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Novel Domino Processes for Asymmetric Construction of Nitrogen and Oxygen Heterocycles

by

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ABSTRACT

The Stevens rearrangement of ammonium ylides has emerged as a powerful tool for accessing nitrogen heterocycles. In this project, several chiral ligands/Cu or Rh complexes and reaction conditions have been surveyed for the catalytic asymmetric ammonium ylide / Stevens [1,2]-shift process. However, these initial efforts did not reveal any suitable conditions.

Marine ladder toxins have attracted much attention in organic synthesis due to their unique nanoscale structures, scarcity, and extremely high biological potency. A cascade method for construction of *trans*-fused cyclic ethers has been developed. Under mild acidic conditions, α-hydroxy ketone substrates undergo several deprotections, subsequent ketalization to form oxygen-containing rings, and trapping of unstable intermediates to terminate the cascade process. α-Hydroxy ketone substrates were prepared via 1,4-hydrosilylation of suitable enones, using Wilkinson or Karstedt's catalysts and trialkylsilane, followed by catalytic dihydroxylation.

After the symmetric 6,6-bis(pyran) compound was synthesized, a second 6,6-bis(pyran) with a geminal dimethyl group was synthesized to determine the relative stereochemistry of bis(pyran) compounds. Furthermore, two new and unexpected rearrangement products were isolated and fully characterized.

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LIST OF ABBREVIATIONS

[α]	Specific rotation
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Anal.	Elemental analysis
APT	Attached proton test
aq	Aqueous
Ar	Aryl
Bn	Benzyl
brs	Broad singlet
Bu	Butyl
t-Bu-box	2,2-Bis[2-[4-(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane
Calcd.	Calculated
cat.	Catalyst
COSY	Homonuclear correlation spectroscopy
conc.	Concentrated
CSA	Camphorsulfonic acid
d	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dddd	Doublet of doublets of doublets of doublets
de	Diastereomeric excess
DIPEA	Diisopropylethylamine
DMAP	4-(*N*,*N*)-Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-2-oxohexahydropyrimidine
DMSO	Dimethyl sulfoxide

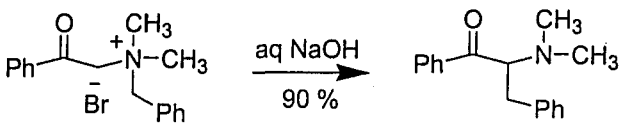
DTBMP	2,6-Di-*t*-butyl-4-methylpyridine
ee	Enantiomeric excess
EI	Electron Impact
eq.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
FTIR	Fourier-Transform Infrared
h	Hour/hours
HMBC	heteronuclear multiple bond coherence
HMQC	Heternuclear multiple quantum coherence
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared
LiHMDS	Lithium hexamethyldisilazide
LA	Generic Lewis acid
m	Multiplet
*m*CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
min	Minute/minutes
mL	Milliliters
mmol	Millimoles
MOM	methoxymethyl
m.p.	Melting point
MS	Mass Spectrometry
Ms	Methane sulfonyl
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
[O]	Oxidation

OTf	Trifluoromethanesulfonate
PDC	Pyridinium dichromate
PG	Protective group
Ph	Phenyl
PhH	Penzene
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
q	Quartet
R	Generic alkyl group
R_f	Retention factor (in chromatography)
Rh_2(*S*-DOSP)$_4$	Tetrakis[1-[[4-alkyl(C_{11}-C_{13})-phenyl] Sulfonyl]-(2*S*)-pyrolidinecarboxylate]dirhodium
R_t	Retention time (in gas chromatography)
rt	Room temperature
s	Singlet
Sharpless AD	Sharpless asymmetric dihydroxylation
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethyl(N, N, N', N')ethylenediamine
TMS	Trimethylsilyl
Ts	Toluenesulfonyl
TsOH	*p*-Toluenesolfonic acid

Chapter 1 The Survey of Chiral Ligands for Stevens Rearrangement of Ammonium Ylides

1.1 Introduction

In 1928, Stevens and co-workers discovered a new [1,2]-shift of a benzyl group when they studied the amine protecting groups (Scheme 1).[1] As a result, the [1,2]-shift rearrangement of ammonium ylides was called the Stevens rearrangement, or Stevens [1,2]-shift.



1 2

Scheme 1. First example of the Stevens rearrangement.

To date, there are mainly three methods to form ammonium ylides:

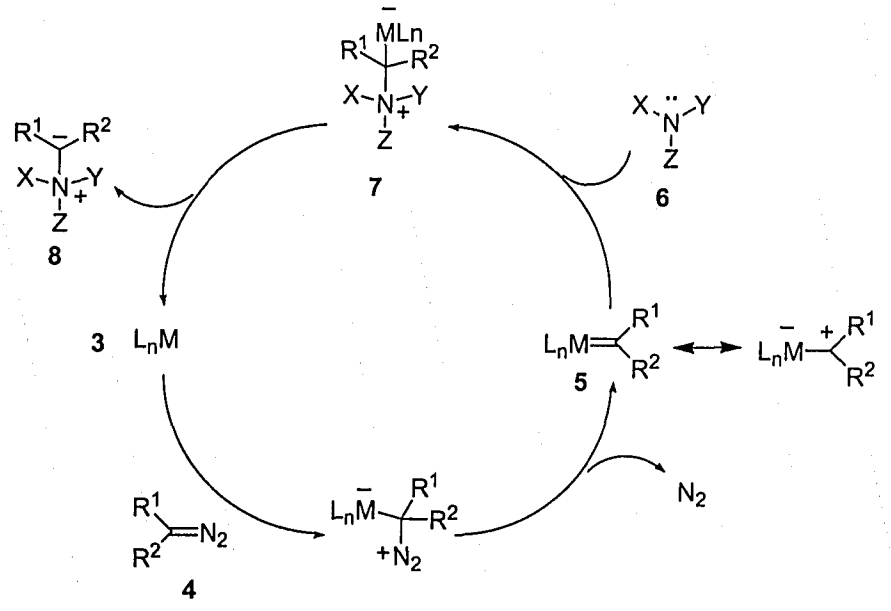
1) the deprotonation of the *N*-quaternary ammonium salts, which is the earliest method. The potential problems with this method are the regioselectivity of the deprotonation and the Hoffman elimination of the amine;[2]

2) the fluoride-mediated desilylation of trimethylsilyl-substituted ammonium salts, which has good regioselectivity and minimizes the elimination process;[3]

3) the electrophilic attack of carbenes on a tertiary amine. Carbenes that are generated through photochemical or thermal decomposition of diazo precursors are too reactive to have good chemoselectivity.[4] Transition-metal-mediated carbene formation is much mild and the resulting metallocarbenes can chemoselectively react with the most electron-rich moiety.[5,6]

The Stevens rearrangement has since proven to be a useful synthetic tool, especially in the synthesis of nitrogen-containing alkaloid natural products.

The catalytic cycle of ammonium ylide formation involves coordination of diazo compounds **4** with an empty d orbital of the transition metal, subsequent loss of nitrogen gas to generate the electrophilic metallocarbenes **5**. A Lewis basic amine **6** adds to the metallocarbene **5** to form the adduct **7**. The adduct **7** can undergo rearrangement, or can dissociate to provide free ylide **8**, regenerating the catalyst **3** and concluding the catalytic cycle.[7]

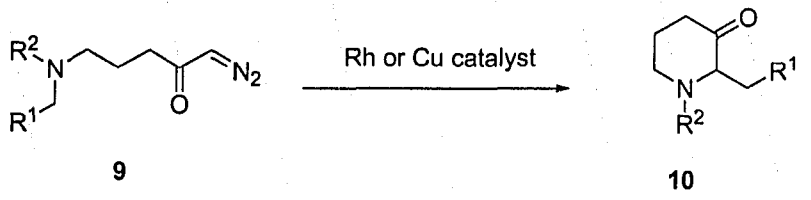


Scheme 2. Catalytic cycle for generation of ammonium ylides via metallocarbenes.

The most common reactions of catalytically generated ammonium ylides include the [2,3]-sigmatropic rearrangement and the Stevens rearrangement. Ammonium ylides can be formed by combination of metallocarbene and tertiary amine, either intermolecularly or intramolecularly. Intramolecular ammonium ylide formation is superior to the intermolecular case because no large excess of amines is required and catalyst deactivation by the amine precursor is greatly reduced.

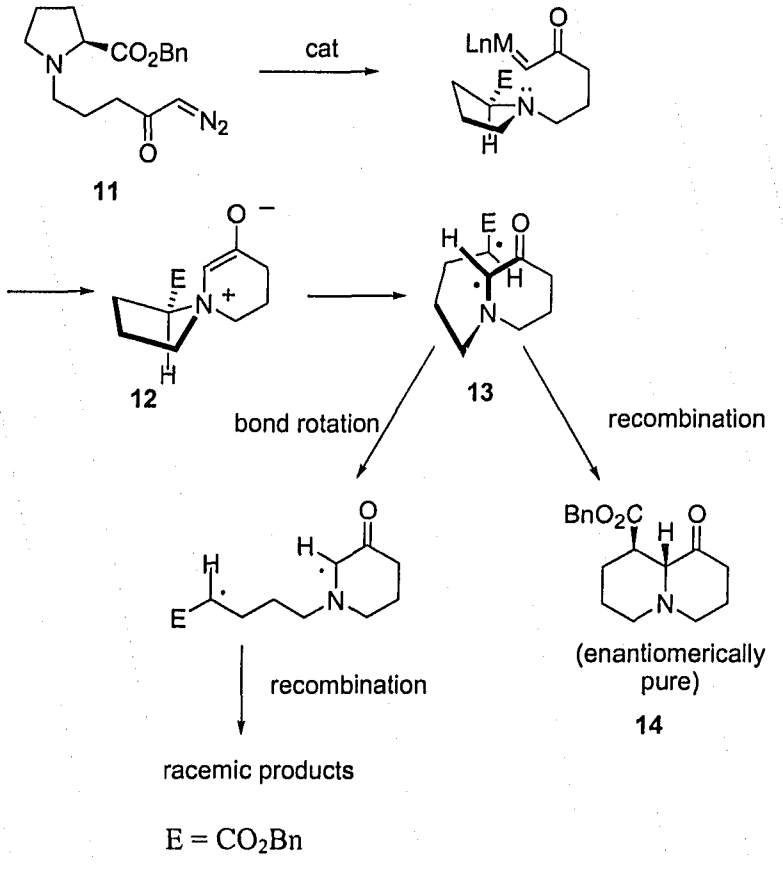
West and co-workers carried out an extensive investigation on the intramolecular ammonium ylide formation followed by Stevens rearrangement and its applications in the synthesis of alkaloid natural products. They first reported the methodology in the synthesis of 2-substituted piperidin-3-ones by the Stevens rearrangement (Scheme

3).[7a] Exposure of the substrate to catalytic rhodium(II) acetate in dichloromethane at room temperature provided the corresponding piperidin-3-one in good to excellent yields.



9 10

Scheme 3. The general equation of synthesis of 2-substituted piperidin-3-one by the Stevens rearrangement.

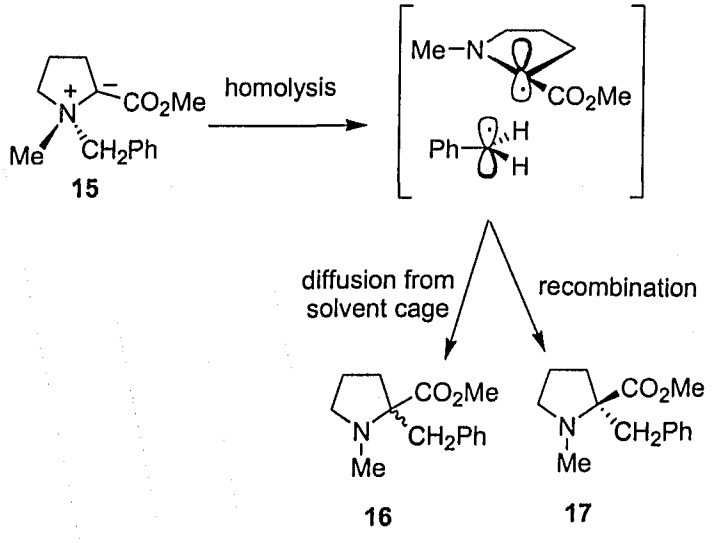


Scheme 4. Rationale for diastereoselectivity seen in [1,2]-shift.

The Stevens ring-expansion method was also used in an efficient total synthesis of epilupinine.[8] The key step is shown in Scheme 4. Formation of a spiro-cyclic ylide

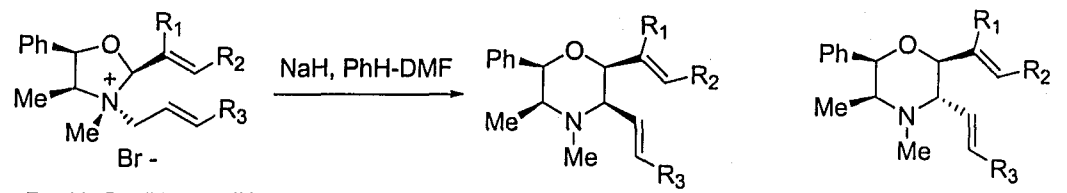
was followed by a [1,2]-shift to provide the desired quinolizidine ring system in high yields and with good diastereoselectivity (Scheme 4). The diastereoselectivity seen in the [1,2]-shift was explained as follows: diastereomeric ylide **12** dominated due to the steric interaction between the benzyl ester and the diazo side chain. C-N bond homolysis gave biradical **13**, which upon fast recombination gives enantiomerically pure **14**. Should the biradical recombination be a slow process, in which bond rotation may occur, recamization would happen to erode the enantioselectivity.

Subsequently, West and Glaeske developed a stereoselective route to α-amino acid derivatives through chirality transfer from the nitrogen to the neighboring carbon atom. The configuration at the quaternary nitrogen was controlled by the adjacent C-2 stereogenic center because the lone pair of electrons in the *N* pyramidal form in the starting material, praline, prefers to be *cis* to the carbomethoxy group. Proline derived **15** was treated with base in THF giving products **16/17** in an average ratio of 1:3 (Scheme 5). This indicates that radical pair recombination from the same face is favored over the process of diffusion out of the solvent cage and recombination on the opposite face of the proline ring.[9]



Scheme 5. The rationale of the chirality transfer in the chiral proline salt **15**.

Pedrosa and co-workers reported the Stevens ring-expansion process of ammonium ylides prepared from the deprotonation of chiral quaternary ammonium salts.[10] Chiral ammonium salts **18a-c** were treated with the strong base to afford ring-expanded products **19** and **20** in about 2:1 diastereomeric ratio. After formation of the biradical intermediate by the homolytic cleavage of the C-N bond, rapid recombination from the same face was kinetically faster than the alternative bond rotation and recombination to give product **20** (Scheme 6).

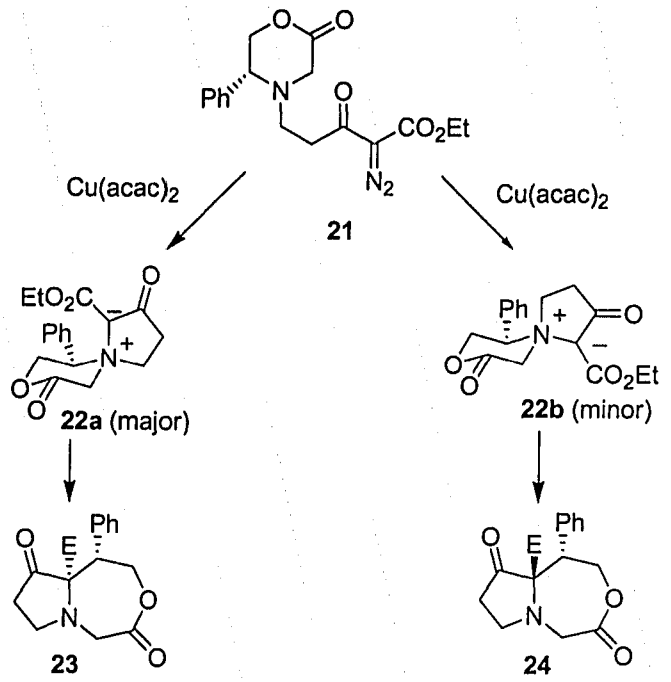


a R_1=H, R_2=Ph, R_3=Ph
b R_1=Me, R_2=H, R_3=Ph
c R_1=H, R_2=Ph, R_3=H

18 **19** a-c **20** a-c

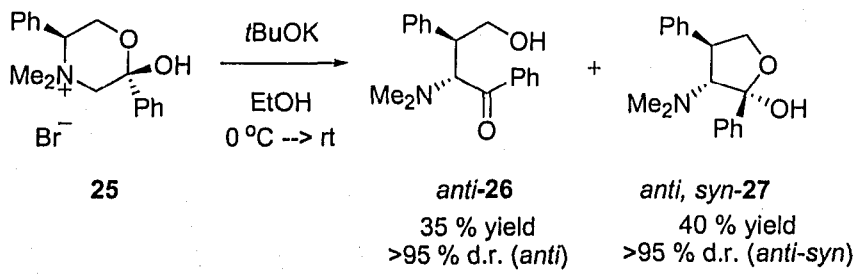
Scheme 6. Stevens ring-expansion process of ammonium ylieds **18.**

Saba and co-workers utilized the Stevens rearrangement of morpholinone compound **21** during their synthesis of 5,7-fused bicyclic amine ring systems.[11] Isolation of the rearrangement products **23** and **24** in enantiomerically pure form suggested the complete retention of configuration during the ring-expansion (Scheme 7).



Scheme 7. Stevens rearrangement of morpholinone **21**.

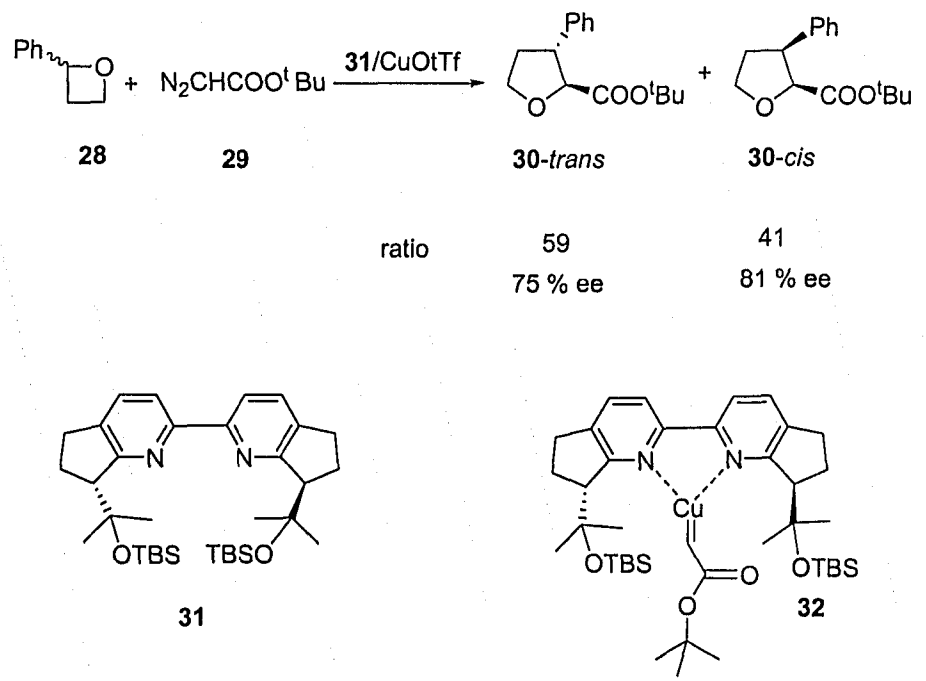
Tomooka and co-workers reported a novel Stevens rearrangement of a cyclic hemiacetal system in their diastereoselective approach to chiral α-amino ketones.[12] Utilizing the optically active hemiacetal **25**, and subjecting it to *t*-BuOK in ethanol at room temperature provided the expected hydroxy ketone **26** in 35% yield as a single diastereomer, as well as hemiacetal **27** in 40% yield also as a single diastereomer (Scheme 8).



Scheme 8. Stevens rearrangement of a cyclic hemiacetal system.

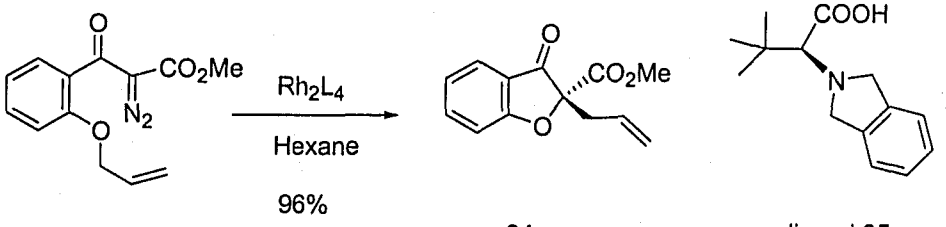
Based on the above knowledge about the Stevens rearrangement, one hypothesis is that the chirality of the quaternary ammonium salt could be transfered to the newly-formed carbon center in this type of rearrangement. As indicated by many experimental data, the Stevens [1,2]-shift of oxonium ylides proceeds through a metal-associated oxonium ylide complex instead of through free oxonium ylides. So the chiral metal complex stereoselectively transfers one enantiomer of the oxonium ylide to the rearranged product.

In 1966, Nozaki and co-workers first reported the asymmetric Stevens [1,2]-shift of oxonium ylides to prepare tetrahydrofurans.[13] Katsuki and co-workers reported that tetrahydrofurans **30** could be prepared from oxetane **28** and diazocarbonyl compound **29** with high enantiomeric purity, using the air-stable chiral catalyst, copper (I) bipyrindine complex **31**.[14] The author proposed the metallocarbene structure **32** as shown in Scheme 9.



Scheme 9. Synthesis of tetrahydrofurans from oxonium ylides.

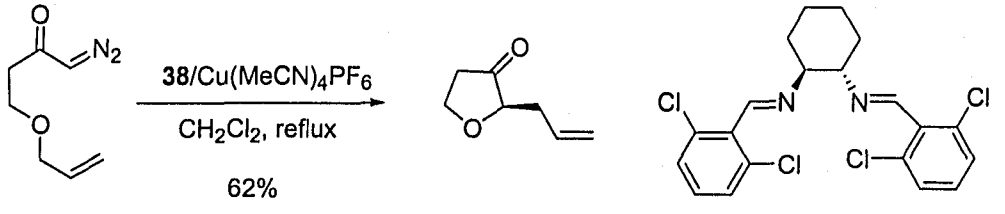
McKervey and co-workers evaluated eight different chiral ligands used in asymmetric oxonium yield formation / [2,3] sigmatropic rearrangement of diazocarboyl substrate **33**. The best ee observed was 60% when ligand **35** was used (Scheme 10).[15] The authors noted that this result indicated that the chiral catalyst was not fully dissociated from the ylide during the sigmatropic rearrangement step.



33 **34** ligand **35**

Scheme 10. Asymmetric oxonium ylide formation / [2,3] sigmatropic rearrangement of compound **33**.

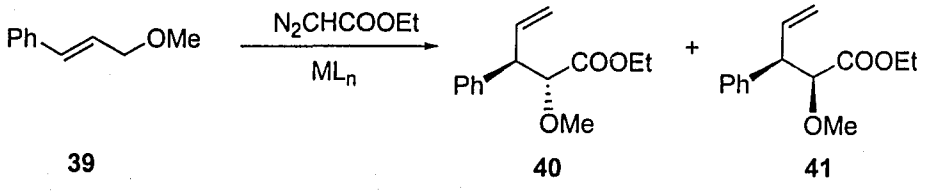
Clark and co-workers demonstrated that asymmetric induction up to 57% ee in the formation of compound **37** by intramolecular oxonium ylide and subsequent [2,3]-sigmatropic rearrangement. A series of chiral copper complexes was screened and the most efficient catalyst was the complex generated from ligand **38** and $Cu(CH_3CN)_4PF_6$ (Scheme 11).[16]



36 **37** 57% ee **38**

Scheme 11. Synthesis of tetrahydrofuran-3-one by oxonium ylide formation/[2,3] sigmatropic rearrangement.

Doyle and co-workers reported that chiral catalysts controlled the formation of oxonium ylide by directing the approach of the Lewis basic ether oxygen atom onto the carbene center (Scheme 12).[17] When $Rh_2(4S\text{-MEOX})_4$ and $Rh_2(4R\text{-MEOX})_4$ were used as the catalyst instead of $Rh_2(OAc)_4$, the diastereoselectivity was reversed and each of the ylide-derived distereoisomers was formed with high enantiocontrol.



39 40 41

	yield (% ee)	
$Rh_2(OAc)_4$	83	17
$Rh_2(4S\text{-MEOX})_4$	15 (94% ee)	85 (98% ee)
$Rh_2(4R\text{-MEOX})_4$	15 (94% ee)	85 (98% ee)

Scheme 12. [2,3] - rearrangement of metal stabilized oxonium ylides.

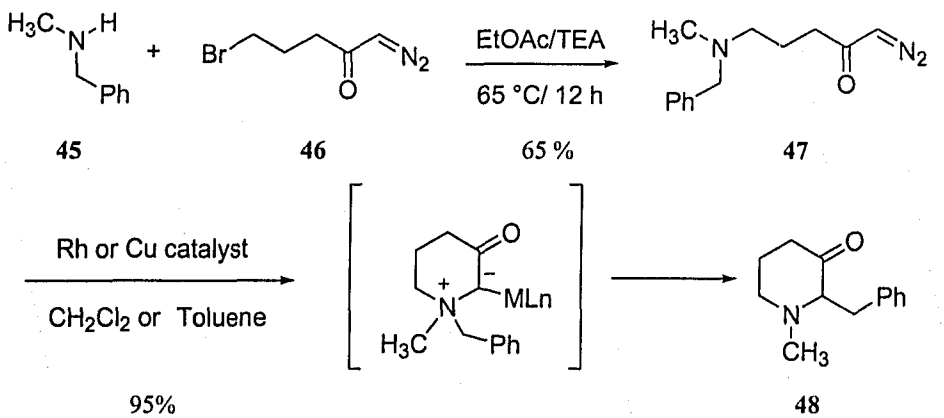
It is proposed that if the chiral transition metal catalyst could function in the ammonium ylide formation just as in the oxonium ylide formation, providing chiral quaternary ammonium ylides, then subsequent stereoselective rearrangement should lead to the enantiomerically enriched product. To probe this hypothesis and stereoselectively prepare the 2-substituted piperidin-3-one by chiral ligands/transition metal-catalyzed Stevens rearrangement, chiral ligands used in the oxonium ylide formation were tested in this project. Due to lack of understanding about the catalytic asymmetric Stevens rearrangement of ammonium ylides, several chiral ligands used in the asymmetric C-H insertion and cyclopropanation reaction of diazo compounds were also tested.[18]

1.2 Chiral transition metal catalyst mediated Stevens rearrangement of ammonium ylides

West and Naidu developed a route to substituted piperidin-3-ones, utilizing a domino sequence.[7a,19] In this approach, diazoketones containing pendant tertiary amine groups can be obtained simply in a one-step process. Reaction of secondary amine **45** with bromide **46** provided tertiary amine **47** in good yield (Scheme 13).

Subsequent treatment of the tertiary amine **47** with $Rh_2(OAc)_4$ or $Cu(acac)_2$ led to the metallocarbene, which underwent intramolecular attack by the amine to form a cyclic ammonium ylide. The ylide, in turn, underwent a [1,2]-shift of the benzyl substituent to form compound **48** in good yield.

In the following section, several chiral transition metal catalysts were screened in order to perform the same reaction in the asymmetric version.

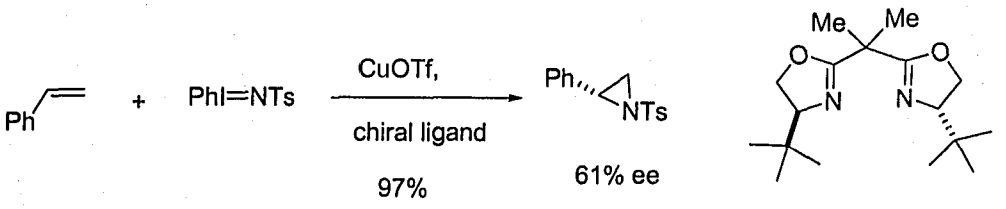


Scheme 13. Formation and Stevens rearrangement of diazoketone **47.**

1.3 Chiral Copper catalysts

1.3.1 Chiral bis-oxazoline-based catalysts

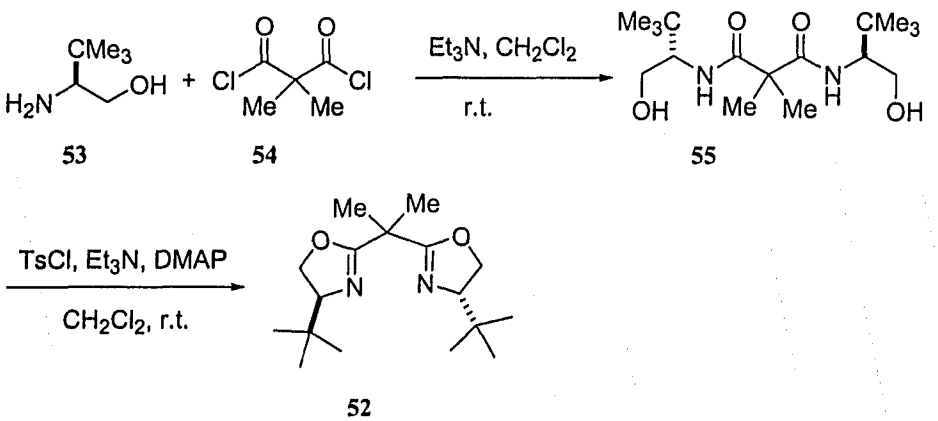
In 1991, Evans and co-workers utilized the chiral complex **52**/Cu(I) to achieve the first catalytic, asymmetric aziridination of styrene **49** in good yield (Scheme 2).[20] The enantiomeric excess of the aziridine compound **51** was 61%.



49 **50** **51** **52**

Scheme 14. The first catalytic and asymmetric aziridination reaction.

2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane (*t*-Bu-box) **52** was prepared in two steps from (*S*)-*tert*-leucinol **53**.[21] Acylation of compound **53** with dimethylmalonyl dichloride **54** afforded the dihydroxy malonodiamide **55** in 87% yield. The subsequent ring closure step was performed with *p*-toluenesulfonyl chloride and triethylamine in the presence of catalytic amount of 4-(dimethylamino)pyridine (yield 80%).



53 **54** **55** **52**

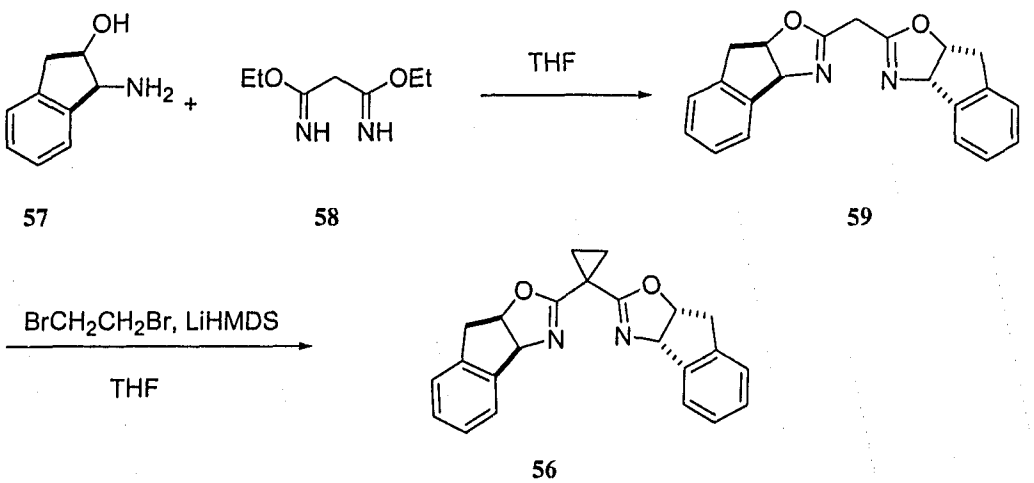
Scheme 15. The synthesis of Bis-oxazoline ligand **52**.

t-Bu-box **52** was used as the chiral ligand to complex with $Cu(CH_3CN)_4PF_6$ to catalyze the Stevens rearrangement of compound **47**. The results are summarized in Table 1. While the yield of this reaction increased at the higher reaction temperature, unfortunately, no significant ee was observed in either dichloromethane or toluene at reflux. The ee was determined by chiral HPLC (Chrialpak OJ-H column, 210 nm UV detector, the eluent IPA/hexane = 4/96, the flow rate 0.4 mL/min).

solvent / T (° C)	ee % (yield, CH_2Cl_2)	ee % (yield, Toluene)
40	~ 0 (20%)	N.A.
120	N.A.	~ 0 (76%)

Table 1 Enantiomeric excess using (*t*-Bu-box)/Cu(I) catalyst.

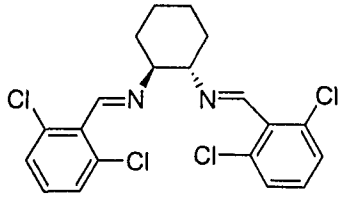
The other bis(oxazoline) ligand **56** studied was inda-box which was prepared as shown in Scheme 16.[22, 23] Compound **59** was prepared by the condensation of optically pure aminoindanol **57** with diethyl malonimidate **58** in THF (80% yield). The cyclopropane bridge was installed by double alkylation with 1,2-dibromoethane to afford ligand **56** in good yield.



Scheme 16. The synthesis of inda-box **56.**

The complex formed by inda-box **56** and $Cu(CH_3CN)_4PF_6$ was tested under the same reaction conditions as *t*-Bu-box and, again, about 0% ee was observed.

1.3.2 Chiral diimine-based catalysts



38

Jacobsen and co-workers discovered that benzylidene derivatives of 1,2-diamino-cyclohexane **38**/CuOTf catalyzed the enantioselective aziridination of unfunctionalized alkenes.[24] Clark used this ligand in the asymmetric [2,3] sigmatropic rearrangement of oxonium ylides.[17] So this ligand was tested in this project.

Ligand **38** was easily prepared by the condensation between the chiral 1,2-diaminocyclohexane and the corresponding halide substituted benzaldehyde in good yields. The complex formed by diimine ligand **38** and $Cu(CH_3CN)_4PF_6$ was tested in the same reaction conditions as *t*-Bu-box and , again, ~ 0% ee was observed.

1.4 Chiral rhodium catalysts

Davies and co-workers reported the Rh_2(*S*-DOSP)$_4$-catalyzed intermolecular C-H insertion reaction with moderate to good enantioselectivity (ee 51–93%).[25] In the reaction mixture, the only chiral source was the chiral rhodium catalyst, Rh_2(*S*-DOSP)$_4$, and the chiral metallocarbene transferred its chirality to the C-H inserted product. Commercially available Rh_2(*S*-DOSP)$_4$ was tested in the Stevens rearrangement of the ammonium ylide.

The results are summarized in Table 2. The starting material was not consumed when the reaction was performed at room temperature. While in dichloromethane or hexane at reflux, the starting material was consumed and the rearrangement product was formed as a racemic mixture.

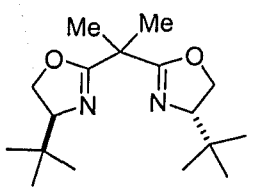
solvent / T (° C)	ee % (yield, CH_2Cl_2)	ee % (yield, Hexane)
r. t.	No reaction	No reaction
reflux	~ 0 (73%)	~ 0 (30%)

Table 2 Results using Rh_2(*S*-DOSP)$_4$ catalyst.

In summary, no positive results were obtained from the screening of chiral catalysts for asymmetric Stevens rearrangement. The possible reasons for the lack of stereoselectivity in the Stevens rearrangement could be attributed to two factors. First, based on the radical pair mechanism of 1,2-shift, if bond rotation of the biradical intermediate was faster than recombination inside the solvent cage, the chirality of the chiral ammonium ylide would be lost. According to the results from the synthesis of epilupinine,[8] the Stevens rearrangement of chiral proline salts **15**,[9] chiral ammonium salts **18**,[10] and morpholinone **21**, [11] this possible reason could not be used to explain lack of stereoselectivity. Secondly, the chiral ligand/trisition metal complex might not effectively direct the ylide formation in a stereoselective manner, resulting in a racemic ylide, and leading to the racemic rearrangement product. This latter explanation is more likely in explaining the lack of enantioselectivity in this project. It is worth noting that this survey was only the initial effort of this project. Only two kinds of transition metals, four chiral ligands, and three solvents have been surveyed. More experiments are necessary to discover the appropriate chiral catalyst and reaction conditions for the catalytic asymmetric Stevens rearrangement of ammonium ylides.

1.5 Expermental section

General. Reactions were carried out in oven-dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven dried glass syringes with stainless steel needles or stainless steel cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, THF, benzene, and diethyl ether from sodium/benzophenone ketyl. Toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash chromatography was packed with 230-400 mesh silica gel (Merck). Melting points were obtained in open capillary tubes and were uncorrected. Ethereal diazoethane was prepared from Diazald according to literature procedures.[26] Proton NMR spectra were recorded on Varian instruments at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz), chemical shifts are reported (ppm) relative to chloroform-*d* or benzene-*d*. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. Optical rotation were recorded in the unit of ° ·mL/g·dm. HPLC analyses were performed on a Gilson HPLC with UV detector. Chiral columns include Chiralpak AD-H, AS-H, OJ-H, and OD-H.



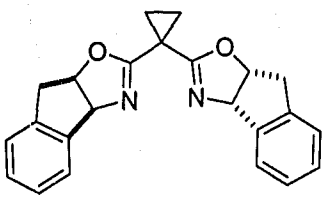
52

2,2-Bis[2-[4-(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [22]

To a solution of (*R*)-*tert*-leucinol **53** (3.52 g, 30.0 mmol) in 35 mL of anhydrous dichloromethane in a 250 mL of round bottom flask in an ice bath was added triethylamine (6.1 mL, 75 mmol) via syringe. A solution of dimethylmalonyl dichloride (2.0 mL, 15 mmol) in 15 mL of dichloromethane was solwly added via cannula to the vigorously stirred reaction mixture over 20 min. The ice bath was

removed, and the reaction mixture was stirred at room temperature for 30 min. Dichloromethane (90 mL) was added to dissolve the white solid. The solution was washed with 1N HCl (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL) separately. Each aqueous layer was back-extracted with 15 mL of dichloromethane. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo to give a white solid, which was recrystallized from ethyl acetate to afford 3.9 g (80 %) of compound **55.** ^1H NMR (500 MHz, $CDCl_3$) δ 6.41 (br d, J = 9.6 Hz, 2H), 3.78-3.85 (m, 4H), 3.55 (br s, 2H), 3.38-3.43 (m, 2H), 1.51 (s, 6H), 0.92 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 62.1, 59.5, 50.3, 33.5, 26.8, 23.8.

A 100 mL of round-bottom flask was charged with compound **55** (2.0 g, 6.0 mmol), 4-DMAP (74 mg, 0.60 mmol), and 24 mL of dichloromethane. Triethylamine (3.7 mL, 26 mmol) was added via syringe. A solution of *p*-toluenesulfonyl chloride (2.3 g, 12 mmol) in 5 mL of dichloromethane was added via cannula, followed by 10 mL of dichloromethane rinse. The solution was stirred at room temperature for 24 h. The solution was diluted with dichloromethane (20 mL) and water (20 mL), and then washed with 25 mL of saturated aqueous NH_4Cl. The aqueous layer was back-extracted with dichloromethane (3 X 20 mL). The combined organic layers were dried over Na_2SO_4. Filtration and concentration in vacuo gave a white solid, which was recrystallized from pentane to afford 1.5 g (82%) of the desired compound **52**: mp 88-90 °C; $[\alpha]^{25}{}_D$ -113.3 (*c* 1.22, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.17–4.05 (m, 4H), 3.84 (dd, J = 10.0, 8.7 Hz, 2H), 1.51 (s, 6H), 0.87 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 75.3, 68.9, 38.6, 33.9, 25.6, 24.4.



56

Inda-BOX 56

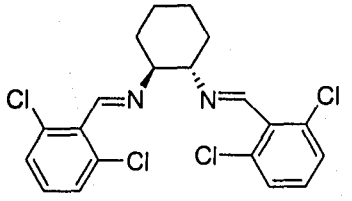
Under Ar, diethyl malonimidate dihydrochloride **58** (1.53 g, 0.66 mmol) was dissolved in 20 mL of anhydrous THF, then (1*S*, 2*R*)-aminoindanol **57** (1.79 g, 12.0 mmol) was added. The reaction mixture was heated to 45-55 °C for 4h.

When the reaction was complet, the temperature was adjusted to < 5 °C and 60 mL of 0.5 N aqueous sodium bicarbonate was added at such a rate that the internal temperature remained <15 °C. After cooling the mixture to < 5 °C, the white solid was filtered and thoroughly washed with water. The filter cake was dried *in vacuo* to yield 1.6 g of compound **59** (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.27-7.22 (m, 6H), 5.55 (d, J = 7.7 Hz, 2H), 5.36-5.30 (m, 2H), 3.38 (dd, J = 18.0, 7.0 Hz, 2H), 3.26 (s, 2H), 3.16 (d, J = 18.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 141.6, 139.6, 128.5, 127.4, 125.5, 125.2, 83.6, 76.7, 39.7, 28.7.

A round-bottom flask (50 mL) was charged with compound **59** (0.74 g, 2.2 mmol), followed by 10 mL of anhydrous THF. Dibromoethane (0.39 mL, 4.5 mmol) was added. LiHMDS solution (1 M in THF, 2.3 mL, 2.3 mmol) was added over 30 min. Then 3.7 mL of 1 M LiHMDS solution was added over 4h via a syringe pump.

After the overnight reaction, 14 mL of 20% aqueous ammonium chloride solution was added slowly. The mixture was diluted with 30 mL of THF. The organic layer was dried over Na_2SO_4. After the solvent was removed *in vacuo*, the product was recrystallized from ethanol to give 0.48 g (61%) of a light yellow solid. mp 164-165 °C; $[\alpha]^{25}_D$ +330.3 (*c* 3.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.27-7.22 (m, 6H), 5.52 (d, J = 8.0 Hz, 2H), 5.33 (ddd, J = 17.9, 7.0, 2.0 Hz, 2H), 3.38 (dd, J = 17.9, 7.0 Hz, 2H), 3.16 (dd, J = 17.8, 1.6 Hz, 2H), 1.38-1.25 (m, 4H);

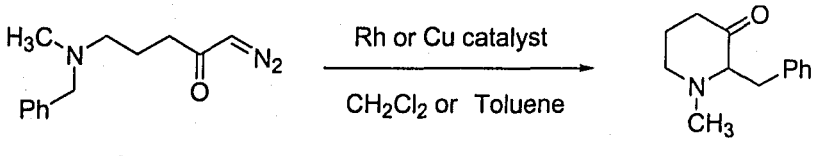
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 141.6, 139.6, 128.5, 127.4, 125.5, 125.2, 83.6, 76.7, 39.7, 28.7.



38

(1*R*, 2*R*)-*N*,*N*'-Bis-(2,6-dichlorobenzylidene)-diaminocyclohexane 38 [25]

A mixture of 2,6-dichlorobenzaldehyde (Aldrich, 464 mg, 2.66 mmol) and (1*R*, 2*R*)-diaminocyclohexane (152 mg, 1.32 mmol) in 10 mL of absolute ethanol was heated to reflux for one hour and then allowed to cool to room temperature. Compound **38** crystallized from the cooled solution, and it was collected by filtration and dried in a vacuum dessicator overnight to give 0.39 g (70%) of a white crystal. mp 148-150 °C; $[\alpha]^{25}_{D}$ +15.0 (*c* 2.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 2H), 7.25 (d, *J* = 8.2, Hz, 4H), 7.14 (dd, *J* = 8.7, 7.3 Hz, 2H), 3.62-3.59 (m, 2H), 1.88 (br s, 6H), 1.52 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 134.8, 132.9, 129.9, 128.6, 74.9, 32.9, 24.2.



9 10

Preparation and catalytic decomposition of compound 9

To a mixture of triethylamine (2.0 mL) and *N*-benzylmethylamine (2.6 mL, 20 mmol) in a 50 mL of dry round-bottom flask was added a solution of freshly prepared 5-bromo-1-diazo-2-pentanone (5.0 mmol) in 20 mL of EtOAc. After stirring for 12 h at 65-67 °C, the reaction mixture was taken into 40 mL of 2 N NaOH solution and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with

brine (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The yellow residue was purified by flash column chromatography (EtOAc/ hexane = 1:4 to 100% EtOAc as the eluent) to afford 0.95 g (78%) of a yellow liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.19 (br s, 1H), 3.46 (s, 2H), 2.37 (t, J = 7.0 Hz, 4H), 2.18 (s, 3H), 1.84 (quintet, J = 7.0 Hz, 2H).

Method A. Chiral ligands and $Cu(CH_3CN)_4PF_6$ complexes catalyzed reactions

In a typical procedure, $Cu(CH_3CN)_4PF_6$ (3.6 mg, 9.6 μmol) and the ligand **52** (3.4 mg, 12μmol) were added to an oven-dried three-neck flask fitted with a reflux conderser and two rubber septa. To this flask was added freshly distilled solvent (10 mL of CH_2Cl_2 or toluene), and the solution was stirred at reflux for 30 min. Diazo compound **9** (22 mg, 96 μmol) in 5 mL of solvent was added over 15 min by a syringe pump. The reaction was stirred at reflux for 2 to 4 h (monitoring the reaction by TLC). After this, the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (1:1 EtOAc/hexane). The ee was determined by chiral HPLC.

Method B. Chiral rhodium complexes catalyzed reactions

Diazo compound **9** (23.1 mg, 100 μmol) in 5 mL of dry solvent (CH_2Cl_2 or hexane) was added dropwise via a syringe over 15 min with stirring to 3 mol % of chiral rhodium complex in 10 mL of dry CH_2Cl_2 at room temperature or at reflux. The reaction was monitored by TLC. After the complete consumption of compound **9,** the reaction mixture was washed with brine (3 x 10 mL), dried over anhydrous $MgSO_4$, fitered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 1:1 to 100% EtOAc). The ee was determined by chiral HPLC.

Chiral HPLC conditions:

Chrialpak OJ-H column, 210 nm UV detector, the eluent IPA/hexane = 4/96, the flow rate 0.4 mL/min.

The detailed results were listed in the section **1.3** and **1.4.**

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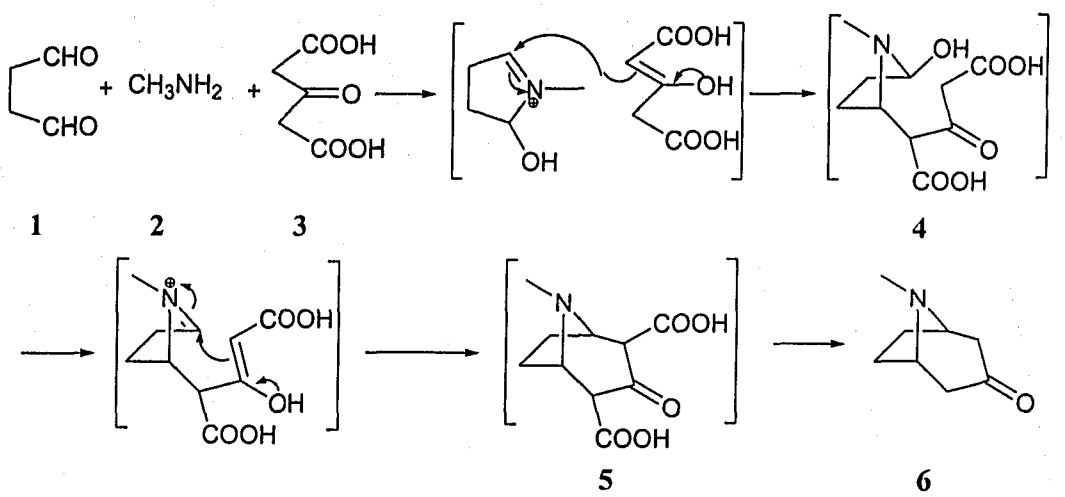
Chapter 2 Cascade Reactions and Major Ring-Forming Methodologies of Polycyclic Ethers

2.1 The cascade reaction

A cascade reaction contains a consecutive series of organic reactions that proceed via highly reactive intermediates. A new functional group generated in situ from the previous chemical transformation will react in the next transformation. The substrate usually consists of an initiative site, a relay moiety and a termination moiety. Broadly definition, a cascade reaction includes both intermolecular and intramolecular reactions. On the other hand, a more strict definition limits the scope only to intramolecular reactions. Multi-component one-pot reaction is excluded from this definition.

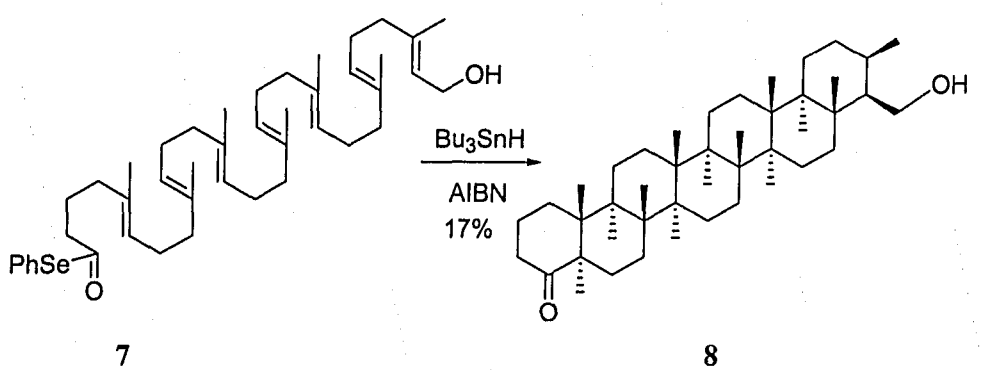
The cascade reaction has long been recognized as a powerful tool and an elegant strategy in synthetic organic chemistry. It displays the efficiency due to fewer work-ups and purifications of intermediates, some of which can be too reactive to be separated from the reaction media. Another aspect after the idea of a cascade reaction is that it may take a long time to prepare the suitable substrate and find out the perfect condition to lead reactions to the desired pathway among numerous possibilities.

The history of cascade reactions can be tracked back to 1917 when Sir. Robert Robinson synthesized tropinone (**6**, Scheme 1) in a one-pot biomimetic synthesis.[1] The bicyclic tropinone (**6**) was synthesized by the double Mannich reaction between succindialdehyde (**1**), methylamine (**2**) and acetonedicarboxylic acid (**3**), followed by decarboxylation. In this sequence, two C-N and two C-C bonds were formed and two carboxylic groups were removed.



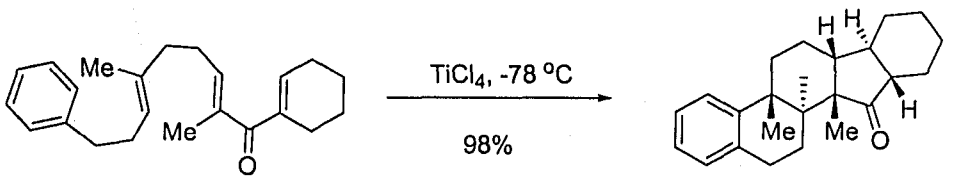
Scheme 1. Rosinson's biomimetic synthesis of tropinone **6.**

The Pattenden group currently holds the record for making seven carbon rings in a single step.[2] (All-*E*)-polyene selenate **7** underwent 6-endo-trig radical cyclizations to afford the heptacycle compound **8** in 17% yield (Scheme 2). Methyl groups on all C=C double bonds played a controlling role in the regio- and stereoslectivity of the polycyclization process. Without the methyl groups on C=C bonds, the 5-exo-trig radical cyclization predominated the reaction process. Mechanistic study of this process remained under investigation.



Scheme 2. Pattenden's synthesis of the "steroid-like" heptacycle compound **8.**

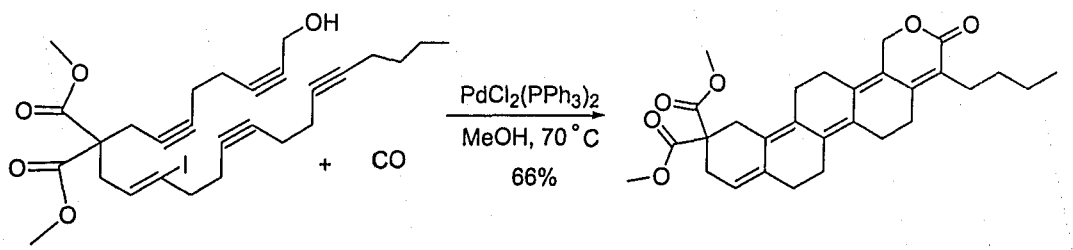
West and co-workers have reported a cascade polycyclization initiated by the Nazorov cyclization (Scheme 3).[3] Under the low temperature, aryl trienone **9** was transformed into polycycle **10** in high yield and with complete diastereoselectivity.



9 **10**

Scheme 3. West's cascade polycyclization intiated by a Nazorov reaction.

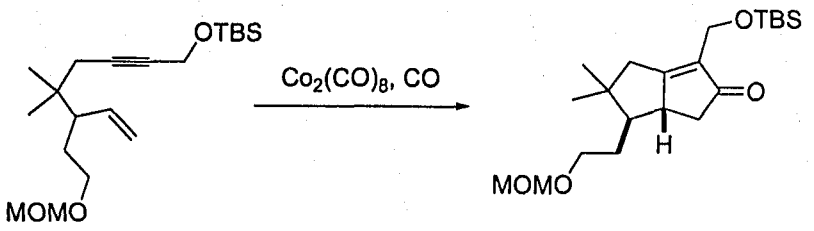
Transition metals play an active role in many cascade processes. Palladium complexes are highly efficient catalysts of the C-C bond formation are widely utilized in cascade reactions. For example, the intramolecular Heck reaction shown in Scheme 4 is called the zipper mode cascade. A mult-ring motif **12** was synthesized from the single carbon-chain starting material **11**.[4]



11 **12**

Scheme 4. Negishi's zipper mode cascade.

Intramolecular Pauson-Khand reactions have been used efficiently and stereospecificly to prepare the cyclic compound **14** (Scheme 5).[5] In the transition state, the silyl ether group occupied one side of the newly-formed cyclopentanone and forced the angular hydrogen and the other side chain to the other side.



13 14

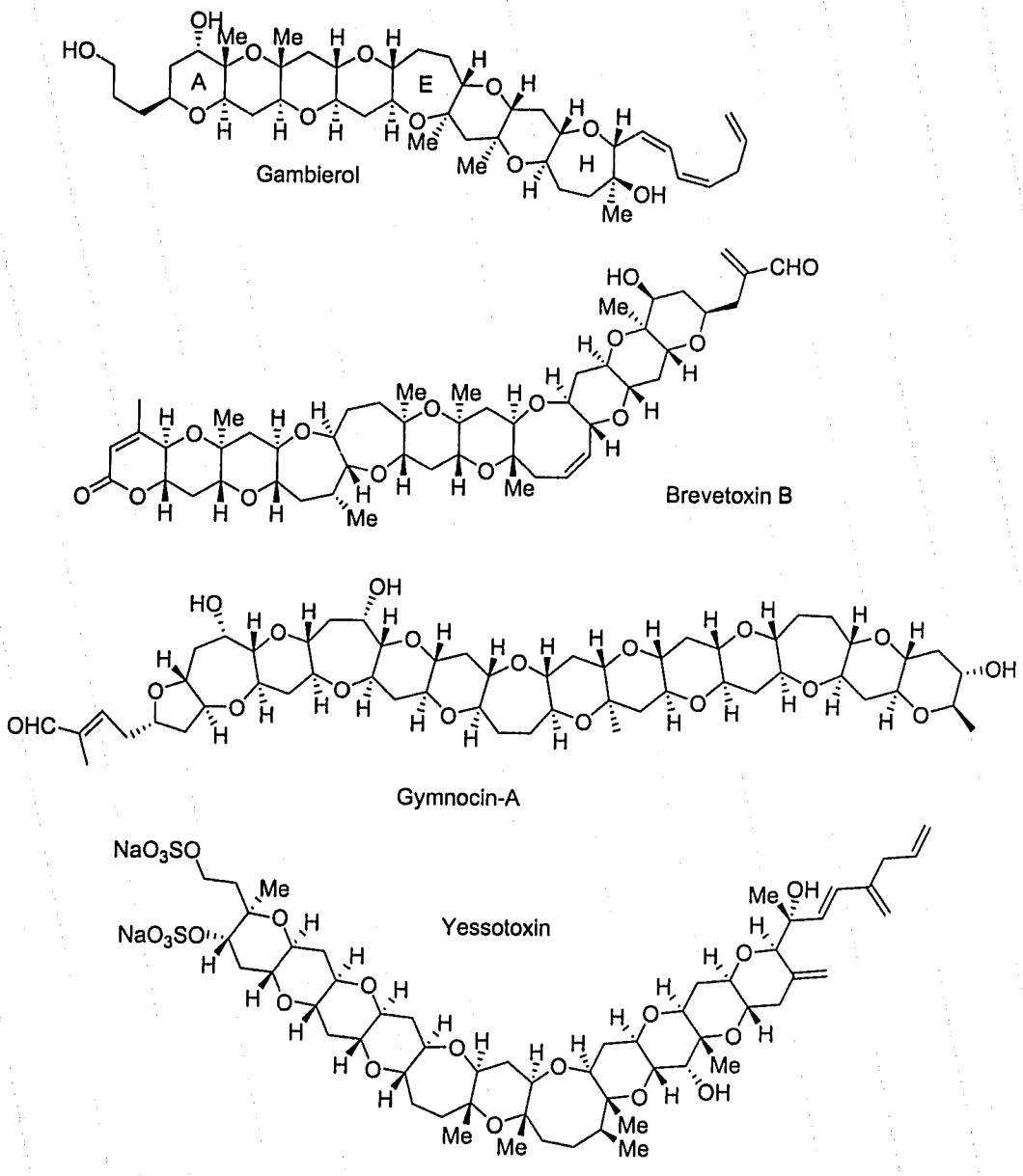
Scheme 5. Magnus's dicobalt octacarbonyl mediated enyne cyclization.

2.2 Marine ladder toxins

2.2.1 Structure and bioactivity of marine ladder toxins

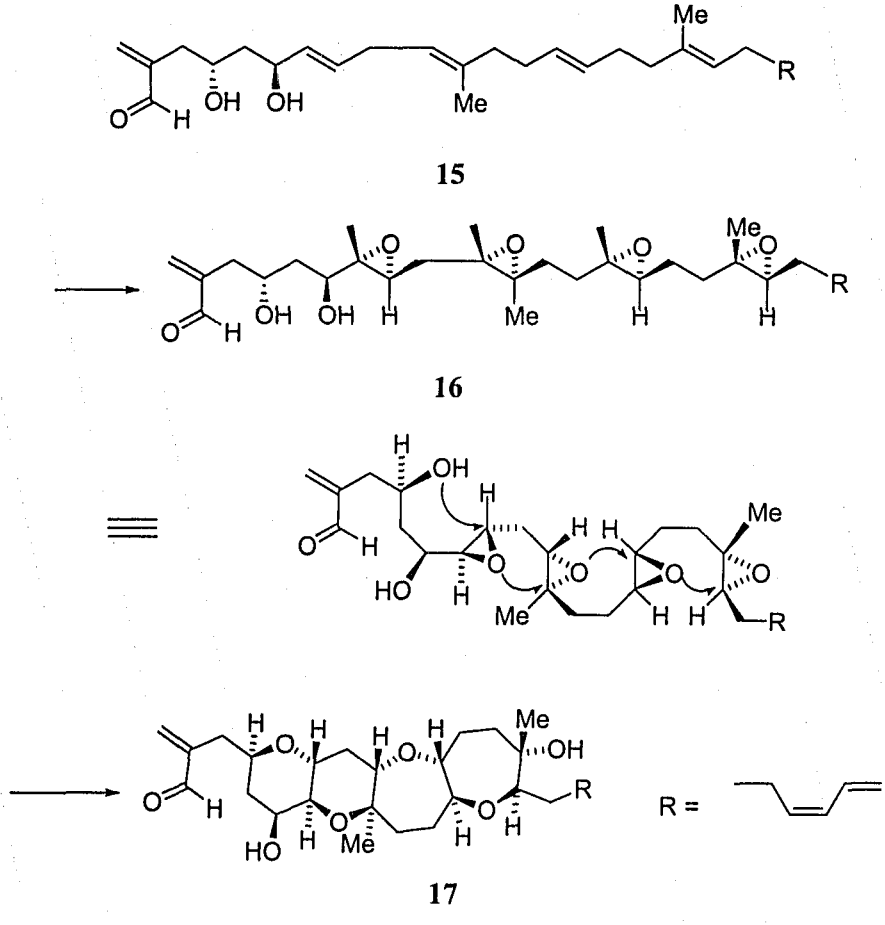
Since the structure of brevetoxin B, a causative agent of Florida red tides, was first reported by the Nakanishi group in 1981,[6] various polycyclic ether marine natural products have been isolated and characterized, using modern spectroscopic techniques. These molecules contain a single carbon chain with the oxygen-bridged polycyclic skeleton. The common moiety is the *trans-syn-trans* fused ether ring system which is essential to the bioactivity. Kadota, Yamamoto and their co-workers synthesized gambierol and its 16-*epi*-diastereomer and discovered that the 16-*epi*-diastereomer was at lest 300 times less toxic than the natural product.[7] This could be explained as that the "*cis*-fused" polycyclic ether compound had a different 3-dimesional structure from the natural *trans*-fused compound.

The marine ladder toxins including brevetoxin, ciguatoxins, gambierol, gambieric acids, yessotoxins, and gymnocins are extremely scarce in nature and accumulated in fish through the food chain, but most of them are highly potent neuorotoxins. The lethal potencies of ciguatoxins were measured as LD_{50} 0.25-4 μg/kg by intraperitoneal injection into mice. They also exhibit antiviral, antifungal,[8] and antitumor activities. To date, brevetoxin, ciguatoxins, gambierol, and gymnocins have been chemically synthesized by linear and convergent synthetic routes.



Scheme 6. Structure of representative polycyclic ethers.

2.2.2 The biosynthesis of marine ladder toxins



Scheme 7. Proposed biosynthesis of hemibrevetoxin.

The hemibrevetoxin biosynthesis was proposed by Shimizu and Nakanishi separately (Scheme 7).[9] In a biological system, an all *trans*-polyene substrate (**15**) is transformed to a chiral polyepoxide (**16**) under enzyme catalysis. A cascade endo-regioselective oxacyclization assembles the polycyclic ether skeleton (**17**), starting from the polyepoxide. The most challenging part of a biomimetic synthesis of a chiral polycyclic ether is the endo-selective epoxide opening because both kinetic and stereoeletronic factors favor exo-selectivity.

2.3 The major ring-forming methodology of polycyclic ethers

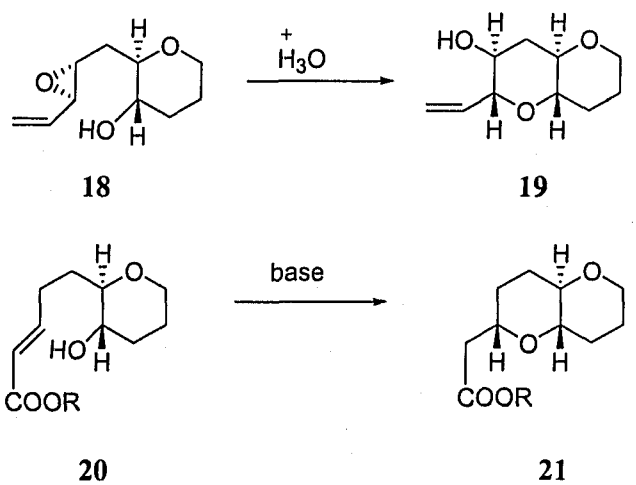
In 1995, Martín and his co-workers published a review titled "Useful Designs in the Synthesis of *Trans*-Fused Polyether Toxins". [10] This review focused on heterocyclization reactions and set two main categories to organize all the methodologies. They were the intramolecular C-O bond and C-C bond-forming reactions. This review covered 146 papers published before 1995.

Later Mori[11] in 1997 and West[12] in 2002 published mini-reviews on the topic of iterative synthesis of marine ladder polyethers.

In the following section, major ring-forming methodologies and their applications in the total synthesis of marine ladder toxins will be discussed. This kind of background knowledge will set the standard for the new methods developing in our lab.

2.3.1 Nicolaou group's methods

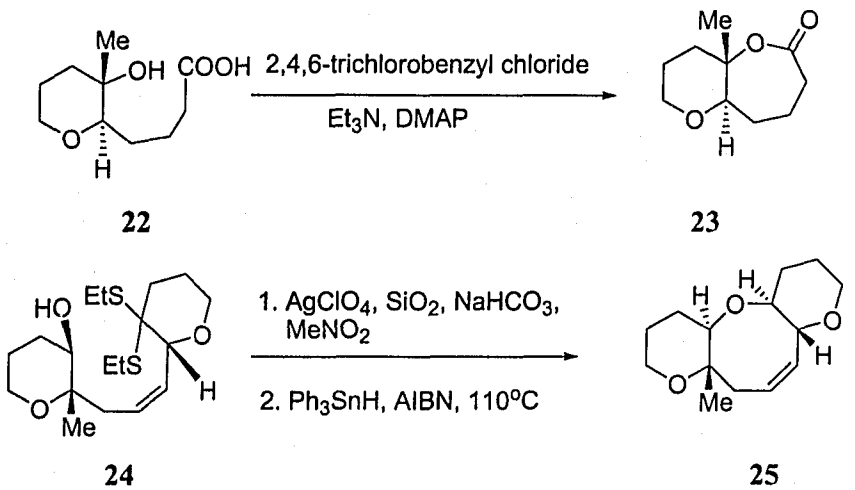
Brevetoxin B[5] was characterized as the first member in the marine ladder toxins family. In 1994, it was first synthesized by Nicolaou and co-workers.[13] Four years later, they synthesized brevtoxin A.[14]



Scheme 8. The ring closure of the tetrahydropyran system.

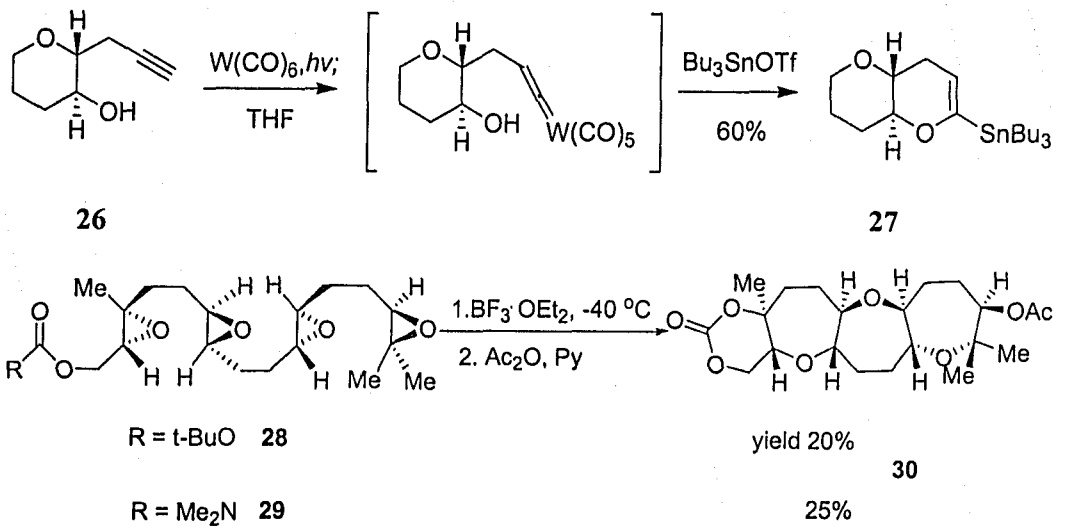
The regioselective and stereospecific formation of the tetraphdropyran (**19, 21**) system was achieved via endo-ring opening from a hydroxyl-allylic epoxide substrate (**18**) due to the stability of allylic carbocation and Michael-type hydroxide addition to the α, β-unsaturated ester (**20**) (Scheme 8). These two methods were widely used in 6-membered ring formation in several total syntheses of marine ladder polyethers.

The bis(oxepane) motif could be obtained by bridging of macrodi(thiolactones) and the reductive etherification of hydroxyketones, but neither method worked in the synthesis of brevetoxin because of steric hindrance. In fact, the problematic oxepane is formed through a 7-membered lactone (**23**) (Scheme 9). The intramolecular cyclization of the hydroxydithioketal **24**, followed by the radical dethiolation was a powerful method for the formation of 6-membered and 8-membered ether rings (**25**). It was this method that closed the last 8-membered ring and furnished the polyether framework in the first total synthesis of brevetoxin B.



Scheme 9. The ring closure of 7-membered and 8-membered ether ring.

2.3.2 McDonald group's method



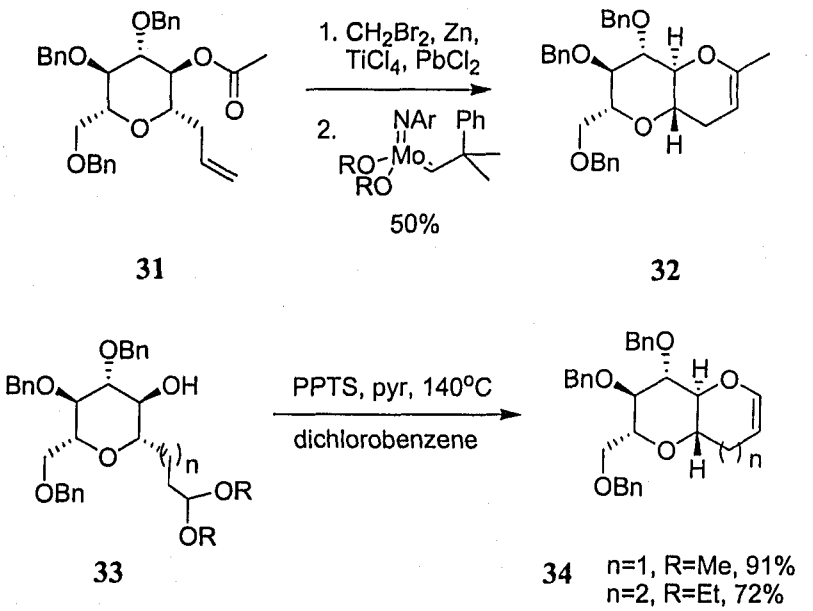
Scheme 10. McDonald group's methodologies.

Two methods have been developed by the McDonald group for application to the synthesis of polycyclic ether rings (Scheme 10). The first one was to utilize the tungsten-promoted endo-cyclization of alkynols (**26**).[15] The second was a biomimetic synthesis, which was achieved by endo-regioselective oxacyclization to provide poly-oxepane motif (**30**).[16] In the starting stage and the terminating stage of this cascade reaction, methyl groups or other trialkylsilyl groups were necessary to differentiate the two carbon atoms of the epoxide ring. Otherwise, undesired exo-products were the major product. This method was not suitable for poly-pyran rings because there was not enough space in the chain substrate to install the epoxide functionalities.

2.3.3 Rainier group's method

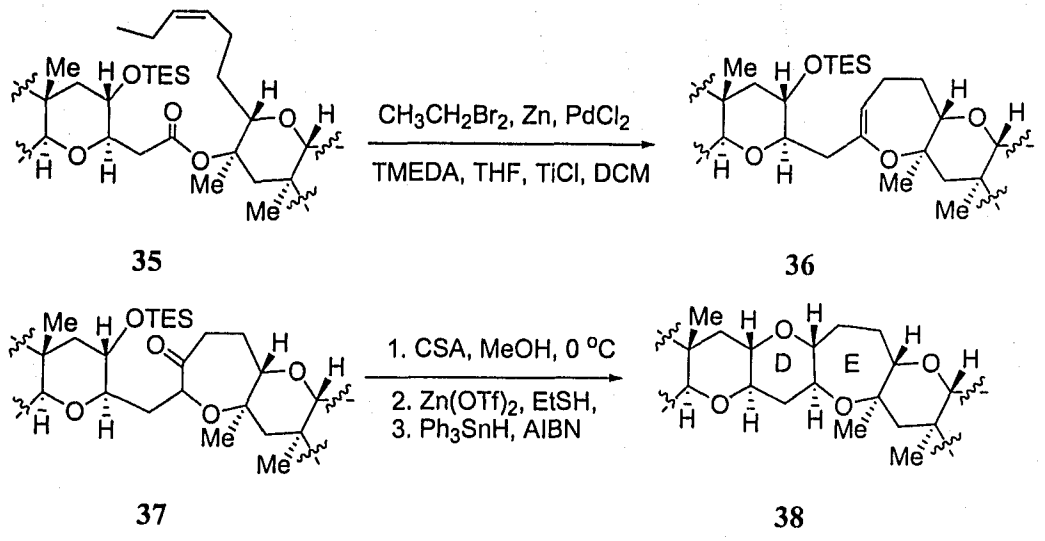
Rainier's general strategy involved olefin ring-closing metathesis (**31**→ **32**)[17]and acid-mediated annulation (**33**→ **34**),[18] commencing with C-glycosides to form 6-membered and 7-membered ring ethers (Scheme 11). In the enol ether-ring closing metathesis

(RCM) protocol, Takai's method was utilized to convert the ester carbonyl group to the acyclic enol ether. Then the Schrock catalyst and the second generation Grubbs catalyst promoted the cyclic enol ether (**32**) formation. The method worked on the 7-membered ring as well. Another efficient method was shown by the transformation from **33** to **34** via the acetalization-elimination process under mild acidic conditions.



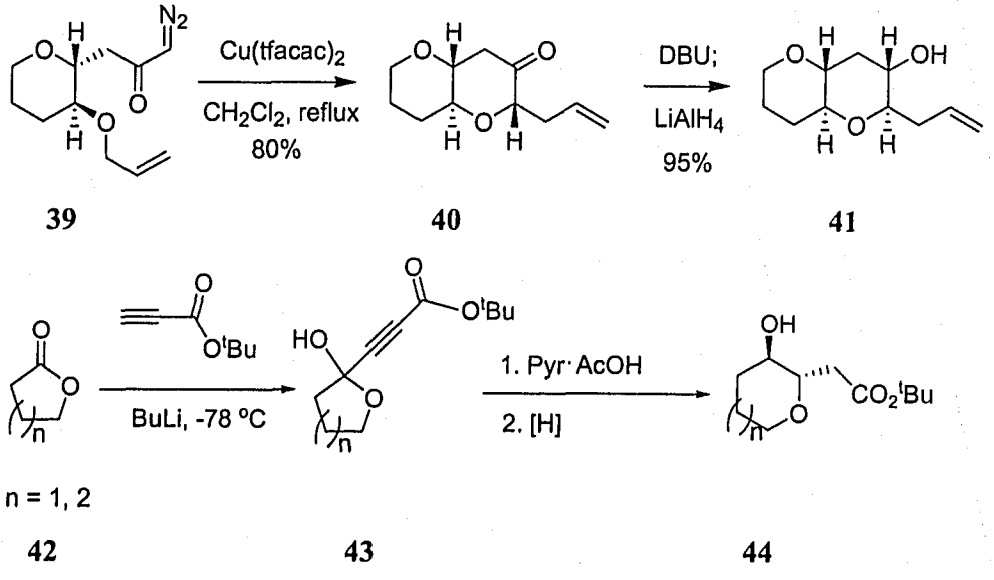
Scheme 11. Rainer's method of ether-ring formation.

In 2004, his group finished the total synthesis of gambierol.[19] The key step was to couple two fragments together via the formation of the middle E and D ring (Scheme 12). The Takai-Utimoto titanium methylidene protocol[20] did not work in this situation. They found that using 1,1-dibromoethane instead of 1,1-dibromomethane in the preparation of the Takai-Utimoto reagent provided the desired 7-membered E ring (**35→ 36**). The following formation of 6-membered D ring was accomplished by Nicolaou's reductive cyclization method (**37→ 38**). In this total synthesis of gambierol, the longest linear route from D-glucal was 44 steps in a 1.2% overall yield.



Scheme 12. Key steps of the total synthesis of gambierol.

2.3.4 West group's method



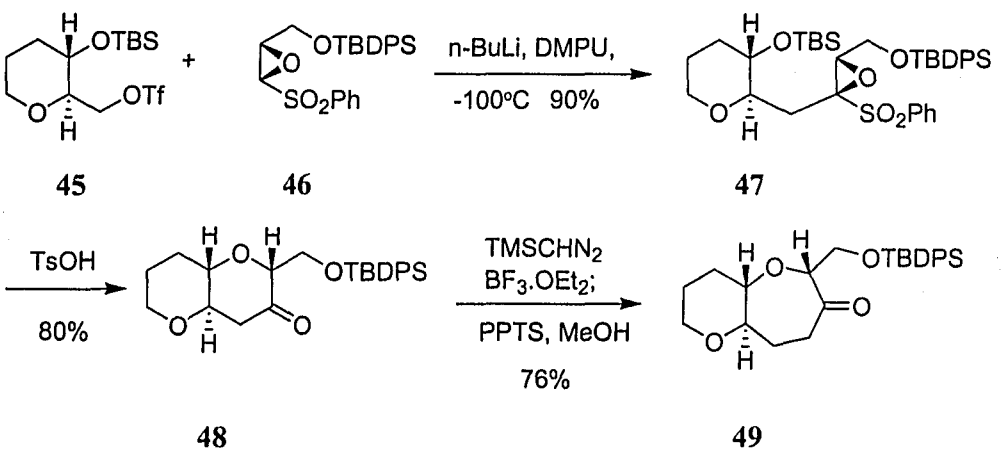
Scheme 13. Polyether ring closure methodologies in West's group.

There are three kinds of methodologies that have been and are being investigated in West's group (Scheme 13). The first one is based on the [2, 3]-shift of oxonium ylides, followed by isomerization and reduction to provide a polypyran system (**39**→ **41**).[21]

The second method includes the organic base-mediated oxacyclization of ketal-propargyl ester (**42**) to provide 6- and 7-membered ether rings (**44**). The third method consists of the regioselective enolation and enantioselective α-hydroxyketone formation, ketalization and reduction to form bis(pyran) compounds. The third method will be discussed in detail in chapter 3 later.

2.3.5 Mori group's methods

In Mori's work, sulfonyl-stabilized oxiranyl anions directly introduced an epoxide ring, followed by 6-endo cyclization to stereoselectively form a new tetrahydropyran ring (**48**) with a carbonyl group (Scheme 14).[22] The carbonyl group was used as a handle to convert the six-membered ring to an oxepane (**49**) by a ring expansion reaction.[23] Sulfonyl-stabilized oxiranyl anions are very reactive so that the extremely low temperature (-100 °C) and *in-situ* fast trapping were necessary for the successful coupling compound **45** and **46**. This methodology was utilized in the formal total synthesis of hemibrevetoxin, which contained 43 steps.[24]

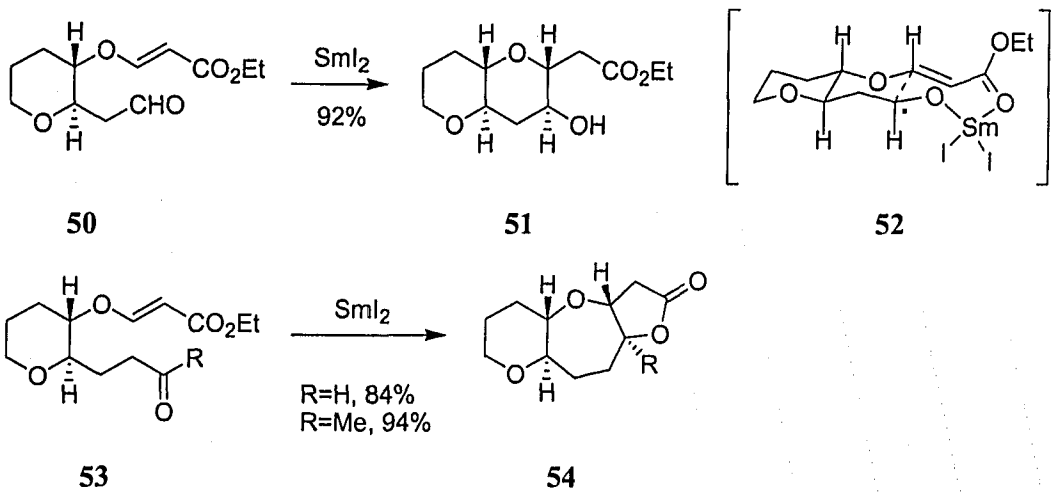


45 **46** **47** **48** **49**

Scheme 14. The ring closure methodology in Mori's group.

2.3.6 Nakata group's methods

In 1999, the Nakata group published a new method using the SmI_2-mediated intramolecular cyclization between aldehydes (or ketones) and an α, β-unsaturated ester to form six- and seven-membered ring ethers (**50→ 51, 53→ 54**) (Scheme 15). The reaction was postulated to process via the transition state **52**. The chelation of Sm (III) between the reduced carbonyl oxygen and the ester was suggested to account for the *trans* stereoselectivity (Scheme 15). A similar transition state was proposed for the 7-membered ring formation. This methodology was used twice in their total synthesis of brevetoxin-B, which required 59 steps as the longest linear sequence and 90 steps overall.[25]

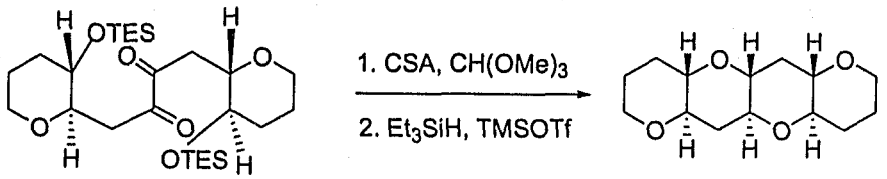


50 **51** **52**

53 **54**

Scheme 15. SmI_2-mediated ether ring formation.

Later, they and two other Japanese groups found another method, intramolecular diketalization and stereoselective Lewis acid-catalyzed silane reduction, provided a bis(tetrahydropyran) motif effectively from a 1,2-diketone with disilyl ether functionality (Scheme 16).[26]

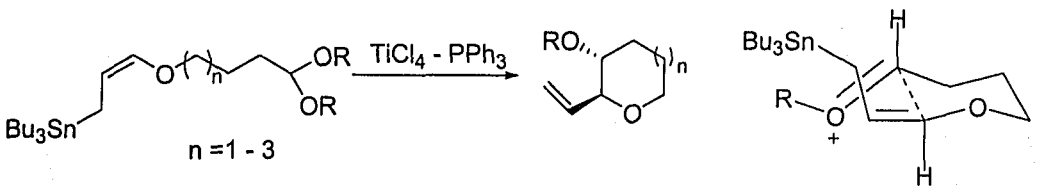


55 56

Scheme 16. The cyclization of dihydroxy diketone compound.

2.3.7 Kadota and Yamamoto group's methods

The intramolecular γ-alkoxyallylstannane-acetal condensation for stereoselectively making ether rings was first illustrated by Yamamoto and co-workers in 1991 (**57** → **58**) (Scheme 17).[27] The cyclization was mediated by Lewis acid and worked on the pyran, oxepane, and oxonane ring system. The allylic stannane and oxocarbenium ion moieties in transition state **59** were both in pseudo-equatorial positions to avoid the 1,3-diaxial repulsion with other axial hydrogen atoms, therefore, these two substituents preferred to be *trans* to each other.

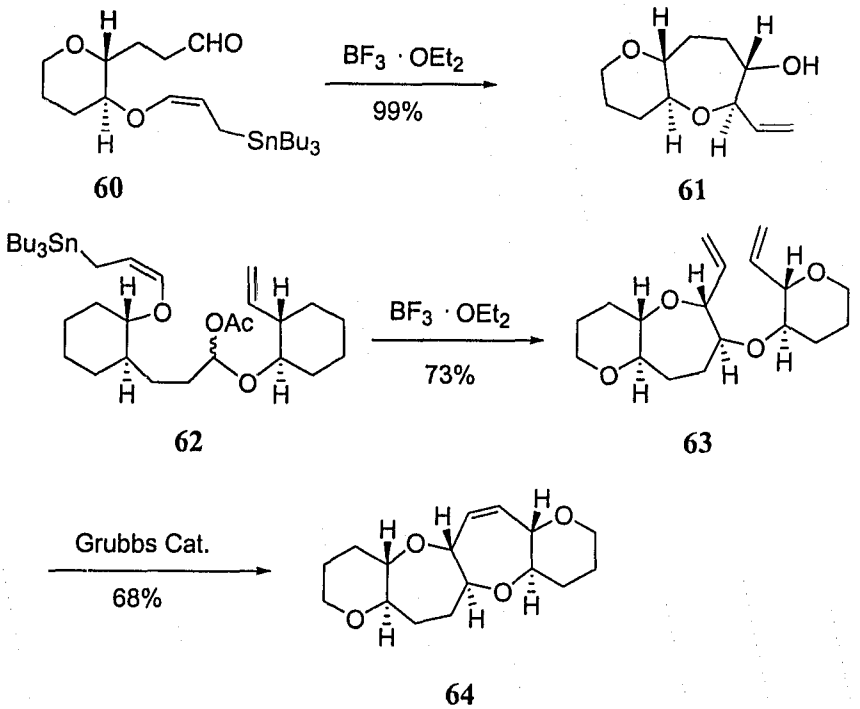


57 58 59

Scheme 17. Yamamoto group's method and proposed transition state.

This method has since been effectively extended. The acetal functionality was replaced by aldehydes **60**, ketals, and *O,S*-ketals , acetoxy ethers **62**, and a α-chloroacetoxy ether. In some cases, they found that the α-chloroacetoxy group functioned as a better leaving group than acetoxy and provided higher yield and the desired stereoselectivity (Scheme 18).[24] After this cyclization, the allylic stannane moiety was converted to the terminal alkene which was utilized in the ring close

metathesis (RCM) to form another ring. 7 to 9-membered rings can be obtained by ring-closing metathesis with about 20 mol% Grubbs catalyst.

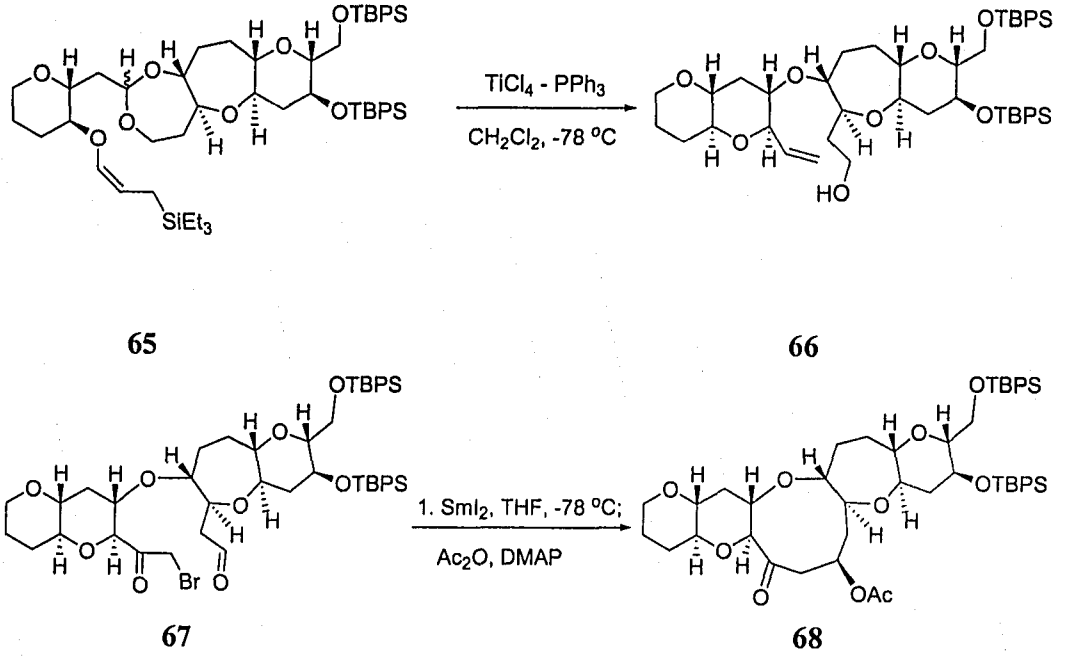


Scheme 18. The extension of intramolecular γ-alkoxyallylstannane-acetal condensation.

In 2003, Kadota and Yamamoto's group published the total synthesis of gambierol and 16-epi-gambierol.[6] The intramolecular γ-alkoxyallylstannane-acetal condensation was the key step to form the 7-membered ring ether by coupling two tricyclic fragments together. The longest linear route contains 66 stepa with 1.2% overall yield, and the total synthesis had 102 steps.

In 2005, they reported the total synthesis of brevetoxin B,[28] following Nicolaou[13] and Nakata's work.[25] This synthesis was highly convergent and three similarly complex fragments were coupled by their method, the intramolecular allylation of *O,S*-acetals, α-chloroacetoxy ethers and subsequent ring-closing metathesis. The longest linear route contained 63 steps with 0.28% overall yield and the total synthesis had 108 steps.

2.3.8 Tachibana, Hirama and Sasaki group's methods



65 66

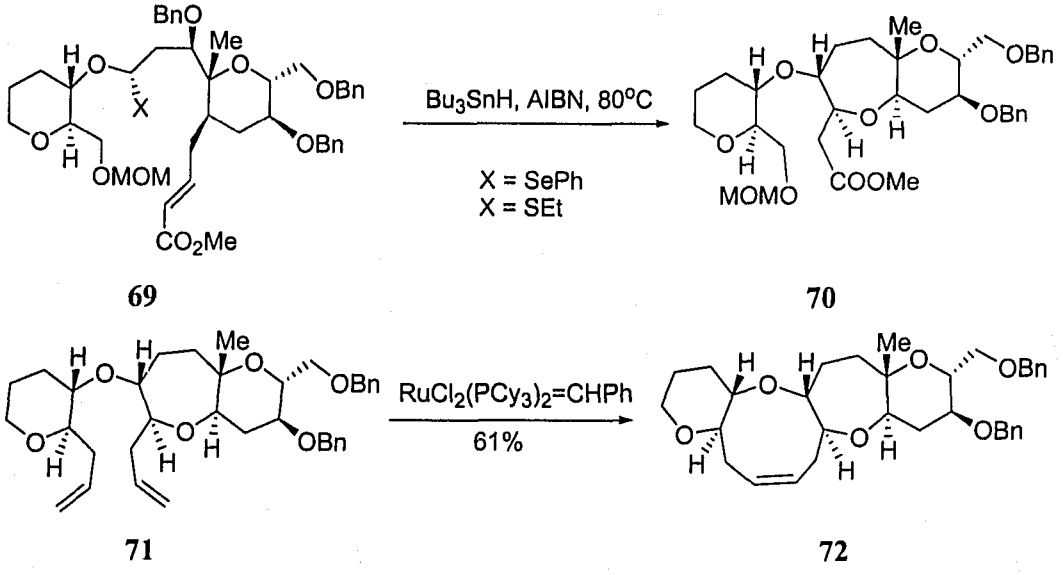
67 68

Scheme 19. The ring closure method in Tachibana and Sasaki's work.

Tachibana and Sasaki's group achieved the construction of 6-membered ring system by the intramolecular γ-alkoxyallylsilane-acetal cyclization (**65→ 66**), and then a SmI_2-mediated Reformatsky reaction to provide the neighbouring 9-membered ring (**67→ 68**) (Scheme 19). [29] The alkoxyallylsilyl group was less reactive than alkoxyallylstannane (**65**), so the reactive 7-membered acetal was used to promote the desired C-C bond formation. The yield of this transformation was only 36% because other epimers were formed. This method was not used the total synthesis because of the low yield.

Later, they found out that they could intramolecularly cyclize a carbon radical to a β-alkoxyacrylate to form the oxepane ring system in the good yield and high stereoselectivity (**69→ 70**) (Scheme 20). The radical was formed by breaking the C-S or C-Se bond as shown in Scheme 20. Then a RCM reaction built the nine-membered

ring in the high yield, using 30 mol% of the first generation Grubbs catalyst (**71**→ **72**). This was the first total synthesis of ciguatoxin.

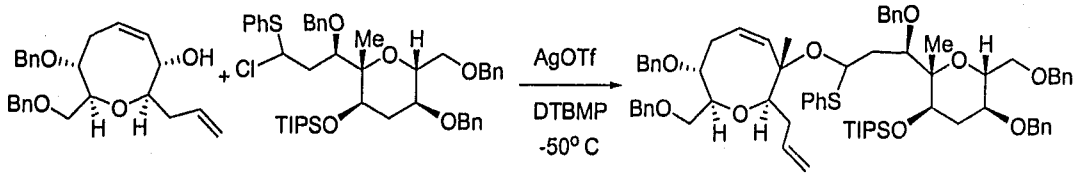


69 **70**

71 **72**

Scheme 20. The formation of ring ethers by radical cyclization.

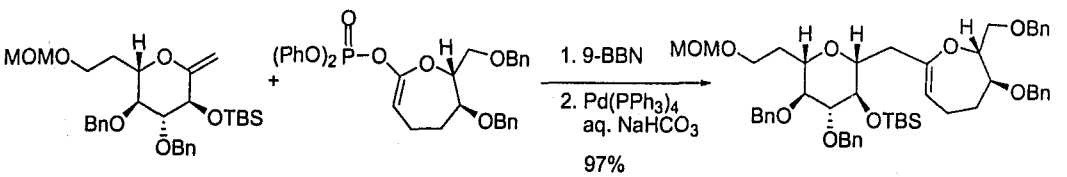
In the second generation of this synthesis, which was reported by the Inoue and Hirama group, the *O*, *S*-mixed acetal **75** was formed by the reaction between the secondary hydroxyl group in one fragment **73** and the α-chlorosulfide group in the other fragment **74** (Scheme 21). AgOTf and DTBMP made this transformation highly chemselective and mildly basic so that acid-sensitive protecting groups could be present in the molecule.[30] At the same time, the two main fragments were coupled by this mixed acetal **75**. This improvement made the second generation synthesis more efficient.



73 **74** **75**

Scheme 21. The formation of *O,S*-mixed acetal **75.**

This group was actively involved in the total synthesis of marine ladder toxins. In 2002 and 2003, they reported the total synthesis of gambierol [31]and gymnocin-A.[32] The other sharp tool they used was a high-yielding palladium(0)-mediated Suzuki cross-coupling reaction of aklylboranes with cyclic ketene acetal phosphates 77 (Scheme 22). A six-membered enol triflate was used in the similar Suzuki cross-coupling reaction. However, the cyclic ketene acetal phosphate **77** was more stable even in aqueous solution and easy to handle.



76 **77** **78**

Scheme 22. The palladium(0)-mediated Suzuki cross-coupling reaction.

Over the past two decades, the strategies and methodologies in the synthesis of marine ladder toxin have made a lot of progress. Because of the size and complexity of this kind of natural product, an average sequence of 100 steps was needed to complete the total synthesis. Biomimetic synthesis has the chance to reduce the number of steps in the total synthesis because multi-ring motifs could be synthesized in a one pot reaction. However, many problems still need to be solved, such as regioselectivity, stereoslectivity, and the generality of the methodology.

2.4 Bibliography

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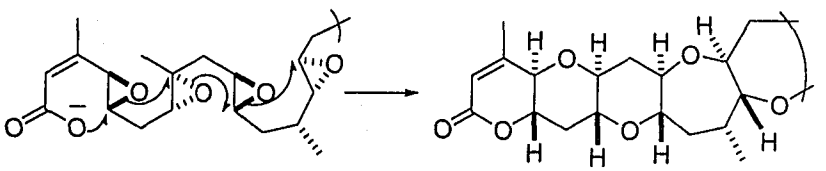
Chapter 3 The Synthesis of Bis(pyran) Compounds

3.1 Perspective and objective of the project

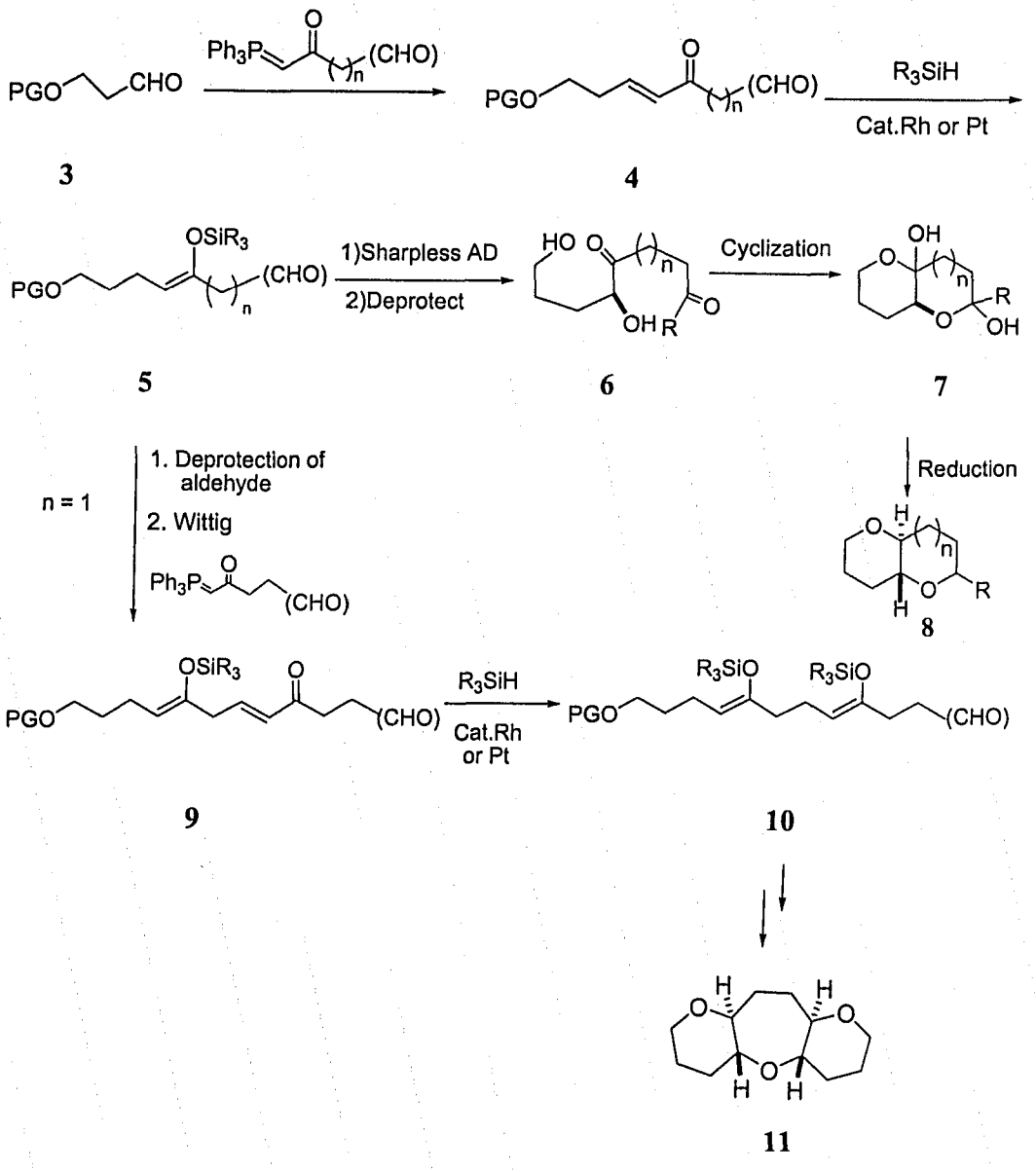
Nature not only contains millions of organic compounds, it also has the ability to efficiently synthesize them. Organic chemists are inspired by nature and attempt to utilize similar routes to synthesize natural products in the laboratory. This is termed biomimetic synthesis. This concept has been applied in recent syntheses of marine ladder polyethers. The biosynthesis of marine ladder polyethers was postulated to occur via a multi-cyclization process from a polyepoxide precursor **1** (Scheme 1).



1 **2**

Scheme 1. The biosynthesis of marine ladder polyether.

We have set out to develop a new method using a multi-α-hydroxy ketone substrate as the polyexpoxide surrogate. The α-hydroxy ketone intermediate **6** can be synthesized from the dihydroxylation of the silyl enol ether compound **5** (Scheme 2). The optical enriched α-hydroxy ketone intermidates could be prepared by the Sharpless asymmetric dihydroxylation,[1] or the Davis chiral oxaziridine reagent.[2] The silyl enol ether would be generated via reduction of an α,β-unsaturated ketone **4** by: 1) conjugate addition of hydride (using Stryker's reagent or Red-Al/CuI), 2) dissolving metal reduction, or 3) 1,4-hydrosilylation. The enone **4** could be formed by a Horner-Wadsworth-Emmons reaction between a stabilized phosphonate anion and the suitable aldehyde **3**.

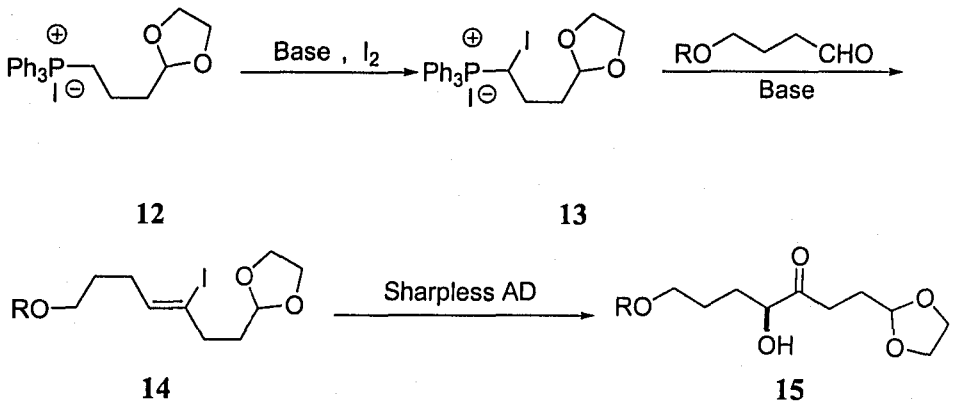


Scheme 2. The original design of this methodology.

Under mild acidic conditions, intermediate **6** should cyclize intramolecularly to form cyclic hemiketals **7**, which could then be transformed *in situ* to the stable ketal compound. Finally, the cyclic ketal intermediate could be reduced to the ether motif **8**. Increasing the number of α-hydroxyketone functional groups in the molecule paves the way to multi-ring formation. Varying the number of methylene groups between the two ketone groups could lead to different size ring formation, such as six-

membered or seven-membered rings, both of which occur frequently in marine polyether ladder toxins.

An alternative strategy would employ synthesis of the vinyl iodide intermediate **14** instead of the silyl enol ether, followed by dihydroxylation to produce the α-hydroxy ketone substrate **15** (Scheme 3). The vinyl iodide intermediate **14** could be prepared by addition of the desired aldehyde to the α-iodo phosphonium salt **13** which in turn could be obtained from *in situ* halogenation of the simple phosphorous ylides **12.** [3]

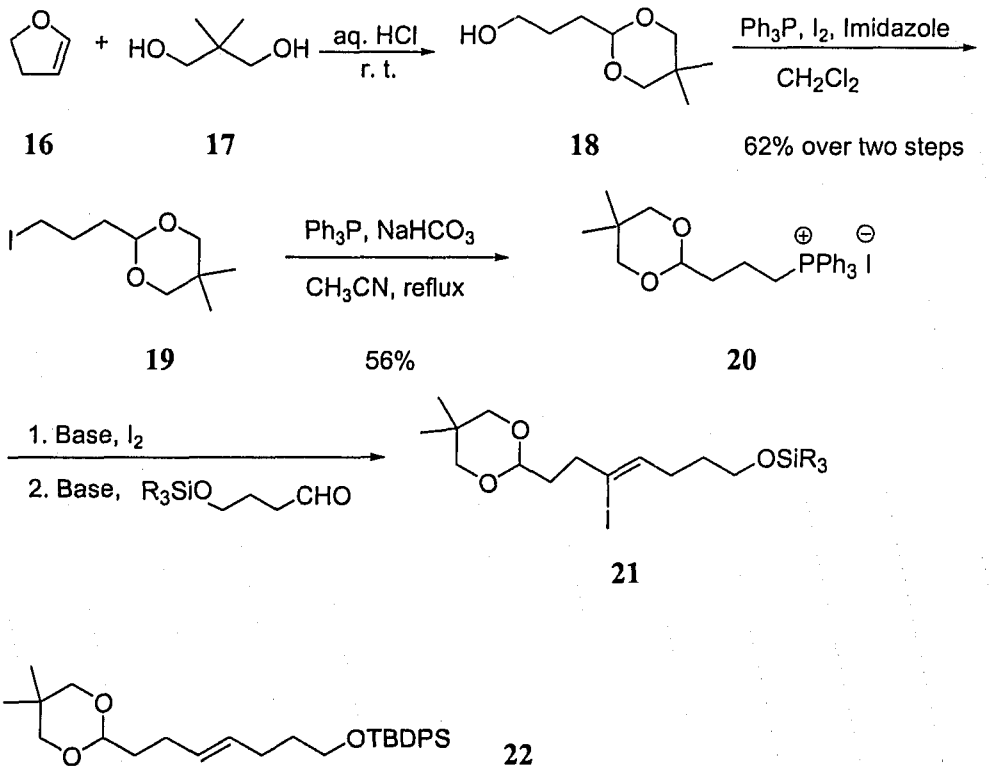


Scheme 3. The synthesis of *Z*-vinyl iodide compound.

3.2 Synthesis of the *Z*-vinyl iodide intermediate 21

4-(4,4-Dimethyl-1,3-dioxane)butyltriphenylphosphonium salt **20** was obtained from 4-(4,4-dimethyl-1,3-dioxane)butyl iodide **19** and triphenylphosphine (Scheme 4). There are several methods to prepare the reactive 4-(4,4-dimethyl-1,3-dioxane)butyl iodide **19** from the corresponding alcohol **18**. Two methods were tested. The first method was to convert the alcohcl **18** into the more reactive tosylate, and then reaction with sodium iodide in acetone to produce the desired alkyl iodide intermediate **19**. The yield of these two reactions was greater than 90% and the purity of the iodide intermediate was high, but the reaction time was longer than 48 h to obtain complete transformation of the tosylate to the iodide intermediate. The second

method involved a Mitsunobu-type reaction, using triphenylphosphine and iodine. The disadvantage of this one-step method was that excess triphenylphosphine cannot be easily separated from the iodide intermediate **19** because of the similar polarity of these two compounds. On the other hand, excess triphenylphosphine was not a problem for the following reaction because it was used as a reagent in excess in the formation of compound **20**. 4-(4,4-Dimethyl-1,3-dioxane)butyltriphenylphosphonium salt **20** should be a solid, but following the work-up procedure, a yellow syrup was obtained. The crude ^{1}H-NMR spectrum showed that the salt was present in the mixture. Finally, the careful and slow recrystallization, using chloroform and ethyl acetate, provided the desired product in moderate yield (68%).[4]



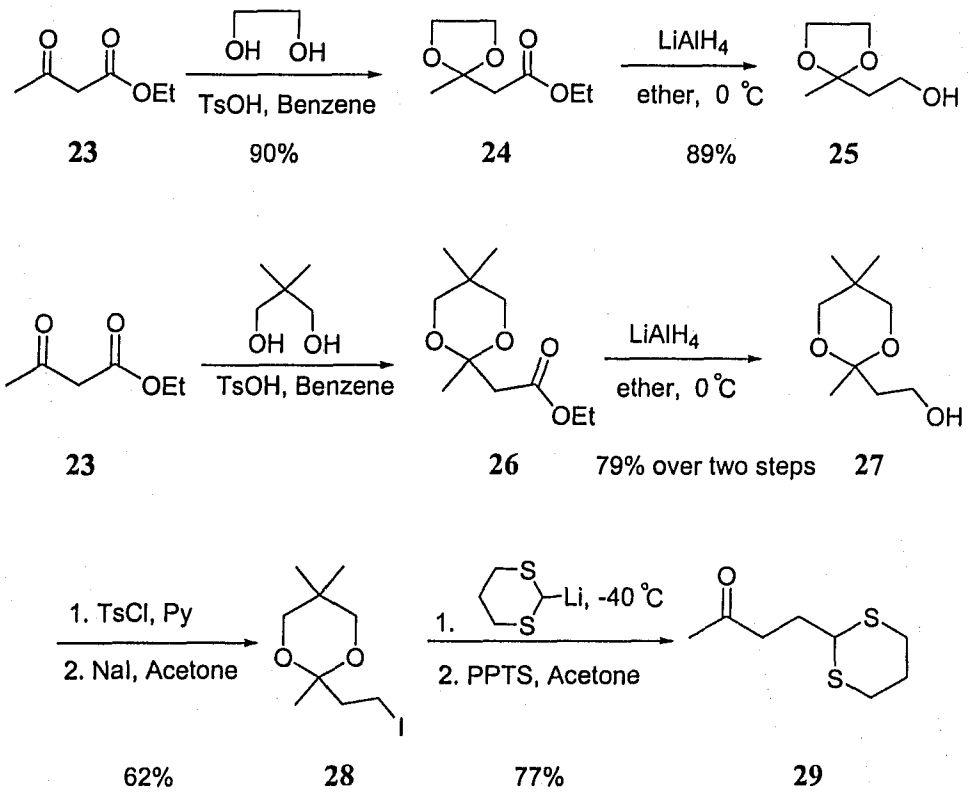
Scheme 4. The synthesis of *Z*-vinyl iodide compound.

With salt **20** in hand, the next step was to prepare the *Z*-vinyl iodide intermediate **21**. Using the strong base (NaHMDS or *n*-BuLi) at -78 °C to room temperature did not

provide the desired product. The crude ^{1}H-NMR spectrum showed that the 1,2-disubstituted alkene, i.e., compound **22** was obtained. The possible reason was that salt **20** was not deprotonated in the first step and the Wittig reaction between the aldehyde and the ylide generated from the salt **20** provided the 1,2-disubstituded alkene **22.**

Later, West and Wan found that using potassium *tert*-butoxide as the base at the higher temperature (50–60 °C) furnished the vinyl iodide intermediate **21**.[5] Unfortunately, it was found not to be a good substrate for the Sharpless asymmetric dihydroxylation.

3.3 Synthesis of the dithioacetal substrate 31



Scheme 5. The synthesis of 1-(1,3-dithiane)-2-pentanone **29.**

Starting from the commercially available ethyl acetoacetate **23**, the ketone carbonyl group was chemoselectively protected as either the 1,3-dioxolane **24** or 4,4-dimethyl-1,3-dioxane **28**. 4,4-Dimethyl-1,3-dioxane was chosen as the ketone protecting group in this route. Comparing with 1,3-dioxolane, 4,4-dimethyl-1,3-dioxane **28** was much easier to deprotect under mild conditions (PPTS as the catalyst in refluxing acetone).

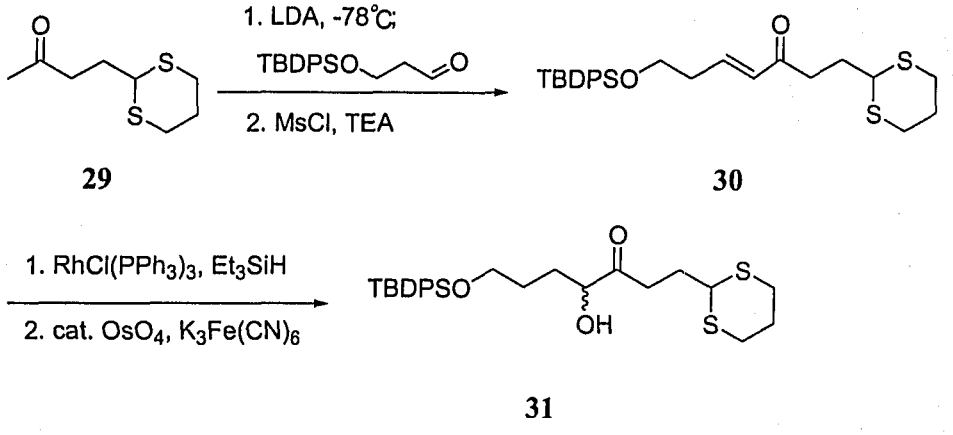
After the ketone carbonyl group was converted into the ketal protecting group, the ester **26** was reduced to the primary alcohol **27** by $LiAlH_4$. Alcohol **27** was then transformed into the iodide **28** by a two-step method. First, the alcohol group was converted into the tosylate, this was then followed by the reaction with sodium iodide to provide the easily purified iodide intermediate **28**. The one-step method using I_2 and PPh_3 was not utilized because purification of the iodide intermediate from the excess PPh_3 was time-consuming and the iodide intermediate was also not stable. The next reaction, the coupling of lithium 1,3-dithiane with the iodide precursor **28** was interfered with residual triphenylphosphine. All these reactions provided the desired product in good yields (Scheme 5).

After the ketal deprotection, an aldol reaction was carried out between the methyl ketone **29** and 3-*tert*-butyldiphenylsilyloxypropanal.[6] Using the bulky and non-nucleophilic base, lithium diisopropylamide at low temperature (-78 °C) secured the kinetically favored enolate as the major intermediate. The desired β-hydroxy ketone product was obtained in 63% yiels. After the scale-up reaction, enough of the β-hydroxy ketone intermediate was prepared to do the next reaction.

The newly-formed hydroxyl group was activated by mesylation with methanesulfonyl chloride (Scheme 6).[7] The subsequent *in situ* E_2 elimination reaction provided the enone **30** in high yield (86%) under mildly basic conditions.

Wilkinson's catalyst mediated 1,4-hydrosilylation was chosen to reduce enone **30** to the corresponding silyl enol ether due to the high chemoselectivity of 1,4-reduction.[8] At the same time, the catalyst is air-stable and easy to handle. The silyl enol ether was then utilized in the following dihydroxylation reaction. Two common oxidizing reagents, potassium ferricyanide and *N*-methylmorpoline *N*-oxide were tested in the dihydroxylation step, which similar results were obtained in both cases. The desired

α-hydroxy ketone **31** was formed as identified by spectral data. However, a side product was formed and it was difficult to separate from the α-hydroxy ketone **31** due to the similar polarity. When 2 mol% of osmium tetroxide was used as the catalyst for the dihydroxylation step, the reaction was slow (24 h to consume all the starting material) and the dithioacetal was also oxidized. Increasing the ratio of osmium tetroxide accelerated the dihydroxylation reaction and also reduced the reaction time. This, in turn, decreased the amount of undesired product.



29 **30** **31**

Scheme 6. The synthesis of α-hydroxy ketone substrate **31.**

3.4 Synthesis of cyclic acetal substrates

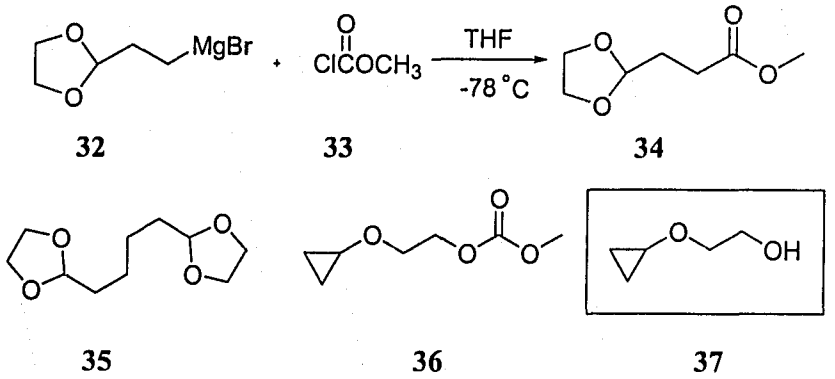
3.4.1 Synthesis of *tert*-butyldiphenylsilyloxy-dioxolane compounds

Starting with the commercially available 2-(2-bromoethyl)-1,3-dioxolane, the Grignard reagent **32** was synthesized (Scheme 7). [9] Alkylation of methyl chloroformate **33** with compound **32** at -78 °C afforded methyl 1,3-dioxolane-3-propanoate **34** in 65% yield.[10]

Due to the Grignard reagent **32** and methyl chloroformate **33** being very reactive, even at the very low temperature, several unexpected side products were obtained.

The first side product **35** was formed during the preparation of the Grignard reagent. When the formation of the Grignard reagent was carried out with external heating, the homocoupling of the Grignard reagent occurred to produce compound **35** as the major

product. Optimized condition, using I_2 and 1,2-dibromoethane to initiate the metallation process,allowed the Grignard reagent to be produced without external heating.

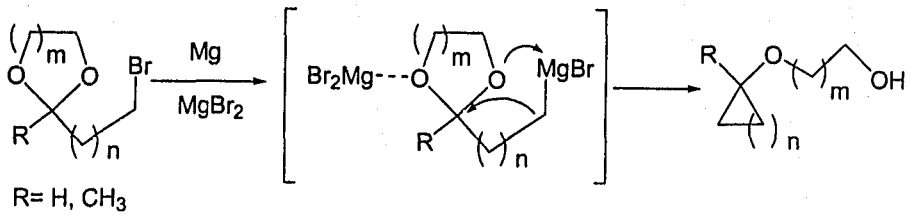


32 **33** **34**

35 **36** **37**

Scheme 7. The reaction of Grignard reagent **32** and side products.

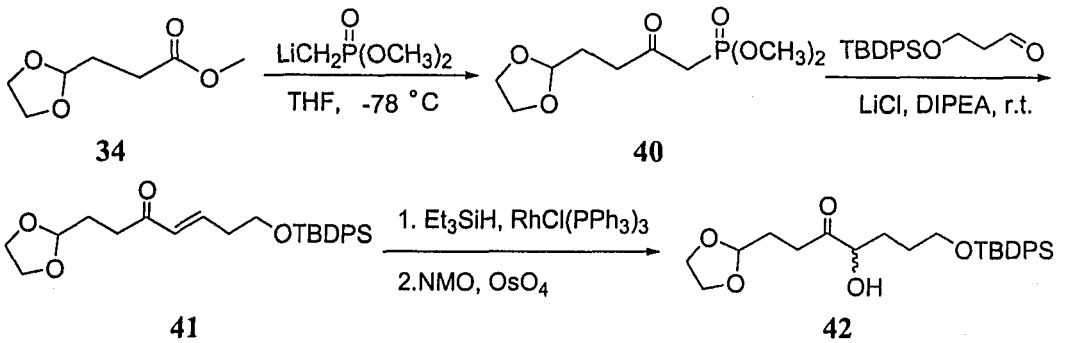
The second side product **36** was formed during the alkylation step. A long reaction time and an increased amount of $MgBr_2$ increased the yield of this side product. The structure of this compound **36** was determined by MS, IR, NMR analysis. A literature search showed this not to be a novel compound. The alcohol **37** was synthesized by Leung's group during their attempts to prepare the same Grignard reagent.[11] They discovered that the side reaction was a Lewis-acid ($MgBr_2$)-promoted kinetically-controlled intramolecular cyclization reaction (Scheme 8). Ring closure was faster in cyclopropyl and cyclopentyl products (n = 1, 3) than in the cyclobutyl ring (n = 2). This indicated a kinetically controlled process. Increasing the amount of $MgBr_2$ generated from $BrCH_2CH_2Br$ provided the higher yield of the side product. They proposed that the acetal group was activated by $MgBr_2$ and the following intramolecular nucleophilic addition of the carbanion provided a new carbo-cyclic product **39** in good yields (Scheme 8).



38 39

Scheme 8. Proposed mechanism for the formation of side product.

The alkylation of ester **34** with dimethyl α-lithio-methanephosphonate at -78 °C provided the suitable phosphonate **40** in 65% yield for the following Horner-Wadsworth-Emmons reaction. Compound **40** was not stable and not easily purified by column chromatography because of its high polarity. According to the ^{1}H NMR spectrum, the crude product was pure enough to be carried through to the next reaction as long as the excess dimethyl methanephosphonate was removed under high vacuum at room temperature (Scheme 9). The NMR spectrum of compound **40** was complex due to the coupling between phosphorus and hydrogen producing large coupling constants and also observable ^{3}J coupling between carbon and phosphorus.



34 40

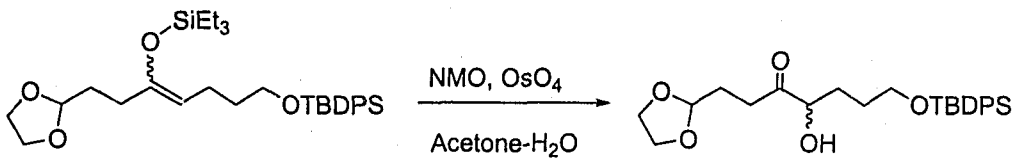
41 42

Scheme 9. The synthesis of α-hydroxyk etone **42.**

The Horner-Wadsworth-Emmons reaction between dimethyl 2-oxo-5-(1,3-dioxolane)-pentylphosphonate **40** and 3-(*tert*-butyldiphenylsiloxy)-1-propanal afforded the desired enone **41**. Strong basic conditions (sodium hydride) and Masamune's mild

conditions (diisopropylethylamine)[12] were used in this reaction and a similar yield (about 80%) was obtained because there were no base-sensitive moieties in this reaction system. The new C=C bond was formed with high (> 95% *E*) stereoselectivity. Using *tert*-butylmethyl ether and hexane as the eluent, the minor *Z*-isomer was separated from the E-isomer by column chromatography.

Having the enone **41** in hand, conjugate reduction provided the enolate equivalent regiospecifically. 1,4-Hydrosilylation with triethylsilane as the hydride source and $(PPh_3)_3RhCl$ (Wilkinson's catalyst) as the catalyst was utilized due to mild reaction conditions.[6] The silyl enol ether **43** was obtained as a mixture of *Z*- and *E*-isomers as shown by the ^1H NMR spectrum of the crude product (Scheme 11). The crude silyl enol ether **43** was used without purification because it was unstable on silica gel and also had a high boiling point.



43 **42**

Scheme 10. The dihydroxylation reaction of silyl enol ether **43.**

Dihydroxylation of the silyl enol ether **43**, using a catalytic amount of osmium tetroxide and NMO afforded the desire α-hydroxy ketone **42** in 50% yield over two steps. When 2 mol% of osmium tetroxide was used in the reaction, the starting material was not completely consumed after 30 h. Using 8 mol% of osmium tetroxide allowed for the completion of the reaction in 24 h.

The optically rich α-hydroxy ketone **42** was prepared from the silyl enol ether **43** and commercially available AD-mix. The original reaction conditions involved stirring the reaction mixture for 16 h at 0 °C. But using the silyl enol ether **43,** the reaction was not complete after 16 h. About 40% of the silyl enol ether **43** was recovered when

the reaction was worked up after 16 h. Optimal conditions were stirring the reaction mixture at 0 °C for 4 h and then at room temperature for 30 h. The enantiomeric excess was 68% determined by chiral HPLC (Chiralpak OJ-H, IPA/hexane = 4/96, flow rate 0.4 mL/min).

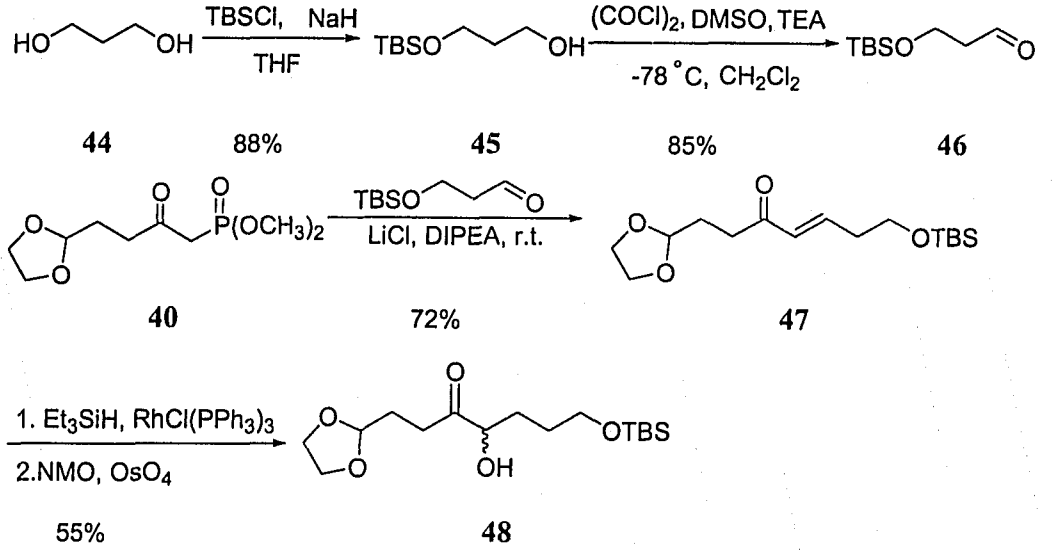
Intramolecular ketalization to cyclize the chain to the bicyclic compound was the key step. The *tert*-butyldiphenylsilyl ether was very stable under mild acidic conditions (TsOH, MeOH). It had to be removed by tetra-*n*-butyl ammonium fluoride. After the primary hydroxy group was deprotected from the *tert*-butyldiphenylsilyl ether, the desired product could not be separated from the reaction mixture due to the equilibration between the acyclic hydroxyl ketone and the cyclic hemiketal. This mixture was subjected to acidic conditions in THF or methanol, but the reaction mixture was too complex to be purified by column chromatography. After the α-hydroxy ketone was stirred with HCl (a catalytic amount) in a 1:1 ratio of methanol and water overnight at room temperature, the proton NMR spectrum of the crude product showed that the 1,3-dioxolane group was still present.

The *tert*-butyldiphenylsilyl ether protecting group could not be removed under mild acidic conditions, which were designed to deprotect both the aldehyde and alcohol functionalities,[13] and also promote an *in-situ* cyclization through the intramolecular ketalization. Therefore, the *tert*-butyldiphenylsilyl ether was replaced by *tert*-butyldimethylsilyl ether which could be deprotected using acidic conditions.

3.4.2 Synthesis of (*tert*-butyldimethylsilyl)oxy -dioxolane compounds

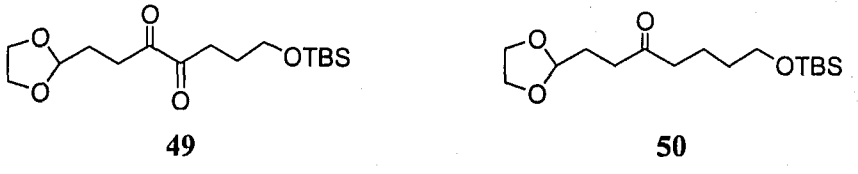
3-[(*tert*-butyldimethylsilyl)oxy]propanal **46** was coupled with dimethyl 2-oxo-5-(1,3-dioxolane)pentylphosphonate **40** using the Horner-Wadsworth-Emmons olefination to give the desired enone **47** (Scheme 11). Masamune's mild conditions (DBU or diisopropylethylamine)[10] were utilized to avoid any side reaction of the *tert*-butyldimethylsilyl ether group. The desired *E*-enone **47** was obtained in 72% yield. 1,4-Hydrosilylation with triethylsilane as the hydride source and $(PPh_3)_3RhCl$

(Wilkinson's catalyst) as catalyst was followed by the dihydroxylation to afford α-hydroxy ketone **48** in 55% yield over two steps.



Scheme 11. The synthesis of (*tert*-butyldimethylsilyl)oxy-dioxolane compounds.

If more than 3 equivalent of oxidant ($K_3Fe(CN)_6$ or NMO) was present in the reaction mixture, the α-hydroxy ketone **48** could be further oxidized to the 1,2-diketone compound **49**, which was separated from the reaction mixture. Due to water being necessary in this reaction to hydrolyze the osmate ester and the triethylsilyl enol ether being labile to water, part of the silyl enol ether was hydrolyzed to the mono-ketone compound **50** after long reaction times.

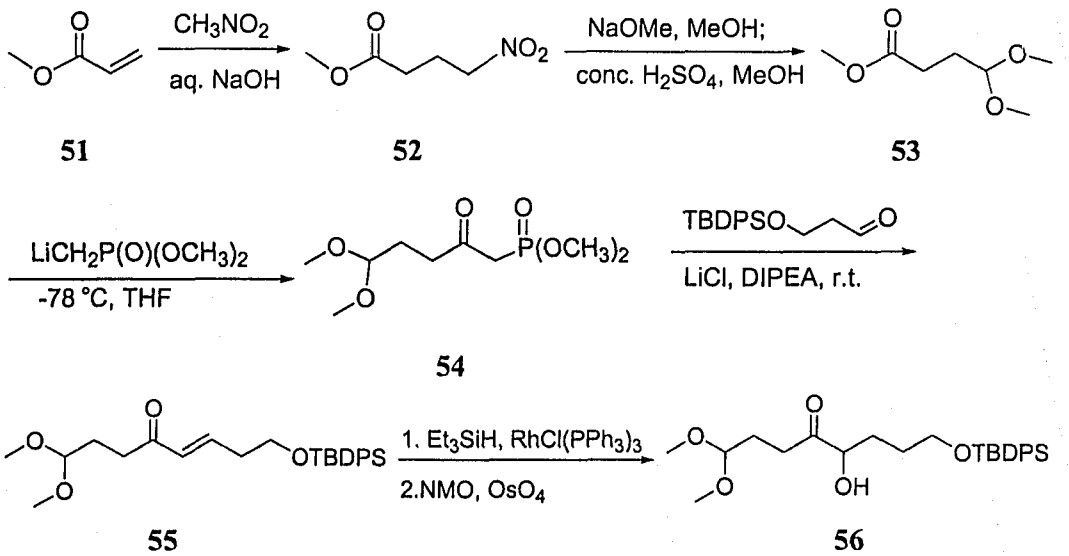


Scheme 12. The side products of dihydroxylation reaction.

3.4.3 Synthesis of silyloxy-dimethyl acetal compounds

The dioxolane protecting group could be substituted for a more labile acyclic acetal, such as dimethyl acetal. Under acidic conditions, a dimethyl acetal can easily lose a methoxy group to form a more electrophilic oxocarbenium cation and further react with hydroxyl group in the same molecule to provide a new cyclic acetal.

A Henry-Michael-type reaction between nitromethane and methyl acrylate **51** using aqueous sodium hydroxide as the base provided methyl 4-nitro-butanoate **52** in 30% yield (Scheme 13). Using Jacobson's modification of the Nef reaction,[14] methyl 4-nitrobutanoate **52** was easily transformed to methyl 4,4-dimethoxybutyrate **53** in good yield (76%) and high purity.[15] Methyl ester **53** was treated with the lithium anion of dimethyl methylphosphonate at -78 °C to afford the *β*-keto-phosphonate **54** in 63% yield. The resulting phosphonate **54** was subjected to a Horner-Wadsworth-Emmons reaction with 3-[(*tert*-butyldiphenylsilyl)oxy]propanal to afford the enone **55** in 68% yield. More than 95% of the newly-formed alkene was the *E* isomer, as shown by the coupling constants of the two vinyl protons (16.0 Hz).

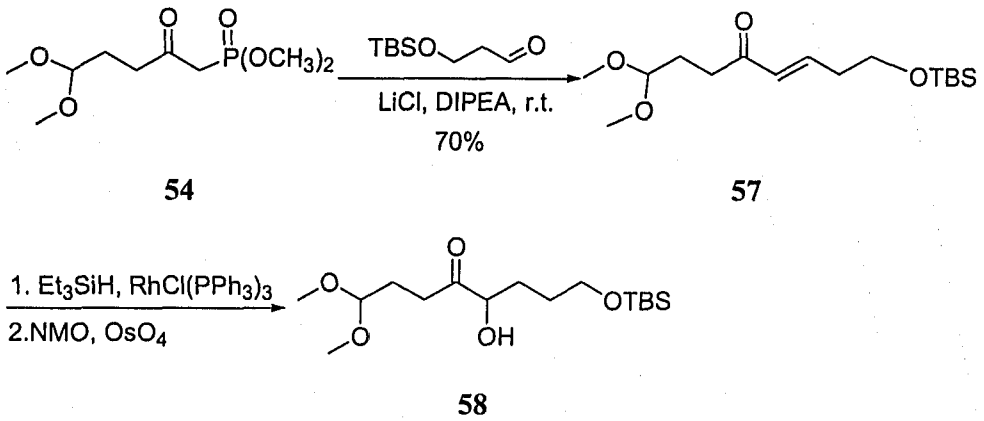


Scheme 13. The synthesis of *tert*-butyldiphenylsilyloxy dimethyl acetal compound.

Reaction of this enone **55** with an excess of triethylsilane and a catalytic amount Wilkinson's catalyst in an oil bath (50 °C) for 1 h yielded the silyl enol ether, which was used as the crude product without purification. The α-hydroxy ketone **56** was prepared by dihydroxylation with NMO as the co-oxidant and 4 mol% of osmium tetroxide. The desired product **56** was obtained in 50% yield over two steps.

α-Hydroxy ketone **56** was then treated with TBAF in anhydrous THF at room temperature. However, the reaction mixture was too complex to be purified by column chromatography.

α-Hydroxy ketone **58** was prepared through the similar method as the compound **56** (Scheme 14). Proton NMR showed that α-hydroxy ketone **58** was present in the crude product. However, purification with silica gel chromatography did not provide any product, even with 1% (v/v) of triethylamine present in the eluent system.



54 **57** **58**

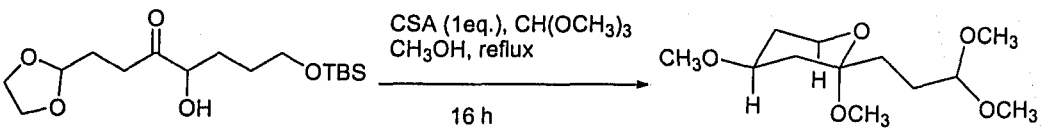
Scheme 14. The synthesis of *tert*-butyldimethylsilyloxy dimethyl acetal compounds.

Comparing all of α-hydroxy ketones **31**, **42**, **48**, **56**, **58**, 1,3-dithiane could be cleaved by a wide range of oxidants and it was not stable in the dihydroxylation step. The dimethyl acetal was too labile and not compatible with some purification procedures. The 1,3-dioxolane was used for further studies. 4,4-dimethyl-1,3-dioxane could be another choice because it was more stable than dimethyl acetal and more labile than 1,3-dioxolane. Among silyl ether protecting groups, *tert*-butyldimethylsilyl ether was

the right selection due to its stability. Combining protecting groups for the aldehyde and the primary alcohol, α-hydroxy ketone **48** was perfect option for the further study.

3.5 Cyclization of cyclic acetal substrates and structure determination of novel products

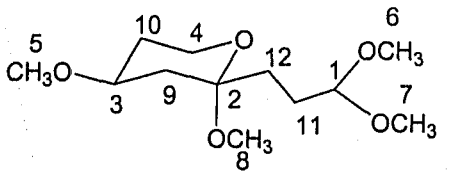
3.5.1 Monocyclic compound 59



48 **59**

Scheme 15. The synthesis of monocyclic compound **59.**

When the TBS protected substrate **48** was stirred with camphorsulfonic acid and trimethyl orthoformate for 16 h in refluxing methanol, one major compound was separated from the reaction mixture (Scheme 15). Its polarity was lower than the starting substrate and it could be stained by anisaldehyde. The electrospray ionization mass spectrum showed the molecular formula, $C_{12}H_{24}O_5$ and the electron impact mass spectrum showed the biggest fragment formula to be $C_{11}H_{21}O_4$. The difference between these two formulas was a methoxy group (CH_3O). The IR spectrum did not indicate the presence of any of the readily identifiable functional groups.



59

Table 1 Chemical shifts of monocyclic product **59.**

Carbon Number	δ_C (ppm)	δ_H (ppm)
1	104.5 (CH)	4.21-4.28 (m, 1H)
2	101.3 (C)	
3	73.5 (CH)	3.62 (dddd, J = 11.0, 11.0, 4.6, 4.6 Hz, 1H)
4	59.6 (CH_2)	3.53 (ddd, J = 11.4, 5.3, 1.8 Hz, 1H), 3.41 (ddd, J = 12.9, 11.4, 2.4 Hz, 1H)
5	55.0 (CH_3)	3.11 (s, 3H)
6	52.6 (CH_3)	3.12 (s, 3H)
7	52.0 (CH_3)	3.10 (s, 3H)
8	47.0 (CH_3)	3.04 (s, 3H)
9	39.6 (CH_2)	2.27 (ddd, J = 12.4, 4.6, 2.0 Hz, 1H), 1.34 (dd, J = 12.4, 10.9 Hz, 1H)
10	32.2 (CH_2)	1.80-1.67 (m, 1H), 1.40 (dddd, J = 12.7, 12.7, 11.1, 5.1 Hz, 1H)
11	31.4 (CH_2)	1.93-1.88 (m, 1H), 1.80-1.67 (m, 1H)
12	27.2 (CH_2)	1.80-1.67 (m, 2H)

The structure of compound **59** was determined by NMR spectral data (Table 1 and 2). One carbon (C1) at 104.5 ppm was a methine whose proton NMR chemical shift was 4.25 ppm, so C1 was postulated to be an acetal carbon. The carbon (C2) at 101.3 ppm without any hydrogen atoms attached was assigned as a ketal carbon. The fact that both carbons had the large chemical shift was consistent with that substitution of C1 and C2 with two oxygen atoms leading to a greater degree of deshielding. C3 was attached to one oxygen atom and its hydrogen coupled with H9 and H10 by two large coupling constants (11.0 Hz) and two small ones (4.6 Hz). Thus methine C3 was apparently adjacent to methylenes C9 and C10. H3 had to be in an axial oriantation

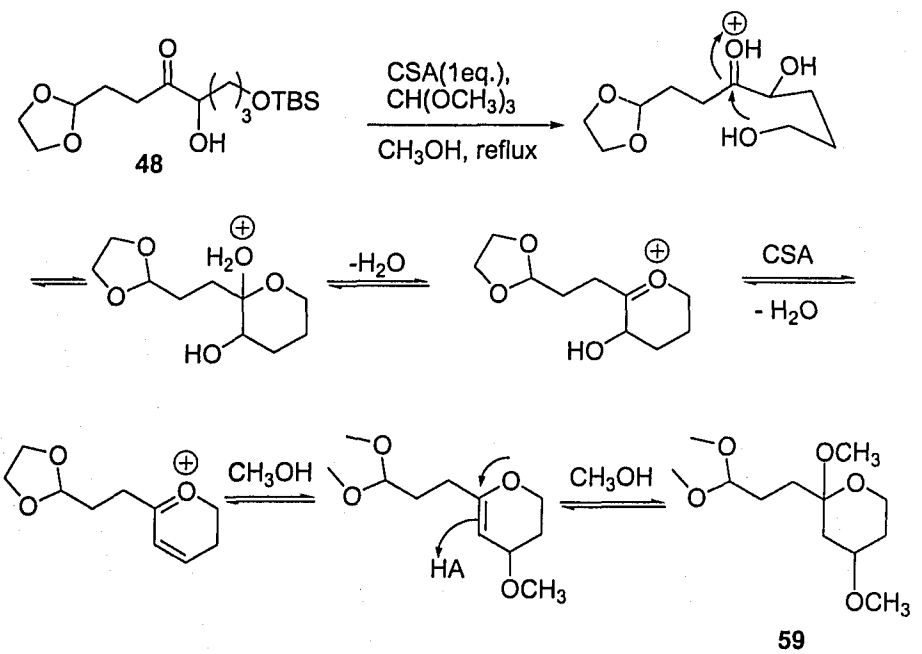
based on above coupling constants. Methylene carbon 4 (59.6 ppm) was attached to one oxygen atom to be in the low field and was the neighbor of methylene C10 based on strong H4 - H10 coupling in the COSY spectrum. The axial H9 coupled with C3 and the equatorial H9'. The equatorial H9' had one weak W long range coupling with the equatorial H10, not present for the axial H. Methylene C10 was proposed to be adjacent to methylene C4 and methine C3 according to the COSY cross peaks and proton coupling constants. So based on the above analysis, the connectivity O-C4-C10-C3-C9 was established.

H1, H11, and H12 were in an isolated coupling system from other protons. H1 coupled with H11, which was adjacent to H12. The second fragment of compound **59** was C1(acetal)-C11-C12.

HMBC data were very informative on the connectivity of the whole molecule. Starting from quaternary carbon C2, five cross peaks were found with H4, H8, H9, H11, and H12. Combining with the two fragments that are already built, C2 must be directly bonded to methoxy C8, metheylene C12 and C9. Based on the chemical shift of methylene C4, methylene C4 was adjacent to an oxygen atom, thus there had to be an oxygen atom between C4 and C2, which was a ketal carbon. Given this information, two fragments, attached by the quaternary C2 and a six-membered ring structure, was established. The position of the other three methoxy groups, except C8, could be determined by the HMBC data, too. Methoxy C6 and C7 were parts of the acetal group due to correlations between C6 and C7 to H1. The cross peak between methoxy C5 and H3 was used to position methoxy C5 to methine C3. Joining all fragments together, the structure of compound **59** was characterized as shown in Scheme 15.

Table 2 Correlations in 2D NMR spectra of monocyclic product **59.**

H & C Number	COSY correlation	HMBC correlation
1	H11, H11'	H11, H12
2		H4, H8, H9, H11, H12
3	H9, H9', H10, H10'	H4, H9, H10
4	H4, H4', H10, H10'	H10
5		H3
6		H1
7		H1
8		H9
9	H9 to H9', H3, H10; H9'to H9, H3	H12
10	H10 to H10', H4, H4',H3; H10' to H10, H4, H4', H3	H4, H9
11	H11, H11', H1	H1
12	H11	H1, H12

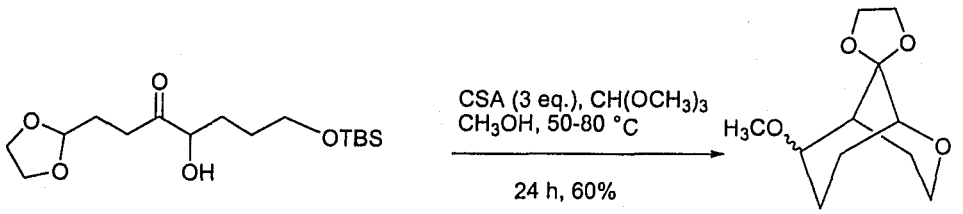


Scheme 16. The proposed mechanism of the formation of compound **59.**

The mechanism for the formation of compound **59** was proposed and shown in Scheme 16. Based on TLC observations, the polarity of the major compound in the reaction mixture dramatically increased after 2 to 3 hours. This phenomenon was the result of the deprotection of *tert*-butyldimethylsilyl ether to the primary hydroxyl

group under acidic conditions. Hemiketal formation and double dehydration gave the cyclic α,β-unsaturated oxocarbenium cation. Methanol as the nucleophile added into this oxocarbenium cation and again to the second newly formed oxocarbenium cation to afford the compound **59** in 60% yield. The elevated temperature could have promoted the dehydration process, so the next reaction was attempted at a lower temperature and higher acid concentration.

3.5.2 Bridged tricyclic compound 60



48 **60**

Scheme 17. The formation of bridged tricyclic compound **60.**

When the TBS substrate **48** was reacted with 3 equivalents of camphorsulfonic acid and 10 equivalents of trimethyl orthoformate in methanol for 5 hours at 50 °C, followed by overnight in methanol at reflux, the bridged tricyclic compound **60** was formed as the major product in 60% yield. The structure of compound **60** was determined by 1D NMR, 2D NMR, MS, and IR analysis. The high resolution mass spectrum provided the molecular formula, $C_{11}H_{18}O_4$. The IR spectrum did not indicate the presence of any of the readily indentifiable functional groups.

COSY and HMBC spectra were very useful for the determination of the connectivity (Table 3). Carbon 1 was a quaternary center without any hydrogen atom and its chemical shift (108.0 ppm) showed that it was connected to two electronegative oxygen atoms, i.e., a ketal carbon. Methylenes 4 and 5 were in an isolated environment according the COSY spectrum and had correlations with C1 in the HMBC spectrum, so carbon 1 and these two methylenes were presumed to form the

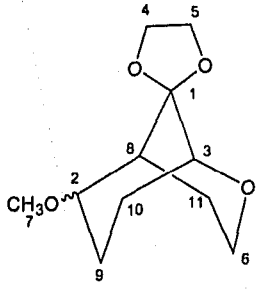
1,3-dioxolane unit. Following COSY and HMBC correlations, another fragment was found, consisting of C6-C11-C8-C2-C9-C10-C3. An oxygen atom joined C3 and C6 together since each had cross peaks with the other's associated hydrogen in the HMBC spectrum and their chemical shifts in ^{13}C and ^{1}H NMR all indicated that one electron-withdrawing atom was directly attached to them. If methines C8 and C3 were connected to each other, then there was no reasonable position for the 1,3-dioxolane to fit in, so their COSY correlation could be explained as a long-range W-coupling. The configuration of methoxy C7 could not be determined using the available spectral data. Because this was an undesired pathway, no further effort was put into determining the relative stereochemistry.

Table 3 Chemical shifts of compound **60** in C_6D_6.

Carbon Number	δ_C (ppm)	δ_H (ppm)	COSY correlation	HMBC correlation
1	108.0			H10, H11, H4, H5
2	79.0	3.82-3.77 (m, 1H)	H8, H9	H7, H8, H11, H9
3	70.4	3.62-3.60 (m, 1H)	H8, H10	H10, H6
4	64.4	3.39-3.29 (m, 2H)	H5	
5	63.9	3.51-3.46 (m, 2H)	H4	
6	61.2	3.96-3.88 (m, 2H)	H11	H11, H8, H3
7	55.6	3.10 (s, 3H)		H2
8	38.6	2.30-2.28 (m, 1H)	H11	H11, H9, H6
9	27.0	1.92-1.74 (m, 2H)	H10, H2	H10
10	26.0	1.92-1.74 (m, 2H)	H9, H3	H9
11	23.3	2.15-2.11 (m, 2H)	H6, H8	H6, H2

The choice of deuterated solvent had a significant influence on the NMR spectra of this tricyclic compound. The chemical shifts in deuterated benzene are listed in Table 3 and were mainly used to deduce the structure. Table 4 shows all NMR data in

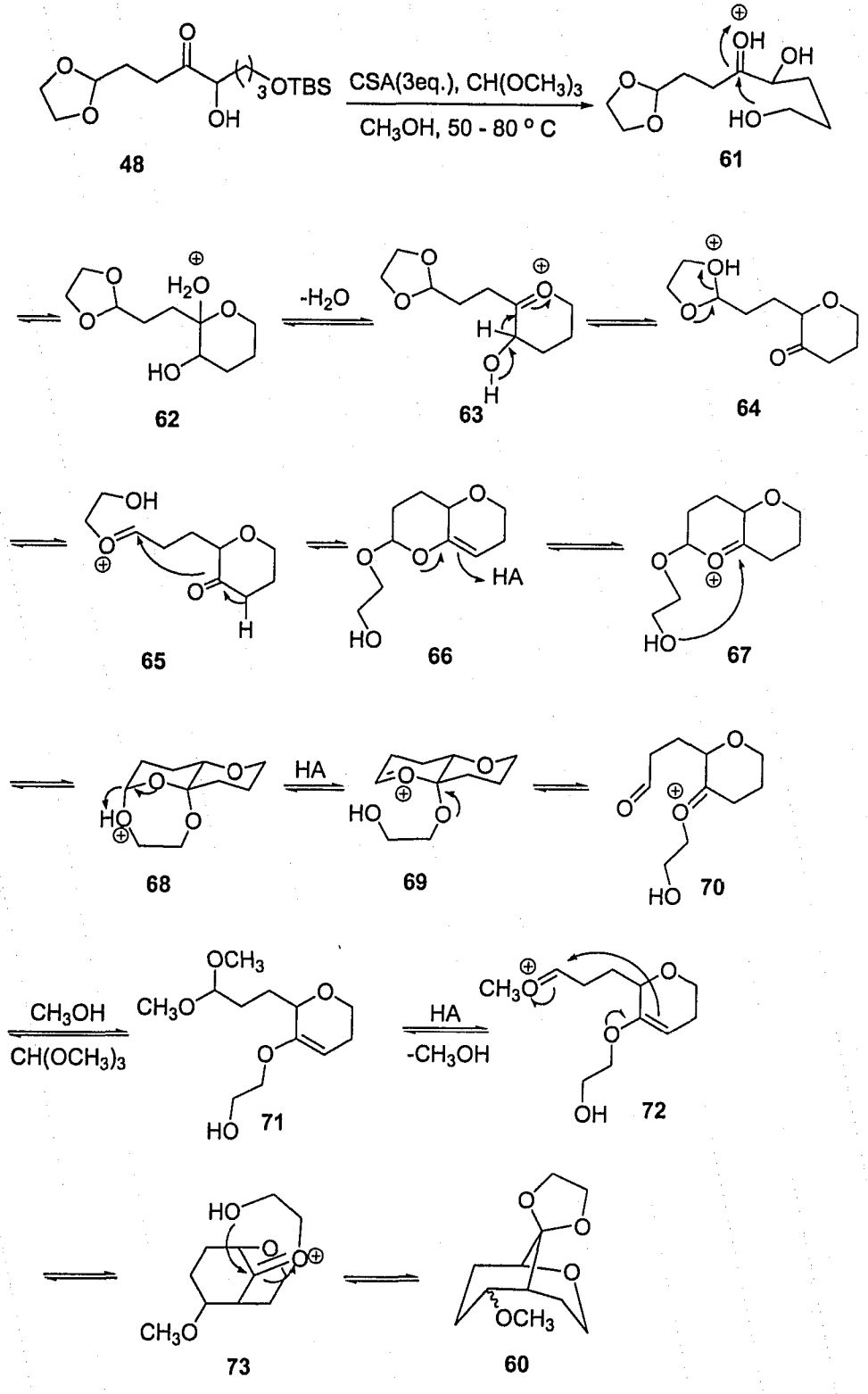
deuterated chloroform. These were consistent with the proposed structure of the tricyclic compound.



60

Table 4 Chemical shifts of compound **60** in $CDCl_3$.

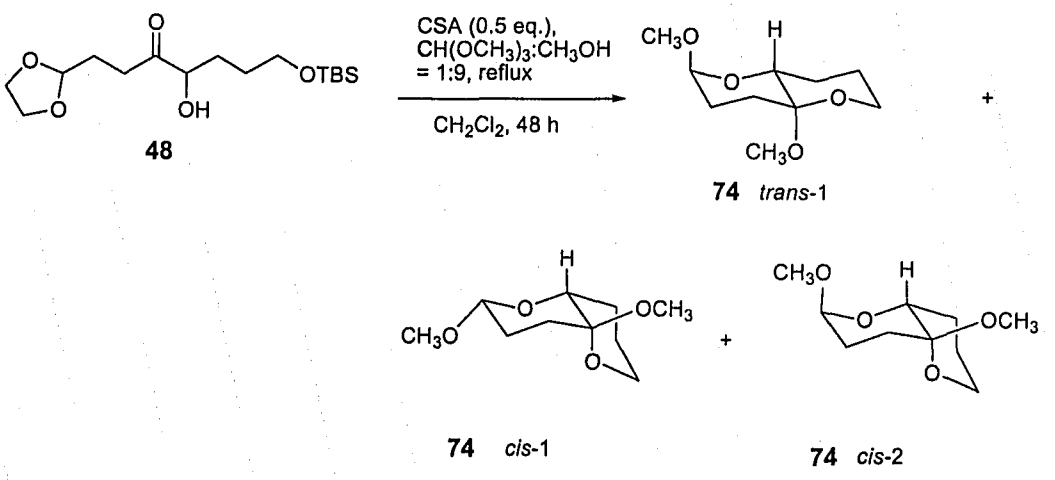
Carbon Number	δ_C (ppm)	δ_H (ppm)	COSY correlation
1	107.3		
2	78.6	3.81-3.73 (m, 1H)	H8, H9
3	70.4	3.53-3.51 (m, 1H)	H8, H10
4	64.7	4.03-3.91 (m, 2H)	H5
5	64.2	4.03-3.91 (m, 2H)	H4
6	61.5	4.03-3.91 (m, 1H), 3.81-3.73 (m, 1H)	H11
7	55.9	3.35 (s, 3H)	
8	37.7	2.24-2.22 (m, 1H)	H11
9	26.3	1.90-1.81 (m, 1H), 1.75-1.64 (m, 1H)	H2
10	26.2	2.16-1.90 (m, 2H)	H3
11	22.8	2.16-1.90 (m, 2H)	H6, H8



Scheme 18. The proposed mechanism for the formation of the tricyclic compound **60**.

The proposed mechanism for the formation of the tricyclic compound **60** is shown in Scheme 18. Under acidic conditions, the primary hydroxyl group was released from the silyl ether and attacked the protonated carbonyl group to form the hemiketal, which was protonated and lost a molecule of water to form oxocarbenium cation **63**. 1,2-hydride shift in compound **63** leads to the neutral intermediate **64**. Again, the protonated 1,3-dioxolane opened the ring to form a new oxocarbenium cation, which reacted with the enol to provide the neutral intermediate **66**. Then several equilibria between hydroxyl- oxocarbenium cation and cyclic ketals provided intermediate **72**, which underwent the intramolecular aldol reaction to afford intermediate **73**. Subsequent ketalization gave the compound **60**.

3.5.3 Bis(acetal) compound 74



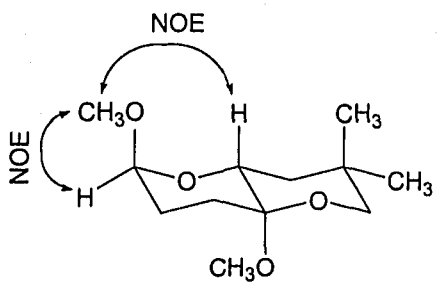
Scheme 19. The cyclization reaction and products.

Camphorsulfonic acid (0.5 equivalent) and a 1:9 ratio of trimethylorthoformate and anhydrous methanol were added to α-hydroxyketone **48** in dichloromethane (0.02 M). The reaction mixture was stirred at room temperature for 3 to 5 hours and then heated at refluxe for 2 days. The desired bis(acetal) compounds **74** were obtained in 60%

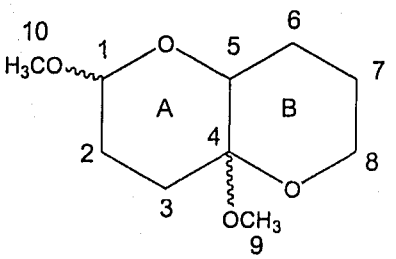
yield. There were three isomers *trans*-1, *cis*-1, and *cis*-2, which were formed in a ratio of 10:1:20. The structures of these three isomers were assigned by MS, NMR, IR spectra.

The relative configuration of these three isomers was determined by the one-dimensional NOE experiments and the coupling constants. The two methoxy groups in the bis(acetal) were easily differentiated by the corresponding correlation between methoxy carbon atoms and hydrogen atoms in HMBC spectra. For example, in compound **74** *trans*-1, there was a cross peak between the acetal methoxy carbon 10 (54.4 ppm) and the acetal hydrogen 1 (4.57 ppm).

The coupling constants of the angular methine hydrogen and the acetal hydrogen are listed on Table 5 for comparison. In compound **74** *trans*-1, the acetal hydrogen H1 had two small coupling constants, so it was in the equatorial position on the ring A. The angular methine H5 was positioned axially to ring B indicated by one large axial-axial coupling and one small axial-equatorial coupling to the methylene H6. On the NOE spectrum, H1 and H5 showed 2.2% and 1.4% enhancement when methoxy 10 was irradiated; but no significant NOE effect when methoxy 9 was irradiated. The similar analysis supported the determination of the configuration of the other two isomers, *cis*-1 and *cis*-2.



74 *trans*-1



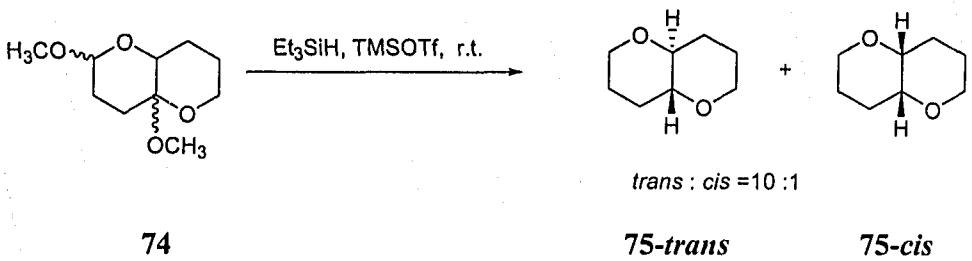
74

Scheme 20. The NOE effect in **74** *trans*-1 and the numbering system in **74.**

Table 5 Chemical shifts and coupling constants of three bis(acetal) **74** isomers

Isomers / Hydrogen	trans-1	cis-1	cis-2
Acetal hydrogen H1	4.57 (dd, J = 3.8, 3.7 Hz, 1H)	4.17 (dd, J = 9.7, 2.0 Hz, 1H)	4.60 (dd, J = 3.4, 1.0 Hz, 1H)
Angular methine H5	3.83 (dd, J = 12.1, 4.0 Hz, 1H)	3.34 (dd, J = 2.9, 2.9 Hz, 1H)	3.81 (dd, J = 2.5, 2.5 Hz, 1H)

3.5.4 *Trans*-fused bis(pyran) 75

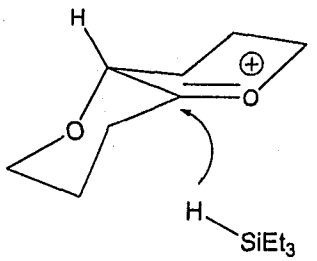


74 **75-*trans*** **75-*cis***

Scheme 21. The reduction reaction and products.

The bis(acetal) compound **74** was reduced by triethylsilane and TMSOTf at room temperature. A 10:1 mixture of *trans* to *cis* bis(pyran) compounds **75** was obtained in 75% yield, regardless of whether a single isomer of a mixture of starting material was used (Scheme 21). Based on the mechanism of this type of reduction, the pyran oxocarbenium cation intermediate was presumed to form by loss of a methoxy group with the aid of the Lewis acid, TMSOTf. Then the stereoselective reduction was realized by the preferred axial addition of hydride to the cation. Thus, the configuration of methoxy group should have no effect on stereochemical outcome of the reduction process (Scheme 22).[16] Before the reduction, the starting material **74**

was dried by adding anhydrous benzene followed by azeotrope distillation. This procedure increased the desired reduction yield by more than 10%.



Scheme 22. The pyran oxocarbenium cation intermediate.

The reduced bicyclic ether compound **75** was volatile and not easy to visualize by general TLC stains. After column chromatography, the desired ether compounds **75** were detected by GC with FID detector.

Due to the symmetry of the compound, equivalent protons and carbons in each ring led to very simple NMR spectra. The *cis*-fused bis(pyran)[17] was a known compound and different from the major reduced product, i.e., the *trans*-fused bis(pyran) **75-*trans***. On the other side, when one of bridgehead carbons was ^{13}C, bis(pyran) **75-*trans*** was not symmetrical and the ^{13}C split the directly bonded proton signal into two parts. Thus the coupling constants between the two angular hydrogens could be extracted from the ^{13}C satellite peaks. This coupling constant was 8.8 Hz and indicated the *trans*-fused configuration. This was the typical diaxial hydrogen coupling constant value due to the electron withdrawing effect of two adjacent oxygen atoms.

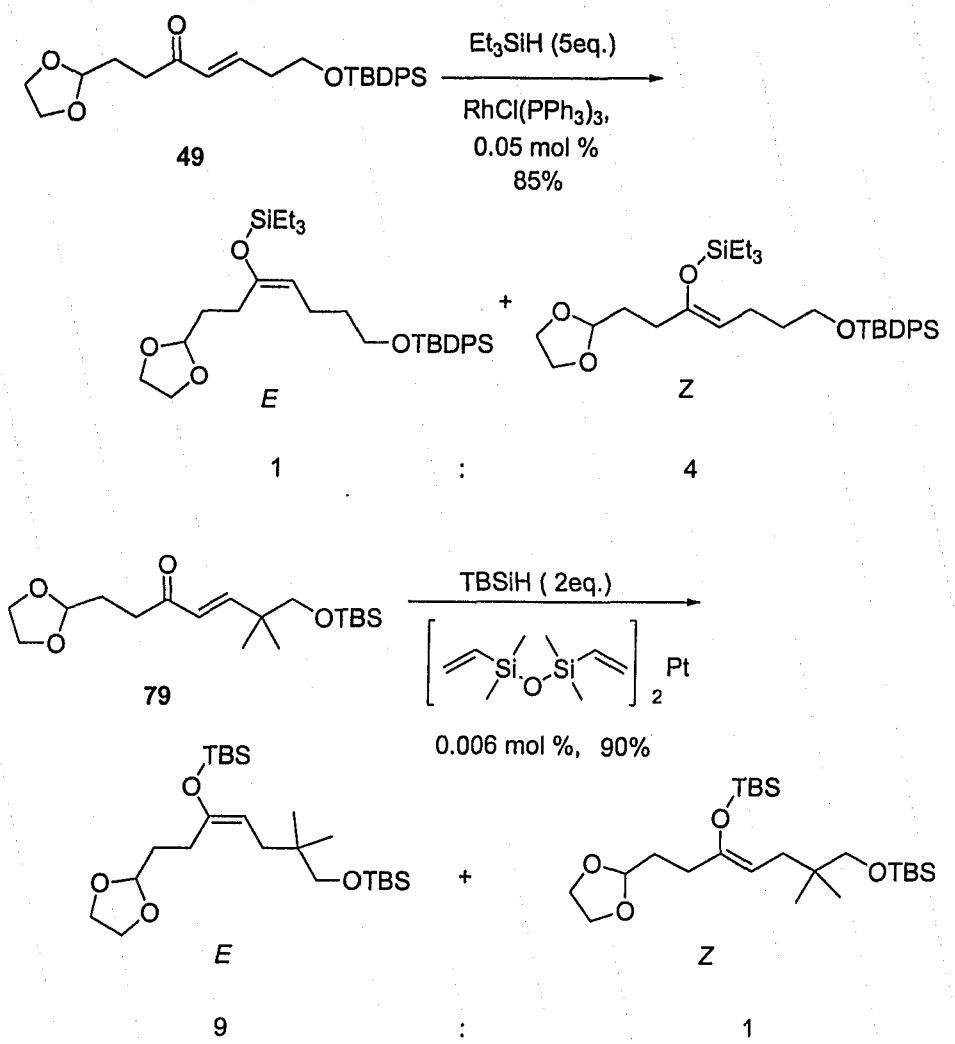
Bis(pyran) **75-*trans*** is achiral due to a S_2 symmetry center on the middle point of ring-fusing C-C bond. Even though the chiral substrate **48** was used as the starting material, no chirality could be preserved in bis(pyran) **75-*trans***.

To unambiguously determine the configuration of the bis(pyran) compound, a geminal dimethyl quaternary carbon was set in one of the ether rings to disrupt symmetry without adding a new chiral center to the system.

3.6 Catalysts for 1,4-hydrosilylation reaction

Among several methods of conjugate reduction of α,β-unsaturated ketones, 1,4-hydrosilylation using Wilkinson's catalyst and trialkylsilane was chosen due to the good chemselectivity and mild reaction conditions.[6] When triethylsilane was used as the hydride source, the ratio of two isomers (*E/Z*) was 1 to 4, estimated by the proton NMR (Scheme 23). As the bulkiness of trialkylsilane was increased from triethyl to *tert*-butyldimethyl or triisopropyl, the rate of reduction decreased significantly, and higher reaction temperatures led to serious side reactions.

A careful review of the literature revealed that Karstedt's catalyst can effectively catalyze conjugate reduction with bulky silanes.[18] When *tert*-butyldimethylsilane was used, the reduction reaction occured at room temperature in one hour, but the resulting silyl enol ether was mainly the *E* isomer (90%).

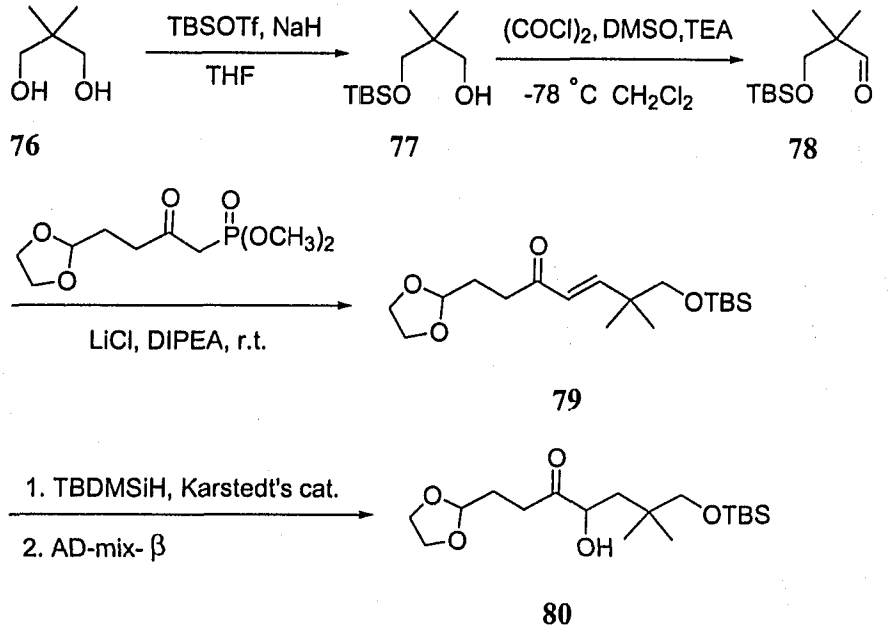


Scheme 23. The conjugate reduction of enones.

3.7 Synthesis of the bis(pyran) ether with a geminal dimethyl group

3.7.1 Synthesis of cyclic acetal substrate with a geminal dimethyl group

3-*tert*-Butyldimethylsiloxy-2,2-dimethyl-propanal **78** was prepared from neopentyl glycol **76** via the mono-protection of one of the hydroxyl groups and oxidation of the other hydroxyl group to the aldehyde using a Swern oxidation.[19] This gave the desired aldehyde **78** in 82% yield (Scheme 24).

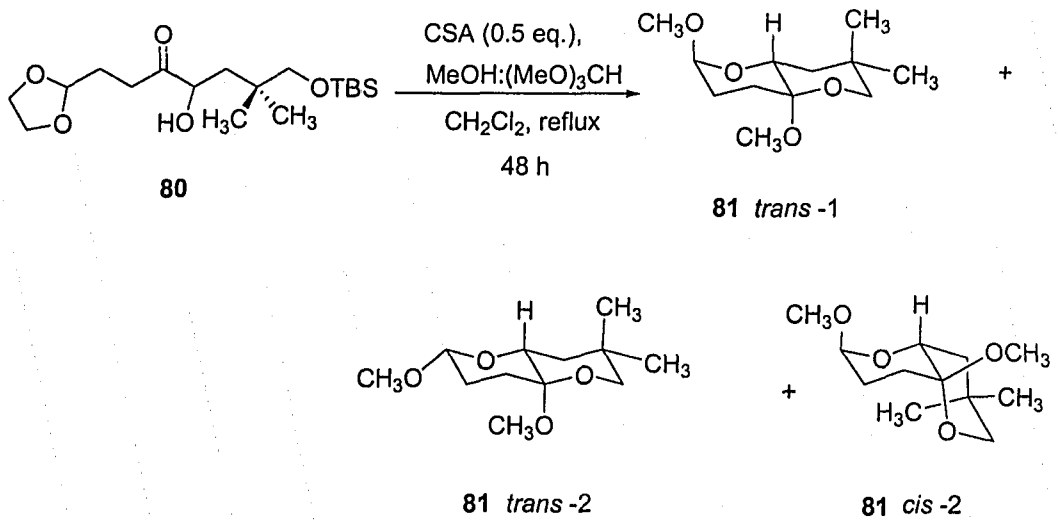


Scheme 24. The synthesis of α-hydroxyketone **80.**

Dimethyl 5-(1,3-dioxolane)-2-oxopentylphosphonate **40** was obtained by the same method as shown in section **3.4.1** from 2-bromoethyl 1,3-dioxolane. Horner-Wadsworth-Emmons olefination between phosphonate **40** and aldehyde **78** provided the desired *E*-enone **79** in 72% yield. Using Karstedt's catalyst (platinum (0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane),[19] the 1,4-hydrosilylation of enone **79** with *tert*-butyldimethylsilane provided the *tert*-butyldimethyl silyl enol ether chemoselectively. The resulting C=C bond was mainly in the *E* geometry (90%). The crude silyl enol ether was subjected to freshly-prepared Sharpless AD-mix-*β*, which consisted of 4 mol% (DHQD)PHAL, 4 mol% OsO_4, 3 equivalents of potassium ferricyanide and potassium carbonate, and 1 equivalent of methanesulfonyl amide. The yield was 55% over two steps (Scheme 24). The enantiomeric excess of α-hydroxy ketone **79** was determined by conversion to the Mosher's ester. Based on the integration of ^{1}H NMR and ^{19}F NMR, the ee value was approximately 10%. Chiral HPLC was used in an attempt to quantitate the enatiomeric ratio, but it seemed that the UV absorption of the isolated carbonyl group was not strong and stable enough to be used to determine the concentration of the enantiomer.

3.7.2 Synthesis of bis(acetal) 81

α-Hydroxy ketone **80** was subjected to the known cyclization condition (0.5 equivalent of CSA, excess of trimethylothoformate in the mixed solvent of methanol and dichloromethane) (Scheme 25). Three isomers were obtained in the ratio of *trans*-1 : *trans*-2 : *cis*-2 = 20 : 1 : 10 in total of 64% yield. Due to the geminal dimethyl being attached to a quaternary carbon, the NMR spectra of these three isomers were more informative relative to compound **74**.



Scheme 25. The cyclization of compound **80** and products **81.**

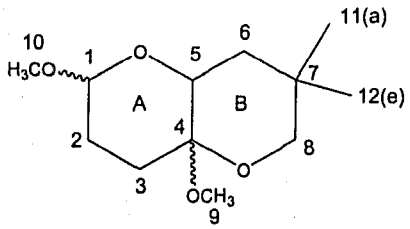
The chemical shifts of two major isomers of compound **81** are listed in Table 6. Their structure and relative configuration were determined by MS, IR, and NMR analysis. As the bis(acetal) compound **81** was in the fused chair configuration, several long-range W couplings were found, such as the coupling between equatorial hydrogen atoms at H6 and H8 in both major isomers. Surprisingly, cross peaks were found between axial H8 and H11, axial H6 and H11 on the COSY spectrum.

In the TROESY spectra, there was a cross peak between H5 and methoxy H10 in both major isomers. The correlation between H5 and methoxy H9 was only present in the *cis* isomer. NOE studies also confirmed the relative stereochemistry shown in Scheme 25.

For the minor isomer, *trans*-2, only ^{1}H NMR data was obtained because this compound could not be separated from the reaction mixture in a pure form.

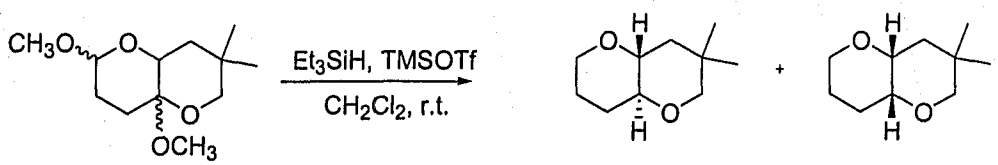
Table 6 Chemical shifts of two major isomers of compound **81.**

Carbon number	δ (*trans*-1)	δ (*cis*-2)
1 (CH)	98.2	97.5
4 (C)	95.2	94.1
8 (CH_2)	70.4	70.8
5 (CH)	67.7	66.8
10 (CH_3)	54.3	54.3
9 (CH_3)	46.8	46.5
6 (CH_2)	37.0	37.2
7 (C)	34.2	28.2
2 (CH_2)	28.2	27.6
11 (CH_3)	27.5	28.5
12 (CH_3)	25.2	27.1
3 (CH_2)	24.7	26.3



Hydrogen number	δ (*trans*-1)	δ (*cis*-2)
H1	4.60 (d, J = 3.8 Hz, 1H)	4.54 (d, J = 1.8 Hz, 1H)
H5	4.10 (ddd, J = 12.6, 4.6, 0.6 Hz, 1H)	3.87 (dd, J = 3.9, 2.3 Hz 1H)
H8(a)	3.43 (dd, J = 10.8, 0.7 Hz, 1H)	3.50 (dd, J = 10.8, 0.6 Hz, 1H)
H8 (e)	3.00 (dd, J =10.8, 2.1 Hz, 1H)	3.21 (dd, J = 10.8, 2.6 Hz, 1H)
H10	3.20 (s, 3H)	3.14 (s, 3H)
H19	3.02 (s, 3H)	3.05 (s, 3H)
H6(a)	2.06 (ddd, J = 12.5, 12.0, 0.6 Hz, 1H)	1.98 (dd, J = 14.0, 4.0 Hz, 1H)
H3(a)	1.95 (ddd, J = 13.7, 13.7, 4.4 Hz, 1H)	1.95-1.78 (m, 3H)
H3(e)	1.86 (ddd, J = 13.6, 4.6, 2.6 Hz, 1H)	
H2(a)	1.76 (dddd, J = 13.6, 13.4, 4.6, 3.8 Hz, 1H)	
H2(e)	1.59 (dddd, J = 13.3, 3.8, 2.6, 1.1 Hz, 1H)	1.66-1.76 (m, 1H)
H6(e)	1.38 (ddd, J = 12.0, 4.6, 2.1 Hz, 1H)	1.51 (ddd, J = 14.0, 2.4, 2.4 Hz, 1H)
H11(a)	1.03 (s, 3H)	1.38 (s, 3H)
H12(e)	0.67 (s, 3H)	0.69 (s, 3H)

3.7.3 Synthesis of bis(pyran) 82



81 **82-*trans*** **82-*cis***

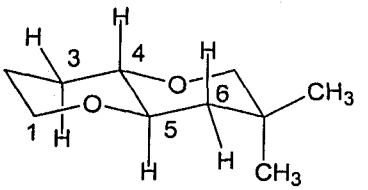
Scheme 26. The reduction of the bis(acetal) compound **81.**

A mixture of isomers of the bis(acetal) compound **81** was reduced by triethylsilane and TMSOTf at room temperature to obtain the desired product **82** in 64% yield. The ratio of the *trans* to the *cis* product was 15:1. The *trans* product was separated from the reaction mixture by silica gel chromatography, using pentane and diethyl ether (20:1 to 10:1) as the eluent. Compound **82** was identified by GC among all the fractions because compound **82** cannot be visualized on TLC and is volatile. By GC, the retention time of the *trans* compound was 7.64 min (Start temperature 100 °C, heating rate 5 °C/min). Only a small amount of **82-*cis*** was found in the mixture with the major **82-*trans***.

The relative stereochemistry of the *trans*-fused bis(pyran) compound **82** was indicated by the coupling constants shown in Table 7. The angular H5 peak overlapped with H1, so the coupling constants between the angular hydrogen H4 and H5 was indirectly deduced from the adjacent hydrogen atoms. The axial H6 had two large coupling constants (12.0 Hz), one of them from the geminal coupling (^2J) and the other one from the axial – axial coupling between H6 and H5, therefore H5 was assumed to be in the axial position. Among the three coupling constants of H4, the smallest one (4.2 Hz) came from H4 and the equatorial H3, one of the two large coupling constants must result from the axial – axial coupling between H4 and H5. Therefore, these two rings must be in the *trans*-fused configuration.

Unfortunately, the enantiomeric excess of the bis(pyran) compound **82-*trans*** was about 10%, as determined by using the chiral shift reagent, $Eu(hfc)_3$. Re-examination the ee of the starting material α-hydroxy ketone **79** showed that the ee of α-hydroxy ketone was about 10%. Further investigation is needed to determine whether the chirality of the α-hydroxy ketone can transfered to the final bis(pyran) compound.

Table 7 The coupling constants used for the determination of the configuration of the bis(pyran) **82-*trans***

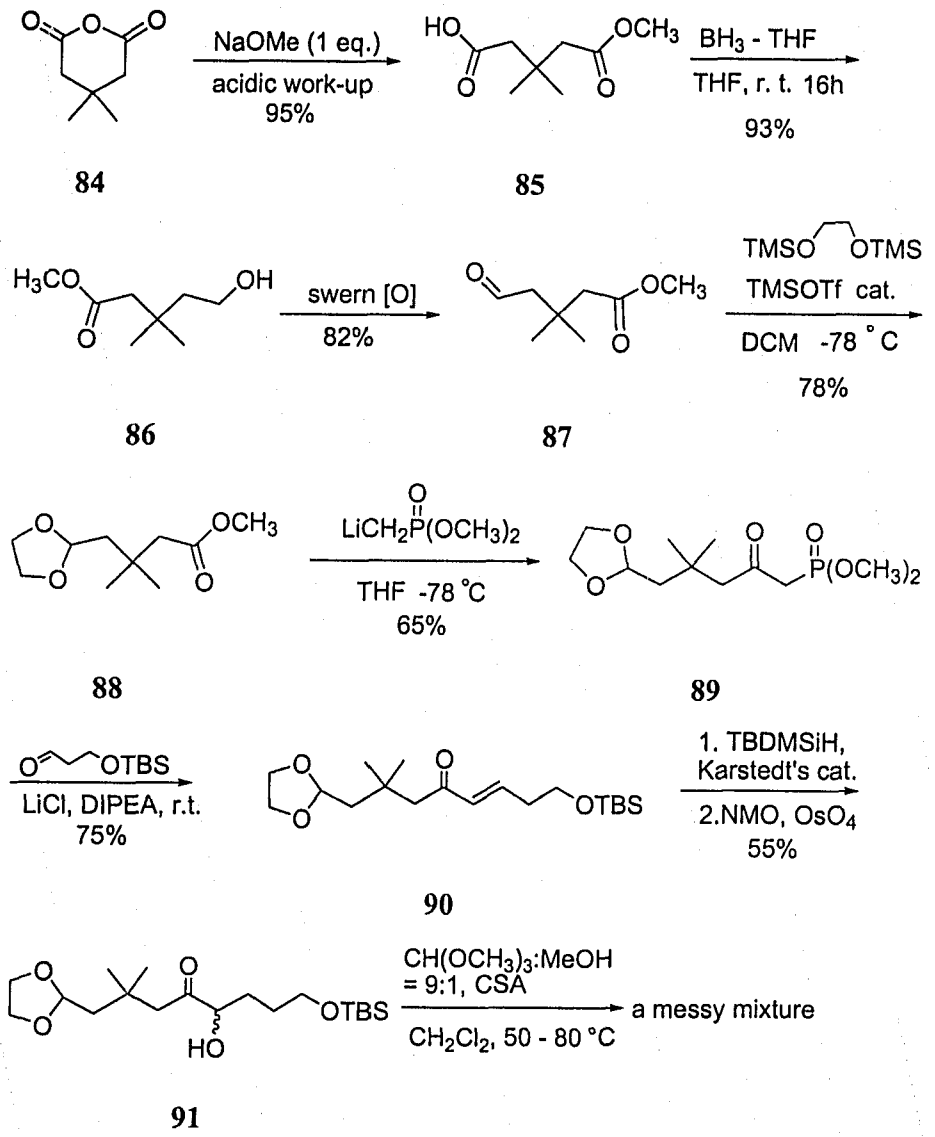


	[a]H6	[c]H6	[a]H4
J (Hz)	dd, 12.0, 12.0	ddd, 12.4, 4.5, 2.4	ddd, 10.8, 8.8, 4.2

3.8 Synthesis of subtrates for 6,7-bicyclic ether

Commencing with 3,3-dimethylglutaric anhydride **84,** methanolysis with sodium methoxide provided 3,3-dimethyl-5-methoxycarbonyl butanoic acid **85** in excellent yield (95%) and very high purity.[20] Crude acid **85** was reduced by BH_3-THF to the alcohol **86,** which was oxidized to the desired aldehyde **87**, using the Swern oxidation in high yield (Scheme 27).[21] After the aldehyde group was protected as the 1,3-dioxolane,[22] the methyl ester **88** was treated with the lithium anion of dimethyl methylphosphonate to afford the desired phosphonate **89** in 65% yield.[23] The Horner-Wadsworth-Emmons reaction between a stabilized phosphonate **89** and 3-*tert*-butyldimethylsilyloxy propanal provided the *E*-enone **90** in 75% yield. 1,4-Hydrosilylation with Karstedt's catalyst followed by dihydroxylation gave the α-hydroxy ketone **91** in 55% yield over two steps.

With the α-hydroxy ketone **91** in hand, the acidic conditions used in the 6,6 fused ether system were tested first. By the GC, more than 15 peaks were detected, but no major product was present. When the reaction conditions were changed to methanol at reflux and 1 equivalent of acid, the starting material **91** was consumed, but a very polar mixture was obtained.

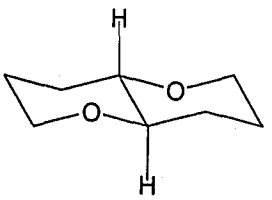


Scheme 27. The synthesis of substrates for 6,7-bicyclic ethers.

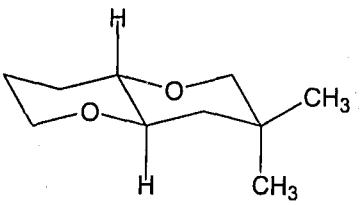
3.9 Conclusions

A cascade method for construction of cyclic ethers has been developed. The substrate was easily prepared using Horner-Wadsworth-Emmons reaction. Then 1,4-hydrosilylation and the Sharpless AD reaction afforded the key α-hydroxy ketone.

Bulky relatively stable silyl enol ethers were accessible with Karstedt's catalyst and silanes. Under mild acid conditions, the α-hydroxy ketone was deprotected and subsequently underwent cyclization to a fused bicyclic bis(acetal). The bis(pyran) **75-*trans*** was obtained efficiently by the cationic reduction, using triethylsilane and Lewis acid (TMSOTf).



75-*trans*



82-*trans*

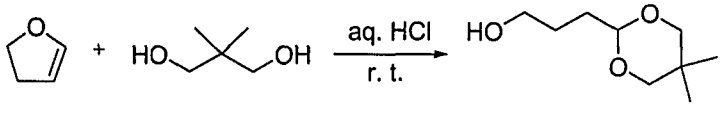
To confirm the configuration and the enantiomeric excess of bis(pyran) compounds, the bis(pyran) compound **82-*trans*** was synthesized. The quaternary carbon with geminal dimethyl group broke the symmetry of bis(pyran) **75** and simplified NMR spectra. The *trans*-fused ring was assigned for the coupling constants and a TROSY spectrum, but the enantiomeric excess of compound **82** still needs further investigation. Also, under different acetal cyclization conditions, two new and unexpected rearrangement products, **59** and **60**, were isolated and characterized.

In the future plan, further investigation is needed to effect better steroinduction during the preparation of α-hydroxy ketone substrates and test whether the chirality of α-hydroxy ketone substrates can be transferred to the final bispyran compound. The method could be extended to prepare different *trans*-fused cyclic ethers.

3.10 Experimental section

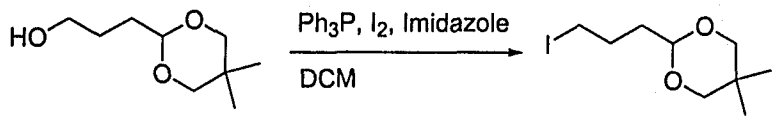
General. Reactions were carried out in oven dried glassware under a positive argon atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven dried glass syringes with stainless steel needles or stainless steel cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, THF, benzene, and diethyl ether from sodium/benzophenone ketyl. Toluene

from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash chromatography was packed with 230-400 mesh silica gel (Merck). Gas chromatograms were obtained on a Hewlett-Packard 5890 series II capillary gas chromatograph with a 30 m HP-5 column and a flame ionization detector. ^{1}H NMR spectra were recorded on Varian instruments at 300 MHz, 400 MHz, or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz), chemical shifts are reported (ppm) relative to chloroform-*d* or benzene-*d*. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. HPLC analysis were performed on a Gilson HPLC with an UV detector. Chiral columns include Chiralpak AD-H, AS-H, OJ-H, and OD-H.



2-(3-Hydroxypropyl)-5,5-dimethyl-1,3-dioxane (18)[24]

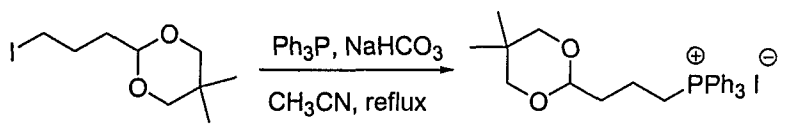
2,3-Dihydrofuran (0.93 g, 13.2 mmol) was added all at once to solution of concentrated HCl (0.3 mL), water (3 mL), and 2,2-dimethyl-1,3-propanediol (1.52 gm, 14.5 mmol) with a cold water bath. The solution was stirred for 10h. Then a drop of phenolphthalein solution was added to the reaction mixture, which was titrated with 4 N NaOH to the pink end point. The organic layer was separated, and the aqueous portion was extracted with $CHCl_3$ (4 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed by the rotary evaporation. This crude compound was used in the next reaction without further purification. A small amount of sample was purified by flash column chromatography, using EtOAc and hexane (1:4) as the eluent. The spectral data were found to be identical with the literature data. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (t, J = 4.4 Hz, 1H), 3.65 (t, J = 5.8 Hz, 2H), 3.63 (d, J = 10.4 Hz, 2H), 3.63 (d, J = 10.4 Hz, 2H), 2.64 (br s, 1H), 1.72-1.76 (m, 4H), 1.19 (s, 3H), 0.73 (s, 3H).



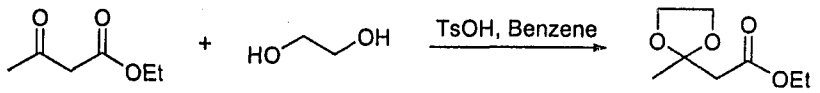
2-(3-Iodopropyl)-5,5-dimethyl-1,3-dioxane (19)

I_2 (15.3 g, 60 mmol) was added to a solution of 2-(3-hydroxypropyl)-5,5-dimethyl-1,3-dioxane (8.7 g, 50 mmol), Ph_3P (19.7 g, 75 mmol), and imidazole (5.9 g, 75 mmol) in dichloromethane (120 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. Then a saturated aqueous solution of $NHCO_3$ was added, followed by adding I_2 until a light yellow color started appearing. The reaction mixture was worked up with hexane and water (50 mL each). The organic layer was washed with a 10% aqueous $Na_2S_2O_3$ and dried over Na_2SO_4. After the solvent was removed under vacuum, the residue was triturated with hexane and the white solid was removed by filtration. Finally, the residue was purified by column chromatography, using hexane and ethyl acetate (20:1). Compound **19** (9.5 g, 67%) was obtained as sticky oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (t, J = 4.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 2H), 3.41 (d, J = 10.4 Hz, 2H), 3.22 (t, J = 5.8 Hz, 2H), 1.72 – 2.24 (m, 4H), 1.19 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.1, 77.3, 35.6, 30.1, 28.0, 22.9, 21.8, 6.6.

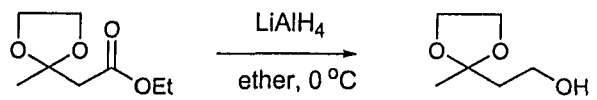


A mixture of the iodide (6.0 g, 21 mmol), Ph_3P (11.0 g, 42 mmol), and $NaHCO_3$ (3.5 g, 42 mmol) in CH_3CN (200 mL) was heated at reflux for 16 h. The solvent was evaporated, and the residue was redissolved in DCM. Inorganic materials were removed by filtration. DCM was removed. The thick residue was dissolved in chloroform and precipitated by adding ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.85 (m, 15 H), 4.72 (t, J = 4.4 Hz, 1H), 3.87 -3.85 (m, 2H), 3.67 (d, J = 10.4 Hz, 2H), 3.41 (d, J = 10.4 Hz, 2H), 1.75 – 2.00 (m, 4H), 1.15 (s, 3H), 0.78 (s, 3H).



(2-Methyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester (24)[25]

A mixture of ethylene glycol (4.2 mL, 75 mmol), ethyl acetoacetate (6.3 mL, 50 mmol), *p*-toluenesulfonic acid (0.5 g), and benzene (50 mL) was heated at reflux with a Dean-Stark trap until no more water azeotroped over. The mixture was washed with saturated aqueous sodium bicarbonate and brine, and dried over Na_2SO_4. After the solvent was removed under vacuum, the crude product was subjected to silica gel chromatography, using hexane and ethyl acetate (6:1) as the eluent. The title product was obtained (7.8 g, 90%). The spectral data are consistent with the literature data. R_f 0.42 (hexane/EtOAc = 4/1), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (q, J = 7.1 Hz, 2H), 3.98 (s, 4H), 2.67 (s, 2H), 1.51 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 107.6, 64.8, 60.5, 44.3, 24.5, 14.2.

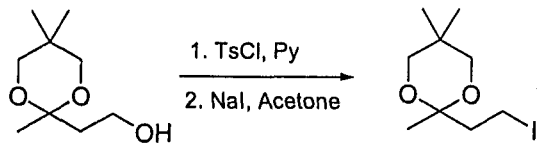


2-(2-Methyl-[1,3]dioxolan-2-yl)-ethanol (25)[26]

The ester **24** (9.0 g, 50 mmol) in anhydrous ether (10 mL) was added dropwise to a mixture of lithium aluminum hydride (1.3 g, 35 mmol) in 25 mL of ether. The resulting mixture was stirred at room temperature overnight. After cooling the reaction flask in the ice-water bath, water (10 mL) was added cautiously to decompose the excess $LiAlH_4$. The inorganic solids were filtered, and the organic layer was separated. The aqueous layer was extracted with ether (3 x 20 mL), and the combined ether layer was washed with water (30 mL), dried over sodium sulfate, and evaporated under vacuum. This product was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 4H), 3.68 (t, J = 4.5 Hz, 2H), 2.61 (br s, 1H), 1.95 (t, J = 5.7 Hz, 2H), 1.27 (s, 3H).

2-(2-Hydroxyethyl)-2,5,5-trimethyl-1,3-dioxane was prepared using a similar method to 2-(2-hydroxyethyl)-2-methyl-1,3-dioxolane. ^{1}H NMR (300 MHz, $CDCl_3$) δ

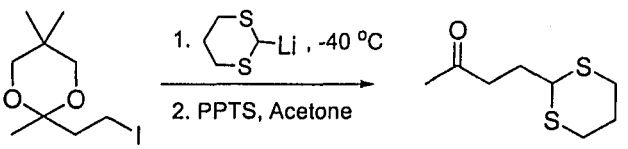
3.99 (s, 4H), 3.77 (t, J = 5.7 Hz, 2H), 2.61 (br, s, 1H), 1.95 (t, J = 5.7 Hz, 2H) 1.37(s, 3H).



2-(2-Iodoethyl)-2,5,5-trimethyl-1,3-dioxane (28)

A solution of the alcohol (2.0 g, 11 mmol), pyridine (1.8 mL, 23 mmol) and p-TsCl (3.3 g, 17 mmol) in dichloromethane (50 mL) was stirred at room temperature for 24 h. The resulting mixture was washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue was purified by flash column chromatography with hexane and ethyl acetate (20:1). This tosylate was obtained (3.0 g, 80%) and used immediately because of its instability. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.24 (t, J = 7.2 Hz, 2H), 3.53 (d, J = 11.4 Hz, 2H), 3.33 (d, J = 11.4 Hz, 2H), 2.45 (s, 2H), 2.07 (t, J = 7.2 Hz, 2H), 1.34 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H).

A mixture of the above tosylate (3.0 g, 10 mmol), NaI (7.7g, 50 mmol), and acetone (100 mL) was stirred for 24 h. After filtration, the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 20 mL). The extract was washed with aqueous $Na_2S_2O_3$ solution, and dried over Na_2SO_4. The residue was used in the next reaction without further purification. The crude product was obtained (1.8 g, 62%).

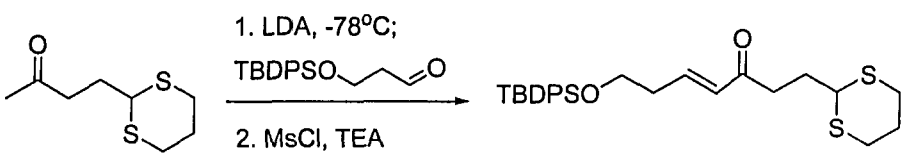


4-[1,3]Dithian-2-yl-butan-2-one (29)

To a stirred solution of 1,3-dithiane (0.72 g, 6.0 mmol) in THF (15 mL) at -40 °C was added n-BuLi (2.8 mL, 2.2 M in hexane) dropwise under Ar. The mixture was stirred for 1 h at -40 °C and then for 3 h at 0 °C. The mixture was again cooled to -40 °C and 2-(2-iodoethyl)-2,5,5-trimethyl-1,3-dioxane (1.6 g, 5.6 mmol) in THF (2 mL) was added dropwise. After stirring for 1 h at -40 °C and for 2 h at 0 °C, the reaction

mixture was quenched by the adding of water (2 mL). THF was removed under reduced pressure and the residue was extracted with ether (3 x 20 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash column chromatography with hexane and ethyl acetate (15:1). 1.2 g (77%) of the dithiane compound was obtained. R_f 0.43 (hexane/EtOAc = 5/1), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (m, 1H), 3.53 (d, J = 11.4 Hz, 2H), 3.45 (d, J = 11.4 Hz, 2H), 2.32-2.08 (m, 1H), 1.93-1.79 (m, 5H), 1.36 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H).

A solution of this ketal (1.2 g, 4.3 mmol) and PPTS (0.4 g) in acetone and water (10:1, 55 mL) was heated at reflux overnight. Then acetone was removed under reduced pressure, and the residue was extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$. Purification with flash chromatography (3 x 20 cm, hexane/EtOAc = 10/1) provided 0.71 g (86%) of the desired product. R_f 0.65 (hexane/EtOAc = 2/1), ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, J = 7.0 Hz 1H), 2.83 (m, 4H), 2.68 (t, J = 7.2 Hz, 2H), 2.08 (q, J = 7.1 Hz, 2H), 2.14-2.08 (m, 1H), 1.92-1.83 (m, 1H). HRMS (EI) [M^+] for $C_8H_{14}O_3S_2$ calcd 190.04861, found: m/z 190.04809.

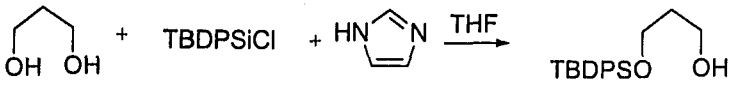


7-(*tert*-Butyldiphenylsilanyloxy)-1-[1,3]dithian-2-yl-hept-4-en-3-one (30)

To a solution of diisopropylamine (354 µL, 2.52 mmol) in THF (5 mL) at -78 °C was added dropwise *n*-BuLi (1.16 mL, 2.18 M in hexane, 2.52 mmol). Then the mixture was warmed to 0 °C for 30 min. At -78 °C, a solution of this ketone (456 mg, 2.4mmol) in THF (3 mL) was added to the LDA solution over 20 min. After 1 h, a solution of the aldehyde (626 mg, 2.1 mmol) in THF (3 mL) was added over 5 min. After stirring for 10 min, monitoring the reaction by TLC until all the starting material disappeared, saturated NH_4Cl (3 mL) was used to quench the reaction. The mixture was stirred vigorously for 10 min and poured into water (20 mL) and diethyl ether (20

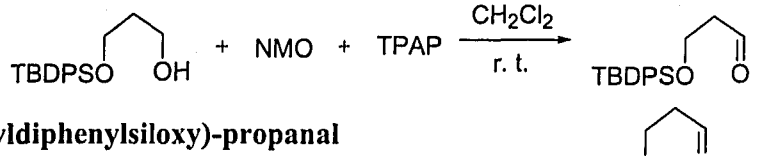
mL). The two layers were separated, and the aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (hexane/ EtOAc = 5/1) to afford the β-hydroxy ketone (760 mg, 63%). R_f 0.52 (hexane/EtOAc = 2/1), IR (Microscope) 3494, 3070, 2930, 2895, 2856, 1710, 1588, 1471, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 4H), 7.44 – 7.38 (m, 6H), 4.31 – 4.35 (m, 1H), 4.04 (t, J = 7.0 Hz, 1H), 3.87 – 3.81 (m, 2H), 3.42 (br s, 1H), 2.85 – 2.83 (m, 4H), 2.68 (t, J = 7.2 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.09 (q, J = 7.2 Hz, 2H), 2.14 – 2.06 (m, 1H), 1.91 – 1.83 (m, 1H), 1.79 – 1.71 (m, 1H), 1.70 – 1.63 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 135.6, 133.3, 129.8, 127.8, 66.8, 62.1, 49.7, 46.4, 40.1, 38.4, 29.9 28.8, 26.9, 25.8, 19.1. HRMS (EI) [M^+] for $C_{27}H_{38}O_3S_2Si$ calcd 502.20316, found: m/z 502.20407.

To a mixture of this β-hydroxy ketone (400 mg, 0.80 mmol) and triethylamine (665 µL, 4.77 mmol) in dichloromethane (5 mL) at 0 °C was added methansulfonyl chloride (123 µL, 1.59 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature for 3 h and stirred until TLC analysis indicated the consumption of the starting material. The reaction mixture was diluted with dichloromethane (15 mL) and washed with water (10 mL). After the layers were separated, the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified with flash chromatography, eluenting with hexane and EtOAc (8:1). 630 mg (86%) of the desired enone **30** was synthesized. R_f 0.73 (hexane/EtOAc = 2/1), IR (CH_2Cl_2 cast film) 3069, 2930, 2895, 2856, 1696, 1674, 1652, 1634, 1457, 1111 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.66 – 7.64 (m, 4H), 7.44 – 7.39 (m, 6H), 6.86 (dt, J = 16.0, 7.0 Hz, 1H), 6.12 (dt, J = 16.0, 1.4 Hz, 1H), 4.06 (t, J = 7.0 Hz, 1H), 3.78 (t, J = 6.3 Hz, 1H), 2.85 – 2.83 (m, 4H), 2.77 (t, J = 7.3 Hz, 2H), 2.45 (qd, J = 6.4, 1.4 Hz, 2H), 2.14 – 2.07 (m, 3H), 1.91 – 1.83 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 144.2, 135.5, 133.5, 131.8, 129.7, 127.7, 62.3, 46.6, 36.4, 35.7, 30.0, 29.3, 26.8, 25.9, 19.2. HRMS (EI) [M^+] for $C_{27}H_{36}O_2S_2Si$ calcd 484.19260, found: m/z 484.19261.



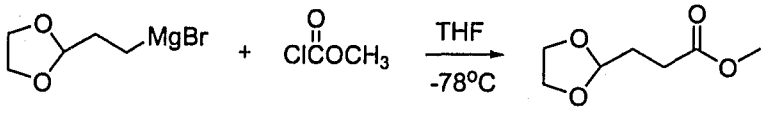
3-(*tert*-Butyldiphenylsiloxy)-1-propanol

A solution of *tert*-butylchlorodiphenylsilane (4.0 mL, 15 mmol) in dichloromethane (15 mL) was added overnight with a syringe pump to a solution of 1,3-propanediol (4.5 mL, 62 mmol) and imidazole (3.1 g, 44 mmol) in dichloromethane (20 mL) at room temperature. After the addition, the mixture was stirred for 4 h. The mixture was diluted with 50 mL of dichloromethane and washed with 1 N HCl (4 x 30 mL), saturated aqueous $NaHCO_3$ (4 x 30 mL), water, brine, and dried over $MgSO_4$. After filtration and evaporation of the solvent under vacuum, the residue was purified with flash chromatography (5.5 x 20 cm) using hexane and ethyl acetate (8:1) as the eluent. 3-(*tert*-butyldiphenylsiloxy)-1-propanol (3.3 g, yield 75%) was obtained as the colorless oil. R_f 0.31 (Hexane:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 - 7.64 (m, 4H), 7.56 - 7.43 (m, 6H), 3.44 – 3.49 (m, 4H), 2.80 (br, s 1H), 1.69 – 1.74 (m, 2H), 1.06 (s, 9H).



3-(*tert*-Butyldiphenylsiloxy)-propanal

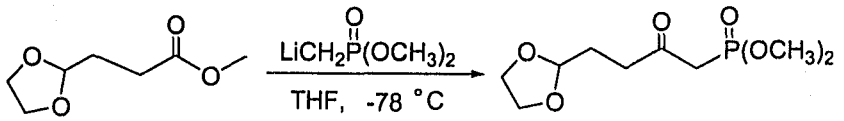
A three-neck flask with powdered molecular sieves was flame dried and flushed with argon. Then CH_2Cl_2 (30 mL), *N*-methylmorpholine *N*-oxide (1.5 g, 13 mmol), TPAP (0.22 g, 0.64 mmol), and 3-(*tert*-butyldiphenylsiloxy)-1-propanol (2.0 g, 6.4 mmol) were added to the reaction flask. The mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum. The residue was filtered through a short plug of silica gel using hexane and EtOAc (6:1) as the eluent. The crude product (3.7 g, 85%) was used without the purification. R_f 0.65 (Hexane:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (t, J = 2.3 Hz, 1H), 7.75 - 7.64 (m, 4H), 7.56 - 7.43 (m, 6H), 4.09 (t, J = 6.0 Hz, 1H), 2.67 (td, J = 6.0, 2.4 Hz, 2H), 1.07 (s, 9H).



Methyl 1,3-dioxolane-3-propanoate (34)

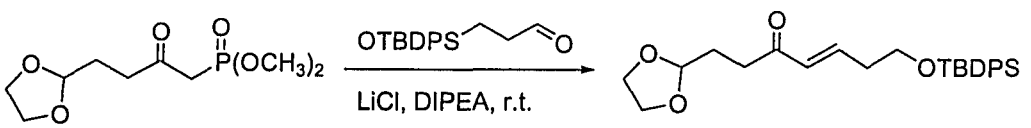
THF (90 mL) and one crystal of iodine were added to 1.5 g (62.5 mmol) of flame-dried magnesium turnings in a three-neck flask (250 mL) under Ar. A solution of 6.0 g (33 mmol) of 2-(2-bromoethyl)-1,3-dioxolane (Aldrich) in 30 mL of THF was placed in an addition funnel, and 5 mL of this solution was added to the magnesium turnings. Then several drops of 1,2-dibromoethane was added to the reaction mixture. The reaction was initiated and the solution began to boil. The remainder of alkyl halide was added at a rate such as to maintain the solvent at reflux. After completing the addition of the halide, the reaction was stirred for 1 h.

The mixture was then cooled to -78 °C and methyl chloroformate (3.4 mL, 44 mmol) in THF (30 mL) was added dropwise to maintain a reaction temperature below -70 °C. The mixture was stirred for another 1 h at -78 °C, and then allowed to warm to room temperature. The resulting solution was decanted from the excess magnesium and quenched with the addition of saturated aqueous ammonium chloride (10 mL). THF was evaporated at room temperature and the residue was diluted with water (30 mL), and then the mixture was extracted with ether (3 x 50 mL). The combined organic layers were dried with potassium carbonate. After evaporation, the residue was subjected to the silica gel column (3.5 x 20 cm), using hexane and ethyl acetate (6:1) as the eluent. 3.4 g (yield 65%) of methyl 1,3-dioxolane-3-propanoate was obtained. R_f 0.59 (Hexane:EtOAc = 2:1); IR (neat) 2953, 2887, 1739, 1438, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (t, J = 4.3 Hz, 1H), 3.97 - 3.83 (m, 4H), 3.67 (s, 3H), 2.44 (t, J = 7.4 Hz, 2H), 2.01 (td, J = 7.4, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 103.1, 65.0, 51.6, 28.8, 28.1.



Dimethyl 2-oxo-5-(1,3-dioxolane)pentylphosphonate (40)

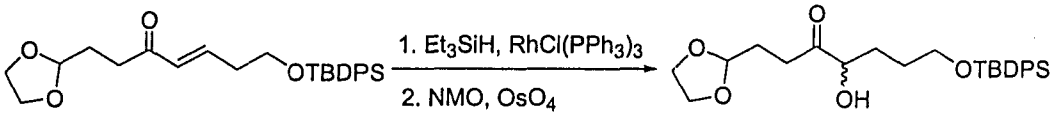
To a hexane solution of *n*-BuLi (7.5 mL, 1.6 M, 12 mmol) in THF (15 mL) was added dimethyl methyl phosphonate (1.62 mL, 15 mmol) at -78 °C under Ar. After 1 h, methyl 1,3-dioxolane-propanoate (0.96 g, 6.0 mmol) was added dropwise. The mixture was stirred at -78 °C under Ar for 3 h, and then poured into saturated aqueous ammonium chloride (10 mL). The mixture was extracted with chloroform (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated at room temperature under vacuum. After dimethyl methyl phosphonate was removed at room temperature under high vacuum, the crude product (0.98 g, yield 65%) was used in the following reaction without farther purification. R_f 0.41 (CH_2Cl_2:MeOH = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (t, J = 4.2 Hz, 1H), 3.96 – 3.82 (m, 4H), 3.78 (d, J = 11.3 Hz, 6H), 3.11 (d, J = 22.6 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 1.99 (td, J = 7.2, 4.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0 (d, J = 6.1 Hz), 103.0, 65.0 (2C), 53.0 (d, J = 6.5 Hz), 41.2 (d, J = 128 Hz), 37.9 (d, J = 1.6 Hz), 27.4 .



7-(*tert*-Butyldiphenylsilanyloxy)-1-[1,3]dioxolan-2-yl-hept-4-en-3-one (41)

To a mixture of dimethyl 2-oxo-5-(1,3-dioxolane)pentylphosphonate (0.91 g, 3.6 mmol) and LiCl (0.46 g, 11 mmol, very hygroscopic, flame-dried) in anhydrous CH_3CN (15 mL) in a flame-dried flask was added diisopropylethylamine (3.74 mL, 20.2 mmol), followed by the addition of a solution of 3-(*tert*-butylphenylsiloxy)-propanal (1.09 g, 3.5 mmol) in 3 mL of CH_3CN under an argon atmosphere. The mixture was stirred overnight. Another portion of the aldehyde (30 mg, 0.10 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ (10 mL), and the enone product was extracted with dichloromethane (3 x 30 mL). The combined organic layer was washed

with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (hexane and *tert*-butyl methyl ether 10:1) gave the pure enone 1.12 g (71%). R_f 0.48 (Hexane:EtOAc = 4:1); IR (neat) 3047, 2930, 2857, 1697, 1674, 1632, 1589, 1472, 1261 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.64 (m, 4H), 7.44 - 7.37 (m, 6H), 6.86 (dt, J = 16.0, 7.0 Hz, 1H), 6.13 (dt, J = 16.0, 1.4 Hz, 1H), 4.94 (t, J = 4.4 Hz, 1H), 3.97 - 3.83 (m, 4H), 3.78 (t, J = 6.3 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 2.45 (qd, J = 6.3, 1.4 Hz, 2H), 2.01 (td, J = 6.3, 4.4 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 144.0, 135.5, 133.6, 131.9, 129.7, 127.7, 103.5, 65.0, 62.4, 35.7, 33.7, 27.9, 26.8, 19.2. HRMS (ESI) $[M+Na]^+$ for $C_{26}H_{34}O_4NaSi$ calcd 461.21186, found: m/z 461.21157.

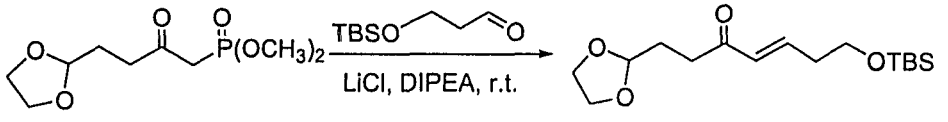


7-(*tert*-Butyl-diphenyl-silanyloxy)-1-[1,3]dioxolan-2-yl-4-hydrocyheptan-3-one (42)

To a mixture of tris(triphenylphosphine) rhodium chloride (4.8 mg, 5.1μmol) and triethylsilane (1.2 mL, 16 mmol) under Ar was added this enone (240 mg, 0.49 mmol). The mixture was heated in 80 °C oil bath. The cooled mixture was filtered through a short Al_2O_3 plug with ether and hexane (1:10). After excess triethylsilane was removed under vacuum, the residue was used in the next step without further purification.

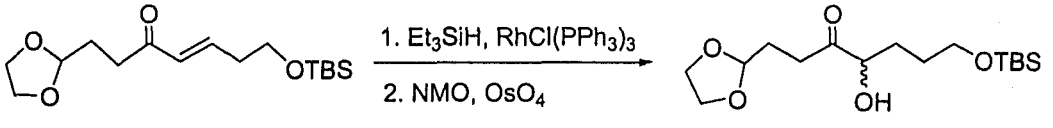
A mixture of this resulting silyl enol ether (0.49 mmol) and *N*-methylmorpholine *N*-oxide (102 mg, 0.75 mmol) in 10 mL of acetone and water (9:1) was treated with 0.40 mL of OsO_4 solution (0.05 mmol/mL in 2-propanol, 0.02 mmol). The reaction mixture was stirred at room temperature overnight. Then solid sodium sulfite (0.5 g) was added to the reaction mixture at 0 °C and the mixture was stirred for 1 h. Methylene chloride (10 mL) was added to the reaction mixture. After the organic layer was separated, the aqueous layer was further extracted with dichloromethane (3 x 10mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give an dark yellow oil, which was purified by flash chromatography

with ethyl acetate and hexane (6:1) to afford the pure product (123 mg, yield 55%). R_f 0.55 (Hexane:EtOAc = 1:1); IR (neat) 3472, 3070, 2955, 2930, 2857, 1712, 1472, 1361cm $^{-1}$; ^{1}H NMR (400 MHz, C_6D_6) δ 4.21 (ddd, J = 7.8, 4.3, 4.3 Hz, 1H), 3.95 – 3.82 (m, 4H), 3.71 (t, J = 6.0 Hz, 2H), 3.54 (d, J = 4.8 Hz, 1H), 2.63 (AB, d, J = 17.6, 7.3 Hz, 1H), 2.58 (AB, d, J = 17.6, 7.3 Hz, 2H), 2.04 (td, J = 7.2, 4.1 Hz, 2H), 2.02 - 1.95 (m, 1H), 1.74 -1.58 (m, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.5, 135.5, 133.7, 129.6, 127.6, 102.9, 76.2, 65.0, 63.4, 31.6, 30.3, 27.9, 27.4, 26.9, 19.2. HRMS (ESI) $[M+Na]^+$ for $C_{26}H_{36}O_5SiNa$ calcd 479.22242, found: m/z 479.22203. Optically-enriched α-hydroxy ketone **42** was prepared by using AD-mix-β. The ee value (68%) was determined by chiral HPLC (OJ, isopropanol/hexane = 4/96, flow rate 0.4 mL/min).



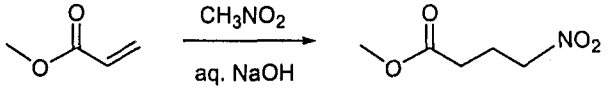
7-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-hept-4-en-3-one (47)

This compound was prepared by the similar method to compound **41**. R_f 0.47 (Hexane:EtOAc = 2:1); IR (neat) 2954, 2929, 2884, 2857, 1740, 1699, 1676, 1633, 1472, 1261, 1099 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dt, J = 16.0, 7.0 Hz, 1H), 6.13 (dt, J = 16.0, 1.4 Hz, 1H), 4.91 (t, J = 4.4 Hz, 1H), 3.97-3.83 (m, 4H), 3.72 (t, J = 6.4 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 2.41 (qd, J = 6.4, 1.5 Hz, 2H), 1.98 (td, J = 7.0, 4.4 Hz, 2H), 0.85 (s, 9H) 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 144.0, 131.7, 103.4, 65.0, 61.6, 35.9, 33.7, 27.8, 25.8, 18.2, -5.4. HRMS (EI) $[M^+]$ for $C_{16}H_{30}O_4Si$ calcd 314.19135, found: m/z 314.19030.



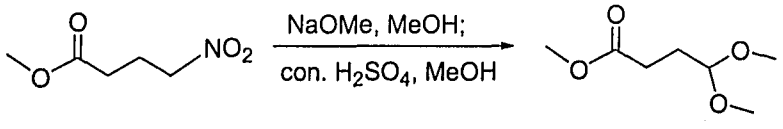
7-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-4-hydrocyheptan-3-one (48)

This compound was prepared by the similar method to compound **42**. R_f 0.37 (Hexane:EtOAc = 2:1); IR (neat) 3472, 2955, 2930, 2857, 2832, 1712, 1472, 1361 cm $^{-1}$; ^{1}H NMR (400 MHz, C_6D_6) δ 4.74 (t, J = 4.4 Hz, 1H), 3.96 (dd, J = 7.9, 3.7 Hz, 1H), 3.47-3.27 (m, 6H), 2.45 (ddd, AB, J = 17.6, 7.8, 6.8 Hz, 1H), 2.28 (AB, ddd, J = 17.6, 7.2, 7.2 Hz, 1H), 2.03-1.98 (m, 2H), 2.04 (td, J = 7.2, 4.1 Hz, 2H), 2.02-1.95 (m, 1H), 1.80 (dddd, J = 13.2, 9.6, 6.1, 3.7 Hz, 1H), 1.67-1.54 (m, 2H), 1.43 (dddd, J = 13.0, 9.4, 7.8, 4.9 Hz, 1H), 0.95 (s, 9H), 0.021 (s, 3H), 0.019 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.3, 103.3, 76.3, 64.8, 62.8, 31.9, 30.6, 28.5, 28.0, 26.1, 18.4, -5.3. HRMS (EI) $[M]^+$for $C_{26}H_{36}O_5Si$ calcd 332.20190, found: m/z 332.20139.



4-Nitro-butyric acid methyl ester (52)[16]

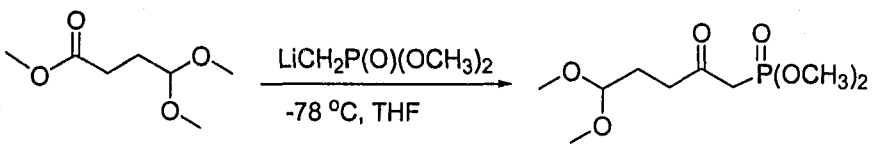
To the mixture of methyl acrylate (56.3 mL, 620 mmol) and nitromethane (33.9 mL, 620 mmol) in dichloromethane (125 mL) in a flask (500 mL) was added a solution of NaOH (6.0 g, 75 mmol) in water (125 mL) at room temperature. The reaction mixture was stirred for 24 h. Then the organic layer was separated, washed with brine, and dried over $MgSO_4$. The crude product (27 g, 30%) was pure enough to be used in the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (t, J = 6.5 Hz, 2H), 3.70 (s, 3H), 2.47 (t, J = 7.0 Hz, 2H), 2.31 (q, J = 7.0 Hz, 2H).



Methyl 4,4-dimethoxy-butanoate (53) [16]

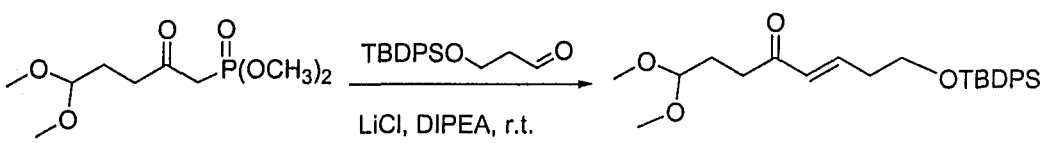
A solution of methyl 4-nitrobutyrate (4.05 g, 27.5 mmol) in 130 ml of 0.5 N methanolic sodium methoxide (65.0 mmol, freshly made from 1.50 g of metal sodium and 130 mL of anhydrous methanol) was added dropwise at a rate of 1 drop per second to sulfuric acid solution (65 mL of concentrated sulfuric acid in 250 mL of anhydrous methanol) at -35 °C. When the addition was finished, the mixture was diluted with methylene chloride (1 L). The mixture was washed with ice water (500

mL), 2N aqueous sodium hydroxide (500 mL), brine (500 mL), dried over potassium carbonate, filtered, and concentrated *in vacuo*. 3.39 g (76%) of highly pure dimethyl acetal compound was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (t, J = 5.6 Hz, 1H), 3.67 (s, 3H), 3.32 (s, 6H), 2.37 (t, J = 7.5 Hz, 2H), 1.92 (td, J = 7.4, 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 103.6, 53.1, 51.6, 29.1, 27.8.



Dimethyl 2-oxo-5,5-dimethoxy-pentylphosphonate (54)

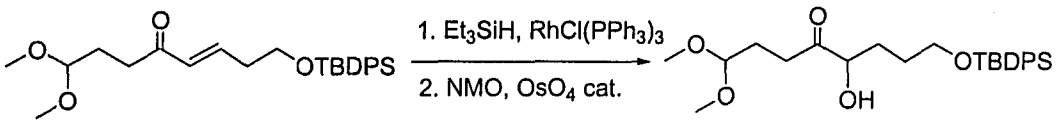
To a hexane solution of *n*-BuLi (7.5 mL, 1.6 M, 12 mmol) in THF (15 mL) was added dimethyl methyl phosphonate (1.7 mL, 15 mmol) at -78 °C under an argon atomsphere. After 1 h, methyl 4,4-dimethoxy-butanoate (0.97 g, 6.0 mmol) was added dropwise. The mixture was stirred at -78 °C under Ar for 3 h, and then poured into saturated aqueous ammonium chloride (10 mL). The mixture was extracted with chloroform (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated at room temperature under vacuum. After dimethyl methyl phosphonate was removed at room temperature under high vacuum, the crude product (0.96 g, yield 63%) was used in the following reaction without farther purification. R_f 0.31 (CH_2Cl_2:MeOH = 20:1).



8-(*tert*-Butyldiphenylsilanyloxy)-1,1-dimethoxy-oct-5-en-4-one (55)

To a solution of dimethyl 2-oxo-5,5-dimethoxy-pentylphosphonate (0.96 g, 3.8 mmol) and LiCl (0.48 g, 11 mmol, very hygroscopic, flame-dried) in anhydrous CH_3CN (30 mL) in a flame-dried flask was added diisopropylethylamine (4.0 mL, 23 mmol), followed by the addition of a solution of 3-(tert-butyldiphenylsilyloxy)-propionaldehyde (1.14 g, 3.7 mmol) in 10 mL of CH_3CN under an argon atmosphere.

The mixture was stirred overnight. Another portion of the aldehyde (0.31 g, 0.1 mmol) was added and the reaction mixture was stirred for 3h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ (10 mL), and the enone product was extracted with dichloromethane. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (hexane and *tert*-butyl methyl ether 8:1, with 1% (v/v) of Et_3N) gave the pure enone 1.1 g (68%). R_f 0.47 (Hexane:t-BuOMe = 1:1); IR (neat) 3071, 3048, 2956, 2932, 2858, 1698, 1676, 1632, 1472, 1112 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.73-7.69 (m, 4H), 7.26-7.19 (m, 6H), 6.64 (dt, J = 16.0, 7.0 Hz, 1H), 5.99 (d, J = 16.0, 1.4 Hz, 1H), 4.32 (t, J = 5.5 Hz, 1H), 3.54 (t, J = 6.4 Hz, 2H), 3.10 (s, 6H), 2.44 (t, J = 7.2 Hz, 2H), 2.07 (qd, J = 6.4, 1.5 Hz, 2H), 1.99 (td, J = 7.2, 5.5 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ199.5, 144.0, 135.5, 133.6, 131.9, 129.7, 127.7, 103.9, 62.3, 53.2, 35.7, 34.5, 26.8(up), 26.8(down), 19.2. HRMS (EI) $[M-H]^+$ for $C_{26}H_{35}O_4Si$ calcd 439.23047, found: m/z 439.23047.

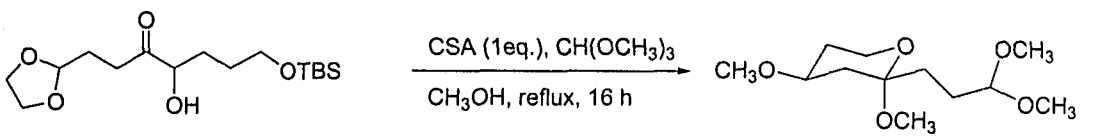


8-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxy-1,1-dimethoxy-octan-4-one (56)

To a mixture of tris(triphenylphosphine) rhodium chloride (9.9 mg, 11μmol) and triethylsilane (3.0 mL, 40 mmol) under Ar was added this enone (0.94 g, 2.1 mmol). The mixture was heated in 50 °C oil bath. The cooled mixture was filtered through a short Al_2O_3 plug with ether and hexane (1:10). After the solvent and excess triethylsilane were removed under vacuum, the residue was used in the next step without further purification.

A mixture of this resulting silyl enol ether (2.1 mmol) and *N*-methyl-morpholine *N*-oxide (0.37 g mg, 3.2 mmol) in 20 mL of acetone and water (9:1) was treated with 1.1 mL of OsO_4 solution (2.5 wt% solution in 2-methyl-2-propanol, 0.084 mmol). The reaction mixture was stirred at room temperature overnight. Then solid sodium sulfite (2.1 g) was added to the reaction mixture at 0 °C and the mixture was stirred for 1 h.

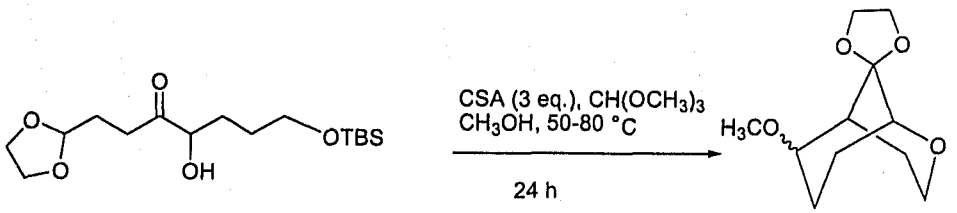
Methylene chloride (30 mL) was added to the reaction mixture. After the organic layer was separated, the aqueous layer was further extracted with dichloromethane (3 x 30mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give an dark yellow oil, which was purified by flash chromatography with ethyl acetate and hexane (6:1, with 1% (v/v) of Et_3N) to afford the pure product (0.48 g, yield 50%). R_f 0.43 (Hexane:t-BuOMe = 1:1); IR (neat) 3470, 3072, 2955, 2932, 2857, 1715, 1652, 1470, 1361cm $^{-1}$; ^{1}H NMR (400 MHz, C_6D_6) δ 7.78-7.65 (m, 4H), 7.26-7.21 (m, 6H), 4.18 (t, J = 45.6 Hz, 1H), 3.92 (dd, J = 8.0, 3.6 Hz, 1H), 3.61 (t, J = 6.0 Hz, 2H), 3.52 (br s, 1H), 3.06 (s, 6H), 2.32 (AB, d, J = 17.6, 7.2 Hz, 1H), 2.14 (AB, d, J = 17.6, 7.2 Hz, 2H), 1.92-1.87 (m, 2H), 1.82-1.58 (m, 3H), 1.42 (ddt, J = 9.6, 8.0, 4.8 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 211.4, 136.0, 134.2, 130.0, 128.0, 103.7, 76.3, 63.8, 52.8, 52.7, 32.5, 30.5, 28.4, 27.1, 26.8, 19.2. HRMS (EP) $[M+Na]^+$ for $C_{26}H_{38}O_5SiNa$ calcd 481.22955, found: m/z 481.23862.



2-(3,3-Dimethoxy-propyl)2,4-dimethoxy-tetrahydro-pyran (59)

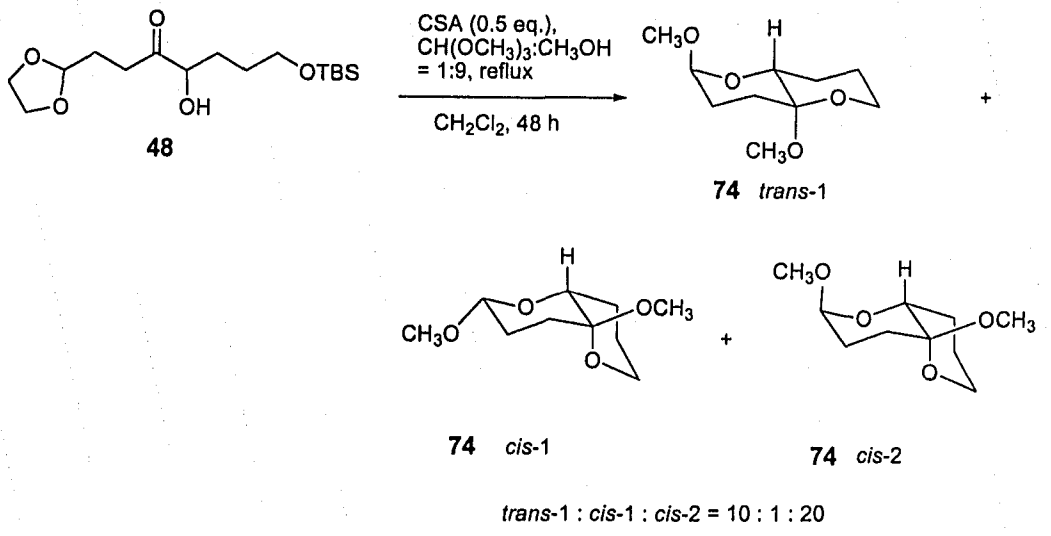
A round-bottom flask was charged with this α-hydroxy ketone (150 mg, 0.45 mmol), camphorsulfonic acid (120 mg, 0.52 mmol) and trimethyl orthoformate (1 mL) in anhydrous methanol (10 mL). The mixture was heated at reflux for 16 h. Then the reaction mixture was neutralized to pH 8 – 10 and extracted with dichloromethane (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified through flash column chromatography (2 x 20 cm), using ethyl acetate and hexane (1:8) as the eluent to afford the title product (66 mg, 60%). R_f 0.55 (Hexane:EtOAc = 1:1); IR (neat) 2955, 2932, 2857, 1161cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 4.21-4.28 (m, 1H), 3.62 (dddd, J = 11.0, 11.0, 4.6, 4.6 Hz, 1H), 3.53 (ddd, J = 11.4, 5.3, 1.8 Hz, 1H), 3.41 (ddd, J = 12.9, 11.4, 2.4 Hz, 1H), 3.12 (s, 3H), 3.11 (s, 3H), 3.10 (s, 3H), 3.04 (s, 3H), 2.27 (ddd, J = 17.6, 7.2 Hz, 1H), 1.93-1.88 (m, 1H), 1.80-1.67 (m, 4H), 1.40 (dddd, J = 12.7, 12.7, 11.1, 5.1 Hz, 1H), 1.34

(dd, J = 12.4, 10.9 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 104.5, 101.3, 73.5, 59.6, 55.0, 52.6, 52.0, 47.0, 39.6, 32.2, 31.4, 27.2. HRMS (EI) $[M\text{-}OCH_3]^+$ for $C_{11}H_{21}O_4$ calcd 217.14398, found: m/z 217.14426; MS (ESI) $[M+Na]^+$ for $C_{12}H_{24}O_5Na$ m/z 271.1.



Tricyclic compound (60)

A round-bottom flask was charged with this α-hydroxy ketone (84 mg, 0.25 mmol), camphorsulfonic acid (186 mg, 0.80 mmol) and trimethyl orthoformate (0.88 mL, 4.0 mmol) in anhydrous methanol (10 mL). The mixture was heated at reflux overnight. Then the reaction mixture was neutralized to pH 8 – 10 and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified through flash column chromatography (1.5 x 20 cm), using ethyl acetate and hexane (1:5) as the eluent to afford the title product (17 mg, 61%). R_f 0.29 (Hexane:EtOAc = 1:1); IR (CH_2Cl_2 cast film) 2929, 2890, 2820, 1338, 1176 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03-3.91 (m, 5H), 3.81-3.73 (m, 2H), 3.53-3.51 (m, 1H), 3.35 (s, 3H), 2.24-2.22 (m, 1H), 2.16-1.90 (m, 4H), 1.90-1.81 (m, 1H), 1.75-1.64 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 108.0, 79.0, 70.4, 64.4, 63.9, 61.2, 55.6, 38.6, 27.0, 26.0, 23.3. HRMS (EI) $[M]^+$ for $C_{11}H_{18}O_4$ calcd 214.12051, found: m/z 214.12056.



trans-1 : *cis*-1 : *cis*-2 = 10 : 1 : 20

2,4-Dimethoxy-octahydro-pyrano[3,2]pyran (74)

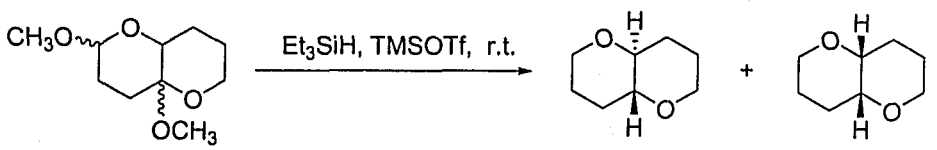
In a flask (100 mL), this α-hydroxy ketone (157 mg, 0.50 mmol) was dissolved in 25 mL of anhydrous dichloromethane and 10 mL of methanol and trimethyl orthoformate (1:9), then camphorsulfonic acid (58 mg, 0.25 mmol) was added. The mixture was stirred at room temperature for 3 h and then was heated in the oil bath (50 °C) for 48 h. When the starting material was consumed based on TLC, the mixture was neutralized with 2 N NaOH until pH 8 -10. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified with flash column chromatography (hexane:t-BuOMe = 10:1 to 5:1) to afford three configurational isomers (61 mg, 61%).

The ratio of *cis*-1, *cis*-2, and *trans*-1 was 1:20:10. The analysis data of compound *cis*-1: R_f 0.71 (Hexane:EtOAc = 1:1); ^{1}H NMR (400 MHz, C_6D_6) δ 4.17 (dd, J = 9.7, 2.0 Hz, 1H), 3.55-3.52 (m, 2H), 3.36 (s, 3H), 3.34 (dd, J = 2.9, 2.9 Hz, 1H), 3.03 (s, 3H), 2.19-2.02 (m, 3H), 1.89 (ddd, J = 13.1, 4.6, 2.7 Hz, 1H),1.74-1.70 (m, 1H), 1.59 (dddd, J = 12.9, 4.8, 2.7, 2.1 Hz, 1H), 1.15 (ddd, J = 14.0, 13.1, 4.6 Hz, 1H), 0.96-0.92 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 103.3, 93.9, 72.2, 61.0, 55.8, 47.0, 30.9, 29.1, 24.8, 19.8.

The analysis data of compound *cis*-2: R_f 0.75 (Hexane:EtOAc = 1:1); IR (film) 2955, 2932, 2857, 1361, 1101 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 4.60 (dd, J = 3.4, 1.0 Hz,

1H), 3.81 (dd, J = 2.5, 2.5 Hz, 1H), 3.64-3.52 (m, 2H), 3.14 (s, 3H), 3.08 (s, 3H), 2.17-2.10 (m, 2H), 2.01 (dddd, J = 12.8, 12.8, 6.0, 3.4 Hz, 1H), 1.84 (ddd, J = 12.5, 12.5, 4.3 Hz, 1H), 1.81-1.76 (m, 1H), 1.66-1.63 (m, 1H), 1.62 (dddd, J = 12.9, 4.2, 2.7, 1.3 Hz, 1H), 1.05-0.94 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 98.0, 94.2, 65.5, 60.9, 54.2, 46.5, 27.7, 26.8, 24.4, 19.7. HRMS (EI) $[M]^+$ for $C_{10}H_{18}O_4$ calcd 202.12051, found: m/z 202.12009.

The analysis data of compound *trans*-1: R_f 0.46 (Hexane:EtOAc = 1:1); IR (film) 2955, 2932, 2857, 1361, 1101 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 4.57 (dd, J = 3.7, 0.5 Hz, 1H), 3.83 (dd, J = 12.1, 4.0 Hz, 1H), 3.50-3.45 (m, 1H), 3.34 (dddd, J = 11.0, 5.1, 1.2, 1.2 Hz, 1H), 3.18 (s, 3H), 3.02 (s, 3H), 2.15-2.10 (m, 2H), 1.92 (ddd, J = 12.8, 12.8, 6.0, 3.4 Hz, 1H), 1.84 (ddd, J = 12.5, 12.5, 4.3 Hz, 1H), 1.82-1.71 (m, 2H), 1.58-1.48 (m, 3H), 1.33-1.26 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 98.1, 95.4, 70.8, 60.4, 54.3, 46.6, 28.1, 26.1, 24.7, 23.8. HRMS (EI) $[M]^+$ for $C_{10}H_{18}O_4$ calcd 202.12051, found: m/z 202.12036.

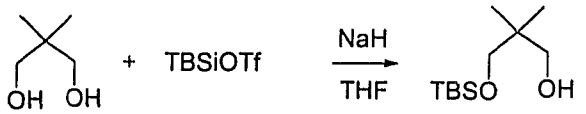


trans:*cis* = 10:1

Octhydro-pyrano[3,2-β]pyran (75)

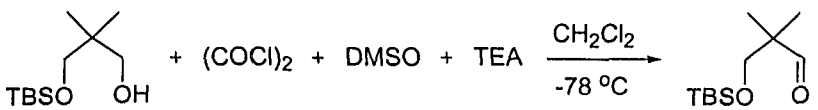
To the mixture of the bisacetal (60 mg, 0.30 mmol), Et_3SiH (0.48 mL, 3.0 mmol) in dichloromethane (15 mL) was added TMSOTf (260 μL, 1.5 mmol) at 0 °C. The mixture was stirred at room temperature for 24 h. Then the mixture was poured into a $NaHCO_3$ (solid)/ice mixture. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by flash chromatography (2 x 20 cm) to yield the bispyran product (about 25 mg, 60%). Pentane and diethyl ether (20:1 – 10:1) was used as the eluent. The ratio of the *trans* to the *cis* product was 10:1. Spectral data of the major *trans*-compound: IR (neat) 2953, 2834, 1093 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 3.70 (dddd, J = 11.2, 4.7, 1.5, 1.5 Hz, 1H), 3.10 (ddd, J =

11.8, 11.3, 2.4 Hz, 1H), 2.91-2.84 (m, 1H), 1.95-1.89 (m, 1H), 1.54-1.44 (m, 1H), 1.42-1.34 (m, 1H), 1.21 (ddddd, J = 13.4, 4.2, 2.8, 2.8, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 79.1, 67.8, 30.3, 26.3. HRMS (EI) [M^+] for $C_{10}H_{18}O_2$ calcd 170.13068, found: m/z 170.13067.



2,2-Dimethyl-3-(*tert*-butyldimethylsiloxy)-1-propanol (77)

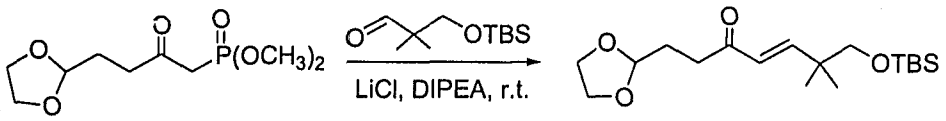
A three-neck flask (250 mL) was charged with NaH (2.1 g, 60% wt % in mineral oil, 53 mmol) in 120 mL of anhydrous THF. To this suspension was added 2,2-dimethyl-1,3-propanediol (5.0 g, 48 mmol) in three portions over 5 min. The resulting thick slurry was stirred at room temperature for 1 h. TBSiOTf (11.0 mL, 48 mmol) was added to the above suspension and the mixture was stirred for 3 h. The mixture was diluted with 100 mL of methyl *tert*-butyl ether and washed with 10% K_2CO_3, brine, and dried over Na_2SO_4. The residue was purified with the flash column (3.5 x 20 cm) using hexane and ethyl acetate (8:1) as eluent. The title compound (5.2 g, yield 50%) was obtained as colorless oil. R_f 0.61 (Hexane:EtOAc = 5:1); IR (neat) 3385, 2955, 2930, 2858, 1472, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.47 (d, J = 5.8 Hz, 2H), 3.47 (s, 2H), 2.80 (br, t, J = 5.8 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 6H) 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.7, 72.2, 36.4, 25.8, 21.4, 18.2, -5.7. HRMS (EI) [M-tBu]$^+$ for $C_7H_{17}O_2Si$ calcd 161.09978, found: m/z 161.09947.



3-(*tert*-Butyldimethylsiloxy)-2,2-dimethyl-propanal (78)[20]

A solution of DMSO (3.3 mL, 42 mmol) in anhydrous dichloromethane (5 mL) was added dropwise at -78 °C to a solution of oxalyl chloride (2.1 mL, 24 mmol) in anhydrous dichloromethane (40 mL) and the mixture was stirred for 30 min. The alcohol (4.35 g, 20 mmol) in dichloromethane (5 mL) was added slowly to the reaction mixture, which was stirred for 1 h. Then the mixture was treated with

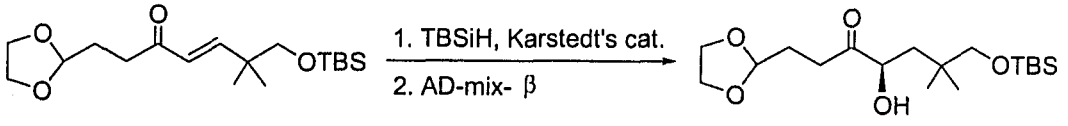
triethylamine (12.2 mL, 88 mmol) and the reaction mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature. The mixture was partitioned between water and dichloromethane, and the organic layer was washed with 5% HCl (20 mL) and saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was filtered through a short plug of silica gel using diethyl ether as the eluent. The crude product (3.7 g, 85%) was used without the purification (The pure product underwent air oxidation to the acid).



7-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-6,6-dimethyl-hept-4-en-3-one(79)

To a solution of dimethyl 2-oxo-5-(1,3-dioxolane)pentylphosphonate (2.38 g, 10.6 mmol) and LiCl (1.35 g, 31.8 mmol, very hygroscopic, flame-dried) in anhydrous CH_3CN (50 mL) in a flame-dried flask was added diisopropylethylamine (11.1 mL, 63.6 mmol), followed by the addition of a solution of 2,2-dimethyl-3-(*tert*-butyldimethylsilyloxy)-propionaldehyde (1.9 g, 9.5 mmol) in 10 mL of CH_3CN under an argon atmosphere. The mixture was stirred overnight. Another portion of the aldehyde (0.20 g, 1.0 mmol) was added and the reaction mixture was stirred for 3h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$, and the enone product was extracted with dichloromethane. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (hexane and *tert*-butyl methyl ether 10:1 to 8:1) gave the pure enone 2.58 g (72%). R_f 0.55 (Hexane:EtOAc = 4:1); IR (neat) 2956, 2930, 2885, 2857, 1699, 1676, 1628, 1472, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, J = 16.3 Hz, 1H), 6.04 (d, J = 16.3 Hz, 1H), 4.93 (t, J = 4.4 Hz, 1H), 3.95-3.83 (m, 4H), 3.36 (s, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.99 (td, J = 7.4, 4.4 Hz, 2H), 1.03 (s, 6H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 154.0, 127.4, 103.5, 71.1, 65.0, 39.1,

33.7, 27.9, 25.8, 23.3, 18.2, -5.5. HRMS (EI) [M^+] for $C_{18}H_{34}O_4Si$ calcd 342.22263, found: m/z 342.22206.

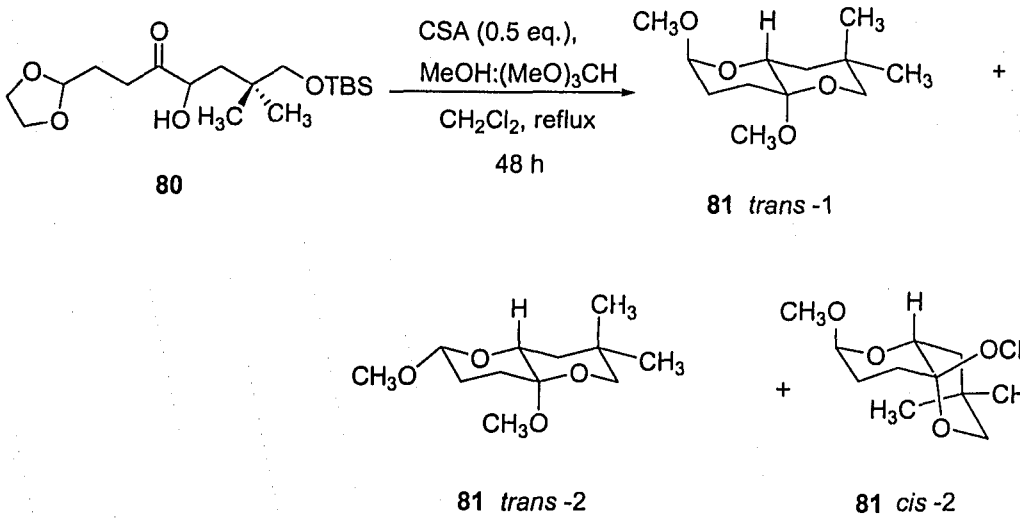


7-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-6,6-dimethyl-4-hydroxy-heptan-3-one (80)

tert-Butyldimethyl silane (TBSiH, 470 μL, 2.0 mmol) and platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Karstedt's catalyst, 20 μL, 0.1 M, xylenes solution) were added into a round bottom flask (15 mL), which was flushed with argon. Then the enone (342 mg, 1.0 mmol) was introduced via a syringe. The mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a short silica plug, using hexane and *tert*-butyl methyl ether (10:1) as the eluent. After the solvent and excess TBSiH were evaporated under vacuum, the residue was directly used in the next reaction.

To a well-stirred mixture of AD-mix-β (1.4 g, Aldrich) and $CH_3SO_2NH_2$ (85 mg, 1.0 mmol) at 0 °C was added this resulting silyl enol ether. The reaction mixture was stirred for 4 h at 0 °C and slowly warmed up to room temperature overnight. Solid sodium sulfite (1.0 g) was added to the reaction mixture at 0 °C. Methylene chloride (30 mL) was added to the reaction mixture. After the organic layer was separated, the aqueous layer was further extracted with methylene chloride. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give an oil, which was purified by flash chromatography (2 x 20 cm) with ethyl acetate and hexane (6:1 – 4:1) to afford the pure product (198 mg, yield 55%). R_f 0.30 (Hexane:EtOAc = 1:1); IR (neat) 3473, 2955, 2930, 2885, 2857, 1714, 1472, 1093cm $^{-1}$; ^{1}H NMR (500 MHz, C_6D_6) δ 4.79 (t, J = 4.4 Hz, 1H), 4.12 (ddd, J = 10.3, 4.2, 1.9 Hz, 1H), 3.96 (d, J = 4.2 Hz, 1H), 3.50-3.36 (m, 4H), 3.34 (d, J = 9.7 Hz, 1H), 3.23 (t, J = 9.7 Hz, 1H), 2.66 (ddd, J = 14.7, 7.9, 6.8 Hz, 1H), 2.50 (ddd, J = 14.7, 7.9, 6.8 Hz, 1H), 1.98-2.10 (m, 2H), 1.76 (dd, J = 14.3, 1.9 Hz, 1H), 1.25 (dd, J = 14.3, 10.3 Hz, 1H), 0.94 (s, 9H), 0.93 (s, 3H), 0.90 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.9, 103.3,

74.9, 71.2, 65.0, 64.9, 43.8, 35.4, 31.8, 27.4, 26.0, 25.9, 24.0, 18.3, -5.5. HRMS (EI) [M^+] for $C_{18}H_{36}O_5Si$ calcd 360.23382, found: m/z 360.23322. Anal. Calcd for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06. Found C 59.99; H, 10.43.



80

81 *trans* -1

81 *trans* -2

81 *cis* -2

trans -1 : *trans* -2 : *cis* -2 = 20 : 1 : 10, 64%

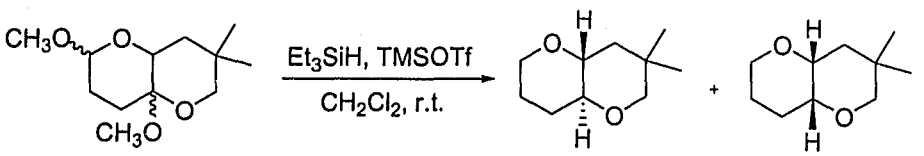
2,4-Dimethoxy-7,7-dimethyl-octahydro-pyrano[3,2]pyran (81)

The mixture of this alcohol (180 mg, 0.50 mmol), camphorsulfonic acid (58 mg, 0.25 mmol) in DCM (25 mL), and trimethyl orthoformate in methanol (10 mL of 1:9 mixture) was stirred at room temperature for 3 h, then it was heated at reflux for 2 days. The cooled mixture was neutralized to pH 8-10 with 2N NaOH. After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous $MgSO_4$. The concentrated residue was purified with the flash chromatography, using *tert*-butyl methyl ether and hexane (1:10 to 1:6) as the eluent. The ratio of *trans*-1 and *cis*-2 is about 2:1. The combined yield was 64% (74 mg).

Spectral data of the *cis*-2 compound: R_f 0.70 (Hexane:EtOAc = 1:1); IR ($CHCl_3$ cast film) 2955, 2930, 2885, 2857, 1472, 1093 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.54 (br, d, J = 1.8 Hz, 1H), 3.87 (dd, J = 3.9, 2.3, Hz 1H), 3.50 (dd, J = 10.8, 0.6 Hz, 1H), 3.21 (dd, J = 10.8, 2.6 Hz, 1H), 3.14 (s, 9H), 3.05 (s, 9H), 1.98 (dd, J = 14.0, 4.0 Hz,

1H), 1.95-1.78 (m, 2H), 1.66-1.76 (m, 1H), 1.51 (dt, J = 14.0, 2.4 Hz, 1H), 1.38 (s, 3H), 0.69 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 97.5, 94.1, 70.8, 66.8, 54.3, 46.5, 37.2, 28.5, 28.2, 27.6, 27.1, 26.3. HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{22}O_4Na$ calcd 253.14103, found: m/z 253.14150.

Spectral data of the major *trans*-1 compound: R_f 0.49 (Hexane:EtOAc = 1:1); IR ($CHCl_3$ cast film) 2953, 2870, 2829, 1470, 1049 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.60 (dd, J = 3.8, 0.6, Hz 1H), 4.10 (ddd, J = 12.6, 4.6, 0.6 Hz, 1H), 3.43 (dd, J = 10.8, 0.7 Hz, 1H), 3.20 (s, 9H), 3.02 (s, 9H), 3.00 (dd, J =10.8, 2.1 Hz, 1H), 2.06 (ddd, J = 12.5, 12.0, 0.6 Hz, 1H), 1.95 (ddd, J = 13.7, 13.7, 4.4 Hz, 1H), 1.86 (ddd, J = 13.6, 4.6, 2.6 Hz, 1H), 1.76 (dddd, J = 13.6, 13.4, 4.6, 3.8 Hz, 1H), 1.59 (dddd, J = 13.3, 3.8, 2.6, 1.1 Hz, 1H), 1.38 (ddd, J = 12.0, 4.6, 2.1 Hz, 1H), 1.03 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 98.2, 95.2, 70.4, 67.7, 54.3, 46.8, 37.0, 34.2, 28.2, 27.5, 25.2, 24.7; HRMS (ESI) $[M+Na]^+$ for $C_{12}H_{22}O_4Na$ calcd 253.14103, found: m/z 253.14121.

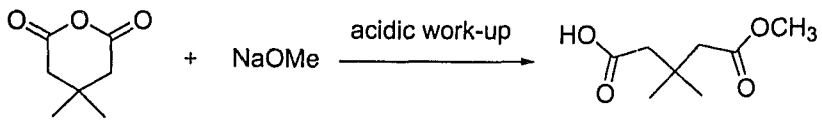


trans:*cis* = 10:1

3,3-Dimethyl-octhydro-pyrano[3,2-β]pyran (82)

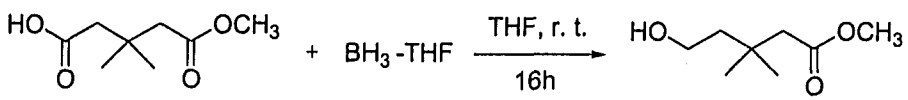
To the mixture of the bisacetal (50 mg, 0.22 mmol), Et_3SiH (350 µL, 2.2 mmol) in dichloromethane (10 mL) was added TMSOTf (189 µL, 1.1 mmol) at 0 °C. The mixture was stirred at room temperature for 24 h. Then the mixture was poured into a $NaHCO_3$ (solid)/ice mixture. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by flash chromatography to yield the bispyran product (24 mg, 64%). Pentane and diethyl ether (20:1 – 10:1) was used as the eluent. The ratio of the *trans* to the *cis* product was 15:1. Spectral data of the major *trans*-compound: IR (neat) 2953, 1093 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ

3.72 (dddd, J = 11.4, 4.8,1.6, 1.6 Hz, 1H), 3.33 (dd, J = 11.1, 2.4 Hz, 1H), 3.14-3.09 (m, 2H), 3.01 (dd, J = 11.0, 0.6 Hz, 1H), 2.80 (ddd, J = 11.0, 9.0, 4.4 Hz, 1H), 1.97-1.94 (m, 1H), 1.75 (ddd, J = 12.3, 4.5, 2.4 Hz, 1H), 1.54-1.36 (m, 2H), 1.30 (dd, J = 11.8, 11.8 Hz, 1H), 0.99 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 79.6, 78.1, 76.4, 67.9, 43.3, 33.1, 30.0, 27.2, 26.3, 25.2; HRMS (EI) [M^+] for $C_{10}H_{18}O_2$ calcd 170.13068, found: m/z 170.13067.



3,3-Dimethyl-5-methoxycarbonyl butanoic acid (84)

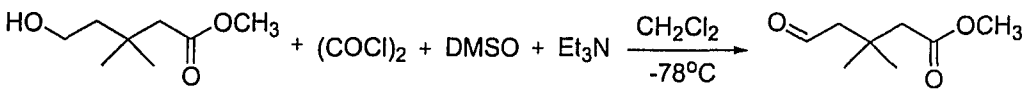
A solution of NaOMe (made from 0.41g Na and 5 mL of anhydrous MeOH) was added to a solution of 3,3-dimethy-glutaric anhydride (2.5 g, 18 mmol) in 9 mL of anhydrous MeOH. After the addition, the solution was allowed to cool to room temperature before removing the methanol by distillation. After most of methanol had been removed, excess benzene was added to the solution and distillation continued to remove all of methanol as the benzene-methanol azeotrope. The residue was cooled and concentrated hydrochloric acid was added until the aqueous layer remained pH 1-3. The layers were separated and the organic layer was dried, and concentrated under reduced pressure. 2.9 g of crude product was obtained as the light yellow oil (yield 95%). ^{1}H-NMR spectrum showed this product was pure enough to use in the next reaction without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.2 (br, 1H), 3.64 (s, 3H), 2.45 (s, 2H), 2.43 (s, 2H) 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 172.4, 51.3, 44.9, 44.8, 32.4, 27.6.



Methyl 3,3-dimethyl-5-hydroxypentanoate (85)

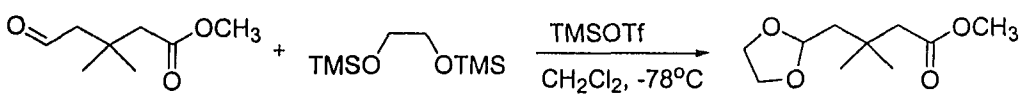
1 M BH_3-THF solution (21.1 mL) was added to the solution of methyl 3,3-dimethyl-5-methoxycarbonyl butanoic acid (3.07 g, 17.6 mmol) in 30 mL of dry THF at -20 °C under argon. The reaction mixture was stirred at ambient temperature overnight. Then

10 mL of water was added to the ice-cooled mixture. The reaction mixture was diluted with 50 mL of ether. After the separation, the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The concentrated residue was purified by flash column chromatography on silica gel using hexane-ethyl acetate (6:1 to 3:1) to give the title compound (2.62 g, yield 93%) as colorless oil. (GC) Retention time: 6.07 min (start temperature 100 °C, heating rate 5 °C/min); ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (br, t, J = 6.5 Hz, 2H), 3.65 (s, 3H), 2.28 (s, 2H), 1.91 (br, s, 1H), 1.64 (t, J = 7.0 Hz, 2H), 1.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 59.5, 51.3, 46.0, 43.9, 32.6, 28.0.



Methyl 3,3-dimethyl-5-oxopentanoate (86)[22]

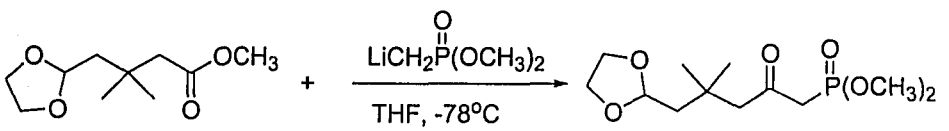
To a solution of oxalyl chloride (1.8 mL, 20 mmol) and dimethyl sulfoxide (2.7 mL, 38 mmol) in anhydrous dichloromethane (45 mL) was slowly added methyl 3,3-dimethyl-5-hydroxypentanoate (2.7 g, 17 mmol) in dichloromethane (5 mL) at -78°C under argon. After stirring for 2h, triethylamine (10 mL, 75 mmol) was added to this solution. The reaction mixture was stirred for 1 h at -78 °C and then warmed to room temperature in 4 h. Then 1N HCl was added to dissolve the salts, the aqueous and the organic phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with saturated sodium carbonate solution, dried with magnesium sulfate. After concentration, the residue was filtered through a short plug of silica gel using hexane-ethyl acetate (4:1) as eluent. The aldehyde (2.2 g, 82%) was used without purification.



Methyl 3,3-dimethyl-5-(1',3'-dioxolane)-pentanoate (88)

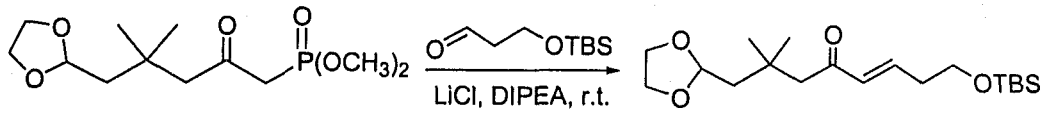
To a solution of trimethylsilyl triflate (6 μL, 0.03 mmol) in dichloromethane (3 mL) were added 1,2-bis(trimethysilyloxy)ethane (0.89 mL, 3.6 mmol) and a solution of

methyl 3,3-dimethyl-5-oxo-pentanoate (0.47 g, 3.0 mmol) in dichloromethane (3 mL) at - 78 °C under argon. After the reaction mixture was stirred for 1h, anhydrous pyridine (70 μL, 0.080 mmol) was added at 0 °C. The resulting mixture was poured into saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give a crude product. Purification by column chromatography (eluent, hexane:ethyl acetate = 10:1) gave the ketal (0.47 g, 78%) as a colorless oil. R_f 0.40 (hexane:ethyl acetate = 4:1). IR (CH_2Cl_2 cast film) 2956, 2883, 2782, 1737, 1434, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (t, J = 5.0 Hz, 1H), 3.97-3.80 (m, 4H), 3.65 (s, 3H), 2.33 (s, 2H), 1.74 (d, J = 5.0 Hz, 2H), 1.09 (s, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 102.6, 64.5, 51.1, 46.1, 45.1, 31.8, 27.8. HRMS calcd. for $C_{10}H_{17}O_4$ $[M-H]^+$ 201.11269, Found 201.11314.



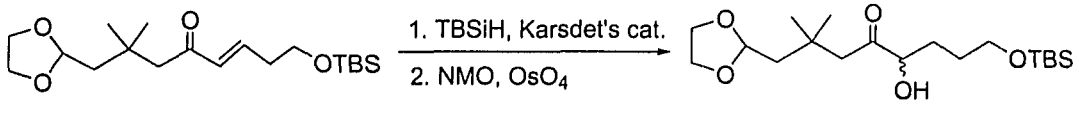
Dimethyl 2-oxo-4,4-dimethyl-6-(1,3-dioxolane)pentylphosphonate (89)

To a hexane solution of *n*-BuLi (17.5 mL, 1.6 M, 28.0 mmol) in THF (40 mL) was added dimethyl methyl phosphonate (3.80 mL, 34.6 mmol) at -78 °C under argon. After 1 h, methyl 3,3-dimethyl-5-(1',3'-dioxolane)-pentanoate (2.70 g, 13.3 mmol) was added dropwise. The mixture was stirred at -78 °C under argon for 3 h, and then poured into saturated aqueous ammonium chloride (10 mL). The mixture was extracted with chloroform (3 x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated at room temperature under vacuum. After dimethyl methyl phosphonate was removed at room temperature under high vacuum, the crude product (2.5 g, yield 65%) was used in the following reaction without further purification. R_f 0.37 (CH_2Cl_2:MeOH = 20:1); ^1H NMR (400 MHz, C_6D_6) δ 4.87 (t, J = 5.1 Hz, 1H), 3.96-3.40 (m, 2H), 3.38 (d, J = 11.9 Hz, 6H), 2.78 (d, J = 22.4 Hz, 2H), 2.54 (s, 2H), 1.92 (d, J = 5.1 Hz, 2H), 1.08 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 201.0 (d, J = 5.7 Hz), 103.0, 65.0 (2C), 54.0, 52.3 (d, J = 6.2 Hz), 44.6, 43.2 (d, J = 126 Hz), 31.9, 28.3.



8-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-2,2-dimethyl-oct-5-en-4-one (90)

To a solution of dimethyl 2-oxo-4,4-dimethyl-5-(1,3-dioxolane)hexanylphosphonate (2.9 g, 9.8 mmol) and LiCl (1.4 g, 32 mmol, hydroscopic, flame-dried) in anhydrous CH_3CN (50 mL) was added diisopropylethylamine (11 mL, 64 mmol), followed by the addition of a solution of 3-(*tert*-butyldimethylsilyloxy)-propionaldehyde (1.8 g, 9.5 mmol) in 10 mL of CH_3CN under an argon atmosphere. The mixture was stirred overnight. Another portion of the aldehyde (0.17 g, 1.0 mmol) was added and the reaction mixture was stirred for 3h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$, and the enone product was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (hexane and *tert*-butyl methyl ether 10:1 to 8:1) gave the pure enone 2.3 g (70%). R_f 0.45 (Hexane:EtOAc = 4:1); IR (neat) 2955, 2929, 2884, 2858, 1684, 1662, 1624, 1472, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.8, 7.0 Hz, 1H), 6.14 (dt, J = 15.8, 1.5 Hz, 1H), 4.94 (t, J = 5.0 Hz, 1H), 3.95-3.74 (m, 4H), 3.73 (t, J = 6.4 Hz, 2H), 2.54 (s, 3H), 2.41 (dq, J = 6.4, 1.5 Hz, 2H), 1.75 (d, J = 5.0 Hz, 2H),1.08 (s, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.1, 142.3, 133.6, 103.2, 64.5, 61.8, 51.1, 45.6, 36.0, 32.4, 28.4, 26.1, -5.2. HRMS (EI) [M^+] for $C_{19}H_{36}O_4Si$ calcd 356.23828, found: m/z 356.23784.



8-(*tert*-Butyldimethylsilanyloxy)-1-[1,3]dioxolan-2-yl-2,2-dimethyl-5-hydroxy-octan-4-one (91)

tert-Butyldimethylsilane (1.16 g, 10.0 mmol) and Karstedt's catalyst (150 μL, platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane, 0.1 M, xylenes solution) were added into a round bottom flask, which was flushed with argon. Then the enone (0.78 g, 3.0 mmol) was introduced via a syringe. The mixture was stirred at room

temperature for 1 h. The reaction mixture was filtered through a short silica plug, using hexane and *tert*-butyl methyl ether (10:1) as the eluent. After the solvent and excess *tert*-butyldimethylsilane were evaporated under vacuum, the residue was directly used in the next reaction.

A mixture of this resulting silyl enol ether (3 mmol) and *N*-methyl-morpholine *N*-oxide (608 mg, 4.50 mmol) in 30 mL of acetone and water (9:1) was treated with 2.4 mL of OsO_4 solution (0.05 mmol/mL in 2-propanol). The reaction mixture was stirred at room temperature overnight. Then solid sodium sulfite (3.0 g) was added to the reaction mixture at 0 °C. Dichloromethane (30 mL) was added to the reaction mixture. After the organic layer was separated, the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a dark yellow oil, which was purified by flash chromatography with ethyl acetate and hexane (6:1 – 4:1) to afford the pure product (0.62 g, yield 55%). R_f 0.34 (Hexane:EtOAc = 1:1); IR (neat) 3475, 2955, 2858, 1712, 1472, 1101cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.84 (dd, J = 5.5, 4.8 Hz, 1H), 4.12 (ddd, J = 8.2, 4.2, 4.2 Hz, 1H), 3.70 (d, J = 4.8 Hz, 1H), 3.52-3.45 (m, 4H), 3.30-3.28 (m, 1H), 2.32 (AB, d, J = 14.2 Hz, 1H), 1.92 (AB, dd, J = 14.2, 5.5 Hz, 1H), 1.90-1.84 (m, 1H), 1.73-1.62 (m, 2H), 1.51-1.44 (m, 1H), 1.08 (s, 3H), 1.01 (s, 3H), 0.96 (s, 9H), 0.035 (s, 3H), 0.032 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.5, 102.9, 77.0, 64.6, 64.5, 62.8, 47.8, 44.7, 32.0, 30.6, 28.7, 28.6, 28.5, 26.2, 18.5, -5.2. HRMS (EI) [M^+] for $C_{19}H_{38}O_5Si$ calcd. 374.24884, found: m/z 374.24839. Anal. Calcd for $C_{18}H_{36}O_5Si$: C, 60.92; H, 10.23; Found C 60.89; H, 10.29.

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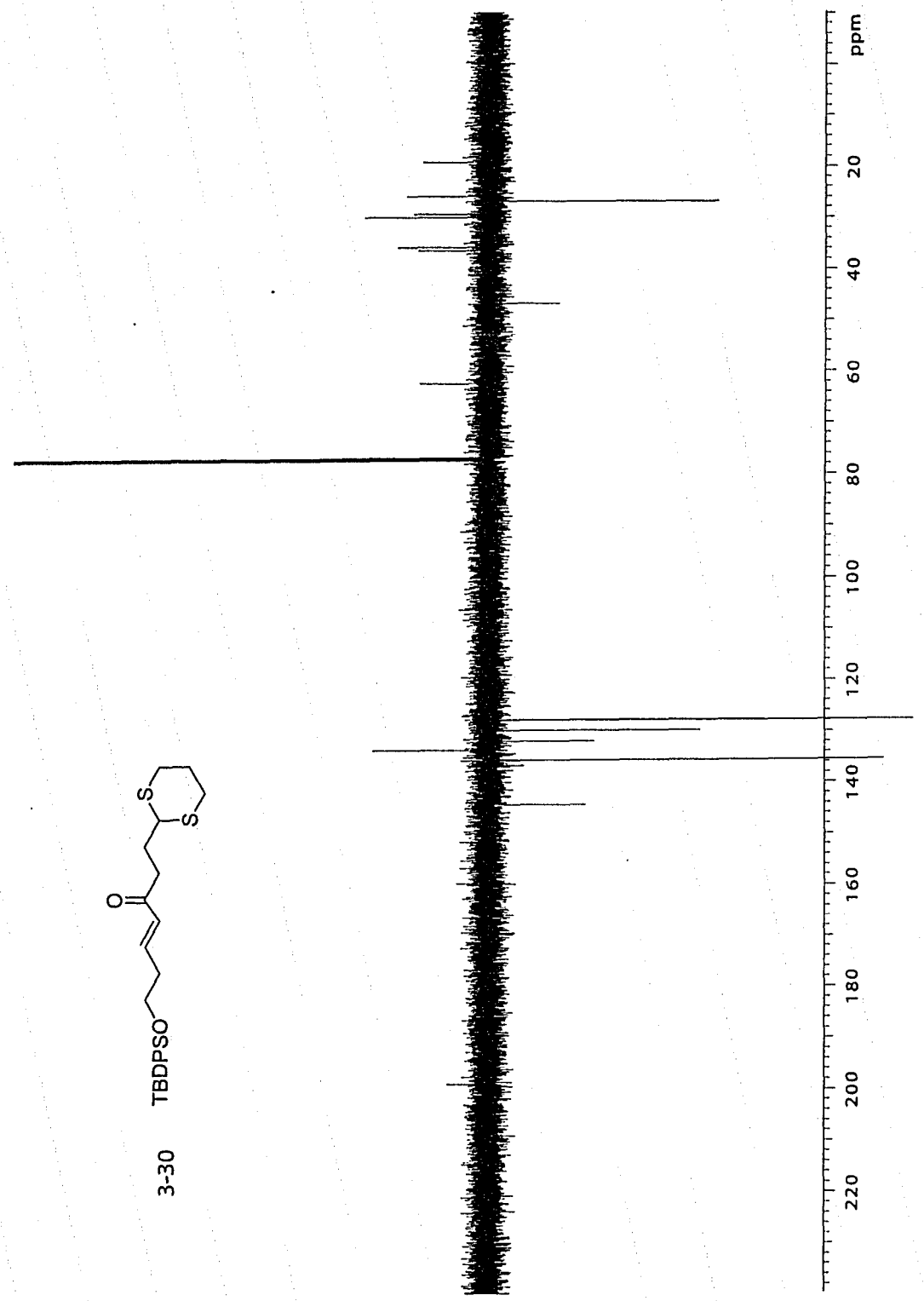
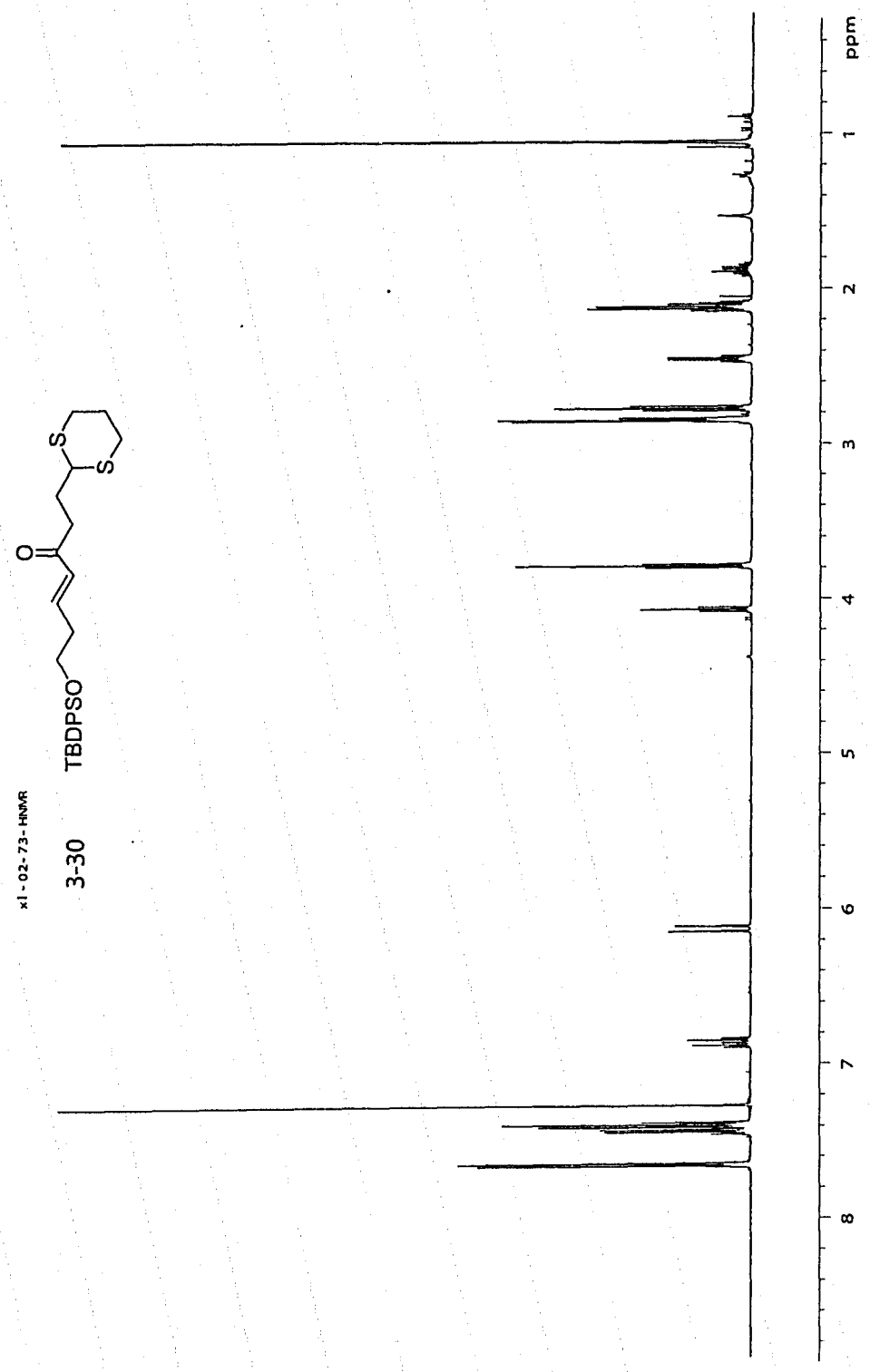
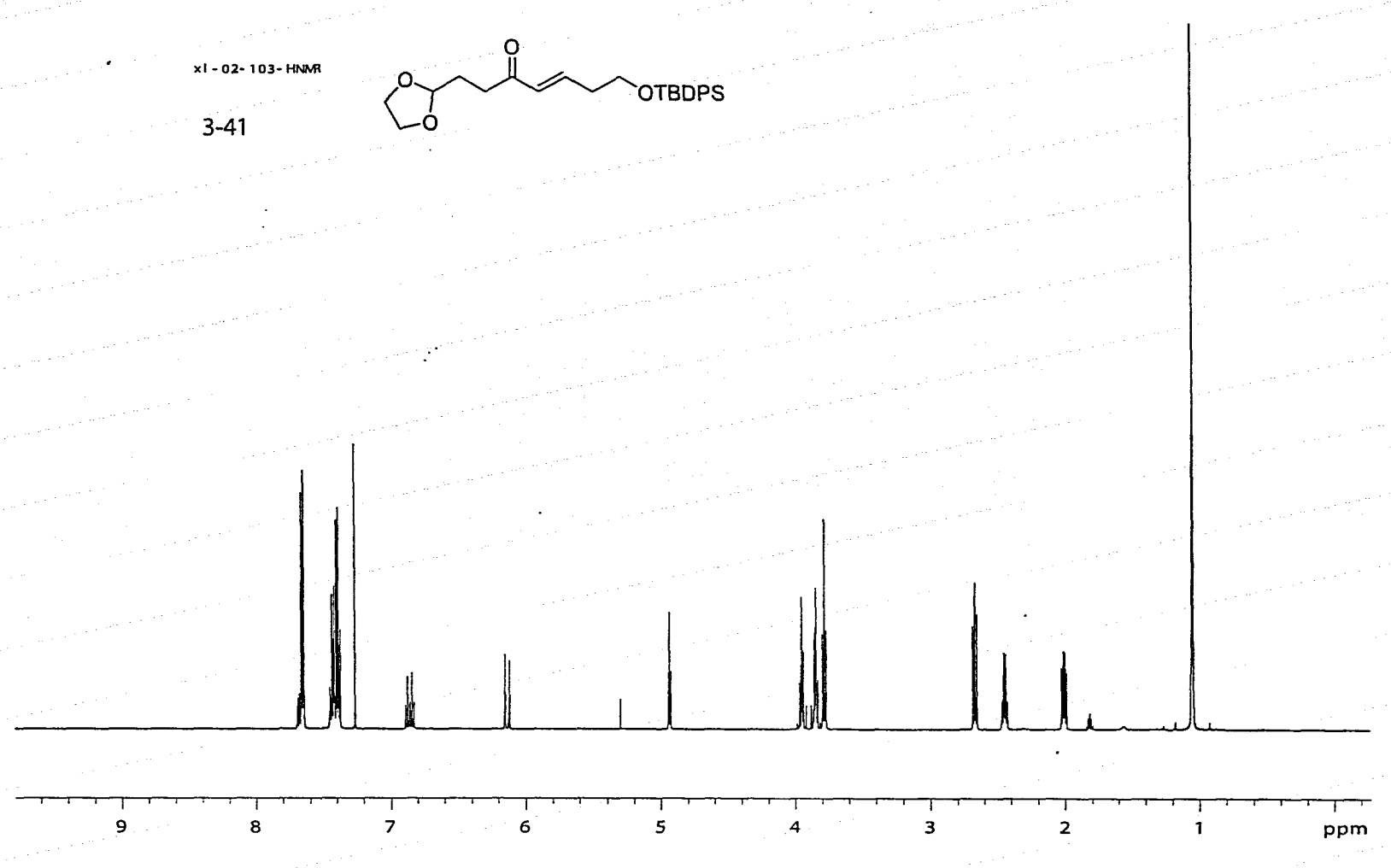
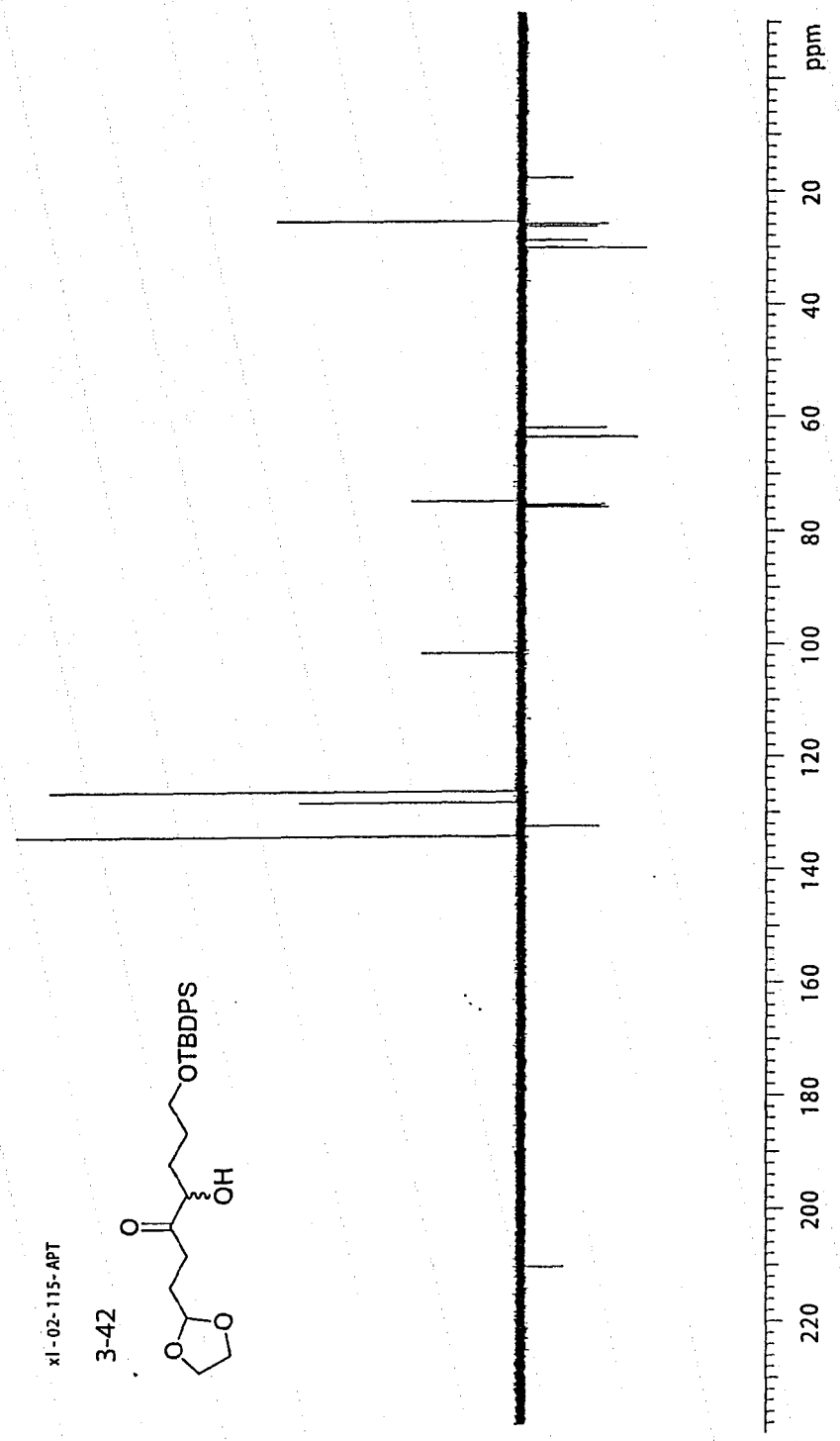
APPENDIX

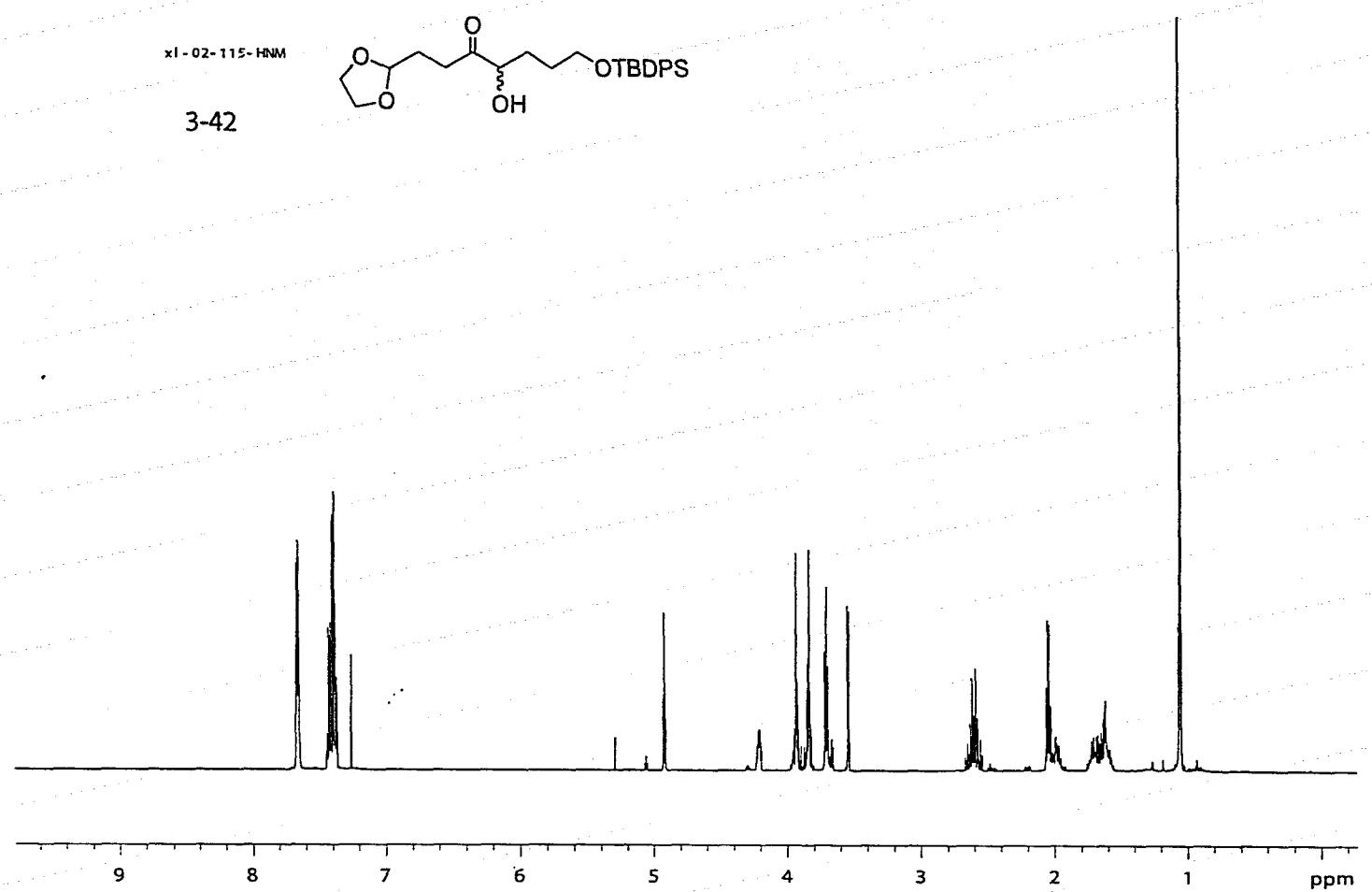
SELECTED NMR SPECTRA

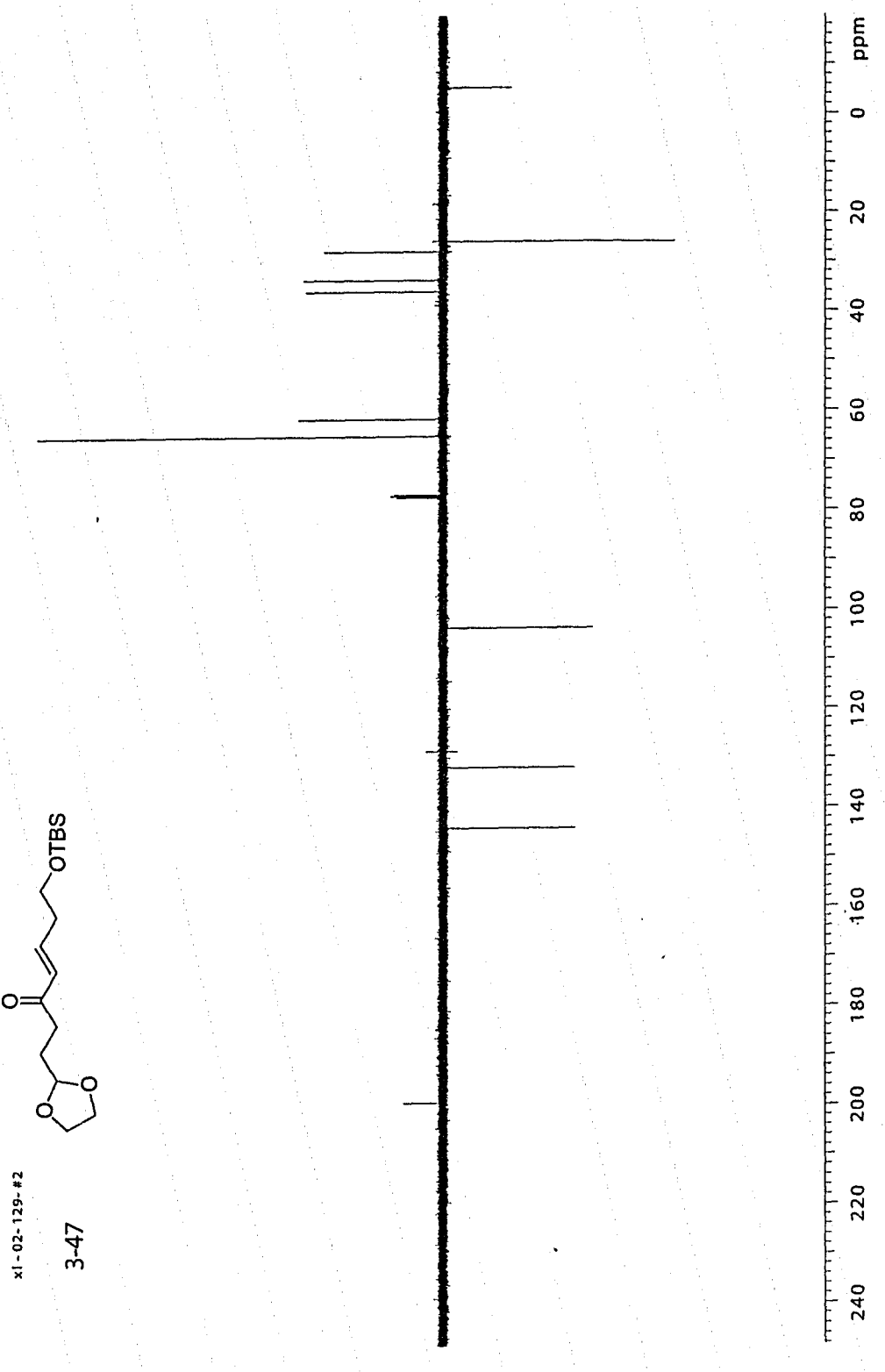


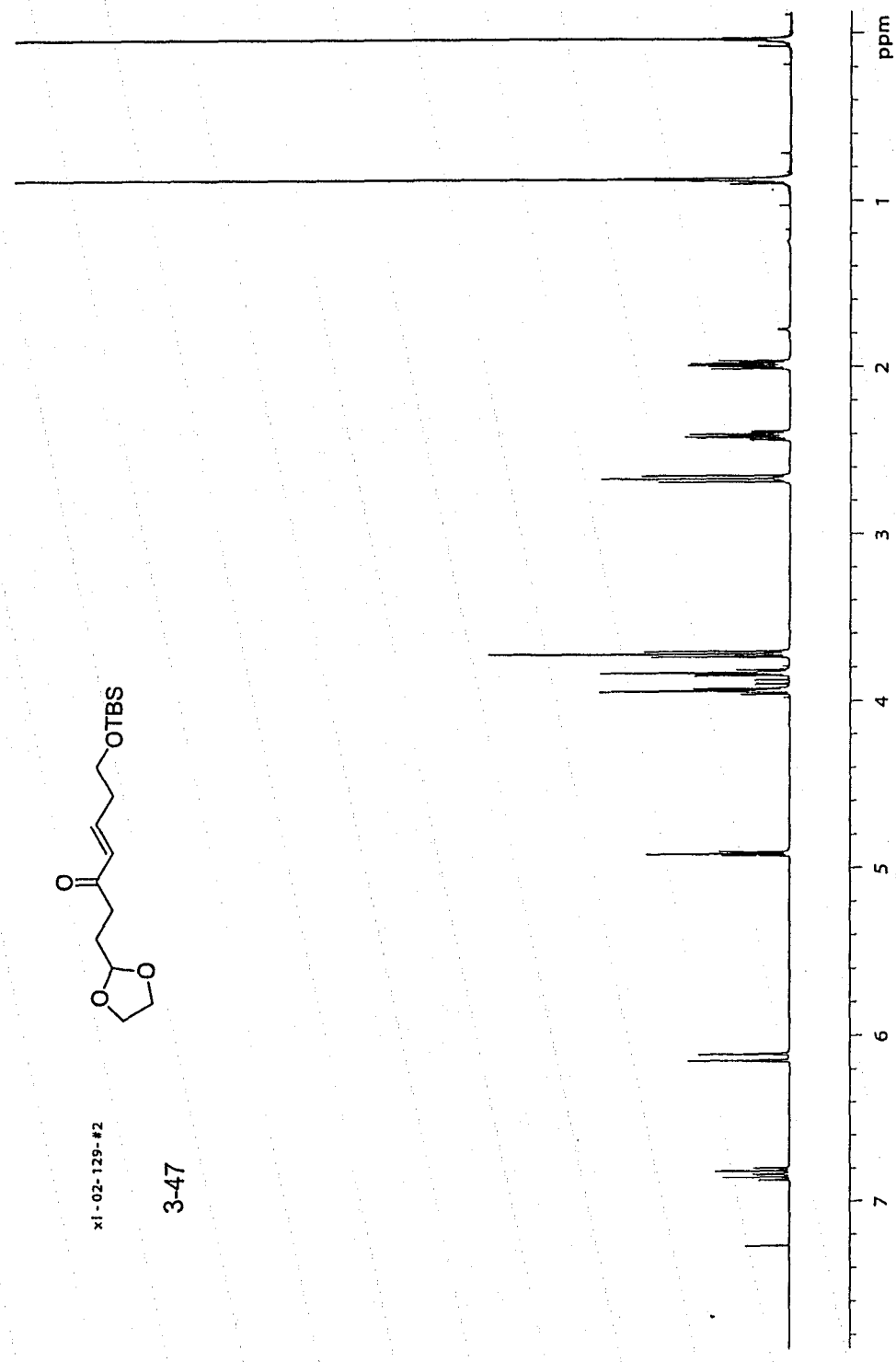


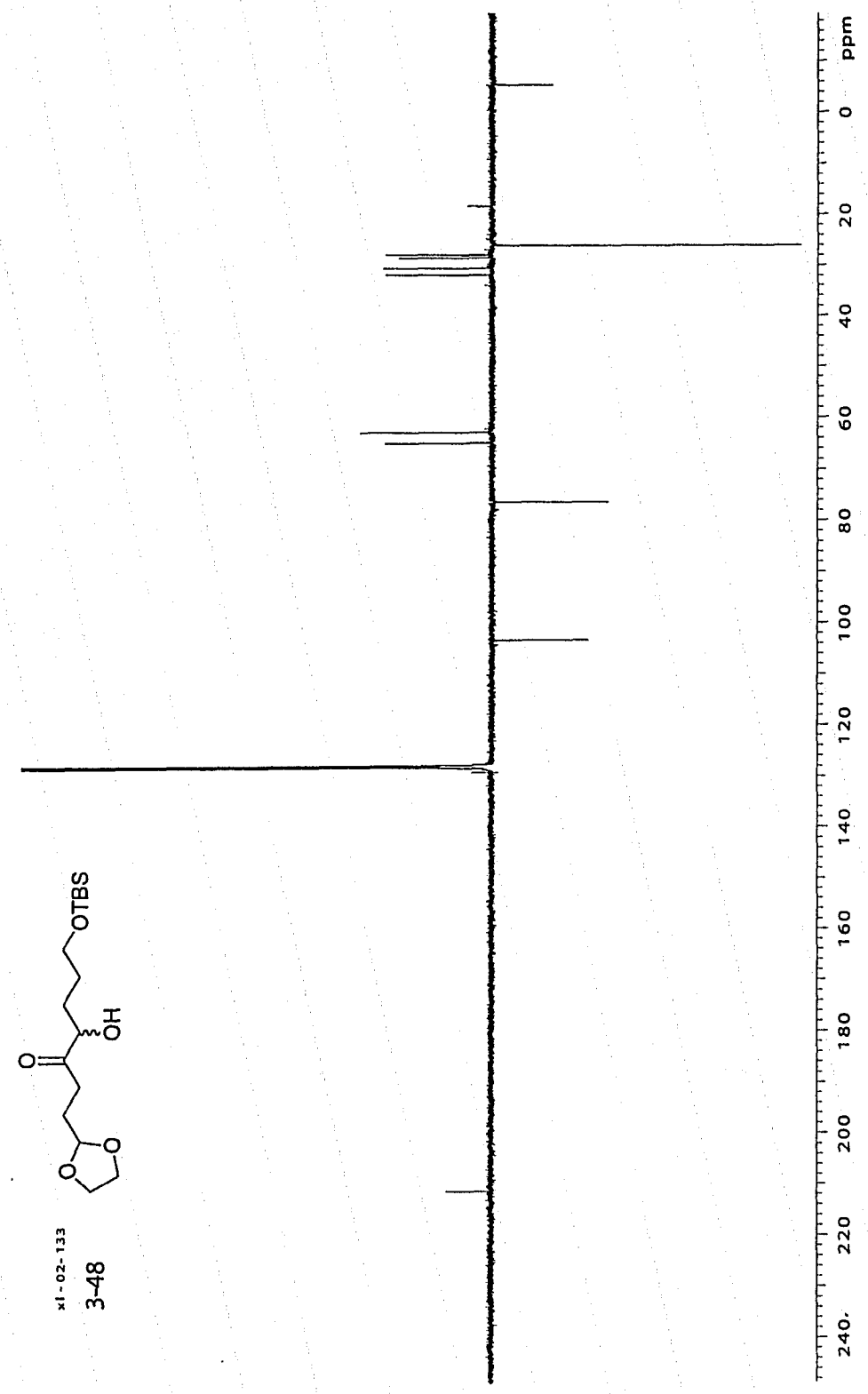


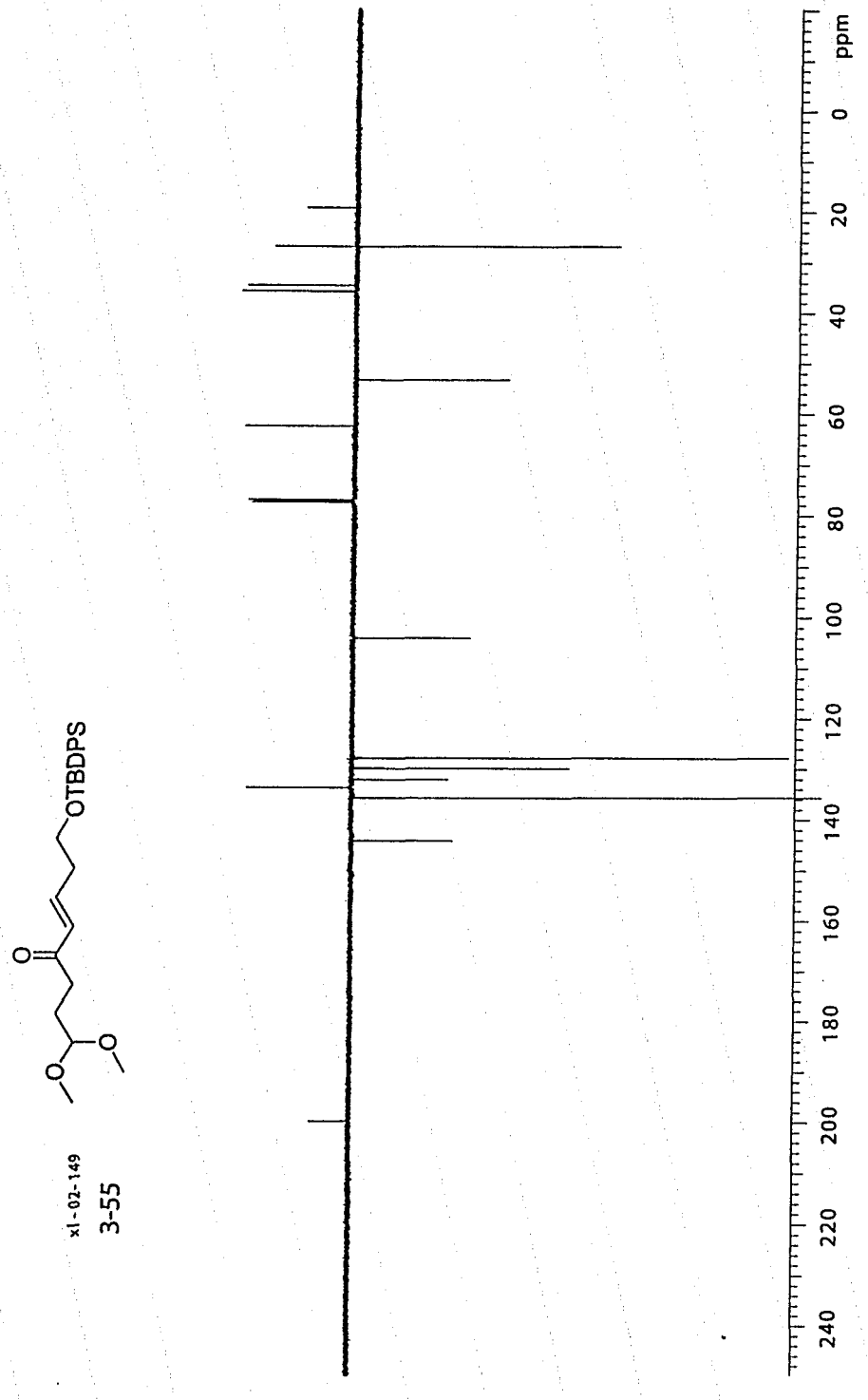


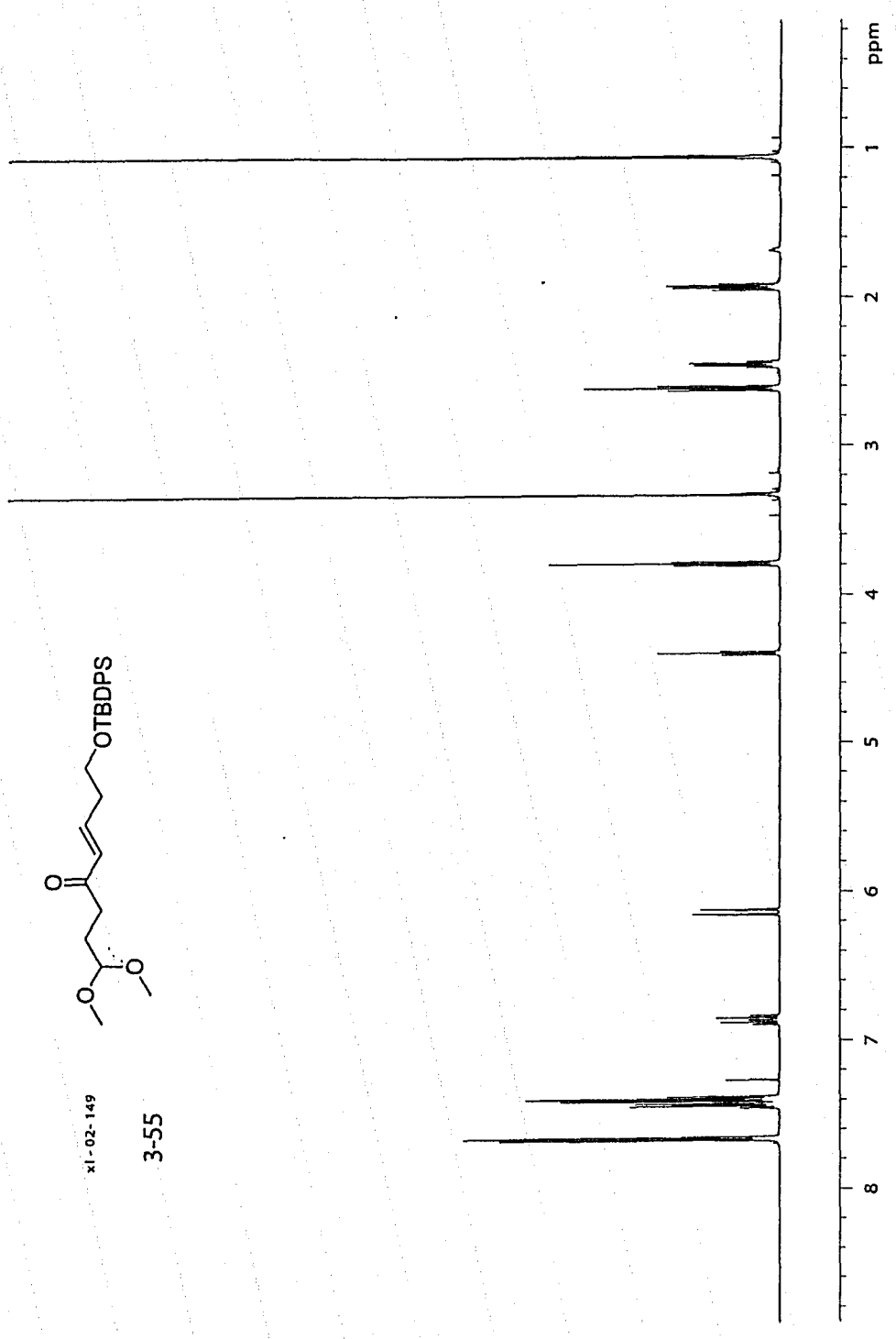


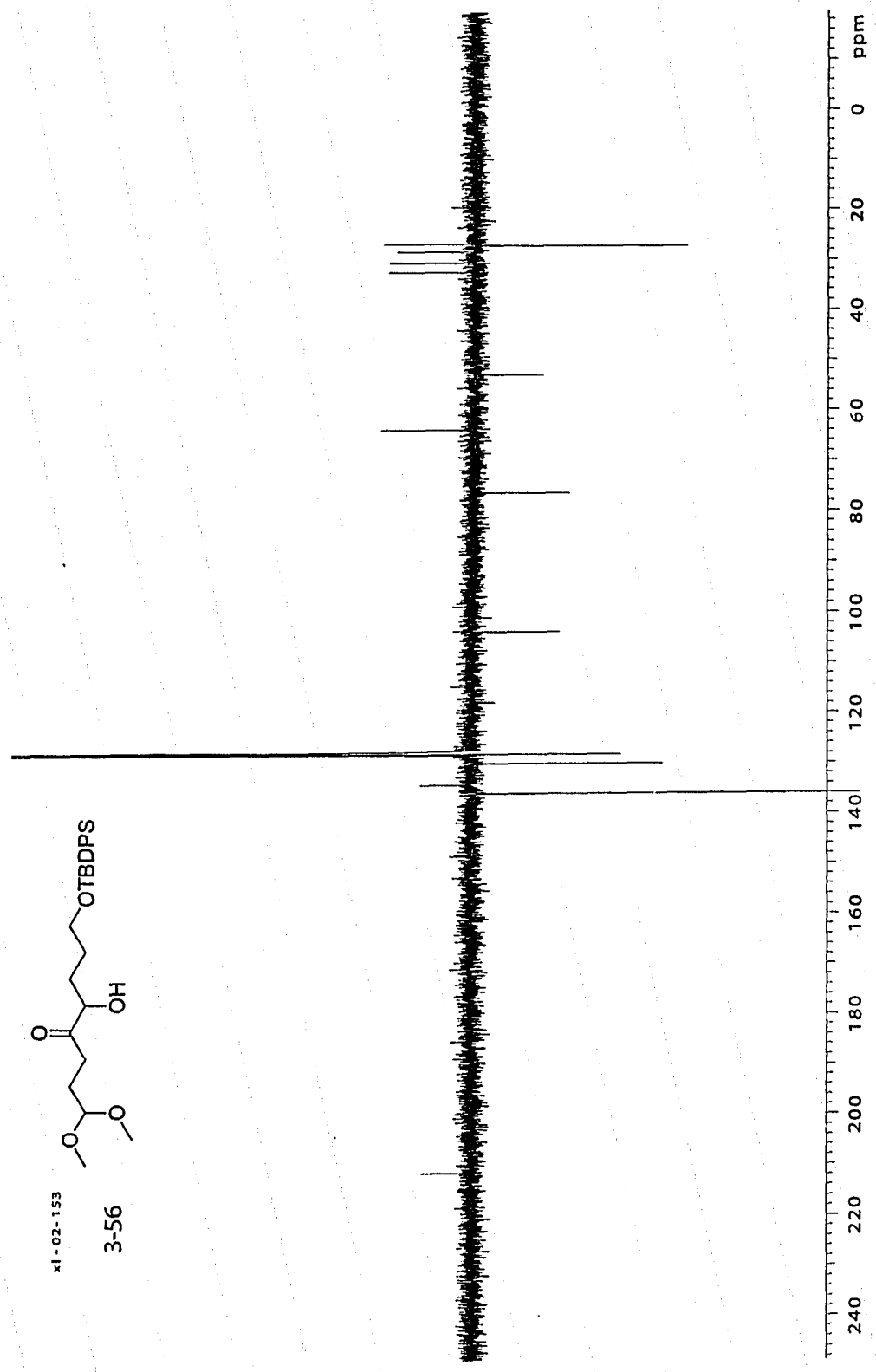


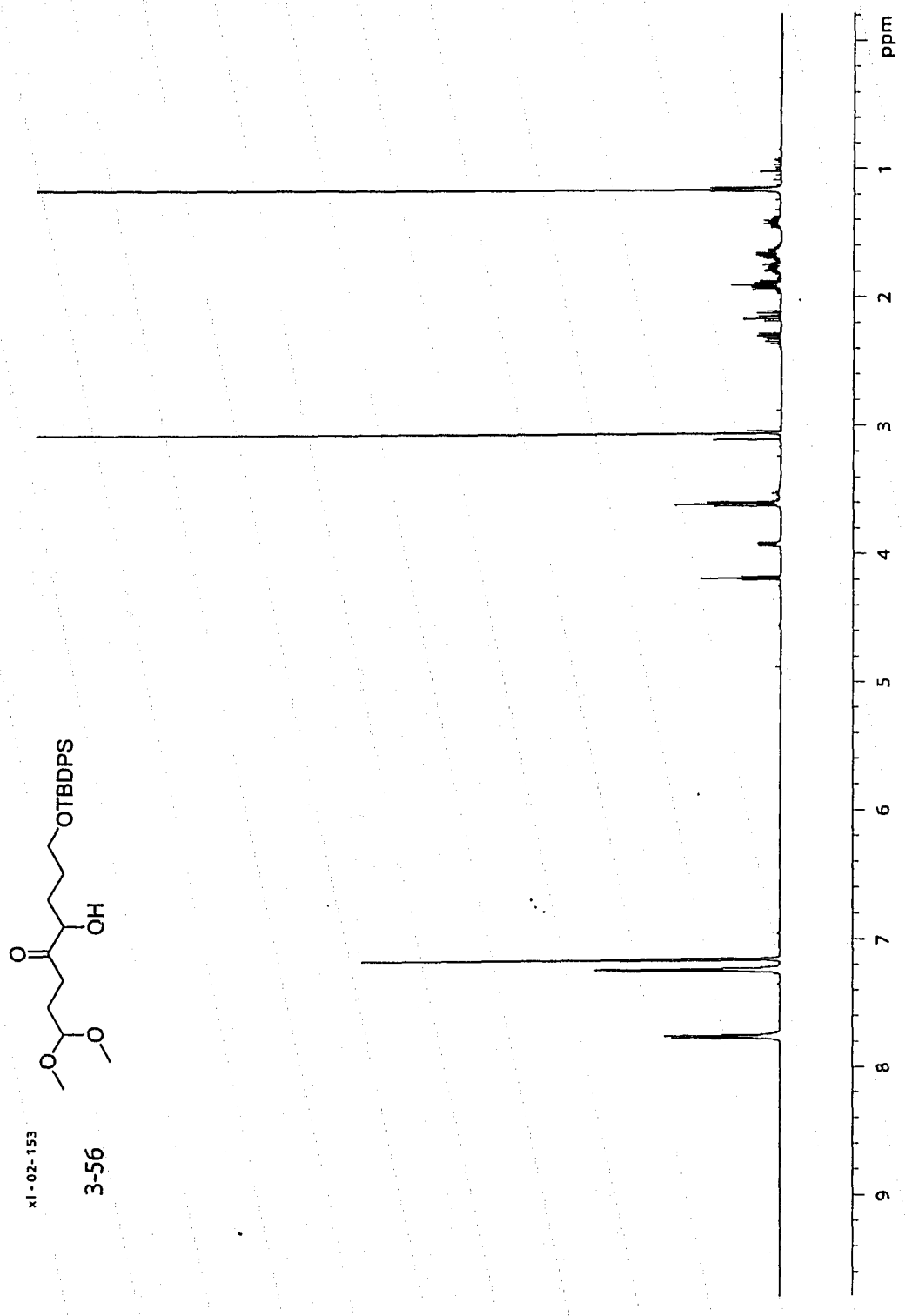


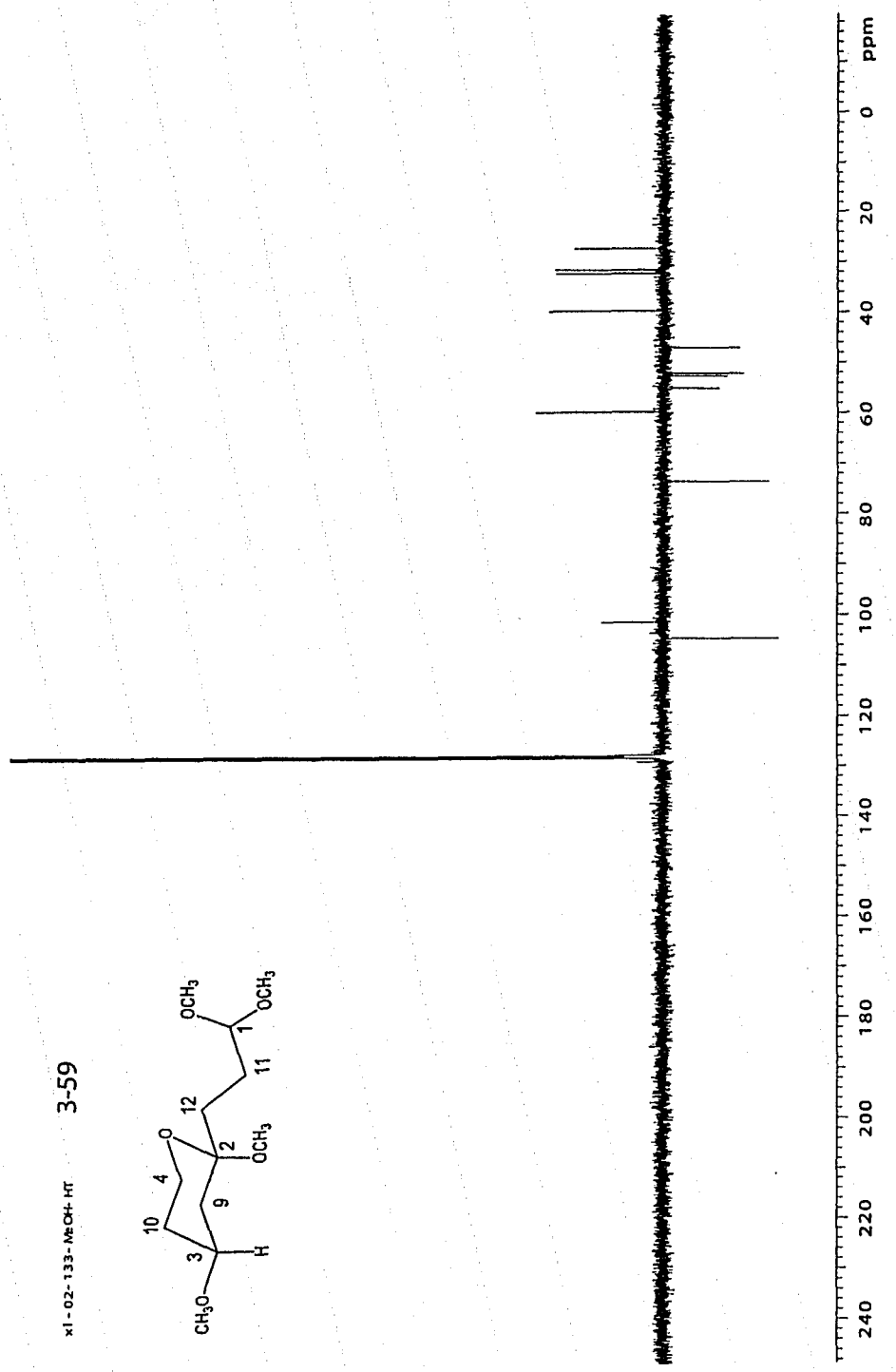


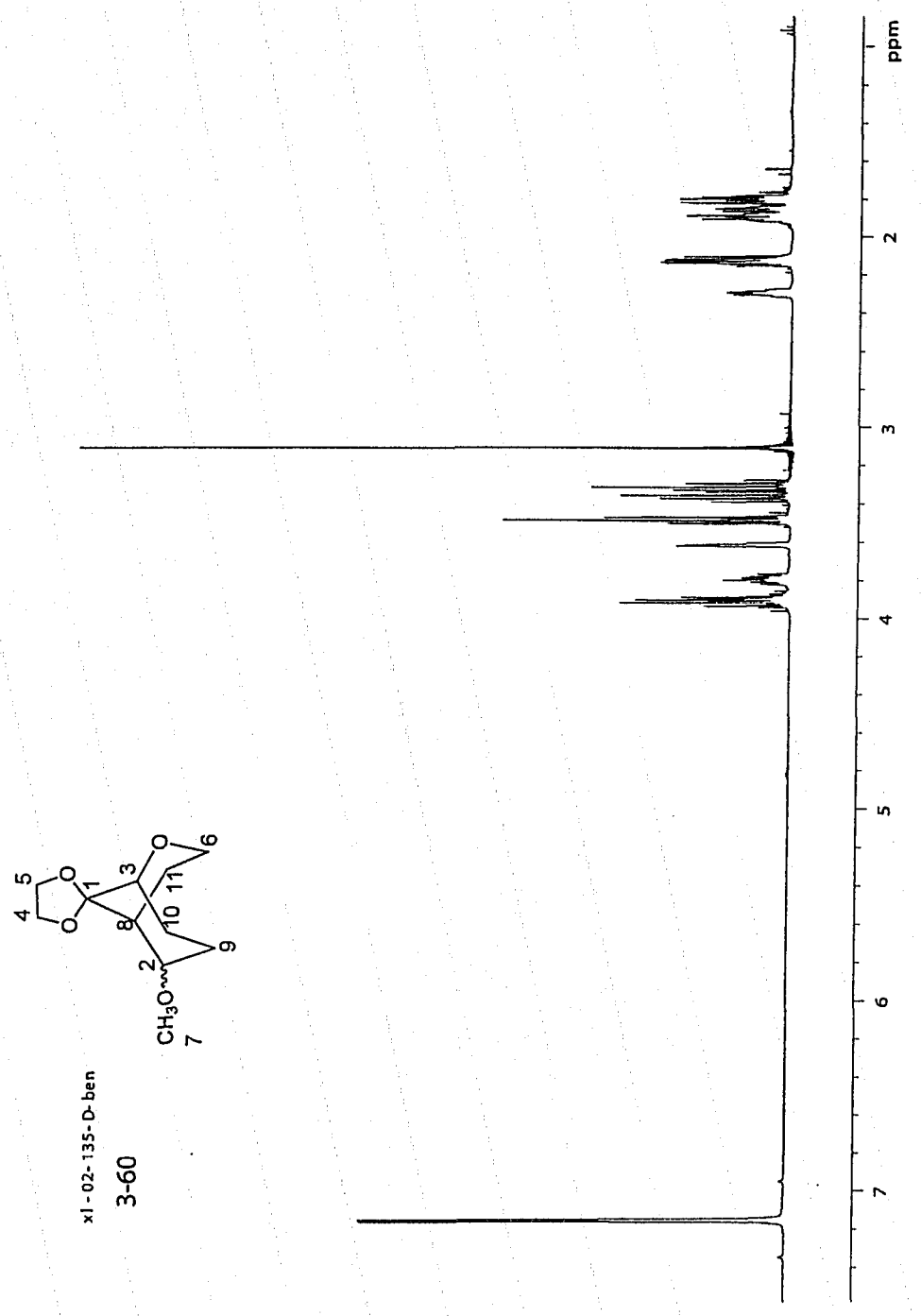












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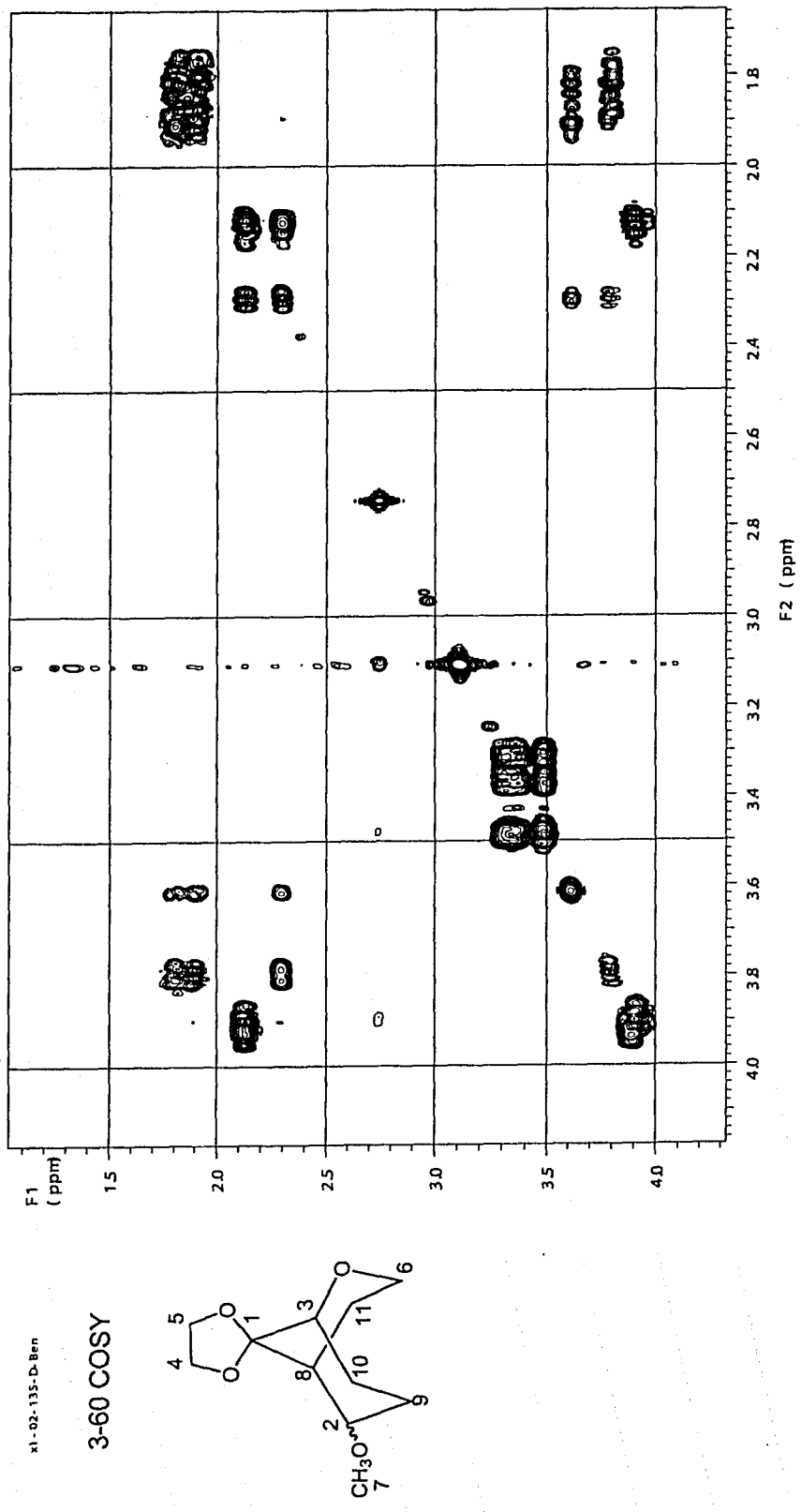

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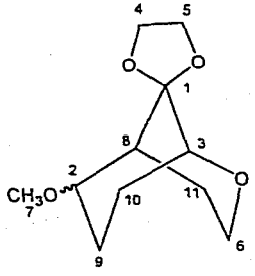

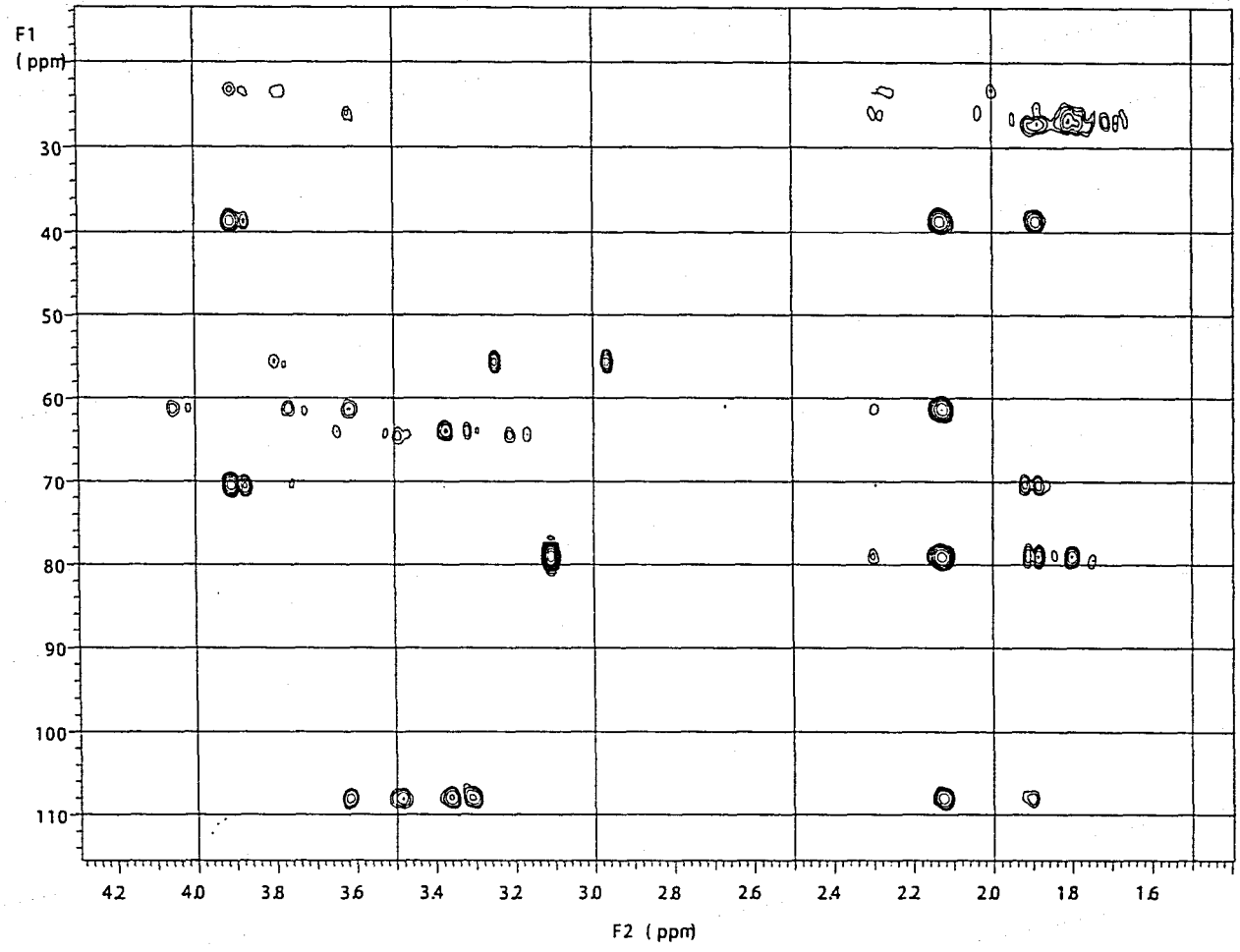

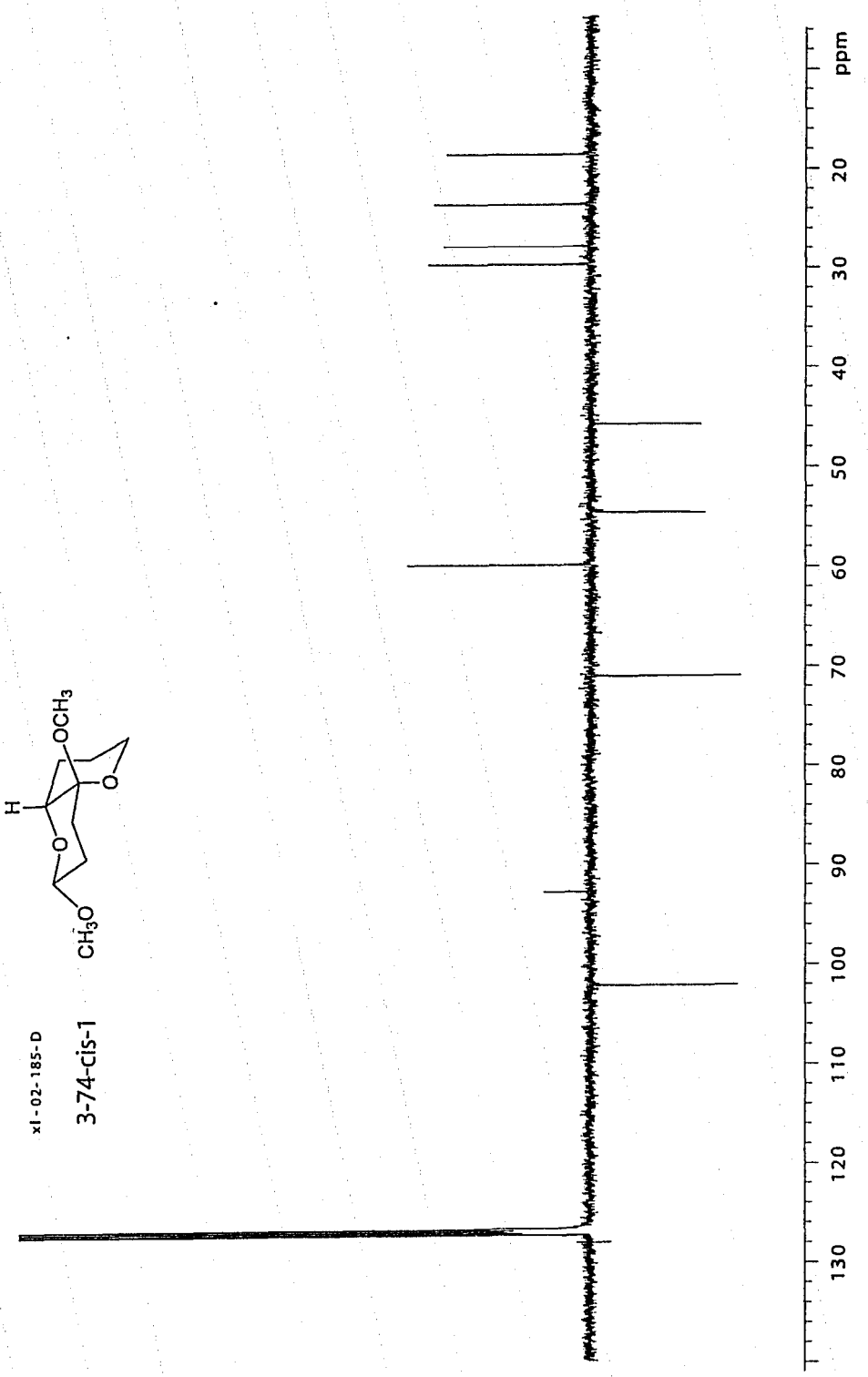

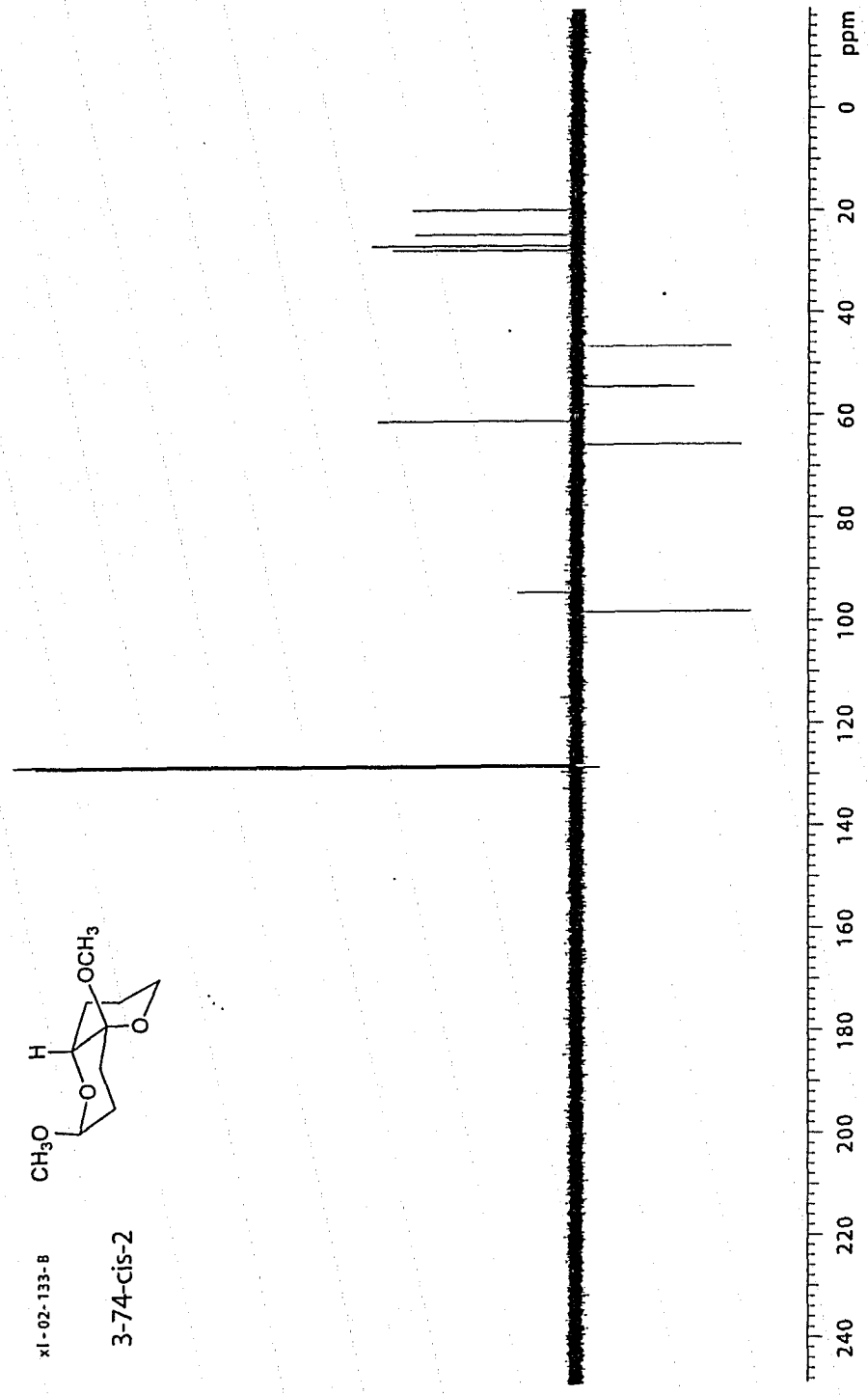

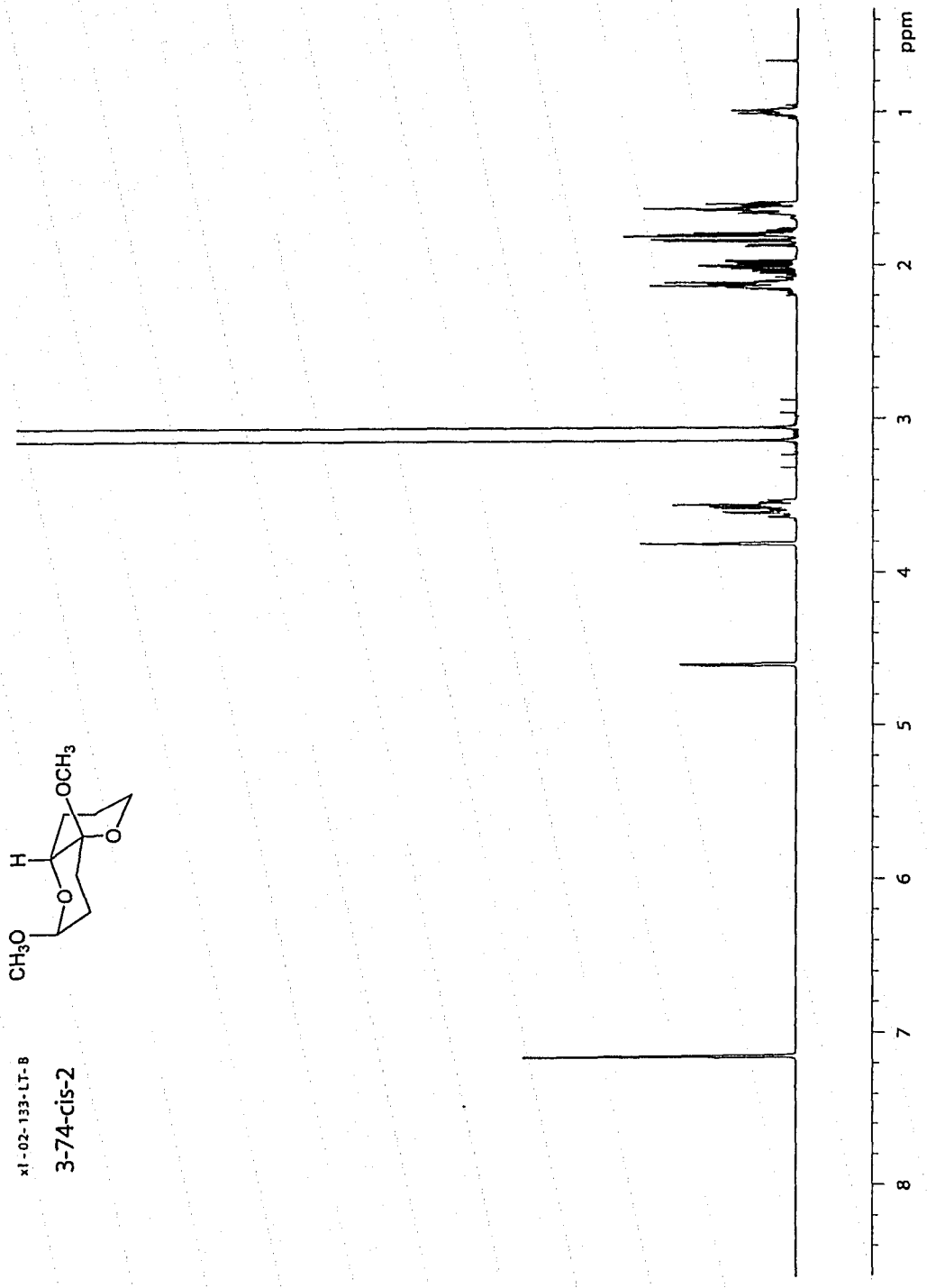

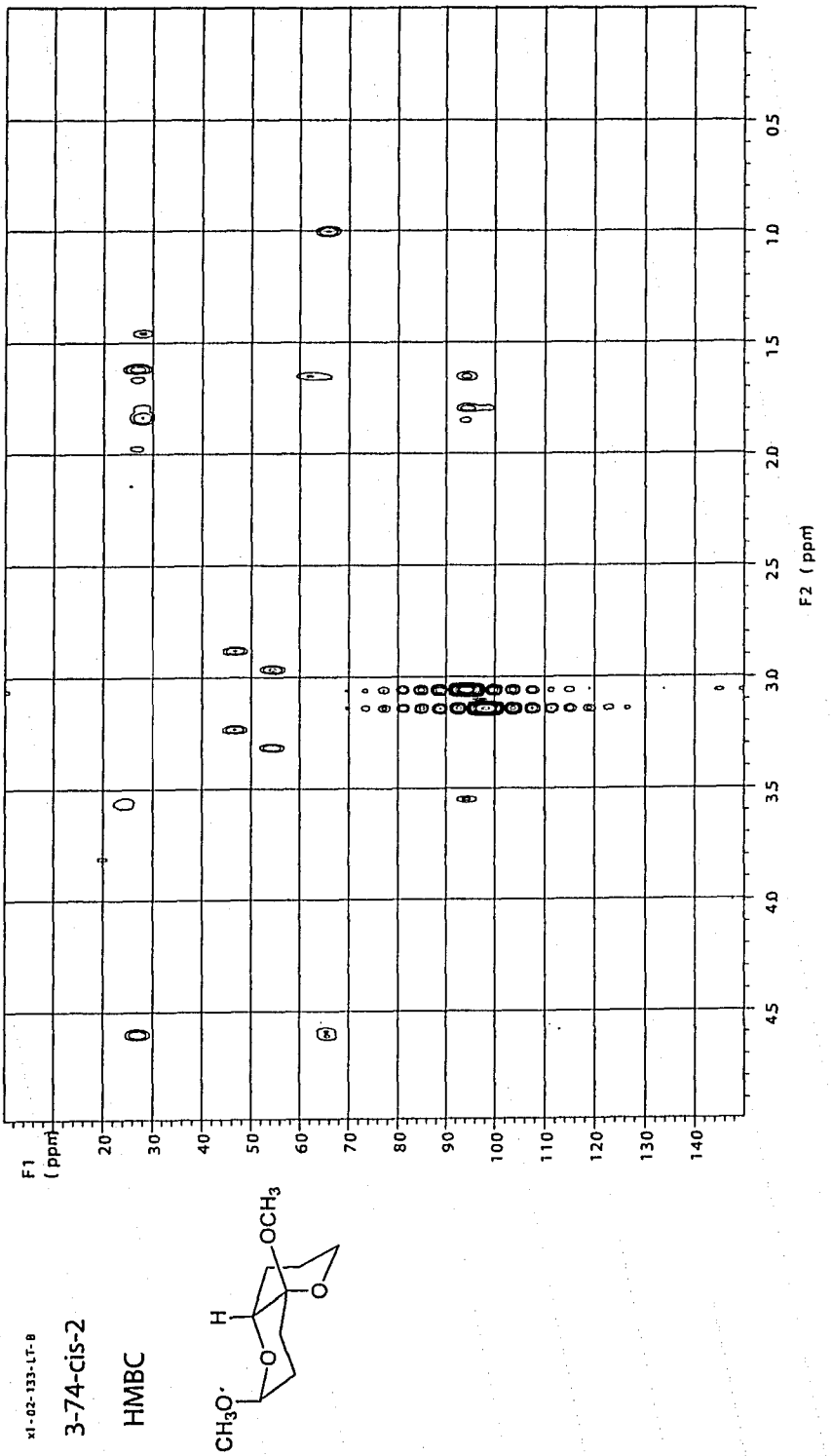

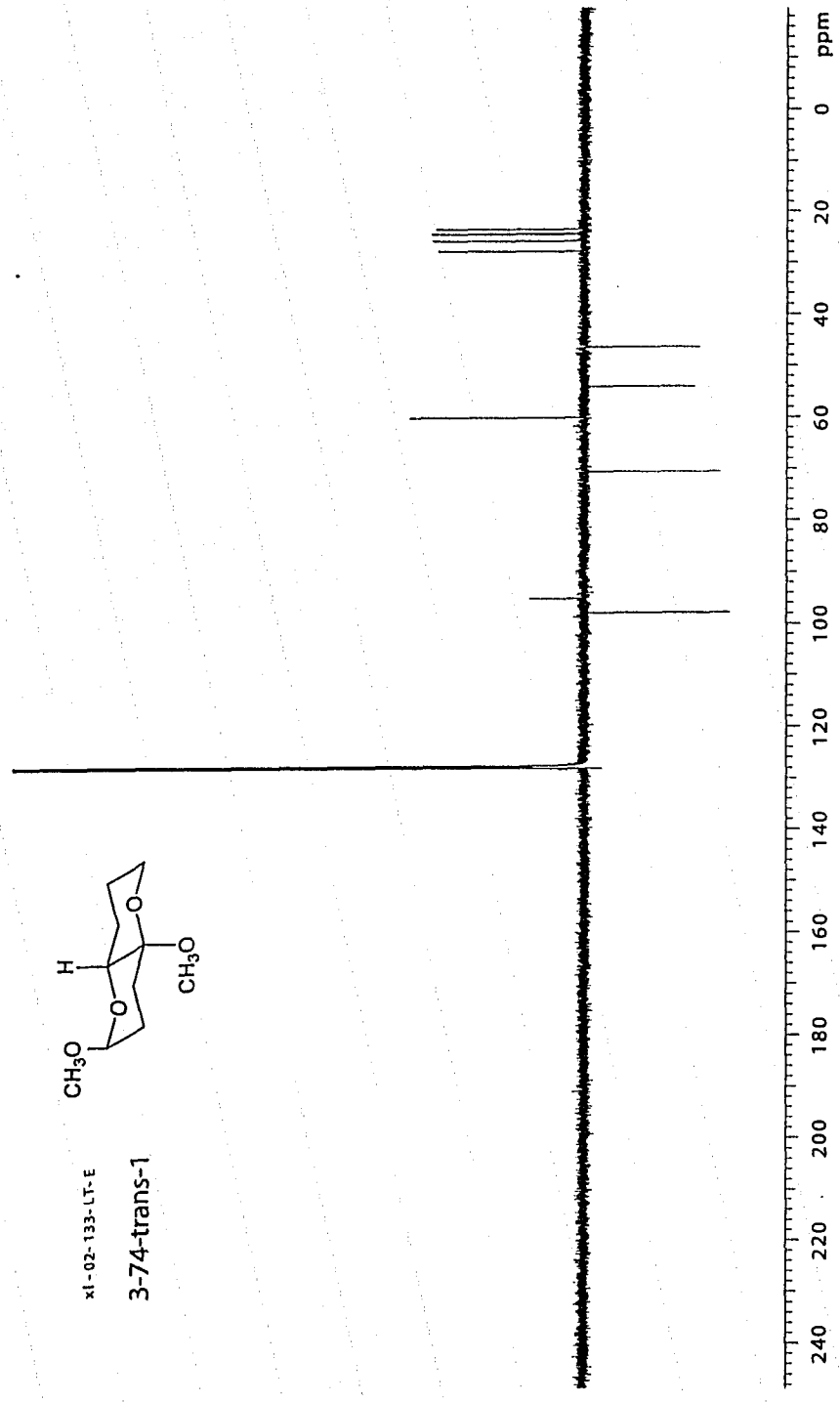

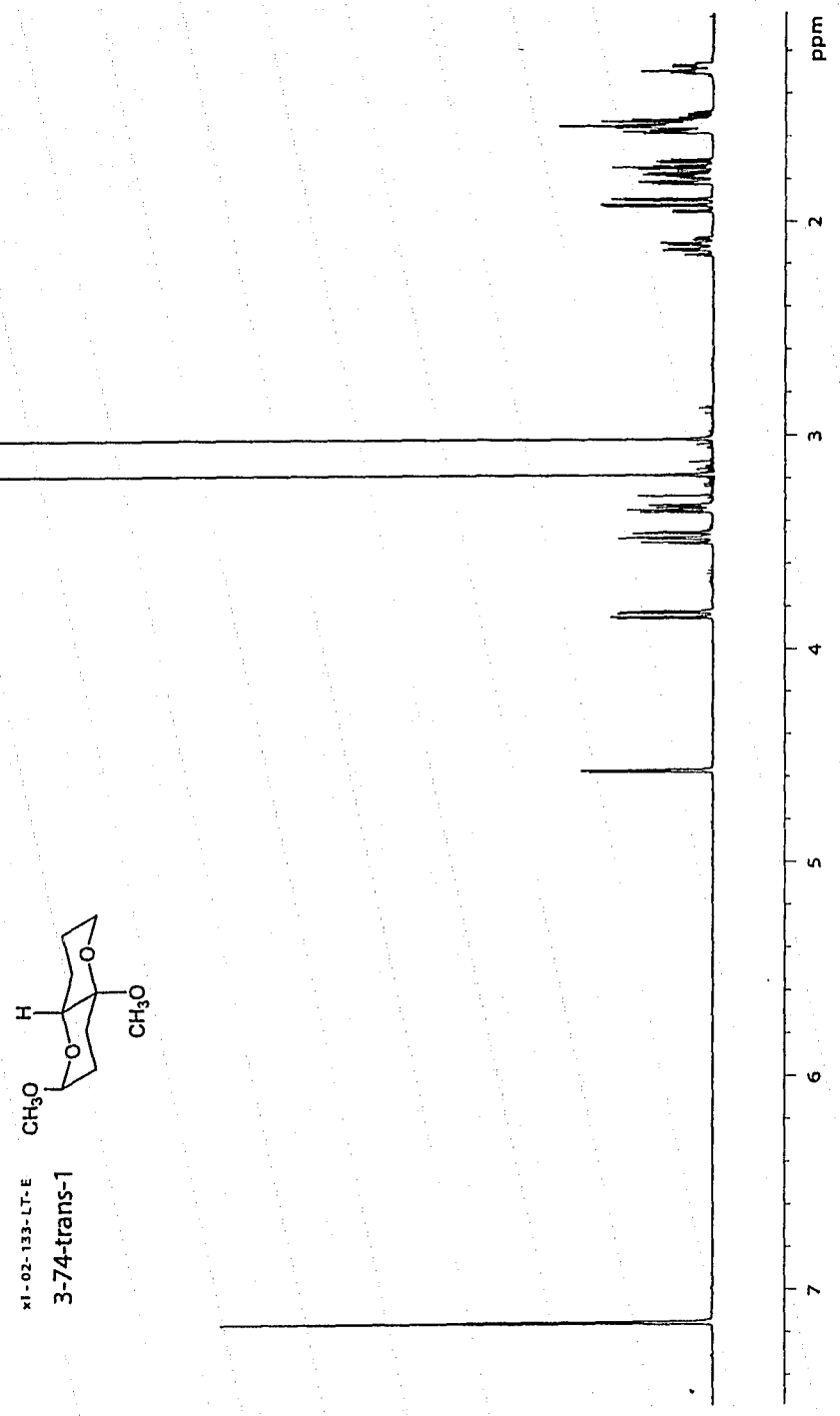

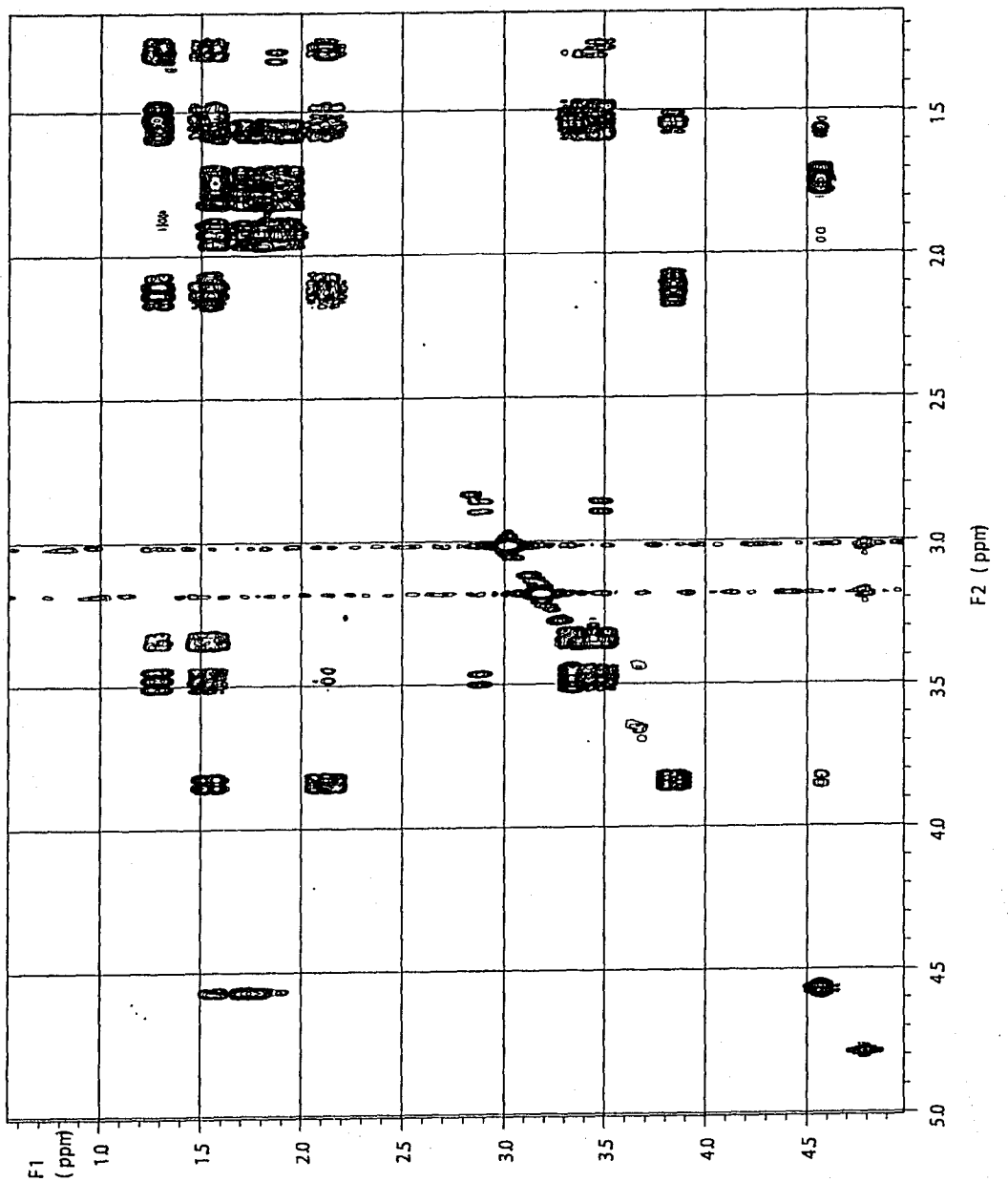

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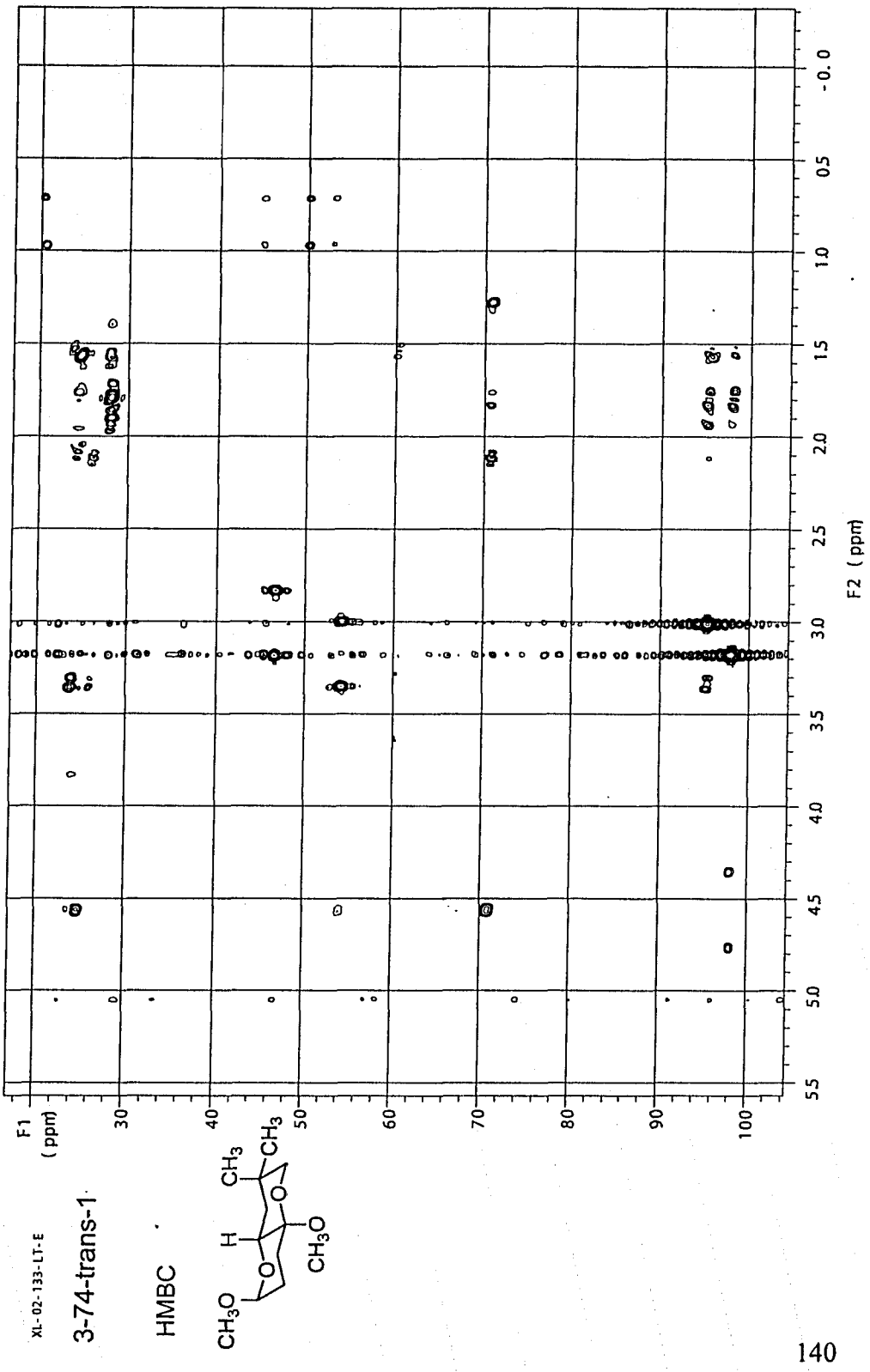
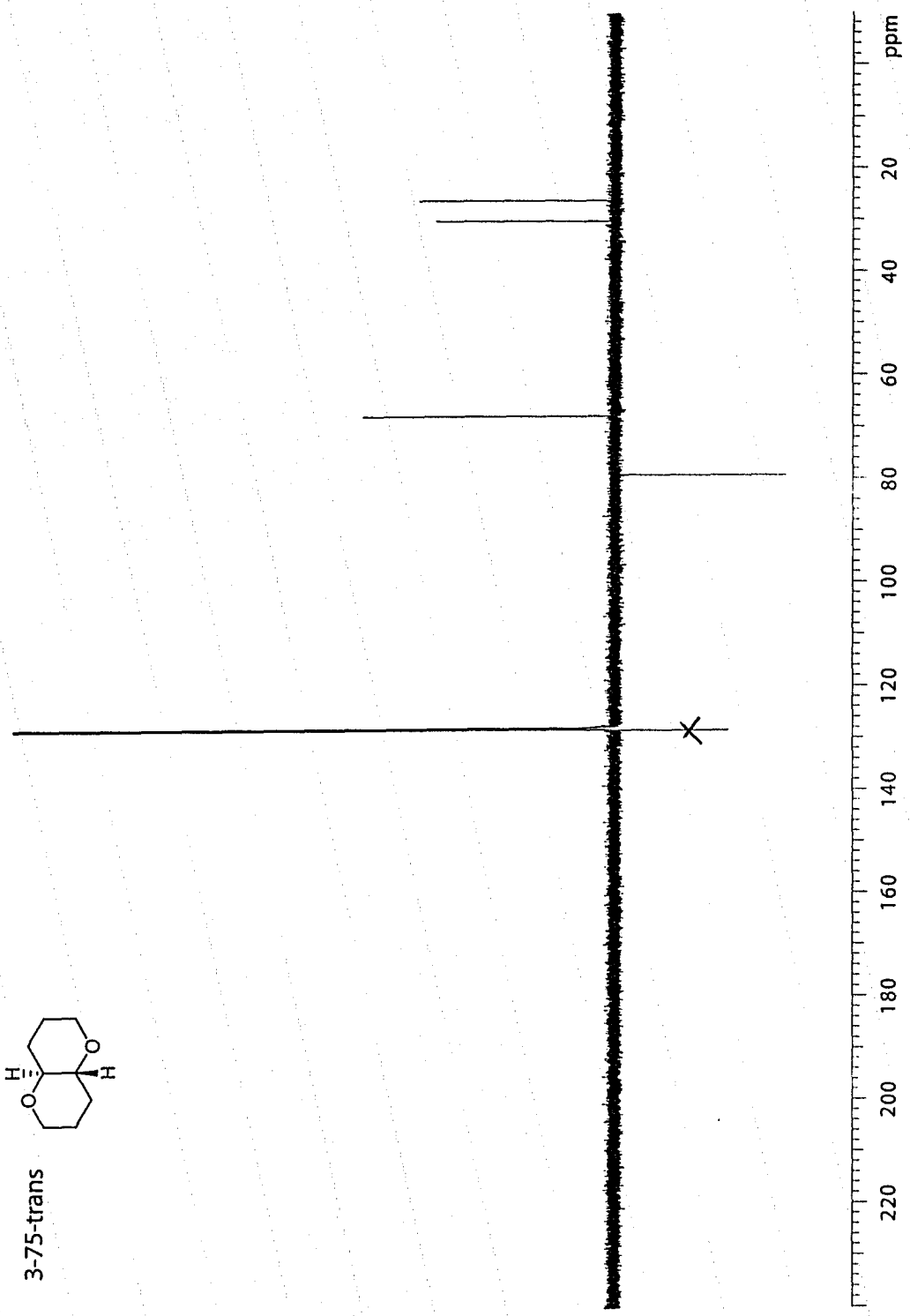
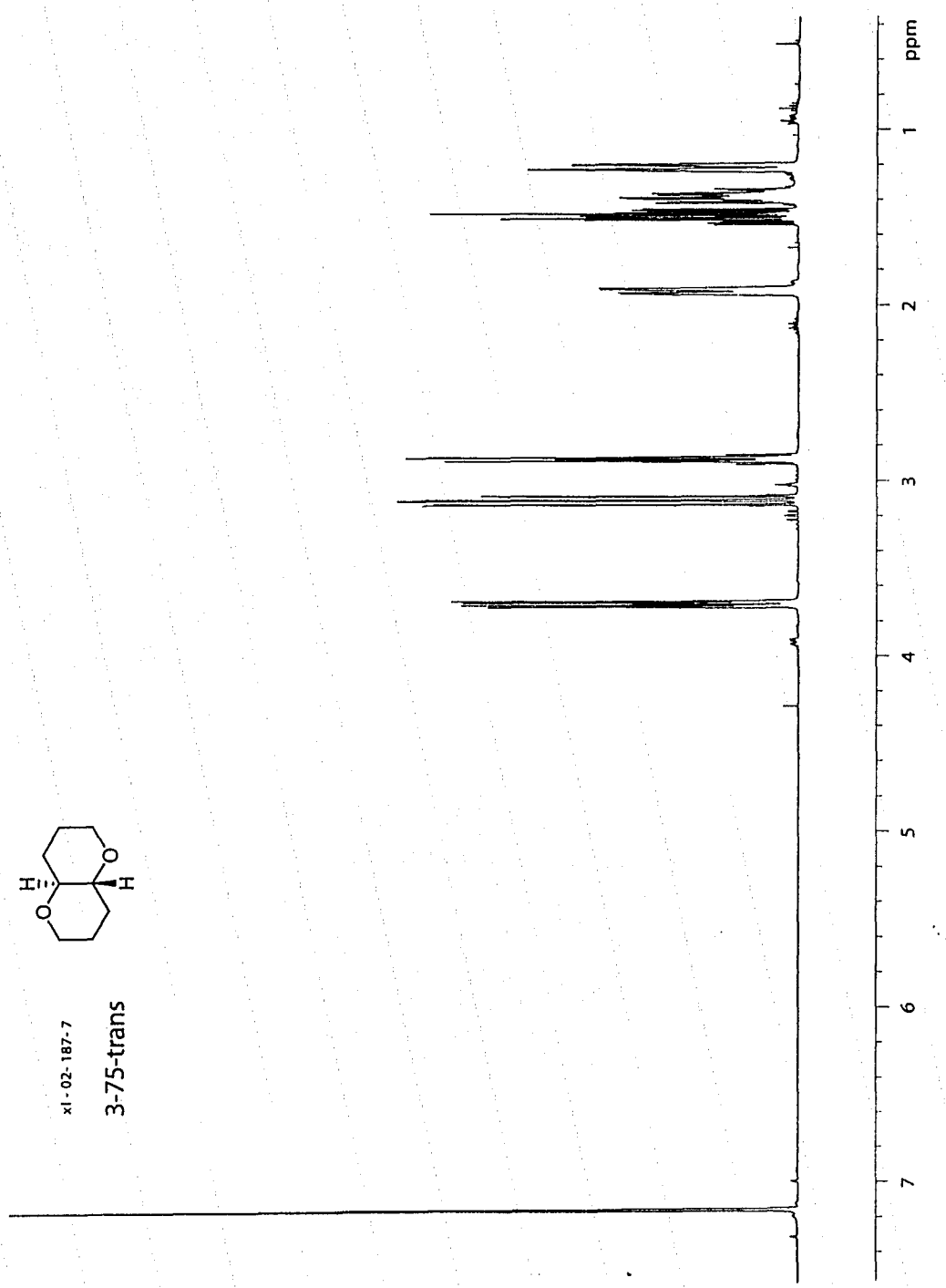
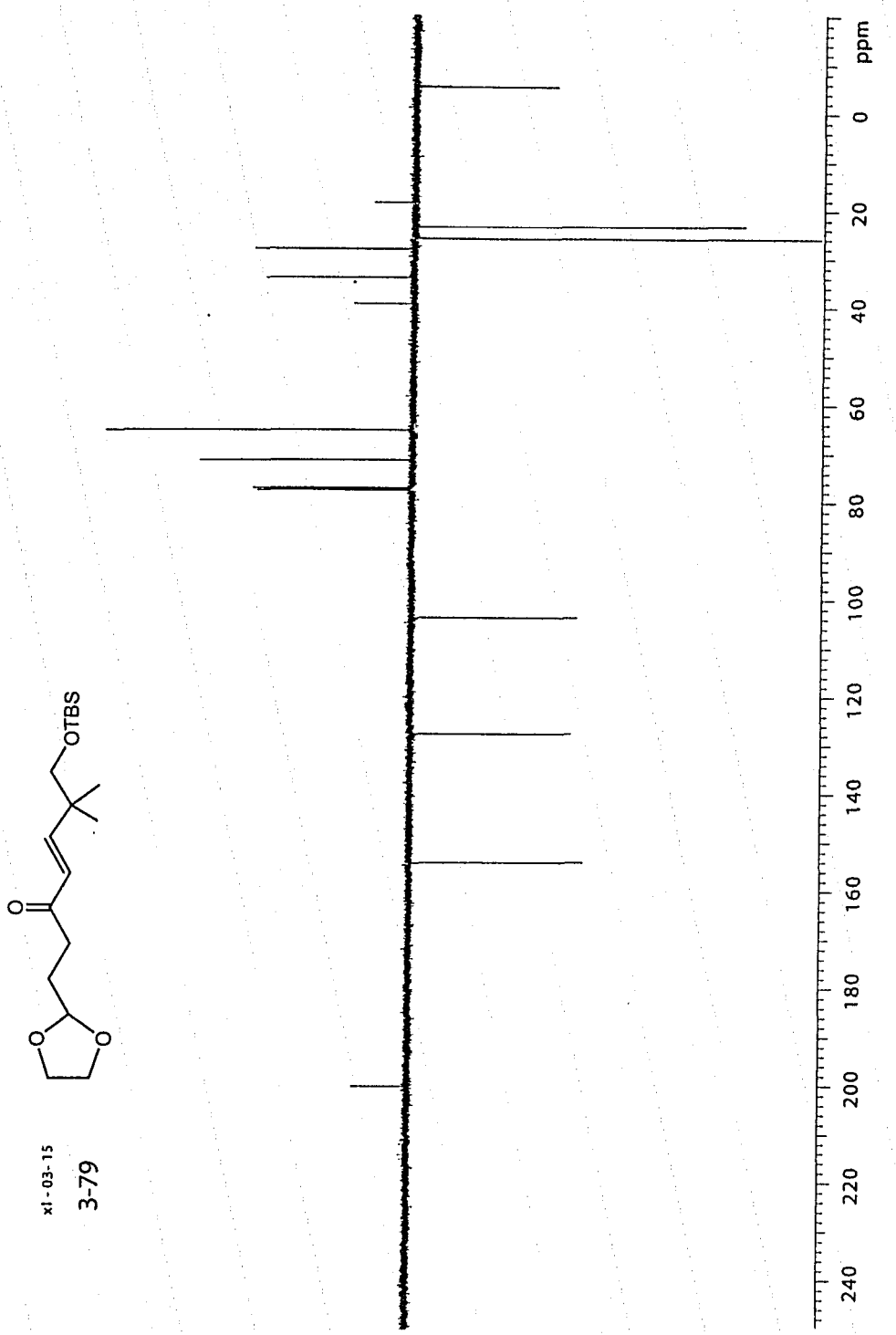
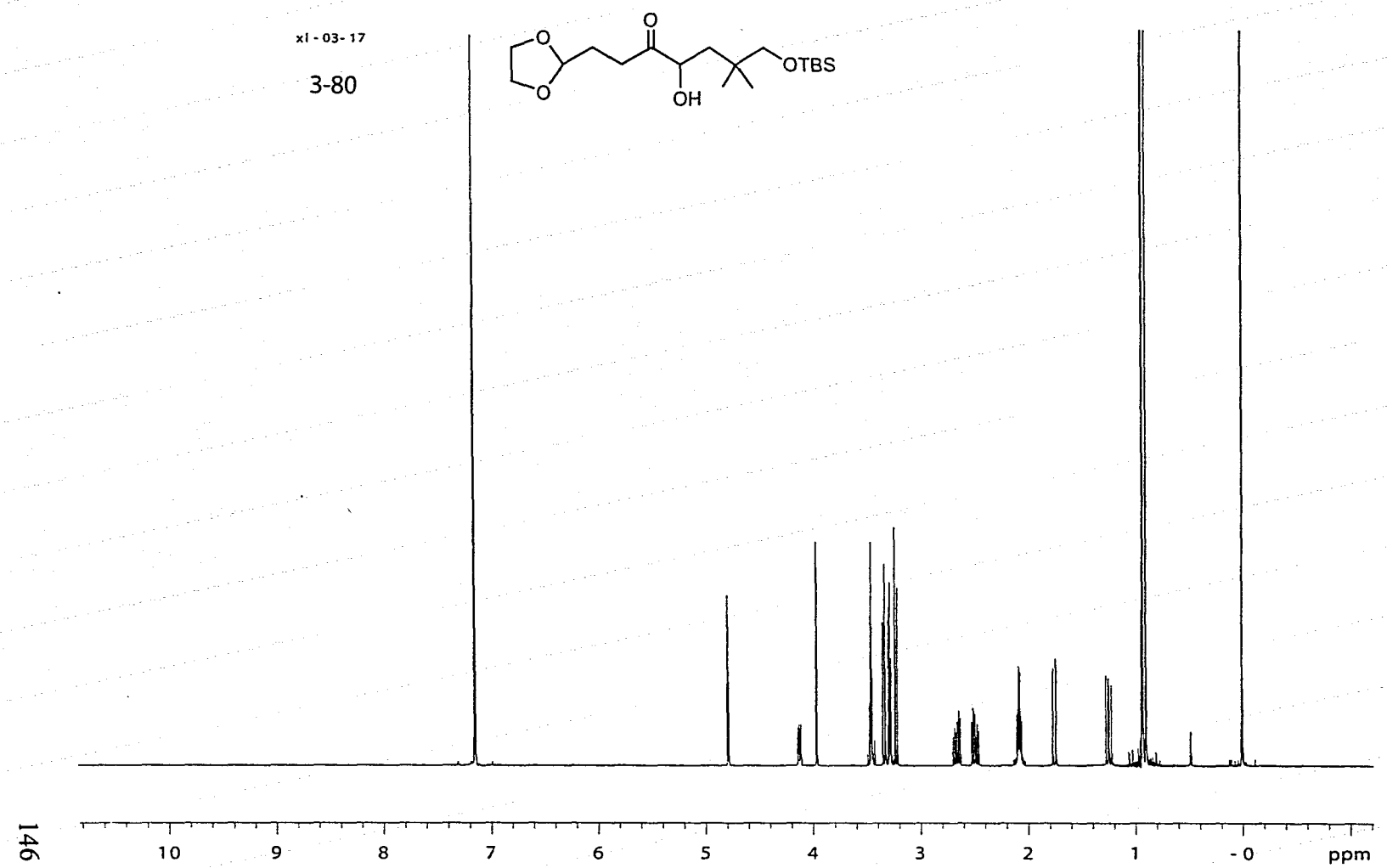
COSY

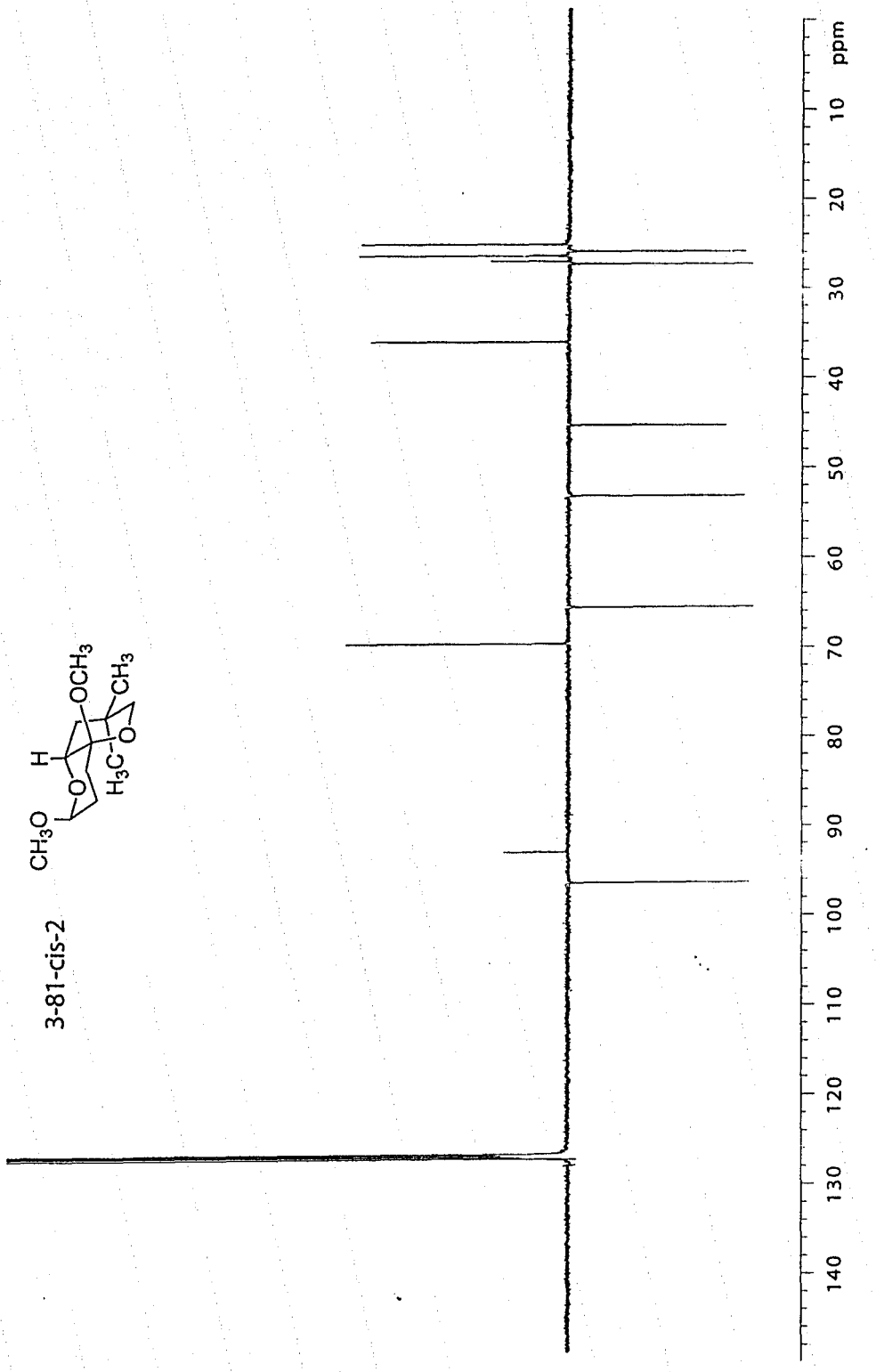


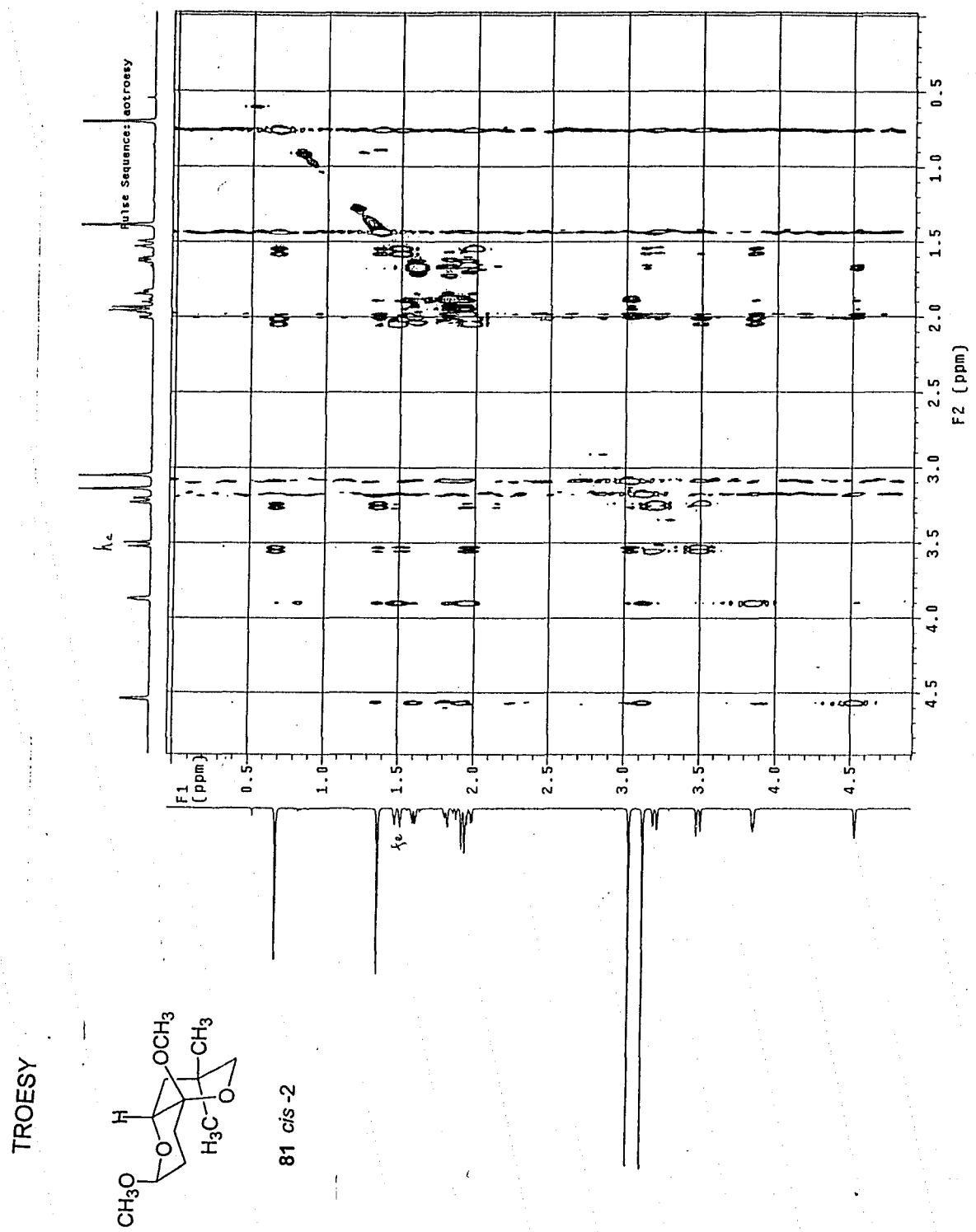


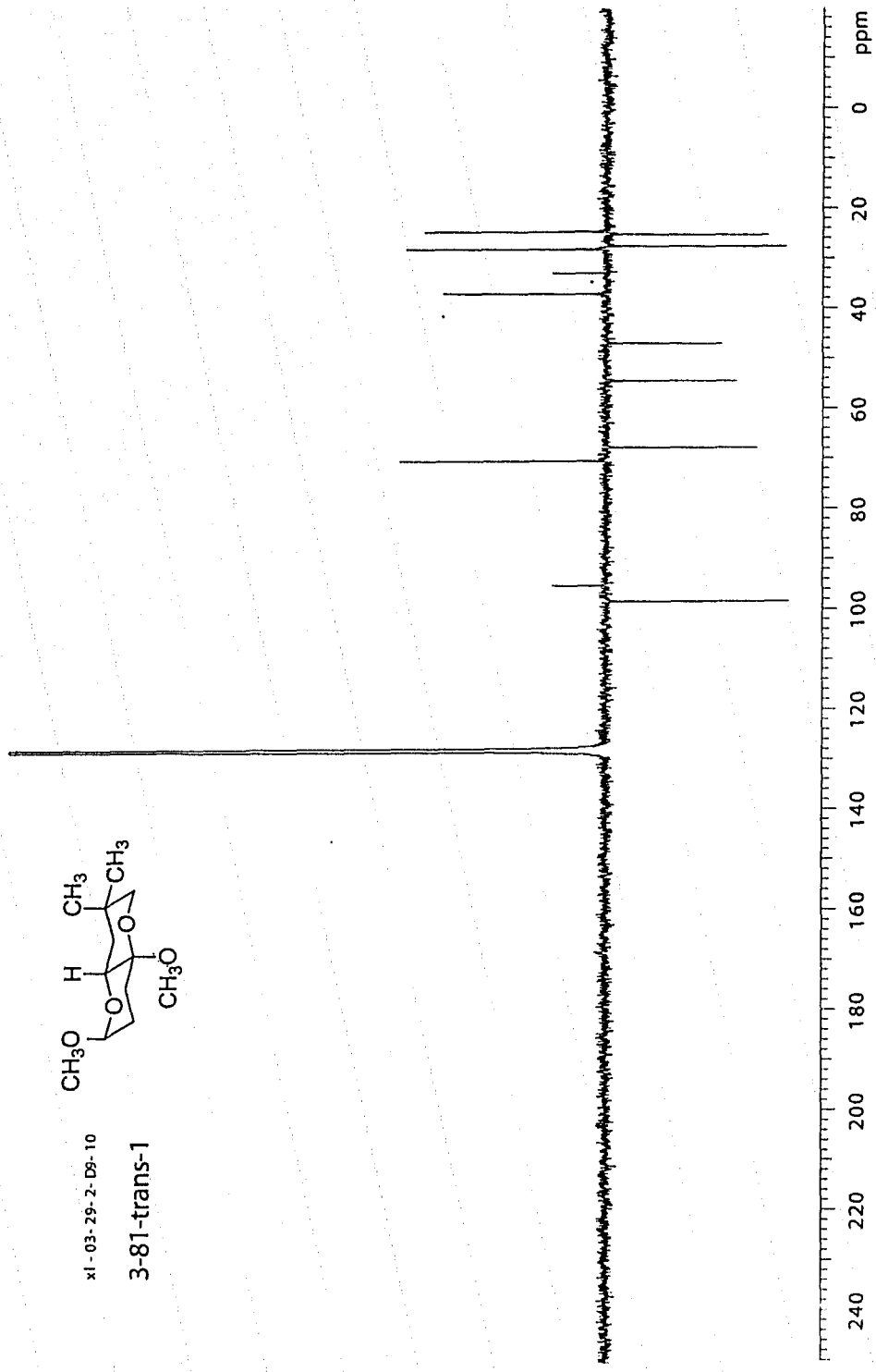


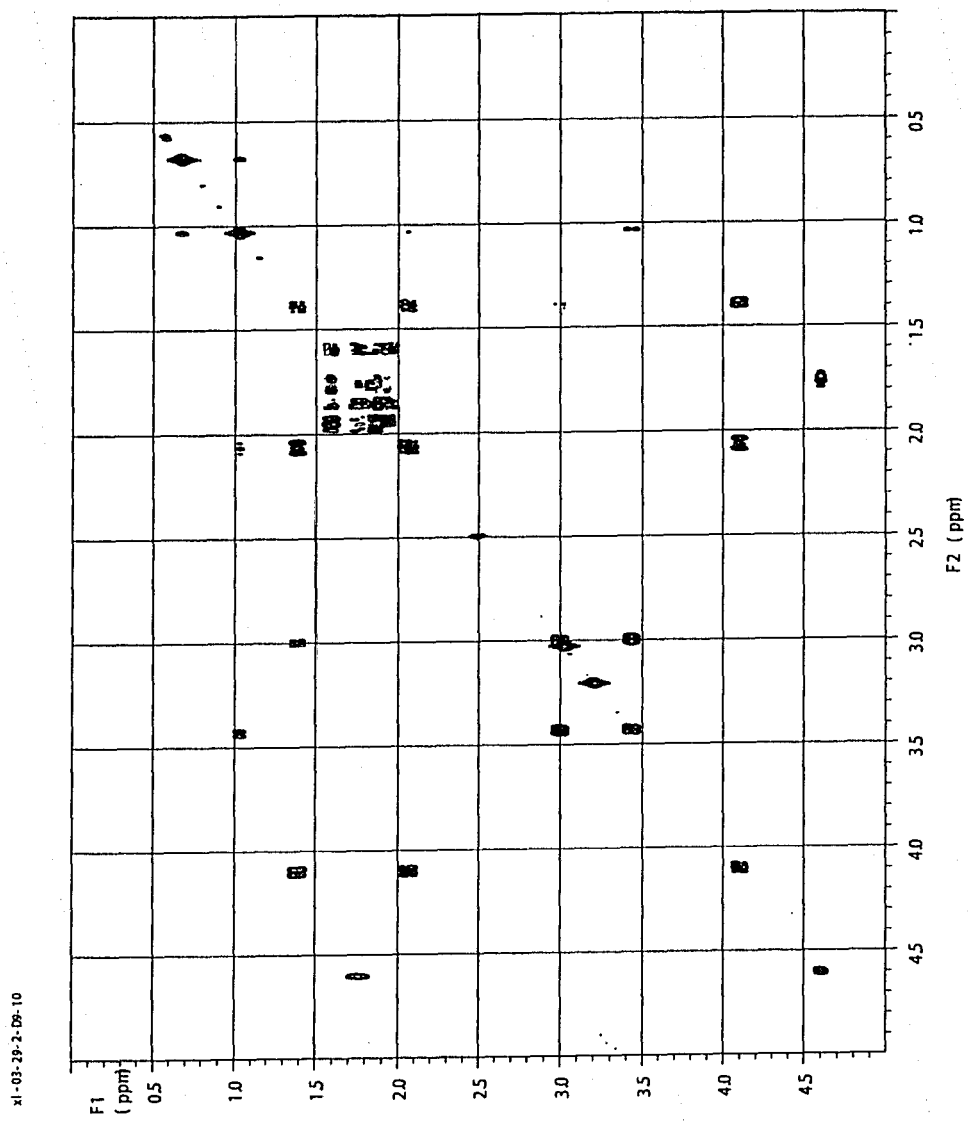












3-81-trans-1

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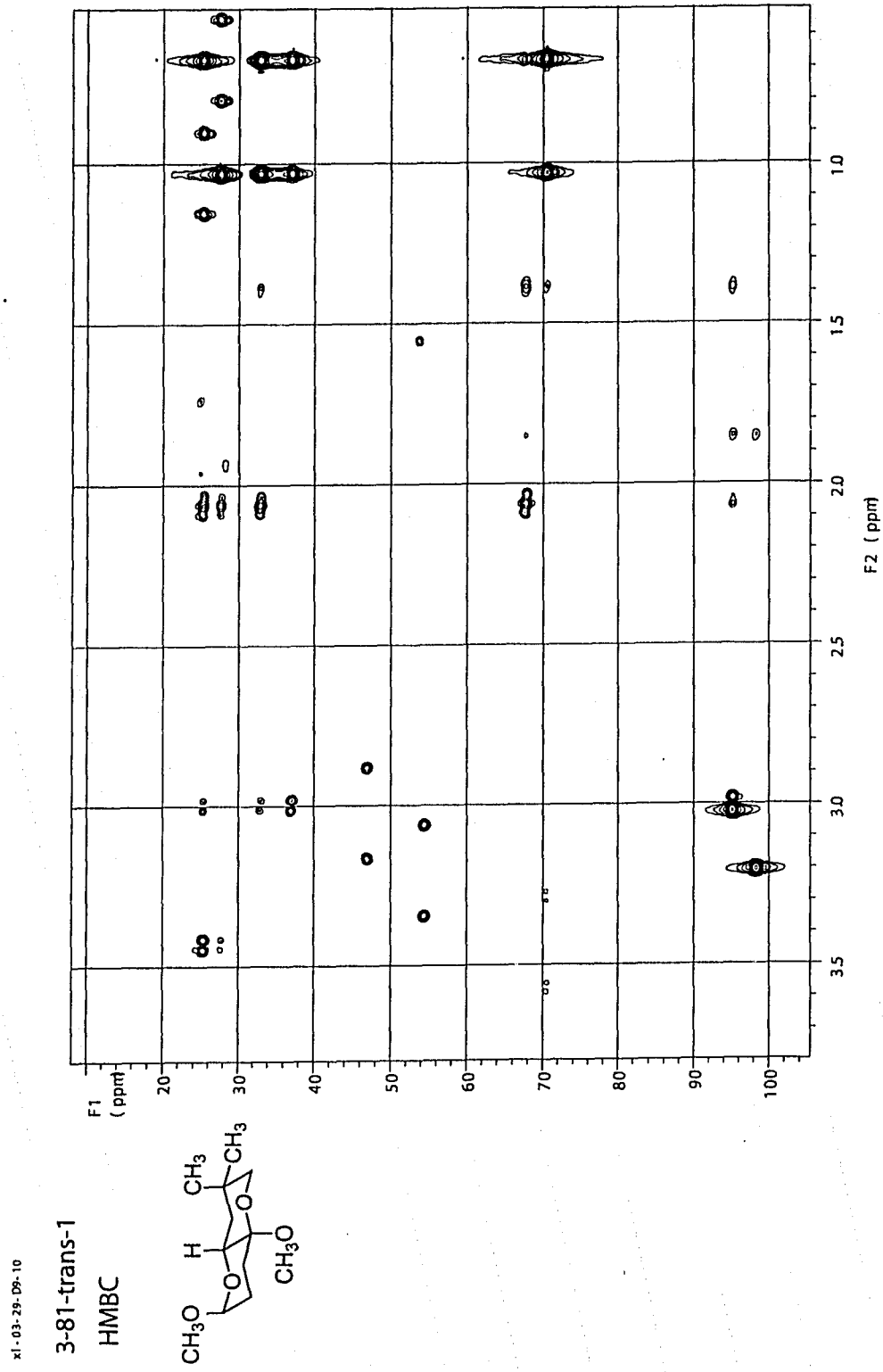

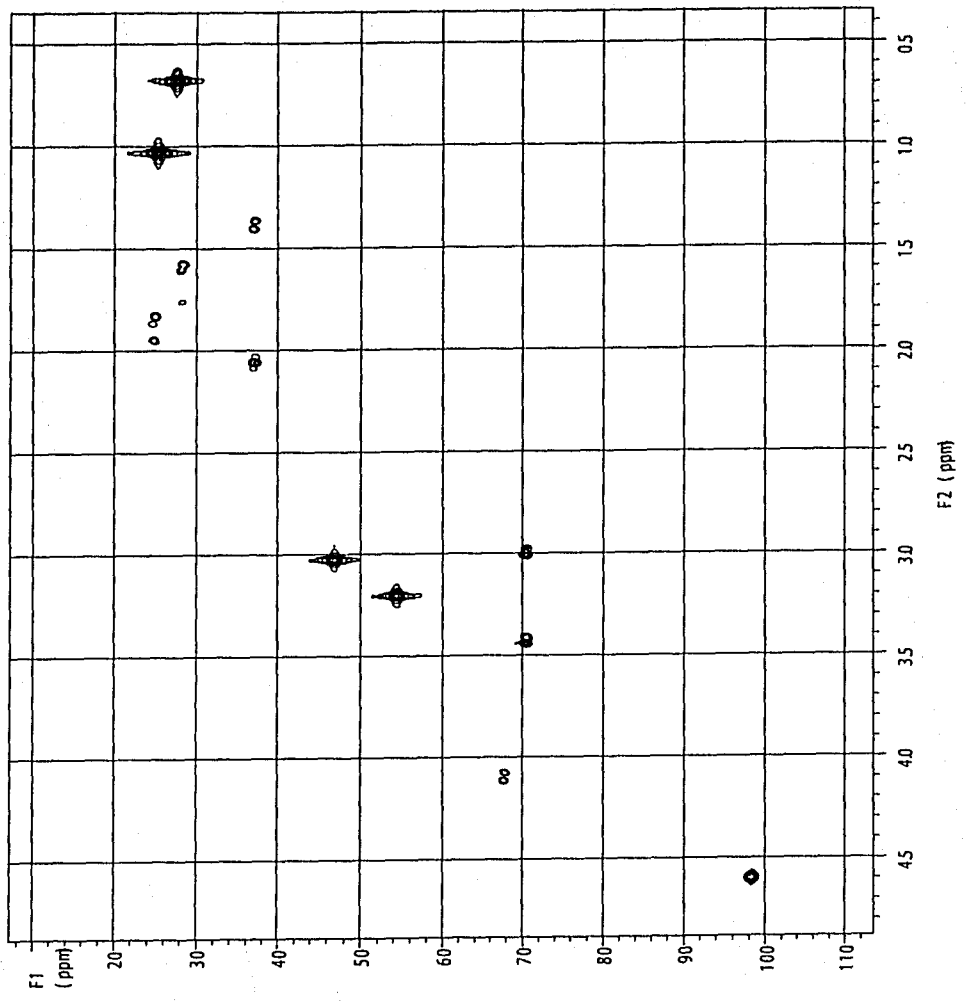

3-81-trans-1

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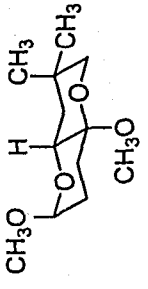

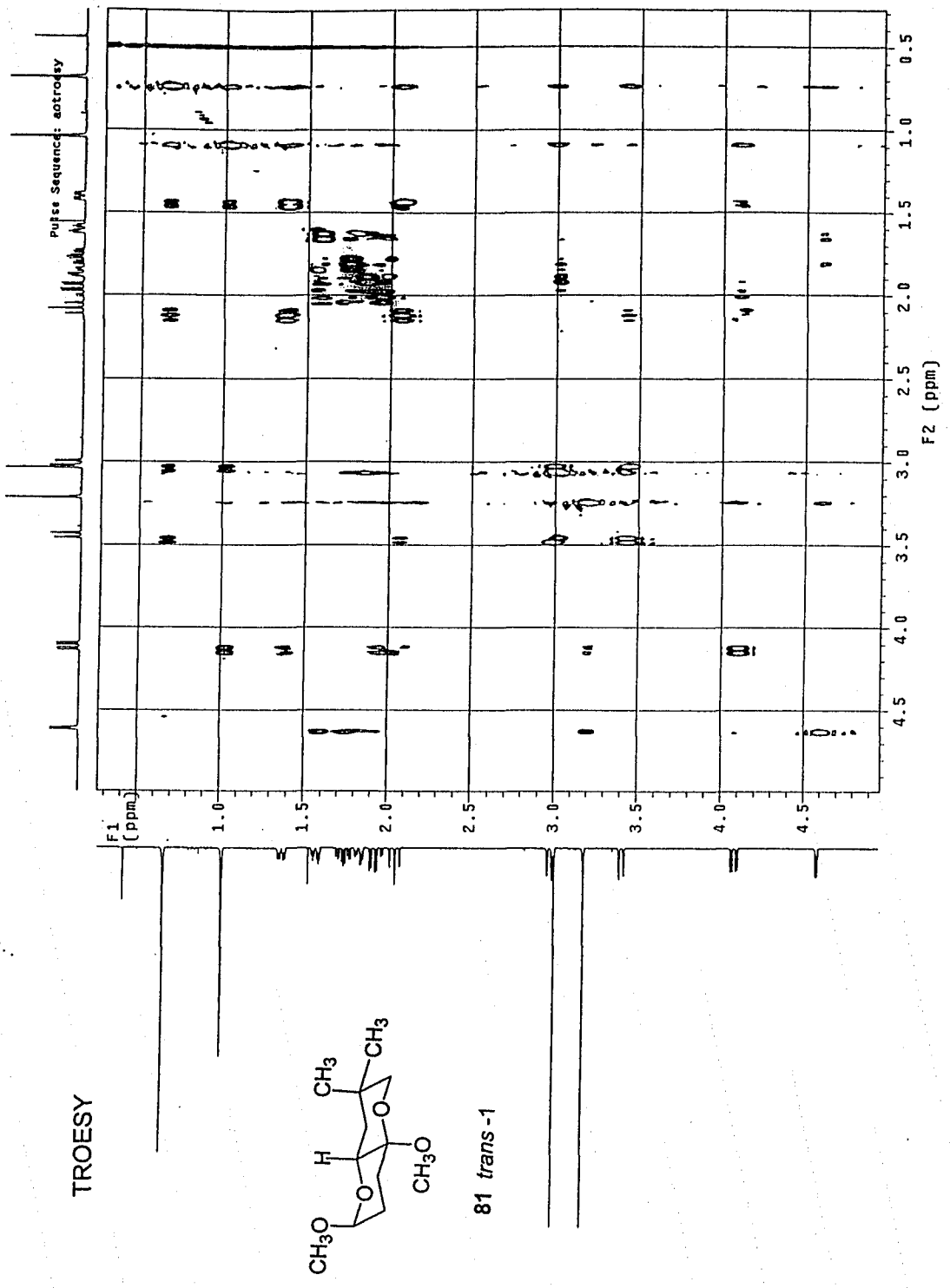

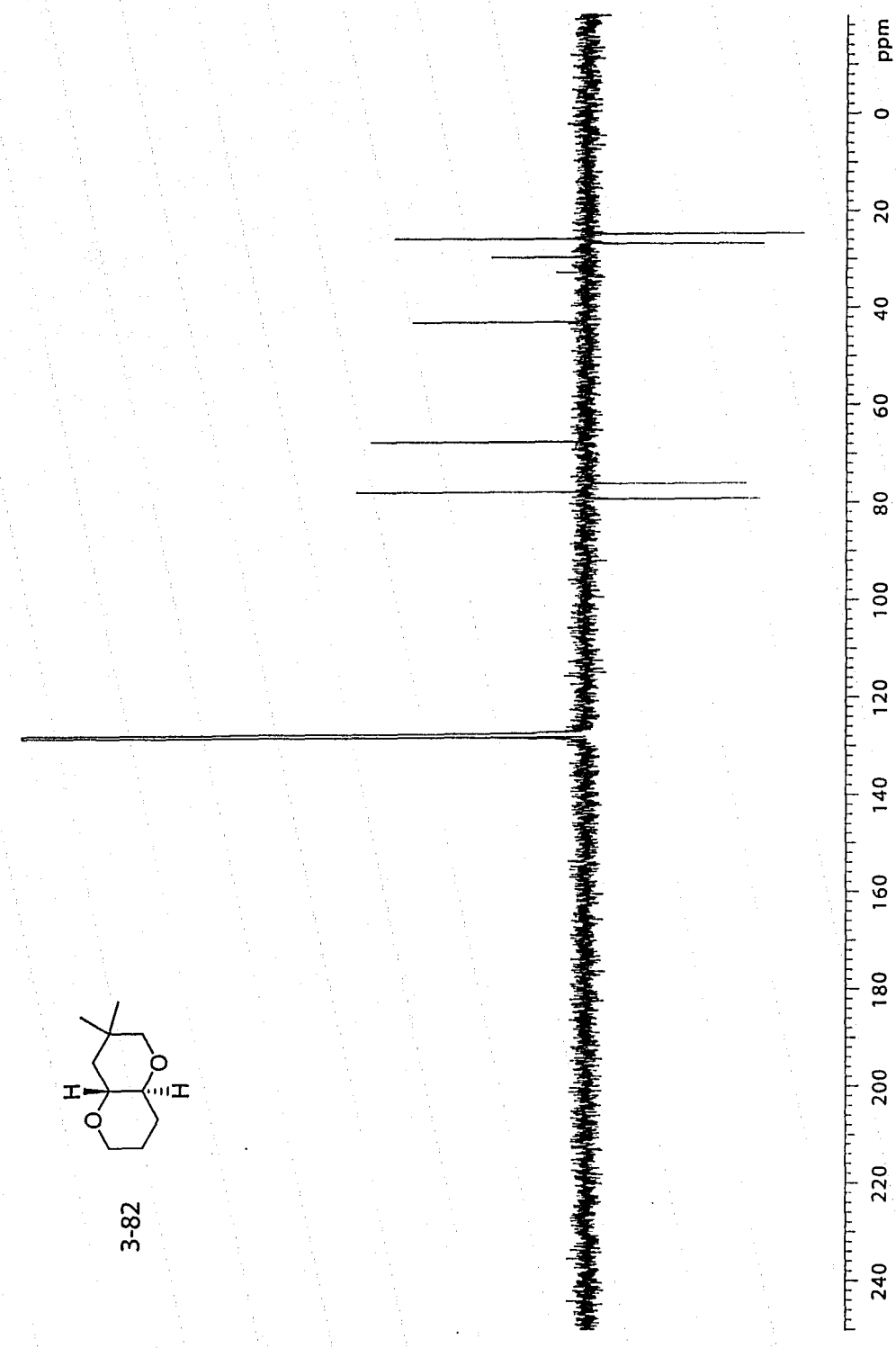

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