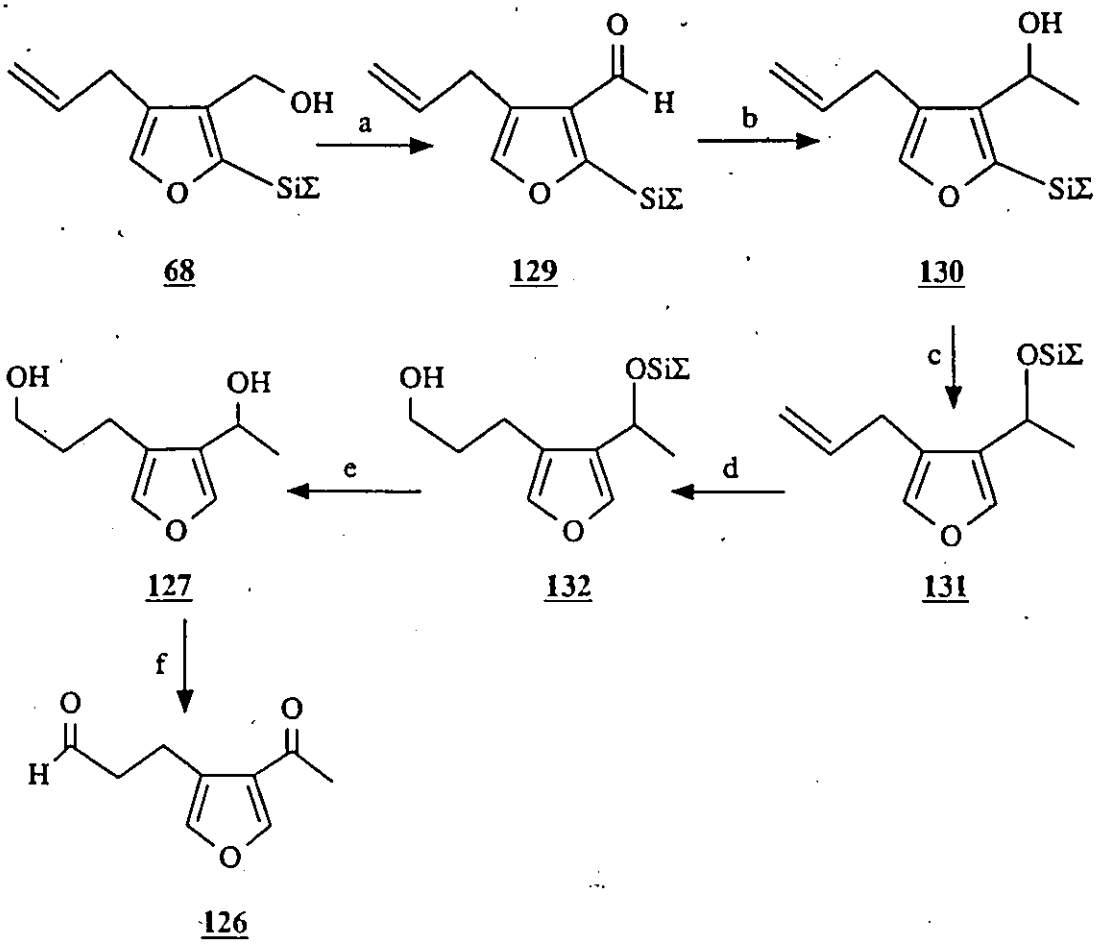
128 127

overlapped with the pattern of the H-10 protons. One other anomaly was observed in the proton spectrum. The silyl group methyl proton signals were separated into two peaks at δ 0.24 and 0.26 indicating that the methyls are nonequivalent and diasteriotopic. The ^{13}C NMR contained a signal due to C-6 which was observed at δ 63.93 and one due to C-7 at δ 26.44. All other signals were consistent with previously assigned data.

Compound 130 was subjected to [1,4] C→O silyl migration conditions (5 equivalents of NaH in DMF) which provided the silyl ether 131 in 95% yield (Scheme 54).

The IR spectrum of the silyl ether 131 did not contain any strong peaks. This reflected the hydroxyl group masked by the silyl moiety. The ^{1}H NMR spectrum exhibited a variety of alterations which resulted from the migration. The shift of the silyl methyl singlets was apparent (from δ 0.25 to -0.017 and 0.028) (vide supra). The second furan proton signal indicated that the silyl group had been removed from the furan ring (δ 7.09 and 7.26). The signal corresponding to H-6 had shifted from δ 5.03 to 4.80 which separated the pattern from the H-10 signal. The ^{13}C NMR spectrum contained the characteristic signals of the furan, silyl group and C-6 to C-10.

Scheme 51

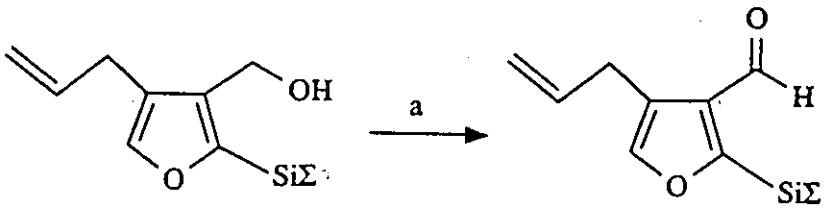


a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N
b) MeLi, THF, -78°
c) NaH, DMF
d) BH_3·DMS, Et_2O; EtOH, NaOH, H_2O_2
e) $(n\text{-}Bu)_4N^+F^-$, THF
f) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

Hydroboration-oxidation[41] of the silyl ether 131 with borane-dimethyl sulfide complex in ether followed by addition of ethanol, sodium hydroxide and hydrogen peroxide provided the alcohol 132 in 86% yield (Scheme 55).

The IR spectrum of alcohol 132 exhibited a broad signal (3367 cm^{-1}) which resulted from the OH group. The ^1H NMR spectrum of the alcohol exhibited a broad multiplet (δ 1.83) assigned to the H-9 protons as well as the hydroxyl proton. The other

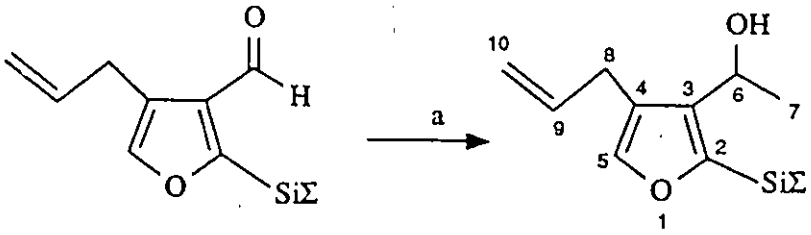
Scheme 52



68 129

a) $(COCl)_2$, DMSO, CH_2Cl_2; ET_3N

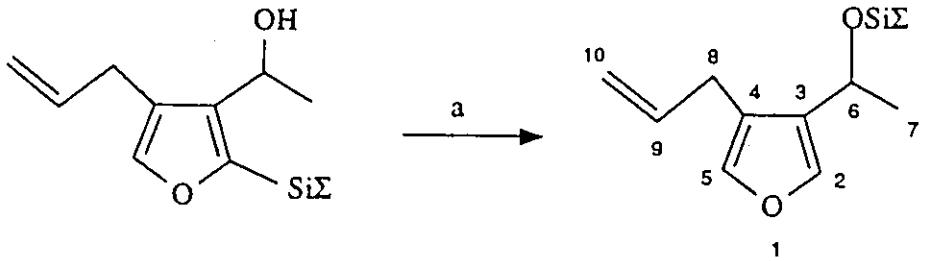
Scheme 53



129 130

a) MeLi, THF

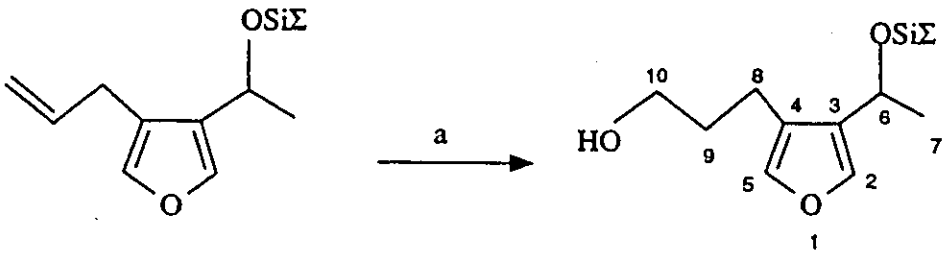
Scheme 54



130 131

a) NaH, DMF

Scheme 55



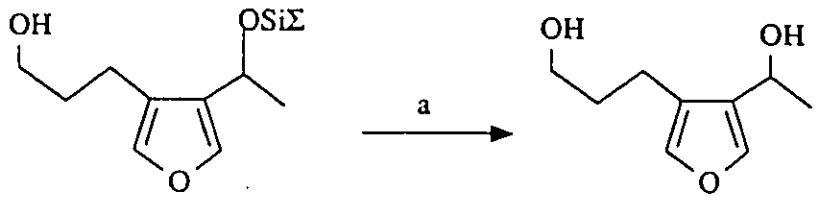
131 132

a) BH_3·DMS, Et_2O

signals elaborated by this reaction resulted from H-8 and H-10 located at δ 3.67 and 2.49 respectively. In the ^{13}C NMR spectrum of alcohol 132 the peaks which resulted from C-8, C-9 and C-10 were observed at δ 20.16, 32.15 and 62.30.

Desilylation of the silyl ether 132 using $(n\text{-}Bu)_4N^+F^-$ in THF resulted in the formation after workup of the diol 127 in 89% yield (Scheme 56).

Scheme 56



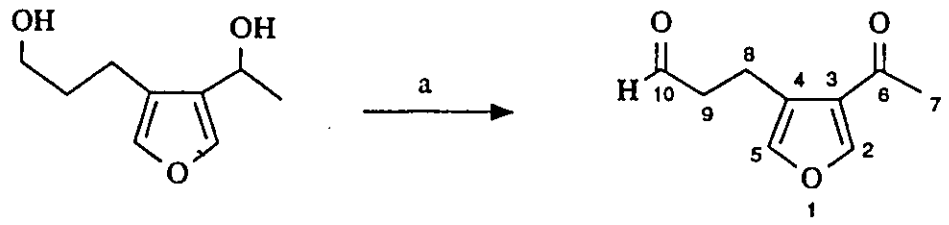
132 127

a) $(n\text{-}Bu)_4N^+F^-$, THF

The IR spectrum of the diol 127 contained an extremely broad signal (3364 cm^{-1}) which corresponded to the two alcohol moieties. The ^1H NMR spectrum of the diol 127 was devoid of the distinctive silyl group protons. The ^{13}C NMR spectrum did not contain the characteristic signals of the silyl group. All other signals in the two spectra remained relatively unchanged by the reaction.

Oxidation of alcohol 127 under Swern[42] conditions with oxalyl chloride-DMSO complex resulted in the formation of the aldehyde-ketone 126 in 89% yield (Scheme 57).

Scheme 57



127 126

a) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

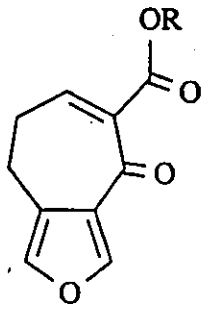
The IR spectrum of the aldehyde-ketone 126 contained two strong absorptions at 1723 and 1675 cm^{-1} which resulted from the aldehyde and ketone moieties respectively. The ^1H NMR spectrum of the system provided direct evidence of the aldehyde group via the signal at δ 9.72. The loss of proton peaks which corresponded to H-6 and H-10 was also observed. The slight shift of almost all peaks (as compared with the diol 127) in the spectrum was observed. A large change in the chemical shift of the H-2 was again observed and the assignments of previous compounds were made as a result. The ^{13}C NMR spectrum exhibited two shifted signals (δ 61.14 and 61.86) at δ 201.83 and 193.27 which resulted from C-10 and C-6 respectively.

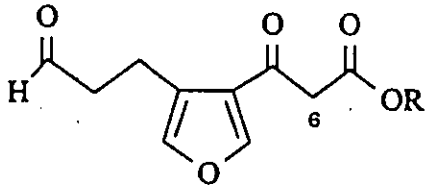
The aldehyde ketone 126 was subjected to a variety of conditions to attempt an Aldol closure. Included among these were NaOMe/MeOH, NaOEt/EtOH and florisil/benzene.[49] The temperature was altered from 25°C to reflux and the solvent concentration was varied. The α,β-unsaturated ketone was never isolated. The reactions generally produced a variety of products which could not be separated; the ^1H NMR spectra of the mixtures indicated compound 126 was not among the melee of products. Since the aldol reaction would not go to completion, an alternative method was required to form the ketone 125.

Ono[48] also reported that the cyclopropanation reaction (Scheme 48) gave the best yields when the system contained a β-keto ester. Yields of the cyclopropyl derivatives were generally 60-70% with these systems. We therefore decided that compound 133 would be the new target. The precursor 134 would most likely be more effective in the Aldol reaction as well, due to the doubly activated protons at C-6.

The synthesis of compound 134 was attempted according to Scheme 58.

Desilylation of alcohol 68 with $(n\text{-}Bu)_4N^+F^-$ in THF provided the alcohol 135





133 134

upon ammonium chloride workup in 84% yield (Scheme 59).[25]

All data was consistent with that previously published.[23] The silyl proton peaks and carbon signals were absent in their respective NMR spectra.

The oxidation of alcohol 135 under Swern conditions with oxalyl chloride-DMSO complex followed by triethylamine provided the aldehyde 136 in 91% yield (Scheme 60).[42]

The IR spectrum of aldehyde 136 exhibited a strong carbonyl signal at 1685 cm^{-1}. The presence of a singlet at δ 9.90 (^1H NMR) resulting from the aldehyde proton as well as the characteristic peak at δ 185.03 (^{13}C NMR) confirmed the existence of the aldehyde group in the system. The absent H-6 proton signal in the ^1H NMR spectrum was also indicative of the oxidation. All other signals remained relatively unchanged.

Oxidation of aldehyde 136 was performed with a mixture of silver nitrate in NaOH and water.[44] The acid 137 was produced in 78% yield (Scheme 61).

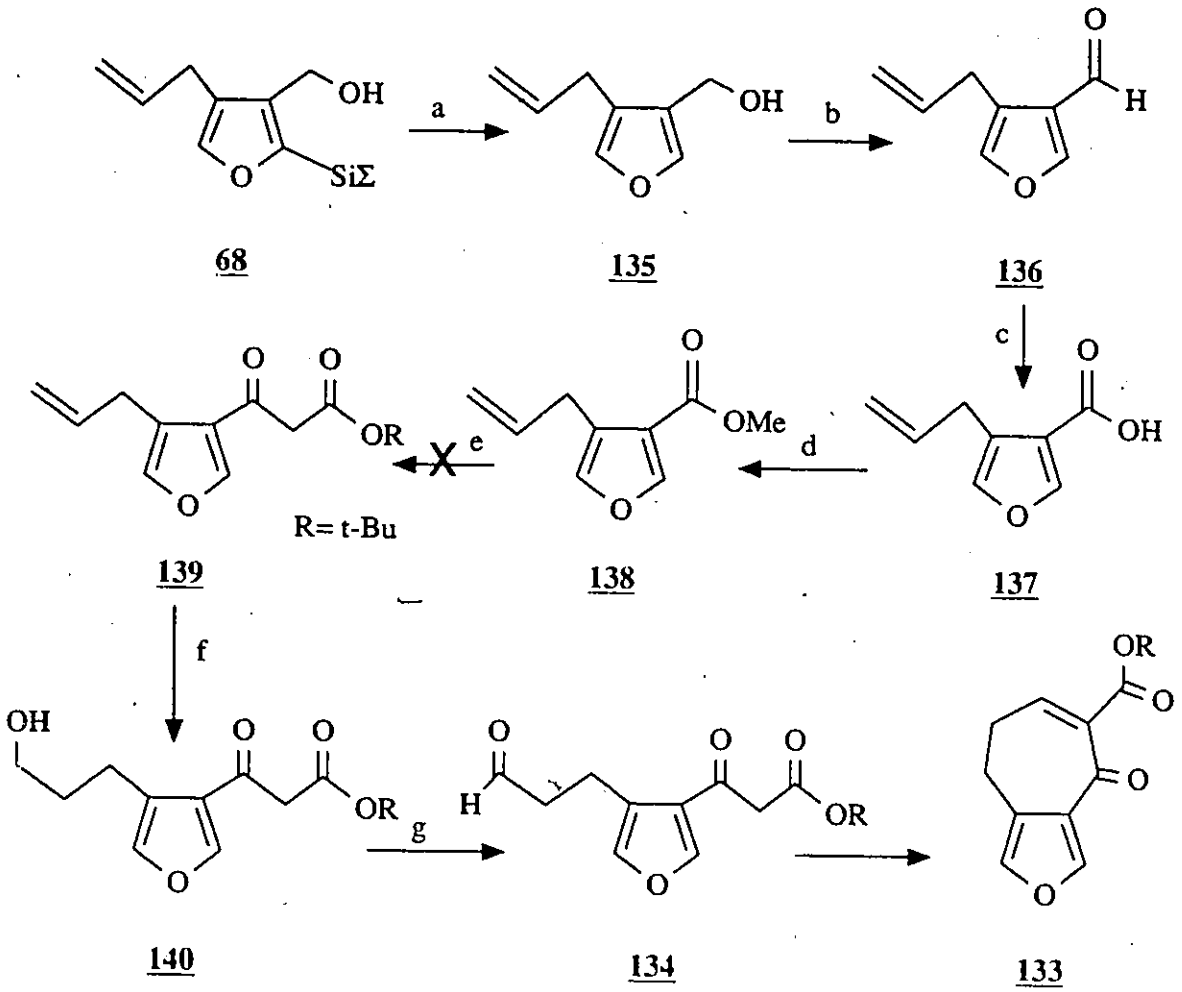
The IR spectrum of the acid 137 contained a hydroxyl signal and a carbonyl signal at 2924 and 1703 cm^{-1} respectively. The existence of the acid moiety was confirmed by the lack of aldehyde proton in the ^1H NMR spectrum. Furthermore the peak observed at δ 169.07 in the ^{13}C NMR spectrum was assigned to the acid carbon.

Esterification of the acid 137 was performed with a mixture of lithium carbonate and MeI in DMF. The ester 138 was produced in 71% yield (Scheme 62).

The IR spectrum of ester 138 contained no hydroxyl signal however a sharp carbonyl peak was observed at 1726 cm^{-1}. The singlet at δ 3.78 in the ^1H NMR spectrum corresponded to the ester methyl protons. The signals at δ 51.23 and 163.85 in the ^{13}C NMR resulted from the methyl and the carbonyl groups respectively.

All attempts at a nucleophilic addition of the anion of t-butyl acetate to ester 138[50] proved futile. In all cases none of the desired β-keto ester 134 was observed and only starting material was recovered.

Scheme 58



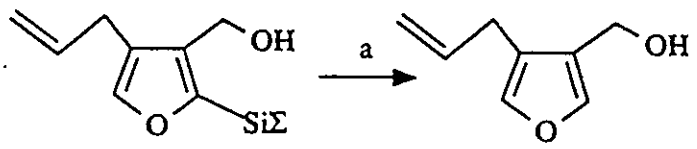
a) $(n\text{-}Bu)_4N^+F^-$, THF b) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N c) $AgNO_3$, NaOH

d) Li_2CO_3, MeI, DMF e) t-BuOAc, LDA, LiOt-Bu, THF

f) BH_3·DMS, Et_2O; H_2O_2, NaOH, EtOH g)$(COCl)_2$, DMSO, CH_2Cl_2; Et_3N

At this point in time a synthesis of furanoplagiochilal has not been presented. Difficulties have been encountered in the 7-membered ring closing steps including the intramolecular cyclopropanation and Aldol reactions. Further problems have been observed with the attempted β-keto ester formation in the last synthesis. Further modifications of this later reaction should be attempted; however, due to time restraints, they were not. Despite these problems significant advances have been made towards the synthesis of furanoplagiochilal. Further investigations will undoubtedly lead to a sucessful end to this project.

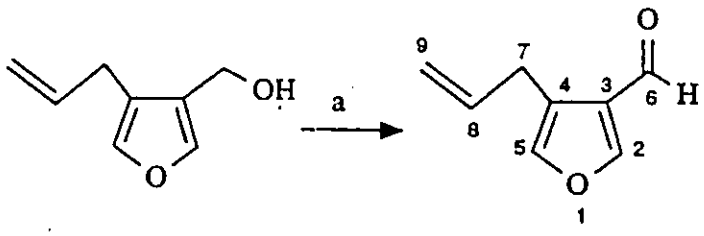
Scheme 59



68 135

a) $(n\text{-}Bu)_4N^+F^-$, THF

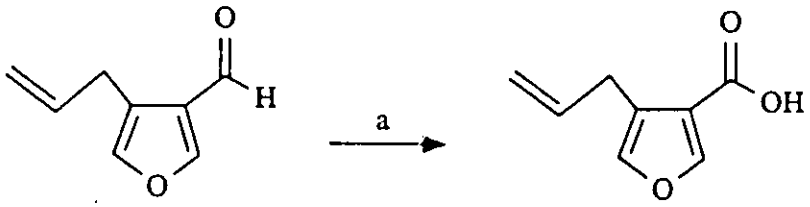
Scheme 60



135 136

a) $(COCl)_2$, DMSO; Et_3N

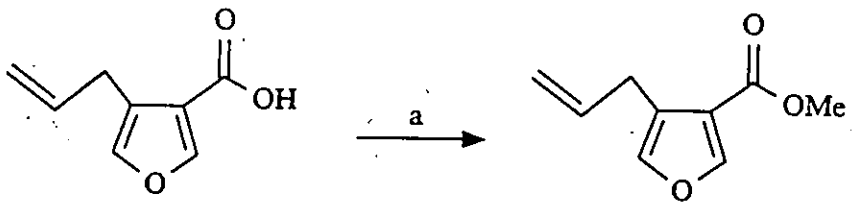
Scheme 61



136 137

a) $AgNO_3$, NaOH, H_2O

Scheme 62



137 138

a) Li_2CO_3, DMF

3.0.0 ***Experimental***

3.1.0 ***GENERAL PROCEDURES***

Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario. Nuclear magnetic resonance spectra were obtained using a Brucker AC300 spectrometer using deuterochloroform as solvent (and internal standard) unless otherwise stated. Spectra listed in this section will have the following format for ^{1}H NMR: chemical shift (in ppm), (multiplicity, number of protons, coupling constants, assignment). All ^{13}C NMR will follow the format: chemical shift (in ppm), (proton multiplicity [as determined by DEPT experiment]). Infrared spectra were obtained using a Nicolet 5DK-FTIR instrument. Solid samples were run as KBr pellets, while oils were run neat on NaCl plates. All mass spectra were obtained using a Varian CH5 spectrometer.

Reactions were monitored by the use of thin layer chromatography (tlc). Tlc plates were purchased from the Merck Frosst Company (catalog #M5735). The developing solvent system will be indicated with each experiment. The plates were developed in the following manner: 1) The plate was coated with a solution consisting of $(NH_4)_8Mo_7O_{24}\cdot 4H_2O$ (118.4g), conc. H_2SO_4 (200ml) and water (2L) and then, 2) heated to over 100°C with a hot air gun. Where column chromatography was necessary E.Merck silica gel (0.040-0.063mm, 230-400 mesh A.S.T.M.) and the method developed by Still[51] was used.

Diethyl ether, THF, benzene and DME were dried (Na/benzophenone) and distilled immediately prior to use. Methylene chloride, HMPA, DMF, and hexane were dried over calcium hydride and distilled prior to use.

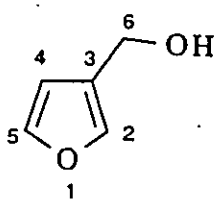
Syringes and glassware were oven-dried at 120°C for 4 hours or longer and either cooled in a desiccator or cooled via the flow of dry argon. All reactions which were sensitive to moisture or atmospheric conditions were conducted under argon.

Cooling baths were prepared using the following solvent/coolant systems : -20°C, 3.5M calcium chloride-dry ice; -60°C, chloroform-dry ice; -78°C, acetone-dry ice. All temperatures are given in degrees Celsius. All boiling points are obtained using a Kugelrohr air bath apparatus while melting points are determined using a Thomas-Hoover capillary apparatus.

3.2.0 *EXPERIMENTAL PROCEDURES*

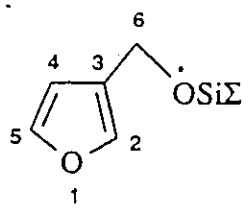
3.2.1 [1,4] C→O Silyl Migration Products and Precursors

3-(Hydroxymethyl)furan(59)



3-Furoic acid (20g, 179mmol) was added to a solution of lithium aluminum hydride (7g, 171mmol) in dry diethyl ether at 0°C. The mixture was stirred 2 hours at 25°C and then cooled to 0°C. The mixture was then treated with water (7ml), 15% sodium hydroxide (7ml), and water (21ml) which produced a slurry. The slurry was filtered through celite and the solvent removed in vacuo to yield after distillation a clear colorless liquid 59(83%). bp 98-100°C/20mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 2.80(bs, 1H, OH), 4.45(s, 2H, H-6), 6.37(s, 1H, H-4), 7.34(d, 2H, J=1.1Hz, H-2 and H-5); ^{13}C NMR($CDCl_3$, 75MHz) 56.21(t), 109.72(d), 125.01(s), 139.76(d), 143.28(d); IR(neat) 3390 cm^{-1}(OH); mass spectrum 98(100, $M^{\cdot+}$).

3-[(t-Butyldimethylsilyl)oxymethyl]furan(54).

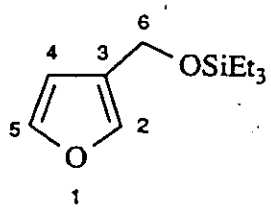


General Silylation Procedure 1

To a solution of t-butyldimethylsilyl chloride (6.1g, 40mmol) in DMF (20ml) at 0°C, was added imidazole (5.7g, 84mmol) and 3-(hydroxymethyl)furan. After 12 hours at 25°C, diethyl ether and aqueous sodium chloride were added. The organic layer was washed (6X's) with saturated aqueous sodium chloride, dried (Na_2SO_4), and the solvent removed in vacuo to afford after distillation a clear colorless oil 54(95%). bp 106-109°C/20mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ -0.04(s, 6H, -Si-Me), 0.81(s,

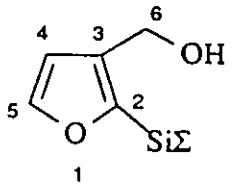
9H, -Si-t-Bu), 4.54(s, 2H, H-6), 6.42(s, 1H, H-4), 7.51(d, 2H, J=6.1Hz, H-2 and H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -2.85(q), 18.21(d), 25.80(q), 57.52(t), 109.66(d), 125.85(s), 139.38(d), 143.14(d); IR(neat) 1063 cm^{-1}(C-O); mass spectrum 212(10%), $M^{\cdot+}$).

3-[(Triethylsilyl)oxymethyl]furan(79).



General silylation procedure 1 was performed on alcohol 59 (1.3070g, 13.3 mmol) with triethylsilyl chloride (2.41g, 16.0 mmol) to yield after distillation a clear colourless oil 79(88%). bp 39-41°C/0.044mm (air bath); ^1H NMR($CDCl_3$, 300MHz) δ 0.60(m, 6H, -Si-CH_2-), 0.95(m, 9H, -Si-CH_2-CH_3), 4.57(s, 2H, H-6), 6.36(s, 1H, H-4), 7.34(d, 2H, J=1.2Hz, H-2 and H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ 4.43(t), 6.67(q), 56.91(t), 109.67(d), 125.53(s), 139.40(d), 143.05(d); IR(neat) 1061 cm^{-1}(C-O); mass spectrum 212(13, $M^{\cdot+}$).

2-(t-Butyldimethylsilyl)-3-(Hydroxymethyl)furan(55).

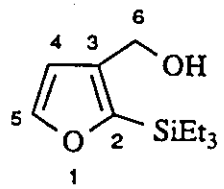


General Migration Procedure 2

To a mixture of furan 54 (0.69g, 3.3mmol), and HMPA (0.62ml, 3.6mmol) dissolved in THF (10ml) and cooled to -78°C, was added n-butyllithium (1.43ml, 2.5M in hexane, 3.6mmol). After stirring for 1h at -20°C saturated aqueous ammonium chloride was added and the solution extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to leave an oil. Silica gel chromatography ((9:1) petroleum ether : ethyl acetate) followed by distillation provided a white crystalline product 55(87%). bp 75-78°C/20mm (air bath); ^1H NMR($CDCl_3$, 300MHz) δ 0.01(s, 6H,

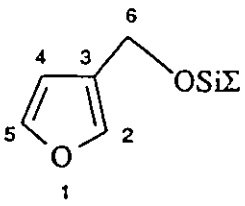
-Si-Me), 0.89(s, 9H, -Si-t-Bu), 1.50(bs, 1H, OH), 4.57(s, 2H, H-6), 6.46(d, 1H, J=1.8Hz, H-4), 7.57(d, 1H, J=1.8Hz, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.73(q), 18.12(s), 25.69(q), 57.10(t), 110.52(d), 135.87(s), 146.69(d), 154.96(s); IR(KBr pellet) 3319(OH), 1070 cm^{-1}(C-O); mass spectrum 212(0.1, $M^{\cdot+}$), 155(100, $M^{\cdot+}$-t-Bu); Anal. calcd. for $C_{11}H_{20}O_2Si$; C, 62.21; H, 9.49. Found; C, 62.56; H, 9.60.

2-(Triethylsilyl)-3-(Hydroxymethyl)furan(66).



General migration procedure 2 was performed on furan 79 to yield after silica gel column (petroleum ether : ethyl acetate (9:1)) and distillation, compound 66(41%). bp 72°C/0.04mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.79(m, 6H, -Si-CH_2-), 0.95(m, 9H, -Si-CH_2-CH_3), 2.10(bs, 1H, OH), 4.52(s, 2H, H-6), 6.43(d, 1H, J=1.4Hz, H-4), 7.55(s, 1H, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ 3.47(t), 7.25(q), 56.95(t), 110.41(d), 135.74(s), 146.77(d), 154.61(s); IR(KBr pellet) 3337(OH), 1045 cm^{-1}(C-O); mass spectrum 212(3.24, $M^{\cdot+}$).

3-[(t-Butyldimethylsilyl)oxymethyl]furan(54).



General Migration Procedure 3

To a solution of furan alcohol 55 (0.45mmol) in DMF or THF (0.05M starting material) was added sodium hydride (2.24mmol). After stirring for 1 hour (in DMF) saturated aqueous sodium chloride and diethyl ether were added, and the organic layer washed (6X's) with brine. After 16 hours in THF, ammonium chloride was added and the solution extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), solvent

removed in vacuo, and the resulting oil 54 distilled (88% in DMF and 86% in THF). All spectral data proved consistant with the data indicated previously.

Catalytic Migration Procedure

General migration procedure 3 was performed on the furan alcohol 55 with only 2 mol% of sodium hydride and 15 minutes in DMF. Furan 54 was obtained in 92% yield.

Silyl Migration Study Using Various Bases

Potassium Hydride

Potassium hydride (35% in mineral oil) was used in place of NaH in general migration procedure 3 with THF. After 48 hours, compound 55 was obtained in 61% yield.

Sodium Hydroxide

Migration procedure 3 was performed with sodium hydroxide in DMF for 1 hour. The product was a mixture of furan 54 (64%) and alcohol 59 (23%).

Vinyl Magnesium Bromide

Vinyl magnesium bromide (1.0M in THF, 1 eqivalent) was used in general migration procedure 3 with THF. After 24 hours, only starting material was observed.

Methyllithium

Migration procedure 3 was used with methyllithium (1.4M in Et_2O, 1 equivalent) in THF. After 24 hours, only compound 55 was recovered.

n-Butyllithium

n-Butyllithium (2.5M in hexane, 1 equivalent) was used in migration procedure 3, but after 24 hours, only starting material (55) was found.

Silyl Migration Study Using Various Solvents

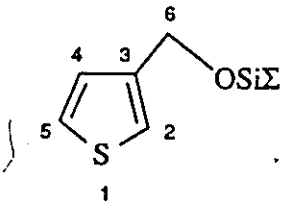
Dimethoxyethane

General migration procedure 3 was performed using DME as the solvent. The solution was stirred for 56 hours providing upon workup 54 (96%).

Diethyl Ether

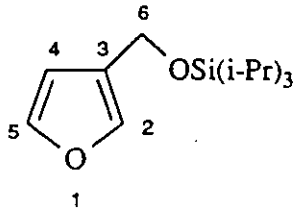
Diethyl ether was used in migration procedure 3. The solution was stirred for 7 days but only compound 55 was observed upon workup.

3-[(t-Butyldimethylsilyl)oxymethyl]thiophene(78).



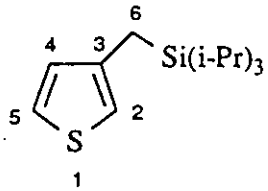
General migration procedure 3 was employed using thiophene 65 which provided after distillation a clear colorless oil 78(76%). bp 88°C/20mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.10(s, 6H, -Si-Me), 0.95(s, 9H, -Si-t-Bu), 4.74(s, 2H, H-6), 7.02, 7.17, 7.26(1H each, H-2, H-4, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.30, 18.32, 25.90, 61.27, 120.42, 125.56, 126.17, 142.75; IR(neat) 1086 cm^{-1}(C-O); mass spectrum 228(100, M^{+}); Anal. Calcd. for $C_{11}H_{20}O_2SSi$; C, 57.84; H, 8.82. Found; C, 57.65; H, 9.06.

3-[(Triisopropylsilyl)oxymethyl]furan(75).



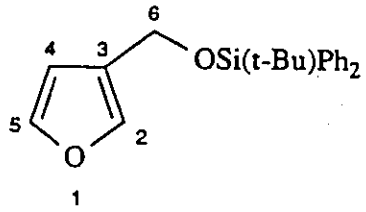
General migration procedure 3 in DMF(89%) and in THF(15%) was performed using furan 62 to afford after distillation a clear colorless oil 75. bp. 95°C/20mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.03(s, 21H, -Si-i-Pr), 4.66(s, 2H, H-6), 6.32(s, 1H, H-4), 7.35(d, 2H, J=1.3Hz, H-2 and H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ 12.28, 17.65, 109.30, 125.99, 139.03, 142.90; IR(neat) 1104 cm^{-1}(C-O); mass spectrum 254(100, M^{+}).

3-[(Triisopropylsilyl)oxymethyl]thiophene(76).



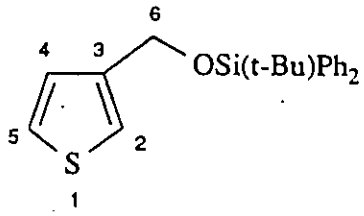
General migration procedure 3 was performed with thiophene 63 to yield a clear colorless oil 76 (in DMF(86%) and in THF(90%)) after distillation. bp. 135°C/20mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.07(s, 21H, -Si-i-Pr), 4.81(s, 2H, H-6), 7.01, 7.16, 7.26(1H each, H-2, H-5, H-4); ^{13}C NMR($CDCl_3$, 75MHz) δ 12.04, 18.00, 61.73, 120.09, 125.50, 125.98, 143.09; IR(neat) 1098 cm^{-1}(C-O); mass spectrum 270(100, M$^{\cdot+}$).

3-[(t-Butyldiphenylsilyl)oxymethyl]furan(73).



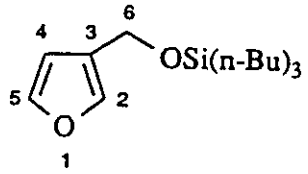
General migration procedure 3 was carried out with furan 60 in DMF(89%) and in THF(91%) providing after distillation compound 73 as a clear colorless oil. bp. 125°C/0.05mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.01(s, 9H, -Si-t-Bu), 4.57(s, 2H, H-6), 6.27(s, 1H, H-4), 7.34(m, 8H, H-2, H-5, Ph), 7.64(m, 4H, Ph); ^{13}C NMR($CDCl_3$, 75MHz) δ 19.22, 26.79, 58.30, 109.54, 125.36, 127.69, 129.70, 133.54, 135.56, 139.34, 142.96; IR(neat) 1089 cm^{-1}(C-O); mass spectrum 336(100, M$^{\cdot+}$).

3-[(t-Butyldiphenylsilyl)oxymethyl]thiophene(74).



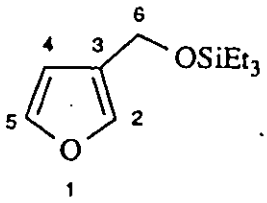
General migration procedure 3 was performed with thiophene 61 in DMF(88%) and THF(93%) to produce a clear colorless oil after distillation 74. bp. 90-93°C/0.04mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.06(s, 9H, -Si-t-Bu), 4.74(s, 2H, H-6), 6.99, 7.14, 7.25(1H each, H-2, H-4, H-5), 7.38(m, 5H, Ph), 7.66(m, 5H, Ph); ^{13}C NMR($CDCl_3$, 75MHz) δ 19.28, 26.83, 62.12, 120.54, 125.59, 126.21, 127.69, 129.70, 133.51, 135.55, 142.41; IR(neat) 1084 cm^{-1}(C-O); mass spectrum 352(2, M$^{\cdot+}$), 295(98, M$^{\cdot+}$-t-Bu).

3-[(Tri-n-butylsilyl)oxymethyl]furan(77).



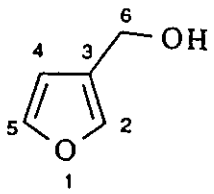
General migration procedure 3 was performed on furan 64 to yield after distillation a clear colorless oil 77 (75% in DMF and 81% in THF). bp. 102°C/0.04mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.60(m, 6H, -Si-CH_2-CH_2-CH_2-CH_3), 0.86(t, 9H, J=3.7Hz, -Si-CH_2-CH_2-CH_2-CH_3), 1.29(m, 12H, -Si-CH_2-CH_2-CH_2-CH_3), 4.55(s, 2H, H-6), 6.35(s, 1H, H-4), 7.34(d, 2H, J=2.7Hz, H-2 and H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ 13.34, 13.76, 25.37, 26.59, 56.94, 109.71, 125.60, 139.43, 143.06; IR(neat) 1087 cm^{-1}(C-O); mass spectrum 296(23, $M^{\cdot+}$), 239(100, $M^{\cdot+}$-t-Bu).

3-[(Triethylsilyl)oxymethyl]furan(79).



Migration procedure 3 was performed on furan 66 for 5 minutes in DMF to give after distillation compound 79(81%). All data was consistant with that indicated above.

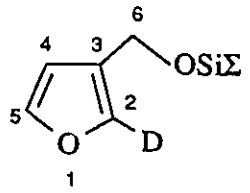
3-(Hydroxymethyl)furan(59).



Each of the following alcohols, when subjected to procedure 3 (in DMF and THF) did not produce the corresponding silyloxy compound but provided 3-hydroxymethylfuran, exclusively.

a)2-(Diphenylmethylsilyl)-3-(hydroxymethyl)thiophene(69)
b)2-(Trimethylsilyl)-3-(hydroxymethyl)furan(70)
c)2-(Dimethylisopropylsilyl)-3-(hydroxymethyl)furan(71).

2-(Deuterio)-3-[(t-Butyldimethylsilyl)oxymethyl]furan(89).



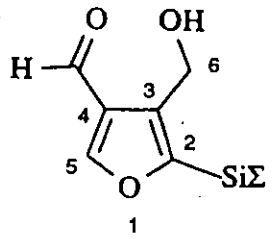
To a solution of furan 55 (0.125g, 0.59mmol) in DME (0.2ml) was added deuterium oxide (0.053ml, 2.9mmol). After 15 minutes the solution was dried (Na_2SO_4), diluted with DMF (5ml) and procedure 3 was followed for only 5 minutes. Silica gel column (petroleum ether : ethyl acetate (9:1)) followed by distillation produced a clear colourless oil 89(82%). bp. 61-63°C/0.033mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.07(s, 6H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 4.58(s, 2H, H-6), 6.35(d, 1H, J=1.4Hz, H-4), 7.35(d, 1H, J=1.4Hz, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.26(q), 18.00(s), 25.89(q), 57.39(t), 109.54(d), 125.71(s), 139.25(3 lines of equal intensity, C-D coupling), 142.95(d); IR(neat) 1082 cm^{-1}(C-O); mass spectrum 156(89, $M^{\cdot+}$-t-Bu).

Mixed Migration Experiment.

General migration procedure 3 was performed on a mixture of furan alcohol 55 (0.0410g, 0.19mmol), and thiophene alcohol 63 (0.0522g, 0.19mmol) in DMF (10ml). The resulting ^{1}H, ^{13}C NMR spectra and mass spectra data indicated that only compounds 54 and 76 were produced. For NMR data see Figure 3.

3.2.2 Furanoplagiochilal Experimental

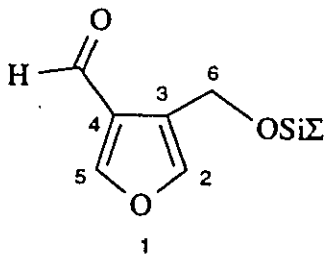
2-(t-Butyldimethylsilyl)-3-(Hydroxymethyl)-4-Furaldehyde(67).



General C-4 Anion Formation Procedure 4

To a solution of alcohol 55 (0.045 g, .21 mmol) in DME (1.5ml) at -78°C, was added n-butyllithium (.19 ml of 2.5M in hexane, .47 mmol). After 15 minutes at 0°C, DMF (0.052 ml, 0.64 mmole) was added and the mixture maintained at 0°C for 12 hours. Saturated aqueous sodium chloride was added and the solution extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and the solvent removed in vacuo to afford a white crystalline solid, after distillation 67(91%). mp. 76-78°C, bp 68°C/0.056 mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.27(s, 6H, -Si-Me), 0.86(s, 9H, -Si-t-Bu), 4.08(bs, 1H, OH), 4.57(s, 2H, H-6), 8.26(s, 1H, H-5), 9.90(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.89(q), 17.11(s), 26.10(q), 55.42(t), 128.31(s), 133.93(s), 158.31(d), 162.92(s), 186.63(d); IR(KBr pellet) 3415(OH), 1678 cm^{-1}(CO); mass spectrum 183(100, $M^{\cdot+}$-t-Bu). Anal. calcd. for $C_{12}H_{20}O_3Si$; C, 59.96; H, 8.39. Found; C, 59.66; H, 8.65.

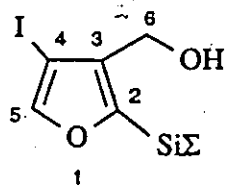
3-[(t-Butyldimethylsilyl)oxymethyl]-4-Furaldehyde(80).



General migration procedure 3 was performed on aldehyde 67 for 1 hour to produce, after distillation, a clear colourless liquid 80(90%). bp 60°C/0.052 mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.08(s, 6H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 4.83(d, 2H, J=1.4Hz, H-6), 7.41(s, 1H, H-2 or H-5), 7.99(d, 1H, J=1.4, H-5 or H-2), 9.91(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.49(q), 18.27(s), 25.83(q), 57.82(t), 125.65(s), 126.36(s),

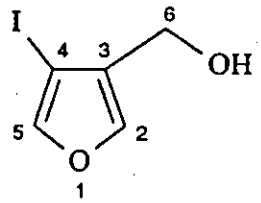
142.02(d), 152.73(d), 185.03(d); IR(neat) 1692(CO), 1095 cm^{-1}(C-O); mass spectrum 239(0.03, $M^{\cdot+}$), 182(100, $M^{\cdot+}$-t-Bu).

2-(t-Butyldimethylsilyl)-3-(Hydroxymethyl)-4-Iodofuran(105).



To the dianion produced via general anion procedure 4 was added iodine crystals (0.6M in DME). Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) followed by distillation produced a white crystalline solid 105(92%). mp 67-69°C; bp 84-86°C/0.02mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.27(s, 6H, -Si-Me), 0.87(s, 9H, -Si-t-Bu), 4.45(s, 2H, H-6), 7.56(s, 1H, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.64(q), 17.20(s), 26.42(q), 56.75(t), 69.42(s), 136.38(s), 149.68(d), 157.89(s); IR(KBr pellet) 3388(OH), 1047 cm^{-1}(C-O); mass spectrum 338(0.2, $M^{\cdot+}$), 281(100, $M^{\cdot+}$-t-Bu).

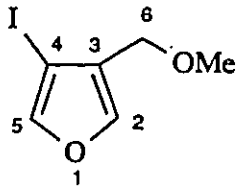
3-(Hydroxymethyl)-4-Iodofuran(106).



General Desilylation Procedure 5.

To furan 105 (0.0090g, 0.031mmol) in THF (0.8ml) was added $(nBu)_4NF$ (0.090ml, 1M soln in THF, 0.093mmol) at 25°C. After 24 hours, aqueous ammonium chloride was added and the solution extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and the solvent removed in vacuo to leave an oil. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) followed by distillation provided a white crystalline solid 106(92%). mp. 77°C; bp. 80°C/0.02mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 4.45(s, 2H, H-6), 7.38(s, 1H, H-2 or H-5), 7.40(s, 1H, H-5 or H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 57.00(t), 67.03(s), 127.11(s), 140.98(d), 146.12(d); IR(neat) 3378 cm^{-1}(OH); mass spectrum 224(1, $M^{\cdot+}$).

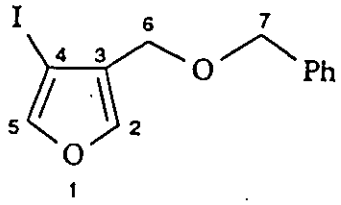
3-(Methoxymethyl)-4-Iodofuran(107a).



General Protection Procedure 6

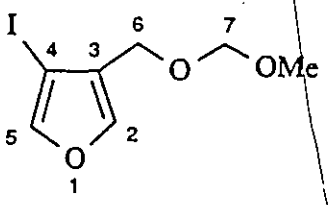
To a solution of alcohol 106(0.1348g, 0.59mmol) in DMF (15ml) was added sodium hydride (0.14g, 5.9mmol). After 5 minutes iodomethane (0.18ml, 3.0mmol) was added followed by ether (15ml) and saturated NaCl (15ml). The organic layer was washed (6X's) with brine, dried (Na_2SO_4), and the solvent removed in vacuo to obtain after distillation 107a(78%). bp 42-45°C/0.025mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 3.35(s, 3H, -OMe), 4.21(s, 2H, H-6), 7.37(s, 1H, H-2 or H-5), 7.40(s, 1H, H-5 or H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 57.89(t), 65.87(q), 124.18(s), 141.36(d), 142.32(s), 145.85(d); IR(neat) 1040 cm^{-1}(C-O); mass spectrum 238(61, $M^{\cdot+}$).

3-[Benzyloxymethyl]-4-Iodofuran(107b).



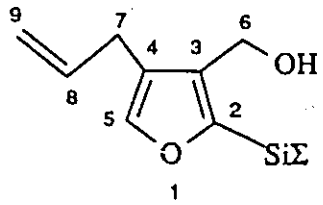
General protection procedure 6 was performed on furan 106 with benzyl bromide. After silica gel chromatography (petroleum ether : ethyl acetate (20:1)) and distillation a clear colourless oil 107b was obtained(79%). bp 88°C/0.023mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 4.33(s, 2H, H-6 or H-7), 4.56(s, 2H, H-7 or H-6), 7.35(m, 7H, H2, H-5 and Ph); ^{13}C NMR($CDCl_3$, 75MHz) δ 63.70(t), 72.34(t), 124.56(s), 127.73(d), 127.92(d), 128.41(d), 137.92(s), 141.70(d), 146.10(d); IR(neat) 1035 cm^{-1}(C-O).

3-[(Methoxymethyl)oxymethyl]-4-Iodofuran(107c).



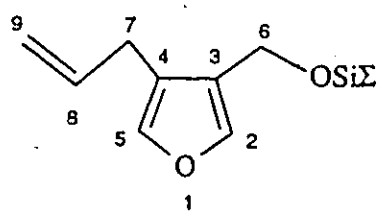
General protection procedure 6 was performed on furan 106 with chloromethyl methyl ether to give, after silica gel chromatography (petroleum ether : ethyl acetate(20:1)) and distillation furan 107c(77%). bp 73°C/0.032mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 3.40(s, 3H, -Me), 4.36(s, 2H, H-6 or H-7), 4.67(s, 2H, H-7 or H-6), 7.41(s, 1H, H-2 or H-5), 7.42(s, 1H, H-5 or H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 55.52, 60.73, 67.91, 95.57, 124.26, 141.76, 146.17; IR(neat) 1048 cm^{-1}(C-O); mass spectrum 268(23, $M^{\cdot+}$).

2-(t-Butyldimethylsilyl)-3-(Hydroxymethyl)-4-(2-Propenyl) furan (68).



To the anion of general procedure 4 was added lithium chloride (.35 g, 8.2 mmol) and allyl bromide (0.24 ml, 2.7 mmol). After stirring at 0°C for 6 hours a mixture of 55 and 68 was obtained. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) and distillation produced a clear oil 68(83%). bp 108°C/0.025 mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.28(s, 6H, -Si-Me), 0.89(s, 9H, -Si-t-Bu), 1.48(bs, 1H, -OH), 3.24(dd, 2H, J=6.3, 1.0 Hz, H-7), 4.50(s, 2H, H-6), 5.08(m, 2H, H-9), 6.00(m, 1H, H-8), 7.37(s, 1H, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.68(q), 17.15(s), 26.31(q), 27.70(t), 55.32(t), 115.74(t), 122.73(s), 134.92(s), 137.03(d), 144.08(d), 156.79(s); IR(neat) 3324(OH), 1038 cm^{-1}(C-O); mass spectrum 195(100, $M^{\cdot+}$-t-Bu). Anal. calcd. for $C_{14}H_{24}O_2Si$; C, 66.61; H, 9.58. Found; C, 66.31; H, 10.00.

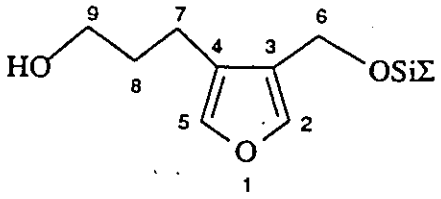
3-[(t-Butyldimethylsilyl)oxymethyl]-4-(2-Propenyl)furan(81).



General migration procedure 3 was performed on compound 68 for 24 hours to yield after distillation a clear colorless liquid 81(83%). bp 72°C/0.028 mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.076(s, 6H, -Si-Me), 0.91(s, 9H, -Si-t-Bu), 3.17(d, 2H, H-7),

4.54(s, 2H, H-6), 5.07(m, 2H, H-9), 5.93(m, 1H, H-8), 7.15(s, 1H, H-5), 7.30(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.37(q), 18.28(s), 25.86(q), 28.02(t), 56.52(t), 115.63(t), 122.15(s), 125.14(s), 136.04(d), 140.11(d), 140.21(d); IR(neat) 1048 cm^{-1}(C-O); mass spectrum 252(0.05, $M^{\cdot+}$), 196(70, $M^{\cdot+}$-t-Bu).

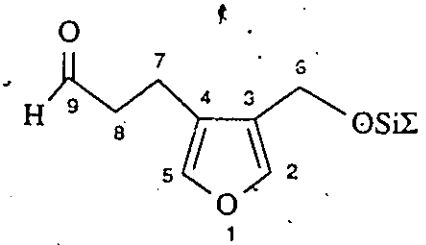
3-[(t-Butyldimethylsilyl)oxymethyl]-4-(3-Hydroxypropyl)furan (112).



General Hydroboration Procedure 7.

To a solution of furan 81 (2.1g, 8.3mmol) in diethyl ether (25mL) at 0°C was added borane-dimethyl sulphide complex (1.7 ml, 2M in THF, 3.3 mmol). After 4 hours at 25°C, ethanol(35 ml), aqueous sodium hydroxide (3.4 ml, 3M, 10 mmol), and hydrogen peroxide (2.8ml, 30%, 25 mmol) were added at 0°C. Following 30 minutes at 25°C saturated aqueous ammonium chloride was added and the solution extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and solvent removed in vacuo to leave a cloudy oil. Silica gel chromatography (petroleum ether : ethyl acetate (4:1)) and distillation produced a clear liquid 112(91%). bp 84°C/0.040mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.066(s, 6H, -Si-Me), 0.89(s, 9H, -Si-t-Bu), 1.81(m, 3H, -OH and H-8) 2.50(t, J=7.4Hz, 2H, H-7 or H-9), 3.64(t, J=6.2Hz, 2H, H-9 or H-7), 4.53(s, 2H, H-6), 7.16(s, 1H, H-5), 7.27(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.31(q), 18.35(s), 19.47(q), 25.88(t), 32.41(t), 56.40(t), 61.89(t), 123.72(s), 125.00(s), 139.84(d), 140.34(d); IR(neat) 3379(OH), 1047, 1088 cm^{-1} (C-O); mass spectrum 213(80, $M^{\cdot+}$-t-Bu).

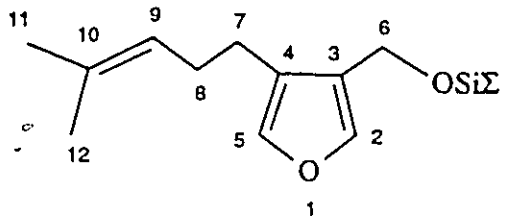
3-[(t-Butyldimethylsilyl)oxymethyl]-4-(3-Oxopropyl)furan(113).



General Swern Oxidation Procedure 8.

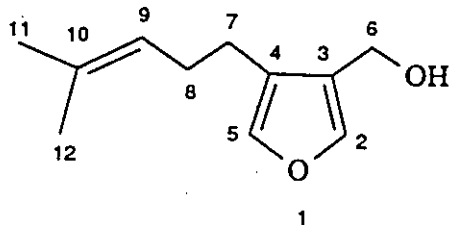
To a solution of oxalyl chloride (0.018ml, 0.21mmol) in methylene chloride (1.5ml) at -60°C, was added DMSO (0.027ml, 0.41mmol). After two minutes furan 112 (0.051g, 0.19mmol) in methylene chloride (0.5ml) was added dropwise and stirred for 15 minutes. Following addition of triethylamine (0.13ml, 0.94 mmol), water was added, and the solution extracted with CH_2Cl_2. The organic layer was washed (NaCl, HCl, Na_2CO_3, water), dried (Na_2SO_4), and the solvent removed in vacuo. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) and distillation produced a clear colourless liquid 113(91%). bp 73°C/0.038mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.056(s, 6H, -Si-Me), 0.88(s, 9H, -Si-t-Bu), 2.74(bs, 4H, H-7, H-8), 4.52(s, 2H, H-6), 7.14(s, 1H, H-5), 7.26(s, 1H, H-2), 9.78(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.46(q), 16.12(t), 18.15(s), 25.73(q), 43.39(t), 56.10(t), 122.79(s), 124.62(s), 139.83(d), 140.28(d), 201.52(d); IR(neat) 1726(CO), 1045 cm^{-1}(C-O); mass spectrum 211(25, M$^{\cdot+}$-t-Bu).

3-[(t-Butyldimethylsilyl)oxymethyl]-4-(4-Methyl-3-Pentenyl) furan(100).



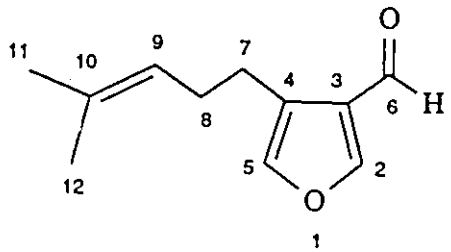
To a solution of isopropyltriphenylphosphonium iodide[43] (0.055g, 0.13mmol) in Et_2O (1ml) at -78°C was added phenyllithium (0.064ml, 0.013mmol). The solution became ruby red in colour when warmed to 0°. After 10 minutes, furan 113(0.023g, 0.086mmol) in diethyl ether (1ml) was added dropwise across 2 minutes. After 1 hour saturated aqueous ammonium chloride was added, the mixture filtered and extracted with ethyl acetate. The organic layer was then dried (Na_2SO_4) and the solvent removed in vacuo. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) and distillation produced a clear liquid 100(74%). bp 74°C/0.04mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.090(s, 6H, -Si-Me), 0.92(s, 9H, -Si-t-Bu), 1.60(s, 3H, H-12 or H-11), 1.70(s, 3H, H-11 or H-12), 2.24(t, J=7.2Hz, 2H, H-7), 2.42(m, 2H, H-8), 4.56(s, 2H, H-6), 5.17(m, 1H, H-9), 7.16(s, 1H, H-5), 7.27(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.33(q), 17.70(q), 18.35(s), 23.82(t), 25.68(q), 25.89(q), 27.90(t), 56.62(t), 123.94(d), 124.20(s), 125.19(s), 132.10(s), 139.63(d), 139.99(d); IR(neat) 1049, 1070 cm^{-1}(C-O); mass spectrum 294(0.06, M$^{\cdot+}$), 237(32.7, M$^{\cdot+}$-t-Bu).

3-(Hydroxymethyl)-4-(4-Methyl-3-Pentenyl)furan(114).



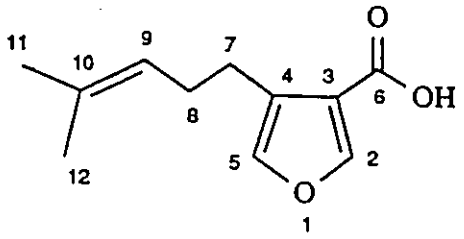
General desilylation procedure 5 was performed on furan 100 which provided after distillation, a clear colourless oil 114(85%). bp 62°C/0.05mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.57(s, 3H, H-11 or H-12), 1.67(s, 3H, H-12 or H-11), 1.88(bs, 1H, OH), 2.24(m, 2H, H-7), 2.43(m, 2H, H-8), 4.48(s, 2H, H-6), 5.15(t, J=7.0Hz, 1H, H-9), 7.15(s, 1H, H-5), 7.32(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 17.61(q), 23.56(t), 25.59(q), 27.99(t), 55.51(t), 123.77(d), 124.30(s), 124.89(s), 132.31(s), 139.91(d), 140.56(s); IR(neat) 1049(C-O), 3365 cm^{-1}(OH); mass spectrum 180(2.65, M$^{\cdot+}$).

4-(4-Methyl-3-Pentenyl)-3-Furaldehyde(117).



General Swern oxidation procedure 8 was performed on furan 114 which provided a clear colourless oil 117 after distillation (95%). bp 62°C/0.042mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.56(s, 3H, H-11 or H-12), 1.66(s, 3H, H-12 or H-11), 2.24(m, 2H, H-7), 2.66(m, 2H, H-8), 5.15(m, 1H, H-9), 7.22(s, 1H, H-5), 7.96(s, 1H, H-2), 9.94(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ 17.58(q), 23.98(t), 25.57(q), 27.70(t), 123.45(d), 123.96(s), 127.46(s), 132.38(s), 141.65(d), 153.11(d), 185.12(d); IR(neat) 1691 cm^{-1}(CO); mass spectrum 178(59.2, M$^{\cdot+}$).

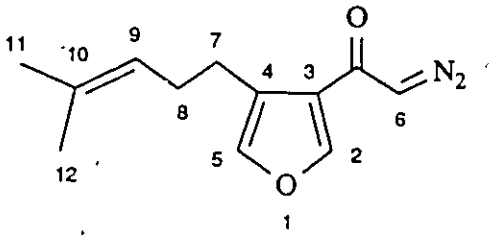
4-(4-Methyl-3-Pentenyl)-3-Furoic Acid(115).



General Silver Oxidation Procedure 9

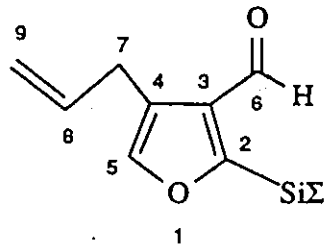
To a mixture of silver nitrate (0.109g, 0.64mmol) in sodium hydroxide (9ml, 3M soln in H_2O) was added aldehyde 117 (0.052g, 0.29mmol). After 6 hours hydrochloric acid (2M) was added and the mixture extracted with diethyl ether. The organic layer was dried (Na_2SO_4), and the solvent removed in vacuo to obtain a light brown solid 115(77%). mp. 156°C; ^{1}H NMR($CDCl_3$, 300MHz) δ 1.57(s, 3H, H-11 or H-12), 1.67(s, 3H, H-12 or H-11), 2.26(m, 2H, H-7), 2.65(m, 2H, H-8), 5.15(m, 1H, H-9), 7.21(s, 1H, H-5), 7.91(bs, 1H, OH), 8.04(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 17.64(q), 24.08(t), 25.66(q), 27.84(t), 117.67(s), 123.68(d), 125.41(s), 132.32(s), 141.10(d), 150.36(d), 169.23(s); IR(KBr pellet) 2918(OH), 1696 cm^{-1}(CO); mass spectrum 194(28.6, M$^{\cdot+}$).

4-(4-Methyl-3-Pentenyl)-3-(2-Diazo-1-Oxoethyl)furan(99).



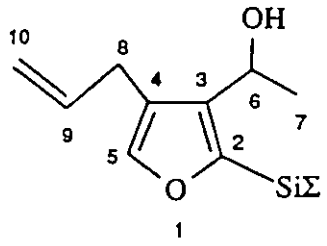
To a solution of the acid 115 (0.0810g, 0.42mmol) in hexane (2ml) was added oxalyl chloride (0.109ml, 1.26mmol). After refluxing for 2 hours, the solvent was removed in vacuo. After distillation (bp 72°C/0.054mm [air bath]), diethyl ether (3ml) and diazomethane (100ml, 0.15M solution in Et_2O) were added. After 6 hours the solvent was removed in vacuo to give a clear liquid 99(76%). ^{1}H NMR($CDCl_3$, 300MHz) δ 1.51(s, 3H, H-11 or H-12), 1.61(s, 3H, H-12 or H-11), 2.20(m, 2H, H-7), 2.62(m, 2H, H-8), 5.08(m, 1H, H-9), 5.56(s, 1H, H-6), 7.16(d, 1H, J=1.0Hz, H-5), 7.72(d, 1H, J=1.4Hz, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 17.51(q), 24.13(t), 25.47(q), 27.70(t), 123.56(d), 124.63(s), 124.90(s), 132.09(s), 141.23(d), 145.49(d), 181.46(s).

2-(t-Butyldimethylsilyl)-4-(2-Propenyl)-3-Furaldehyde(129).



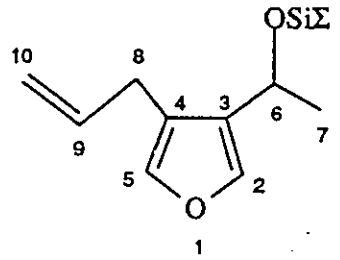
General Swern oxidation procedure 8 was performed on furan 68 which provided a clear colourless liquid after distillation 129(83%). bp 72°C/0.06mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.34(s, 6H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 3.42(d, 2H, J=6.5Hz, H-7), 5.07(m, 2H, H-9), 5.95(m, 1H, H-8), 7.37(s, 1H, H-5), 10.09(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.40(q), 17.15(s), 26.24(q), 28.51(t), 115.95(t), 123.00(s), 135.84(d), 136.39(s), 144.99(d), 172.17(s), 187.20(d); IR(neat) 1684.7 cm^{-1}(CO); mass spectrum 193(100, M$^{\cdot+}$-t-Bu).

2-(t-Butyldimethylsilyl)-3-(1-Hydroxyethyl)-4-(2-Propenyl) furan(130).



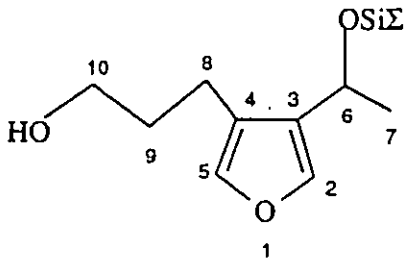
To a solution of furan 129 (0.6013g, 2.4mmol) in THF (30ml) was added methyllithium (2.6ml, 1.4M soln in diethyl ether, 3.6mmol) at -78°C. After 1 hour saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give, after distillation, a white amorphous solid 130(94%). mp 73-75°C, bp 90°C/0.036mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 0.24(s, 3H, -Si-Me), 0.26(s, 3H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 1.46(d, 3H, J=6.6Hz, H-7), 2.08(bs, 1H, OH), 3.35(m, 2H, H-8), 5.03(m, 3H, H-6 and H-10), 5.95(m, 1H, H-9), 7.30(s, 1H, H-5); ^{13}C NMR($CDCl_3$, 75MHz) δ -5.20(q), -5.40(q), 17.28(s), 23.65(q), 26.44(q), 28.91(t), 63.93(d), 115.78(t), 122.19(s), 137.05(d), 138.92(s), 145.00(d), 154.41(s); IR(KBr pellet) 3323.8 cm^{-1}(OH); mass spectrum 209(100, M$^{\cdot+}$-t-Bu).

3-[1-(t-Butyldimethylsilyloxy)ethyl]-4-(2-Propenyl)furan(131) .



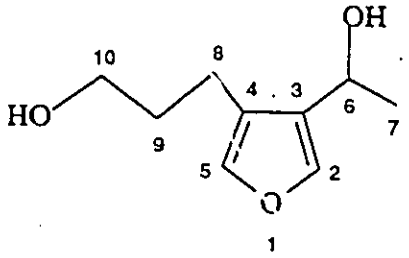
General migration procedure 3 was performed on alcohol 130 which provided after distillation a clear colourless oil 131(95%). bp 69°C/0.056mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ -0.017(s, 3H, -Si-Me), 0.028(s, 3H, -Si-Me), 0.87(s, 9H, -Si-t-Bu), 1.37(d, 3H, J=6.3Hz, H-7), 3.15(m, 2H, H-8), 4.80(q, 1H, J=6.4Hz, H-6), 5.07(m, 2H, H-10), 5.92(m, 1H, H-9), 7.09(s, 1H, H-5), 7.26(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ -4.84(q), 18.19(s), 25.58(q), 25.83(q), 28.40(t), 63.99(d), 115.81(t), 121.31(s), 130.51(s), 136.18(d), 139.36(d), 140.28(d); IR(neat) 1086.3 cm^{-1}(C-O); mass spectrum 209(29, M^{+}-t-Bu).

3-[1-(t-Butyldimethylsilyloxy)ethyl]-4-(3-Hydroxypropyl)furan (132).



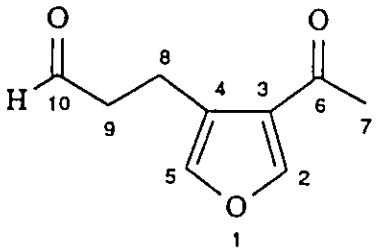
General hydroboration procedure 7 was performed on compound 131 with the following modifications: 1) The BH_3 was added at -78°C and, 2) the mixture was warmed to 0°C for 4 hours. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) followed by distillation produced a clear colourless oil 132(86%). bp 88°C/0.056mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ -0.016(s, 3H, -Si-Me), 0.030(s, 3H, -Si-Me), 0.86(s, 9H, -Si-t-Bu), 1.39(d, 3H, J=6.3Hz, H-7), 1.83(m, 3H, OH, H-9), 2.49(m, 2H, H-10), 3.67(t, 2H, J=6.4Hz, H-8), 4.80(q, 1H, J=6.3Hz, H-6), 7.11(s, 1H, H-5), 7.23(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ -4.79(q), 18.22(s), 20.16(t), 25.53(q), 25.84(q), 32.15(t), 62.30(t), 64.12(d), 122.83(s), 130.41(s), 139.34(d), 139.69(d); IR(neat) 3366.7(OH), 1085.9 cm^{-1}(C-O); mass spectrum 284(0.06, M^{+}), 227(12.34, M^{+}-t-Bu).

3-(1-Hydroxyethyl)-4-(3-Hydroxypropyl)furan(127).



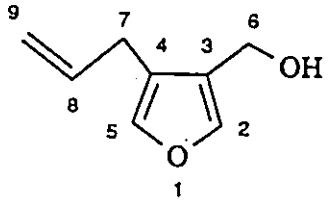
General desilylation procedure 5 was performed on furan 132 which provided a clear oil. After silica gel chromatography ((1:9) petroleum ether : ethyl acetate) and distillation, a colourless liquid 127 was obtained (89%). bp 110°C/0.056mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.44(d, 3H, J=6.5Hz, H-7), 1.75(m, 2H, H-9), 2.50(t, 2H, J=7.5Hz, H-10), 3.42(bs, 1H, OH), 3.55(t, 2H, J=6.0Hz, H-8), 4.73(q, 1H, J=6.4Hz, H-6), 7.12(s, 1H, H-5), 7.25(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 19.29(t), 22.85(q), 32.32(t), 61.14(t), 61.86(d), 123.53(s), 129.30(s), 139.08(d), 140.00(d); IR(neat) 3363.9(OH), 1050.4, 1073.3 cm^{-1}(C-O); mass spectrum 170(15.29, $M^{\cdot+}$).

3-(1-Oxoethyl)-4-(3-Oxopropyl)furan(126).



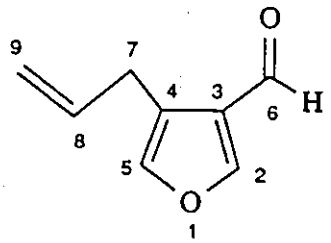
To a solution of oxalyl chloride (0.82ml, 9.30mmol) in methylene chloride (100ml) at -60°C, was added DMSO (1.36ml, 18.5mmol). After two minutes furan 127 (0.72g, 4.21mmol) in methylene chloride (5ml) was added dropwise and stirred for 15 minutes. Following addition of triethylamine (5.90ml, 42.1mmol), water was added , and the solution extracted with CH_2Cl_2. The organic layer was washed (NaCl, HCl, Na_2CO_3, water), dried (Na_2SO_4) and the solvent removed in vacuo. Silica gel chromatography (petroleum ether : ethyl acetate (9:1)) and distillation produced a clear colourless liquid 126 (89%). bp 74°C/0.048mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 2.37(s, 3H, H-7), 2.69(t, 2H, J=7.0Hz, H-9 or H-8), 2.93(t, 2H, J=7.1Hz, H-8 or H-9), 7.21(s, 1H, H-5), 7.95(d, 1H, J=1.3Hz, H-2), 9.72(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ 16.83(t), 28.15(q), 43.45(t), 123.35(s), 126.09(s), 141.80(d), 149.66(d), 193.27(s), 201.83(d); IR(neat) 1723.6(CO), 1675.7 cm^{-1}(CO); mass spectrum 166(100, $M^{\cdot+}$).

3-(Hydroxymethyl)-4-(2-Propenyl)furan(135).



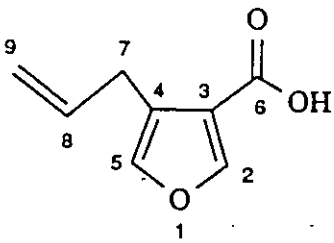
General desilylation procedure 5 was performed on furan 68 which provided, after silica gel chromatography (petroleum ether : ethyl acetate (9:1)) and distillation compound 135(84%). bp 52-53°C/0.025mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 1.72(bs, 1H, OH), 3.20(d, 2H, J=6.3Hz, H-7), 4.47(s, 2H, H-6), 5.08(m, 2H, H-9), 5.94(m, 1H, H-8), 7.17(s, 1H, H-5), 7.35(s, 1H, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 27.83(t), 55.40(t), 115.89(t), 122.19(s), 124.78(s), 136.49(d), 140.45(d), 140.96(d); IR(neat) 3386(OH), 1048 cm^{-1}(C-O); mass spectrum 138(100, $M^{\cdot+}$).

4-(2-Propenyl)-3-Furaldehyde(136).



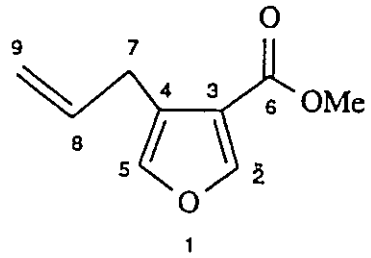
General Swern oxidation procedure 8 was performed on alcohol 135 which provided after distillation a clear colourless oil 136(91%). bp 79°C/0.021mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 3.38(dd, 2H, J=1.2, 6.6Hz, H-7), 5.05(m, 2H, H-9), 5.91(m, 1H, H-8), 7.20(s, 1H, H-5), 7.97(d, 1H, J=1.5Hz, H-2), 9.90(s, 1H, CHO); ^{13}C NMR($CDCl_3$, 75MHz) δ 28.13(t), 116.27(t), 122.38(s), 127.08(s), 135.26(d), 141.96(d), 152.99(d), 185.03(d); IR(neat) 1685(CO), 1045 cm^{-1}(C-O); mass spectrum 136(97, $M^{\cdot+}$)

4-(2-Propenyl)-3-Furoic Acid(137).



General silver oxidation procedure 9 was performed on aldehyde 136 which provided a light brown solid 137(78%). mp 68°C; ^{1}H NMR($CDCl_3$, 300MHz) δ 3.40(dd, 2H, J=1.2, 6.6Hz, H-7), 5.09(m, 2H, H-9), 5.97(m, 1H, H-8), 7.21(d, 1H, J=1.2Hz, H-5), 8.06(d, 1H, 1.6Hz, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 28.28(t), 116.20(t), 117.44(s), 128.08(s), 135.58(d), 141.47(d), 150.47(d), 169.07(s); IR(KBr pellet) 2924 (OH), 1703 (CO), 1089 cm^{-1}(C-O); mass spectrum 152(100, $M^{\cdot+}$).

4-(2-Propenyl)-3-Furoic Acid, Methyl Ester(138).



To a solution of acid 137 (0.0136g, 0.089mmol) in DMF(1.5ml) was added lithium carbonate (0.0075g, 0.10mmol). After 15 minutes, iodomethane (0.0063ml, 0.099mmol) was added. After 12 hours diethyl ether and saturated NaCl were added. The organic layer was washed (6X's) with NaCl, dried (Na_2SO_4), and the solvent in vacuo. The residue was distilled to obtain 138(71%). bp 75°C/0.019mm (air bath); ^{1}H NMR($CDCl_3$, 300MHz) δ 3.38(dd, 2H, J=1.2, 6.5Hz, H-7), 3.78(s, 3H, OMe), 5.06(m, 2H, H-9), 5.95(m, 1H, H-8), 7.18(d, J=1.2Hz, H-5), 7.94(d, 1H, J=1.6, H-2); ^{13}C NMR($CDCl_3$, 75MHz) δ 28.32(t), 51.23(q), 116.01(t), 117.83(s), 123.67(s), 135.75(d), 141.15(d), 148.95(d), 163.85(s); IR(neat) 1726(CO), 1051 cm^{-1}(C-O); mass spectrum 166(1.24, $M^{\cdot+}$).

4.0.0 ***References***

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5.0.0 ***Appendix***

Publications and Presentations of the Work Presented Herein

1. "A Facile Preparation of 3,4-Disubstituted Furans; An Approach Towards the Synthesis of Furanoplagiochilal", E.J.Bures, P.G. Spinazze and B.A.Keay, 3rd Chemical Congress of North America, 1988.

VITA AUCTORIS

Patrick Gianpietro Spinazze

Born: Windsor, March 17, 1961.

Education: F.J. Brennan High School, Windsor, Ont., 1975-1980

University of Windsor, Windsor, Ont., 1982-1986